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CHAPTER 38

Property-Based Drug Design and Preformulation

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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. DiMasi[4] 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.

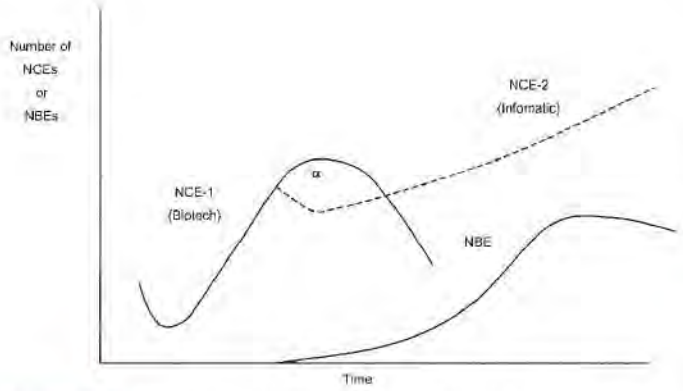


Figure 38-1. Charles Handy's sigmoidal growth curve. (From Handy C. The Age of Paradox. Cambridge, MA: Harvard Business School, 1995: 49-67. Copyright © 1995 by the Harvard Business School Publishing Corporation: all rights reserved.

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 infomatics, 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 increases 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 Informatic NCE-2 curve in Figure 38-1 will most likely need the simultaneous improvements of a number of infomatic-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

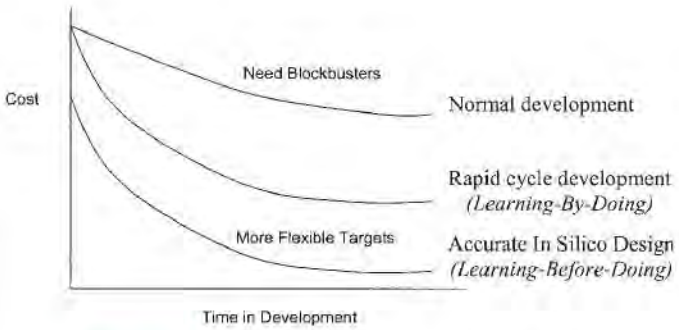


Figure 38-2. Cost savings by learning-before-doing.

foster integration of discovery and development. The ideal development of a NCE optimizes both "property-based" as well as "activity"-based design simultaneously. Continued improvements in efficiency will require that organizations be ready to adapt to new technologies and learnings. However, potential roadblocks to the integration of discovery and development efforts include high throughput (HT) decision-making, attrition, and the management of complexity.

HT Decision-Making

One of the attractive concepts for improving efficiency is that of successive screens. Currently, they come in two flavors, *in vitro* and computational to filter out poor drug candidates so resources are not wasted on unproductive activities.[9] The sequential paradigm

Discovery → Development

can now be replaced by the sequence

Discovery [design → synthesis] →
Selection [screen for activity → absorption → metabolism → toxicology] →
Development [formulation → animal pk testing → regulated toxicology → IND → initial clinical trials]

In essence, screens used in this manner are a way to simplify the complex process of discovering, selecting, and developing NCEs.

As efficient and useful as successive, hierarchical high throughput screens (HTSs) are for simplifying decision making, the question should be asked, "Have HTSs increased productivity?" As we alluded to under a previous section, productivity for IND filings (a measure of preclinical activity) has reached a plateau. This is most likely due to the use of successive filters in a decision-tree that then successively reduces future possibilities. If successive filters are employed, they could be prioritized so that earlier filters have higher quality. This would minimize the loss of potential opportunities.

Consider a situation of form selection in which scientists are trying to select the best molecule for development. In this multitiered approach, decision-making follows a progression of:

Hygroscopicity → thermal analysis & x-ray diffraction → accelerated solid-state stability

One impact of such decision-trees is that hygroscopic salts would rarely be developed (even if they have very advantageous bioavailability properties). If hygroscopicity were a property that prevented development, then any compound with this characteristic would be eliminated immediately. However, it is possible, with a good enough reason, to work with this situation.

Attrition

GAINS—Property-based screens have made tremendous gains over the last 5 years. This is due to the design of NCEs that have both activity and desirable physical properties such as solubility. These advances have been instrumental in reducing pharmacokinetic attrition during clinical trials.[7,10,11] On the other hand, more sophisticated technologies are needed to overcome low productivity problems associated with simple successive filters.

LOSSES—IMPACT OF FILTER IMPERFECTIONS—Reduced compound flow in the pipeline is a possible result of attrition filters. If these filters were perfect, this would not be a concern. Filters, however, hold back: (a) absolute negatives, (b) technical negatives, and (c) false negatives. Absolute negatives are compounds that are incompatible with the body. Consider, for example an insoluble, high affinity trap compound with a very high melting point (>240° C). Even if a pharmaceutical scientist were able to successfully formulate this compound for an intravenous formulation, it would most likely crystallize in the kidney. On the other hand, suppose water solubility was used as a filter. A technical negative that fails for adequate water solubility, may still be biocompatible. A highly lipophilic compound with a melting point of 100° C would be a compound of this type. This compound may be deliverable by special formulations and has the potential to be a viable NCE from the property-design point of view. However, both of these compounds would be screened out if water solubility were used as an attrition filter. The final type of negative is a false negative in which the filter removes a perfectly viable compound.

To appreciate the impact of losing good compounds as false negatives and formulatable technical negatives, consider the following situation. Three filters A, B, and C are to be used in succession. To calculate their impact, assume that each has the following characteristics. Each will pass 50% of the positives correctly, will block correctly the 25% absolute negatives, but will also block 25% of compounds that are either false or technical negatives. For this battery of successive filters the throughput of positives is 12.5%. However, the correct throughput of positives and formulable compounds is 42%. Thus the pipeline possibilities were reduced unnecessarily by 236%. How many compounds are being filtered out that previously might have taken a considerable amount of time to develop but were developable? A key goal for property-design should be not to lose technical negatives that a company has the core competencies to develop rapidly.

PROPERTY-BASED DESIGN IN LEAD SELECTION

One of the keys for continuous improvement and moving into the Informatic α phase of Figure 38-1 is to make better use of existing data and to obtain higher quality data. In addition, the active participation of special groups that have domains of expertise is also needed. As we have seen, simple models can promote efficiency but more sophisticated refinements that take into account complexity are needed to increase productivity.

As an example, one area of extreme complexity is understanding disease. The biotechnology epoch of the 20th century that focused on a single gene–single protein approach just doesn't work well with multi-gene disorders such as cancer or Alzheimer's disease. In order to understand the basis for human genetic variability, the human genome project pooled and sequenced the genes and nucleotides of many individuals to establish a baseline. Single nucleotide deviations from this baseline are termed SNPs (single nucleotide polymorphisms). Although rare diseases can occur from SNPs (eg, sickle cell anemia and cystic fibrosis), the most common diseases (eg, diabetes and asthma) may encompass 20–50 SNPs and may involve 10 or more genes. Research efforts are now ongoing to establish blocks of SNPs that correlate with a given disease predisposition. If such correlations can be found, then drugs can be sought to prevent disease expression. The complexity of this undertaking will require a much more sophisticated approach to drug development. Understanding complexity in property-design will also expand possibilities.

Ideally, a property-based design strategy would be able to anticipate and predict the physical properties of a proposed molecule from structure alone. This would be coordinated with activity-based and safety-based strategies so that predictions would be made on this triad of design characteristics. Proposed molecules could then be evaluated from structure alone to see if they either had (a) the requisite properties, or (b) the potential to be further designed to have the requisite triad of design characteristics: activity, solubility, and safety. For this latter group, knowledge of functional groups that have the flexibility for being modified would have to be identified so that further predictions could be carried out on modified structures for triad characteristics. Property-base possibilities would include compounds that had:

a. Passive diffusion properties (solubility & membrane permeability)
b. Crystal packing disruptive potential for passive diffusion

c. Special vehicle delivery potential
d. Prodrug enhancement potential
e. Stability enhancement potential.

FORWARD-FOCUS VISION

Some of the terminologies that we have inherited from crisis situations like attrition and triage cast images of what is to be avoided and what choices have to be made with limited resources. While it is necessary to recognize these areas, a focus on them may inhibit forward thinking and new solutions to get where we want to go. The 'forward focus' model is an alternative way to think about producing more products that add shareholder value. The principles of the model are[12]:

(1) If we focus on obstacles, we expend time and energy on obstacles rather than on getting where we want to go.
(2) When we clearly focus on where we want to go, we do whatever we need to do to get there with minimal wasted energy.

Ironically, empirical evidence suggests that focusing on obstacles may attract what we want to avoid.[12] The forward-focus vision concentrates on the efficient utilization of resources to enable more NCEs to come to market faster, and with higher quality. Its advantage over an attrition-focus strategy is that more energy is expended using existing knowledge to enlarge property-space possibilities and on the development of novel approaches. It has been said that[13] "In the realm of possibility, we gain our knowledge by invention." We also invent rules, but these must be used with caution.

LIFECYCLE OF RULES—Rules are the compilations of knowledge that enable us to carry out business efficiently. Even the best rules, however, should be viewed in the context of a lifecycle. Changing circumstances or new knowledge can cause rules that were formulated in the past to become inappropriate. One of the most useful roles rules play is that they provide a reference for obtaining a more precise understanding of physical phenomena. Attrition also can be thought of in terms of a lifecycle and be made productive.

MAKING ATTRITION NON-PERISHABLE—While late clinical-stage attrition is very costly, the loss of resources involved in attrition of NCEs prior to Phase I clinical trials is even more costly. It is possible that more that 85% of pre-Phase I activity is taken up by compounds that never progress to clinical trials. While this is accepted as an inevitable part of the research and development process, a program for capturing the knowledge from all of these failed NCEs might very well enhance the efficiency of property-design.

ACCEPTANCE OF COMPLEXITY—Rules that capture the essence of complex phenomenon is one strategy for designing properties. Another approach is to accept that physical systems will be complex and that computational approaches may be needed to design systems that can accurately predict. Such systems can analyze more situations in more detail than an individual. One key element that enhances acceptance of such computational approaches is that the reasoning or scientific basis of the predictions be understandable. For continuous progress, phenomena need to be understood at the molecular level.

MOLECULAR PRINCIPLES

Grasping the structure of a subject is understanding it in a way that permits many other things to be related to it meaningfully. To learn structure, in short, is to learn how things are related.[14] Insight that will lead to improved property-based design will result from using a variety of molecular tools that will give scientists an understanding of the precise interactions that occur between molecules, whether they be interactions between molecules among themselves or between molecules with biological systems. The two types of molecular interactions that we will be focusing on in this section deal with interactions in (1) crystals and (2) membranes.

Crystalline interactions are of interest because they ultimately determine solubility, melting point, and dissolution of NCEs. If we can gain a molecular understanding of the intermolecular interactions that occur between the molecules in a crystal, then we can gain insight into how we can predict and design molecules that have the properties we desire from structure alone. This is the ultimate goal of property-based design. For simple crystals, containing only the same molecules (no solvents or salt counterions), we will use the term *cohesive* to characterize the type of intermolecular interactions of the same type of molecule.

Membrane interactions between an NCE and a biological membrane will be termed *adhesive*, because they are between different types of molecules. Adhesive interactions are those types of interactions that also occur between solvent molecules and the NCE when it is dissolved in the aqueous environment of the digestive tract. Solvent-solute interactions control the familiar like- dissolves-like concept. For example, lipid molecules dissolve in oil more than they do in water. We refer the reader to the work of Abraham[15] for extensive research into the solvation phenomena. In this discussion of molecular property-based design, we will begin to examine the types of cohesive interactions that can occur in a crystal which impact its solubility (or insolubility).

Crystalline Interactions

Molecules in a crystal organize themselves in a limited number of regular arrays, which are termed space groups. There are 230 possible crystalline space groups; however, because pharmaceutical molecules are complex and in general not symmetric, the number of actual space groups for drug-like molecules is only about 3. These are shown in Table 38-1. The impact of regular ordering of molecules in a crystal is that, for a given space group, rules can be stated that allow the entire crystal to be replicated through a sequential series of translation, reflection, inversion, and other analytical geometric operations. For example, the operation for the very common space group for drug-like molecules, P21/c, is shown in Figure 38-3. The fundamental unit that is replicated is the unit cell. This is obtained from single crystal x-ray diffraction evaluations of the NCE. This unit cell (sometimes termed the asymmetric unit) has information regarding the number of molecules in the asymmetric unit and the dimension and angles of the unit cell.

Ultimately, it is the molecular structure of the molecule that determines the space group and the number of molecules in the unit cell of a particular crystal. However, for a given molecule, the crystals that can form are not unique. Because molecules can assume different conformations, and because a variety of crystallization conditions can influence the crystal that forms, a variety of different polymorphic forms are possible (this will be discussed in detail in later sections). Polymorphic forms may have different physical properties, especially dissolution characteristics that could impact bioavailability and very often these different forms can interconvert. One objective of active pharmaceutical ingredient (API) design is to find the most stable crystalline form so that polymorphic changes do not occur once an NCE is formulated into a dosage form. It is the packing of the atoms in a given crystal that will be considered next and the forces that lead to insolubility.

CRYSTAL PACKING

Crystal packing is dominated by two opposing phenomena: (1) maximizing the number of hydrogen bonds (H-bonds) that can be formed for a given molecular structure, and (2) packing the atoms of the crystal as densely as possible (ie, close packing). Ultimately, molecular shape and the distribution of the H-bond donor and acceptor groups in a given molecule determine the most favored polymorphic form chosen by nature.

Table 38-1. Possible 3-Dimensional Crystalline Space Groups

CRYSTAL SYSTEM	NUMBER OF INDEPENDENT PARAMETERS	PARAMETERS	MATHEMATICAL ABUNDANCE	ORGANIC CRYSTAL ABUNDANCE
Triclinic	6	$a \neq b \neq c$; $\alpha \neq \beta \neq \gamma$	2	High ?
Monoclinic	4	$a \neq b \neq c$; $\alpha = \gamma$; >90	13	High $P2_1/c$
Orthorhombic	3	$a \neq b \neq c$; $\alpha = \beta = \gamma = 90$	59	Very Low $P2_12_12_1$
Tetragonal	2	$a = b = c$; $\alpha = \beta = \gamma = 90$	68	~0
Trigonal rhombohedra	2	$a = b = c$; $\alpha = \ = \gamma \neq 90$	6	~0
Trigonal hexagonal	2	$a = b = c$; $\alpha = \ = 90$; $\gamma = 120$	19	~0
Hexagonal	2	$a = b = c$; $\alpha = \ = 90$; $\gamma = 120$	27	~0
Cubic	1	$a = b = c$; $\alpha = \beta = \gamma = 90$	36	~0

H-bonds are non-covalent interactions that can occur within a given molecule (intramolecular) and between different molecules (intermolecular). Essentially they are electrostatic in nature and as such are long-ranging forces (force varies as $1/r^2$). Weak H-bonds usually have a higher multiplicity of interactions than strong H-bonds because they are more flexible, as illustrated Table 38-2. Intramolecular H-bonds form when the atoms in the molecule can be arranged such that a ring of covalently linked atoms (usually 6) is closed with 1 or more H-bond (Fig 38-4A). Intermolecular H-bonds form between different molecules of a crystal (Fig 38-4B–E).

High affinity traps with their associated insolubility and high melting points can be attributed to H-bonding networks and/or close packing. As a general rule, H-bonding network insolubility is associated with the number of H-bonds per molecule as well as the number of H-bond between molecules in a crystal. In Table 38-3, pairs of molecules are shown that have the same water solubilizing groups but differ in their H-bonding motifs. Figures 38-4B and C show molecules that form a dimer and a single chain, respectively. Each has 2 H-bonds per molecule but differ in the number of H-bonding neighbors. Similarly, Figures 38-4D and E show molecules that form single and double H-bonding chains, respectively. In this case, each molecule has the same number of H-bonding neighbors, but has a different number of H-bonds per molecule. For both pairs, Table 38-3 shows that increasing either the number of H-bonding neighbors or the number of H-bond per molecules reduces the effectiveness of the water-solubilizing group. The negative influence of close packing on physical properties is most likely due to the introduction of van der Waals dispersion forces that vary as $1/r^6$. Zwitterion formation, conformationally restricted molecules, or high packing density molecules have the highest intrinsic insolubility potential.

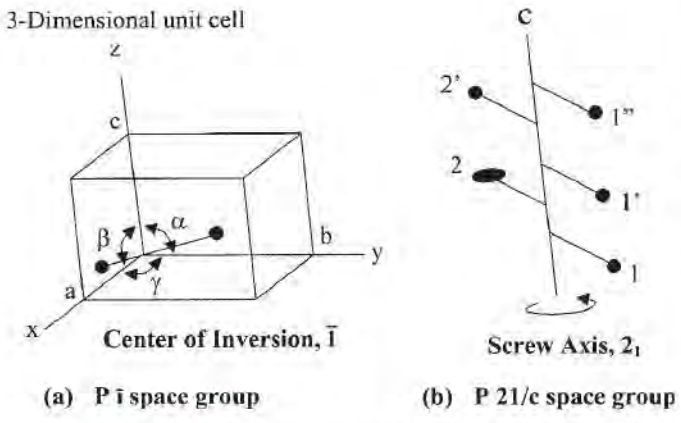


Figure 38-3. Repeat mechanism (space group rules).

Membrane Interactions and Permeability

THEORIES OF PASSIVE PERMEABILITY

The *water of desolvation* hypothesis, explored extensively by Burton and co-workers[16,17] states that the major barrier for passive permeability NCEs across cell membranes is the energy needed to remove bound water from the molecule so it can enter the hydrophobic portion of the lipid bilayer. Although both hydrophobic and hydrophilic NCEs would have some bound water associated with them in solution, the adhesive H-bonding between water and the polar groups of hydrophilic NCEs group would be much stronger and thus need to be broken before transport can take place. Strong supporting evidence for this concept has been found using the peptide bond as the polar moiety and has led to an experimental partitioning system, $P_{\text{heptane/ethylene glycol}}$, that appears to be more predictive of permeability than the widely accepted octanol/water partition coefficient.[16]

The *molecular rigidity hypothesis* posits that molecular weight itself is not a sufficient condition to impart reduced membrane permeability but may itself be a factor that is correlated with the number of rotatable bonds and polar surface

Table 38-2. Comparison of Hydrogen

	BOND CHARACTERISTICS	
	WEAK	STRONG
Bond Character	Electrostatic Broad	Covalent Narrow
Bond Length	1.5 Å–3 Å	1.2 Å–1.5 Å
Directionality	160° ± 20°	~ 180°
Multiplicity	2,3,4 Centered	2 Centered
XH ···· A	A / XH ⋯ A′	A / XH ···· A′
	A′	A″
2 Centered	3 Centered	4 Centered

area. If these two latter parameters are below certain values, then compounds that are sufficiently rigid and non-polar may be absorbed independent of molecular weight.[18] Some factors that can impart rigidity besides fused-ring systems are molecules that have intramolecular H-bonds that form a ring or cyclic peptides.

THEORIES OF ACTIVE PERMEABILITY

NUTRIENT UPTAKE MECHANISMS—The passive permeability limitations discussed above for polar or ionized molecules do not hold for a number of nutrients. Special site-specific transporter proteins are present in membranes that are used to bypass the lipophilic barrier of bilayer membranes.[19] Among these are transporters for peptides, amino acids, nucleoside and nucleobase, ascorbate, and a few other molecules such as glucose and urea. Application of the PEPT1 transporter to prodrug delivery will be discussed below.

XENOBIOTIC EFFLUX MECHANISMS—Membrane transporters belong to one the largest classes of proteins, termed ABC (ATP binding cassette) proteins that can transport against the concentration gradient of the substrate. The characteristics of these membrane proteins are: (a) 2 transmembrane domains [regions of the protein embedded in the membrane], and (b) 2 ABC units [which bind ATP].[20] Defects in ABC proteins are the cause of many human inherited diseases. In most studies, ABC proteins are the multidrug resistance proteins (MDR) that remove therapeutic agents from cells by an active efflux.

MDR1 (or Pgp1) is one of the most extensively studied ABC proteins. Its normal function is believed to protect cells and organisms from toxic substances.[21] There are 7 identified proteins that have been placed in the MDR family, all are organic anion transporters. MDR1, MDR2, and MDR3 have all been associated with multi-drug resistance.

PASSIVE-DIFFUSION DESIGN

One way to reduce conformational restriction is to open up a restricting ring. Alternatively, Figures 38-4 A, D & E discussed in a previous section shows that the substitution of a t-butyl group for a phenyl group dramatically increased solubility by breaking up H-bonding so that each molecule only had 2 rather than 4 H-bonds per molecule. This was due to the bulkiness of the t-butyl group that prevented dimer formation.

PRODRUG DESIGN

Often NCEs have adequate biological activity but do not have the required physical properties to become a drug. For orally administered drugs, the compound needs to dissolve in the gastrointestinal tract and be absorbed by the intestinal membranes; for intravenous drugs, the compound must have adequate solubility in its dosing vehicle and in the blood so it can be delivered safely without causing embolisms. Prodrugs are one way to solve a number of safety and property-design problems and should be considered early in the design phase. Prodrugs are inactive analogs of biologically active compounds that can be converted into active compounds by the body's chemical processes. They are designed to have the critical properties that the parent compound lacks. Poor membrane permeability, poor solubility, and poor dissolution are problem areas that may be addressed by prodrugs. All three of these areas impact the passive absorption of drugs. Prodrug design has also been used to reduce toxicity.

Poor Membrane Permeability

One of the major roles of the outer limiting membranes of cells is to isolate it from its surroundings. Three factors that inhibit the passage of a drug molecule through biological membranes are: (a) charge, (b) water of hydration, and (c) molecular size. The importance of charge is related not only to the hydrophobic environment of the bilayers but also to the asymmetry of plasma membranes. Because these membranes are composed of two layers of phospholipids (a bilayer), the radius of curvature of micron-sized cells requires that phospholipids with small head groups be located in the inner leaflet of the bilayer to prevent excessive tension on the membrane.[22] The anionic phospholipid, phosphatidylserine (PS), resides almost exclusively in the inner leaflet due to an active process.[23] This negatively charged inner leaflet of the plasma membrane has

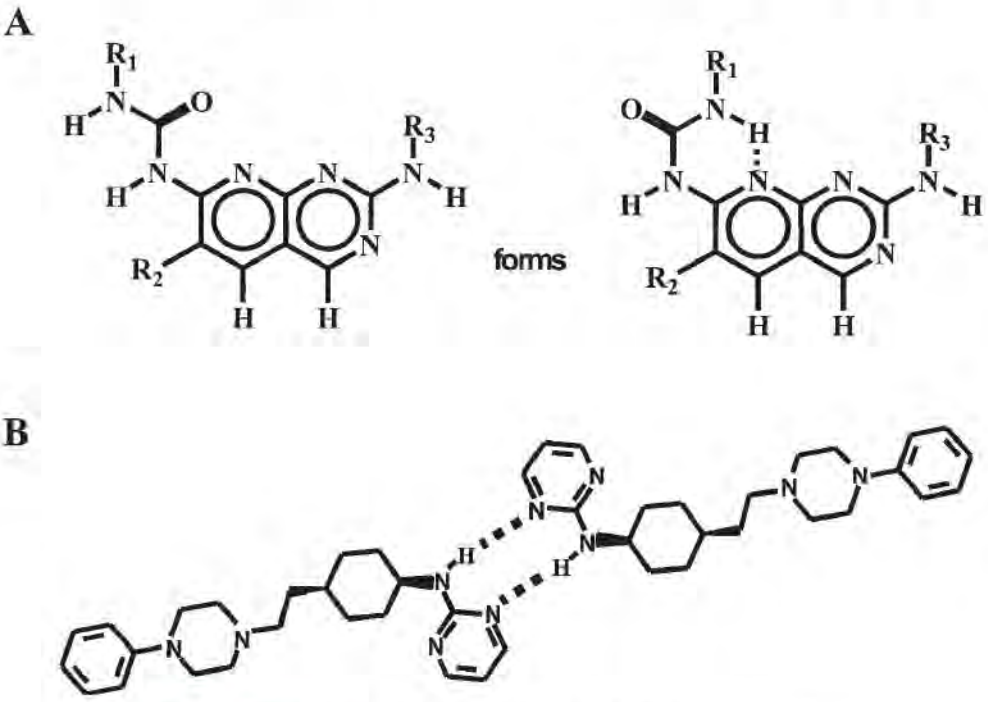


Figure 38-4. Examples of intra- and intermolecular hydrogen bonding.

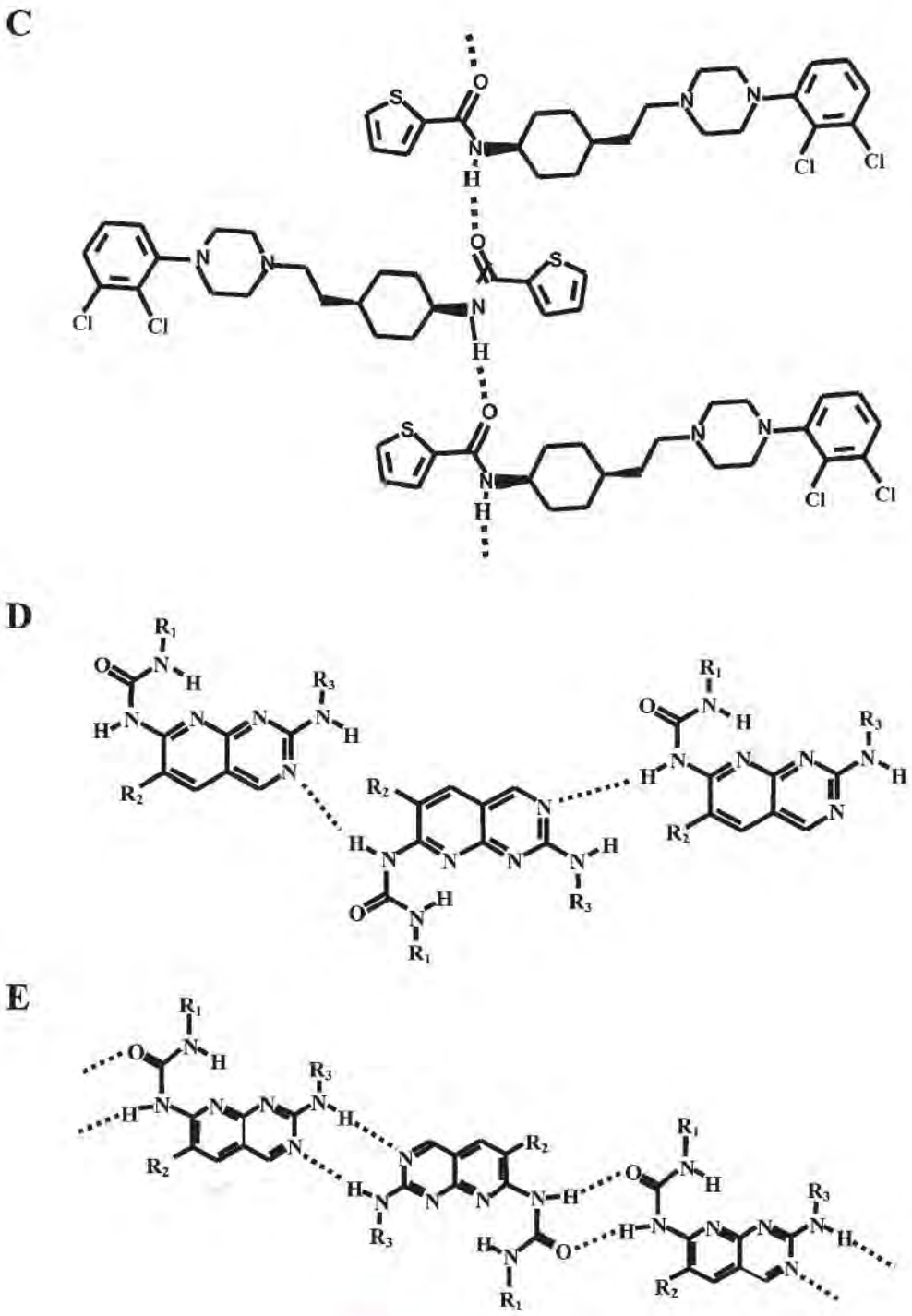


Figure 38-4. *Continued.*

Table 38-3.

pH	SOLUBILITY μg/mL 1	5.6	7.3	13	NETWORK TYPE	# H-BOND /MOLECULE	# H-BONDED NEIGHBORS
B	17600		8		Island	2	1
C	14		0.05		Sgl. Chain	2	2
D		1700	610	25	Sgl. Chain	2	2
E		16	10	6	Dbl. Chain	4	2

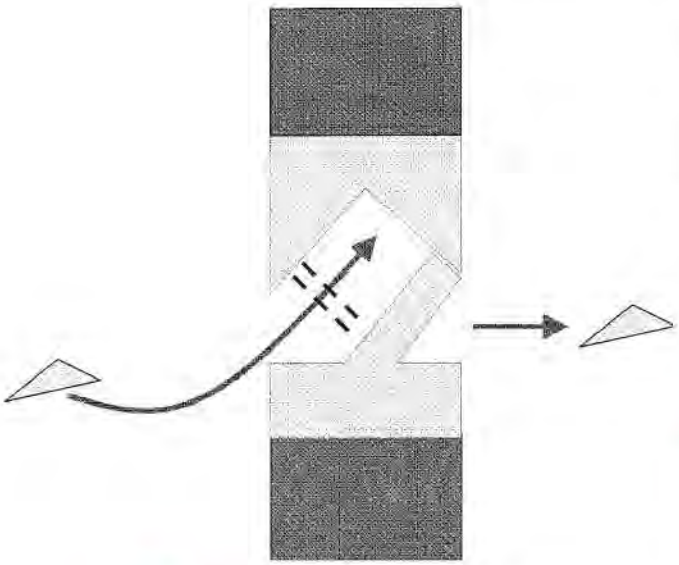


Figure 38-5. PepT1 cattle-gate mechanism.

been shown to control the tissue distribution of basic cationic drugs[24] and the permeability of the anthracycline base, doxorubicin, in a biphasic manner.[25] One might expect this inner leaflet would impact the absorption of anionic drugs. To circumvent these barriers to ionized and polar nutrients like peptides, amino acids, and nucleoside bases, cells developed a number of special transport proteins. Prodrug efforts are now ongoing to exploit these membrane transporters to enhance drug absorption.[26]

Use of Membrane Transporter Systems

Recently, some of the structural requirements of the plasma membrane peptide transporter, PEPT1, have been elucidated.[27-29] The binding requirements and the cattle-gate mechanism for PEPT1 are shown in Figure 38-5. Among the number of drugs reported to be transported by PEPT1 are ACE inhibitors (captopril, enalapril, lisinopril), penicillin, and cephalosporins (ceftibuten, cefadroxil). The advantage of this transporter is its high capacity (grams/meal). Successful prodrug strategies utilizing PEPT1 have been reported. The antiviral agent, Valtrex (valcyclovir-*GlaxoSmithKline*) is a prodrug of Zovirax (acyclovir). It has recently been observed that the H-bonding of the guanidine moiety of L-valaciclovir may enhance its PEPT1absorption.[30]

Reducing Ionization

Most Factor Xa inhibitors for preventing the activation of thrombin and blood clots have utilized a highly charged group, either a guanidine or an amidine group. These groups, however, limit the bioavailability of these compounds when used orally. One strategy to overcome this problem is to synthesize a prodrug which has a reduced charge for oral absorption but which can be converted in the systemic system to the active charged compound. Scientists at *Millennium* have recently designed a Factor Xa inhibitor that utilizes amidoximes as prodrugs for amindines.[31] These prodrugs showed good bioavailability but the conversion to the amidine was only 20%. Although the amidoxime prodrug approach apparently has been successful in masking charge for other chemical entities, in this situation, steric factors evidently retarded activation *in vivo*. This raises another concern with prodrugs: the potential toxicity of the intact prodrug moiety.

The pentamidines are very effective antimicrobial agents against a variety of pathogens and have been used to treat malaria and leishmaniasis. However, their use has been limited to systemic injections since a doubly charged drug is poorly absorbed. Exploration of amidoximes as prodrugs for amidines[32] has led to a new agent, DB 289, that has excellent bioavailability and is currently undergoing phase II clinical trials to treat *Pneumocystis carinii*, a fungal infection in infants that have immune deficiencies and in AIDS patients.[33] Studies with Caco-2 cell monolayers indicate that the greater permeability of the prodrug is due to its ability to transport passively across cell membranes by the transcellular route compared to the pericellular route of the parent compound.

Reducing Water of Hydration

In a previous section, the desolvation hypothesis was discussed in which the impact of strong H-bonds between NCE polar groups and water provides barriers for absorption (due to the need to remove this water before traversing the hydrophobic environment of bilayer acyl chains). Using prodrug strategies to make polar groups more lipophilic is one method to increase permeability and this has been accomplished for peptides by designing cyclic compounds that encourage intramolecular H-bonding and thus reduce water of hydration, make a more compact, rigid molecule, and minimize adhesive interactions with the membrane phospholipid head group.[34]

Size of Molecule

Although molecular weight has always been considered an important determinant of permeability, questions have recently arisen regarding the exact molecular property that determines a reduction of permeability with increasing molecular size as discussed in a previous section. We have discussed the hypothesis that increased molecular rigidity and a reduced polar surface area may enhance permeability. Results with cyclic peptides would seem to be consistent with this hypothesis as the Type I β-turn both reduces the polar surface area and enhances molecular rigidity. In addition, a molecule with more conformational flexibility would appear to present a larger size entity to the membrane.

POOR SOLUBILITY

Using prodrugs for solubility enhancement can take at least two different pathways: (a) increasing water solubility, and (b) disrupting crystal packing. The latter application has as much promise as the first, yet it is less obvious. The reader is referred to the previous discussion on crystal packing. Enhancing ionization with phosphate moieties has been used for both intravenous and oral applications. The intravenous is the earlier.

INCREASING IONIZATION—Fosphenytoin (Cerebyx-*Pfizer*) is an injectable, phosphate prodrug of phenytoin (Dilantin- *Pfizer*) for the treatment of epilepsy that is freely soluble and rapidly cleaved to phenytoin after injection (half-life 8–15 min). The aqueous solubility of the parent drug is 20–25μg/ml while the solubility of the prodrug is significantly greater (approximately 88,000μg/ml). Local toxicity (pain, burning, itching) that is associated with phenytoin administration due to its high pH formulation is greatly reduced since the more highly soluble prodrug can be formulated at physiological pHs.[35]

DISRUPTING CRYSTAL PACKING—Parecoxib sodium (Pharmacia) is a good example of using prodrugs to disrupt H-bonding and crystal packing as well as increasing pK_a to enhance solubility. For post-surgical pain management, a compound must not only be effective and have few side effects, but it must also be formulated so that a minimal injection volume is administered. Although valdecoxib (*Pharmacia*) possessed

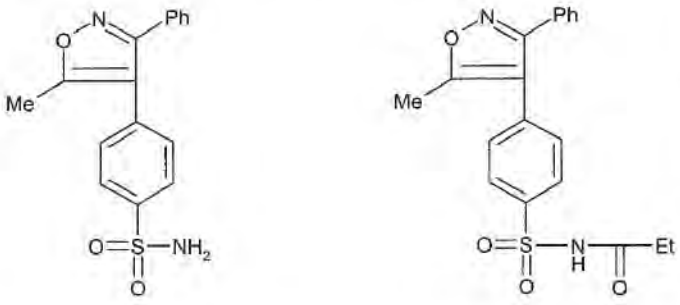


Figure 38-6. Prodrug of valdecoxib increases solubility by decreasing H-bonding.

the required potency and safety profile, its solubility was insufficient for this application. Increased water solubility was imparted to the prodrug, parecoxib, by making a prodrug of valdecoxib (Fig 38-6).[36,37]

POOR DISSOLUTION

Prodrugs may be used to improve dissolution properties. For example, Fosamprevavir (Vertex - *GlaxoSmithKline*) is an oral prodrug of Amprenavir (Agenerase - Vertex - *GlaxoSmithKline*), an anti-viral for HIV infections. Although agenerase is approved for HIV treatment, its poor water solubility necessitated that the drug be formulated with large amounts of excipients for optimal dissolution and bioavailability. Typical clinical dosage routines included dosing at 1200 mg (8 capsules) twice or three times a day when plasma concentrations fell below therapeutic levels. The large number of capsules and the food and water restrictions associated with administration of this drug provide barriers to patient adherence with the prescribed therapeutic regimen. By synthesizing the highly soluble phosphate prodrug, fosamprevavir, it is anticipated that adequate drug levels can be achieved with out food or water restriction at 2-700 mg tablets twice daily.[38] Currently, fosamprevavir is completing Phase III clinical trials.

TOXICITY REDUCTION

Xeloda (capecitabine - *Roche*) is a prodrug of the anticancer drug 5FU.[39] The parent compound has a number of dose-limiting side effects including: myelo-suppression, intestinal toxicity, and reduction in bone marrow function. Capecitabine reduces the intensity of these side effects by utilizing intestinal, liver and tumor enzymes to generate 5FU in the tumor cell. Camptosar (irinotecan HCl - *Pharmacia*) is a second line agent for advanced colorectal cancer. It is a prodrug of the natural alkaloid camptothecin[40] that is activated by carboxylesterase-2 when it occurs in the tumors. This prodrug greatly increases the solubility of camptothecin.

Taxol's (paclitaxel - *Bristol-Myers Squibb*) low aqueous solubility has necessitated that its intravenous formulation include Cremophor EL which has serious side effects. Recently, a prodrug, paclitaxel oleate, has been shown to not only be activated *in vitro* and in rabbits, but also has been shown to have pharmacokinetic parameters superior to paclitaxel.[41] This raises the possibility of using the most widely prescribed anti-cancer agent with much greater safety. In addition, *Merck* scientists have shown that prostate specific antigen (PSA), a serine protease with chymotrypsin-like activities enzyme, can be used to convert the inactive prodrugs of doxorubicin[42] and vinblactine[43] into the active agent within the tumor thereby reducing side effect of the parent drugs.

In summary, Figure 38-7 shows three types of drug possibility spaces for property-design. The first, at the bottom of the triangle, shows the traditional drug space for compounds that have adequate physical chemical properties and have been found by traditional discovery techniques. The second possibility space is shown in the middle section of the triangle. This space requires more active participation by the property designer to utilize all available tools when physical chemical problems arise. The techniques listed here for simplicity include special delivery systems (SDS) such as self-emulsifying drug delivery systems, prodrugs to break up crystal packing or to add water solubilizing or lipophilic groups, SDS for lipophilic prodrugs, and crystal packing disruptions designed to reduce H-bonding interactions and dense crystal packing. Technology will produce even more options for the future. Finally, there is the physiologically negative drug space or the region of high-affinity traps. These molecules usually have extremely high *in vitro* activity, but have been so over-designed for activity that they suffer from poor physical chemical properties. Sometimes these molecules can be delivered to the systemic system with clever formulations or drug delivery systems, but their poor physical properties ultimately reveal themselves when they crystallize out in the renal tubules of the kidney when solubilizing factors have diffused away from the drug molecules. The ability to anticipate the second possibility space and to avoid the negative-property space at the top of the triangle is a worthy goal for property-based design. This is the subject of the next section.

MACHINE LEARNING SYSTEMS

Artificial intelligence (AI) is a computational algorithm that would be called intelligent if a human exhibited it. One of AI's theses is that computers can simulate any effective procedure.

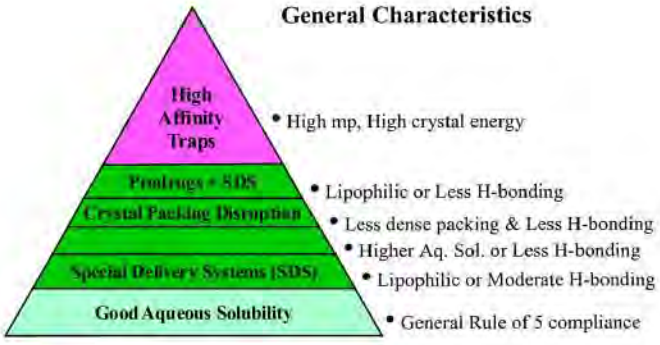


Figure 38-7. Possible and physiological-negative drug spaces. See Color Plate 5.

As John von Neumann once said: "Tell me what a machine cannot do, and I will always be able to make a machine that can do it!" Opponents of AI once defined intelligence as learning. Machine learning is AI's response to that challenge. In the following sections, *machine* will be used synonymously with a computational algorithm.

Machine learning is an area of AI that develops techniques that allow computers to, in some sense, "learn." If the pharmaceutical industry is to become more efficient and reduce cost, it must learn more efficiently. Since 90–95 % of the resources that are expended on NCE development are spent on compounds that will never advance, learning from this experience is an imperative. Machine learning may be the way the industry can reduce cost by learning before doing as we have shown in Figure 38-2. Activity-based design utilizing rapid machine learning techniques would efficiently use the results of high throughput screening to develop highly accurate pharmacophores. In addition, *in silico* activity screening and chemical route design technology would generate structures that are synthesizable, scalable, and match different aspects of these pharmacophores. Safety-based machines would accurately predict different features such as mutagenicity, clastogenicity, or QT-interval prolongation. And finally, property-based machines would be used to ensure that the design of such structures had the requisite physical properties so that traditional or specialized drug delivery could be accomplished. All of these activities would be carried out before a single molecule was synthesized. The impact on cost reduction of such a learning-before-doing paradigm also opens up new markets for NCEs.

Supervised learning is the most prevalent form of machine learning that is currently practiced. Because data in machine learning are termed examples, supervised machine learning is termed *learning by example*. In this type of learning, examples are presented to the machine, and after learning takes place, the machine is tested to see how well it can predict *unseen* examples. Just how accurately the machine can predict unlearned examples is termed the machine's *generalizability*. Example sets are usually subdivided into *training* and *test* sets to carry out the operations stated above. In general, the quality of a machine's future generalizability is highly dependent on how representative the training example set is of examples that are to be predicted in the future.

There are two main types of applications for machine learning, *regression* and *classification*. In regression, the goal is to predict an exact value of a physical property such as solubility or melting point. For classification, the training set is composed of both *positive* and *negative* examples. After training, the machine is asked to correctly separate unseen examples. Classification applications for machine learning are generally *binary* classification i.e. yes/no answers. For example, in the bioinfomatics area, classification is used to predict whether a particular gene codes for a particular protein.

Unsupervised learning deals with learning the *structure* or *topology* of knowledge. Learning that fails to have an ability to grasp the general principles or the structure of a discipline will fall short of learning how things are related and how new information can be related in the future.[44] Learning 'without a teacher' is learning that *adapts* its behavior without being told (supervised learning) the appropriateness (reinforced learning) of an observation. However, by grasping the topology of the subject area, the learning machine will be more able to respond in an improved way in the future. Knowledge discovery and data mining are areas where this type of learning has immediate applications.

One of the major concerns in the machine learning community is the *opaqueness* of some of the algorithms. Humans, and especially physicians, distrust 'black boxes' even if they can be shown to be highly accurate. This concern has lead to new machines that are much more *transparent* in their reasoning. This leads to exciting collaborations between machines and domain experts, humans that are highly specialized in certain technical areas. *Expert systems* are *non-learning* computing systems in which the knowledge of the human domain expert is captured and stored as a set of rules in a knowledge base. A generic inference engine connects the user with the knowledge base so that the machine expert can respond to queries from the user. Machine learning systems, in distinction to expert systems, learn rules from data alone. This is potentially much more powerful since machines can examine data in larger quantities and more consistently than humans. If this process is transparent to humans, it provides a synergistic situation in which the domain expert and the machine can collaborate in solving new problems.

Property-design is based on the premise that all of the information that is needed to predict physical properties is contained in the molecular structure of the molecule alone. This means that the dependent variable (a physical property like solubility) must be computed from factors (independent variables) that are determined from the molecular structure only. The machine learning terminology for these independent variables is *features*; the molecular modeling term for these variables is *molecular descriptors*. There are many computational programs that can generate molecular features and a number of strategies for *feature selection*. The danger, however, is that users get caught up in 'group think' and become so dependent on software programs that innovative thinking is inhibited.

Several mathematical issues are associated with the algorithms of machine learning. The first is the functional relationship of the physical property with features. *Linear* relationships are the simplest type of functional dependence. The advantage of *linear regression analysis* is that humans can easily see and understand the relationships between what is being predicted and the features that are being used to predict (*transparency*). Visual inspection can be used to assess the quality of the prediction. Assuming that there is a linear dependence is both a strength and weakness of this type of analysis. On the one hand, linear system analysis is amenable to many different mathematical analytical methodologies, and, fortunately, many nonlinear systems are linear over a narrow range of feature values. On the other hand, because most physical systems are non-linear over wider ranges, linear dependencies are accurate *locally* but often do not project to the same accuracy over wider ranges (ie, *globally*). Neural networks made the next advance in making predictions. They address the non-linear issue.

Artificial neural networks (ANN) are mathematical abstractions of a simple animal reasoning systems. These systems utilize a non-linear function, usually the hyperbolic tanh function, to model the relationship between the input features with respect to the output physical property. During the learning phase of ANNs, feature selection takes place on the training examples. Learning is a supervised reinforcement that focuses on minimizing error in the training set (empirical risk minimization). The features that have the strongest relationships to the dependent property are selected while taking into account multiple feature interactions. This learning process is often tedious and requires experienced personnel. More over, the complexity of the interactions or the dependence of the dependent property on the input features is hidden, i.e. the reasoning is *opaque*. Another issue with ANNs is that they are subject to *over fitting*. This is a phenomenon in which the ANN model is refined to such a degree that the training examples are very highly correlated to the dependent property but the model as a whole has very poor *generalalizability*. This is a result of learning being dependent on empirical risk minimization. Skilled usage of ANNs, however, can give us some of the most accurate machine learning predictions we have at the current time. In addition, one of the shortcomings of ANNs, a lack of memory, appears to have been addressed. ASNNs were designed with this defect in mind.

Associate neural networks (ASNN) address the issue of training set dependence and knowledge update[45,46] by combining ANN and K-nearest neighbor technology. With such machine learning technology, extensive and laborious training is carried out to generate ensembles of ANNs. The machine has the ability to determine the most appropriate ANN for a

particular compound so that it can obtain the advantage of higher local accuracy while having a global span. In addition, it has the ability to learn new examples on-the-fly. This means that extensive training can be carried out on public databases while updating with respect to proprietary data is possible on an ongoing basis. Recent implementation of an ASNN for calculated LogP has shown 2–5-fold improvements using additional proprietary examples.[47] ASNNs partially address the local/global issue, but still suffer from being opaque. A newer machine learning paradigm has been introduced that addresses both of these issues, *support vector machines* (SVM).

SVMs are statistically constrained machines that were introduced in 1982 to explicitly address *generalizability*, *local/global*, and *linear/non-linear* issues.[48,49] In addition, some SVMs are *very transparent* and are very efficient in *feature selection*.[50] SVMs use mathematical functions, called kernels, that have a very special property: they can act as mediators that allow non-linear data to be processed by linear algorithms. Their major strength is that they promote generalizability explicitly. In addition, SVMs are designed so that they converge on global optima only. They have been shown to give classification results superior to ANNs in the bioinfomatics area and some have regression capabilities. These machines use dual optimization routines that promote generalizability, global, non-linear, and feature efficient predictions, and are just being introduced into the chemoinfomatic arena.[51] In general, however, they are *opaque* techniques that require skill in parameter selection. One machine learning technique, however, excels in its transparency, *inductive logic programming* (ILP).

ACTIVE PHARMACEUTICAL INGREDIENT-BASED DESIGN AND PREFORMULATION

Once a NCE is selected for development, choosing the molecular form that will be the active pharmaceutical ingredient (API) is a critical milestone because all subsequent development will be affected by this decision. For preformulation, physical characterizations should be focused on making decisions that balance solid-state dissolution properties with material consistency under manufacturing and storage conditions. The advantages of having a rapidly dissolving amorphous state have to be balanced against the potential conversion of this state by time, moisture, and heat to a crystalline state that can be less soluble. Similarly, the increased solubility that often can occur with hydrochloride and sodium salts may have to be balanced with a potential for physical or chemical instability due to moisture and heat. These salts are attractive because they are simple to make and are relatively nontoxic. The salt selection process must project its considerations of the "best" properties to encompass dissolution, physical and chemical stability, toxicology, market-image formulations, large scale manufacturing, and product storage.

The following section will outline solid-state changes that might occur with varying moisture content, pH, and temperature. It will be illustrated that water (moisture) is one of the most important environmental factors that influences solid-state stability. The discussion will then focus on identifying the solid-state properties of an NCE that will make it a viable API. Ultimately, the best balance between absorption and material consistency is sought. Later, the discussion of engineering the solid state will explore why these requisite properties should be designed into NCEs from the earliest stages of discovery.

CHALLENGES TO THE SOLID STATE

Solids are a complex state of matter because intermolecular forces can arrange the molecules in a variety of different ways, each producing a different solid with potentially different physical properties. In this section, a symbolic nomenclature is introduced to specifically address changes that can occur in the solid state (Table 38-4). Application of this notation to the effects of moisture, the major environmental factor influencing the solid state, will then be examined.

Table 38-4. List of Symbols

SYMBOL	MEANING
α	Amorphous solid state as left subscript designation
Σ	Surface of solid state as right subscript designation
δ	Defective region of solid state as left subscript designation
ρ	Density
I, II, III	Crystalline polymorphic forms of the solid state as left subscript designation
$+$	Positively charged, cationic species as superscript designation
$-$	Negatively charged, anionic species as superscript designation
0	Uncharged, free species as superscript designation
A	Active ingredient in the solid state
a	Dissolved form of the active ingredient
${}_{j}A_{\Sigma}^{i}$	Surface of active ingredient of charge i and solid state j
B	Reactant of A in the solid state
b	Dissolved form of reactant
C_S	Saturation concentration
h	Monohydrate as left subscript designation
$0h$	Anhydrous as left subscript designation
nh	n-Hydrate as left subscript designation
$<h$	Reduced water content as left subscript designation
$>h$	Increased water content as left subscript designation
m	Mass
An^-	Negatively charged anionic counterion
i	Charge on the active ingredient as superscript designation
j	Solid state form of the active ingredient as left subscript designation
k_d	Dissolution rate constant
k_r	Recrystallization rate constant
P	Permeability
Cn^+	Positively charged cationic counterion
S_a	Surface area

SOLID-STATE CHARACTER

In this chapter, ${}_{j}A_{\Sigma}^{i}$ is a notation that will be used to indicate solid-state changes. The A denotes the active drug entity. This may be a weak acid, a weak base, or a nonelectrolyte. When A dissolves, a denotes the presence of this entity in solution; thus, dissolution of the solid A in water to form a will be shown schematically as

$$A \xrightarrow{H_2O} a \qquad (1)$$

The charge of A is denoted by the usual placement of a right superscript, i. The charge of A is assumed to be zero by default. For emphasis, a lack of charge may be shown explicitly as A^0. For a weak acid, A^0 represents the protonated form (in other notations this might be shown as HA). The ionized form of the weak acid, A^-, represents A^0 minus the weak acid proton. For a weak base, A^0 denotes the uncharged base that can be protonated to A^0H^+. Equations with A, shown with arrows, are not stoichiometric. Instead, they only show essential changes, so the focus can be placed on the relevant chemical, ionic, and solid-state alterations in the chemical entity. For example, in Equation 2, in which a chemical reaction changes the parent entity A into a different molecular solid B,

$$A \rightarrow B \qquad (2)$$

there is no attempt to show the specific details of the functional groups that were changed to bring about the formation of B. In a similar manner, consider a reversible acid–base reaction

$$A \underset{\leftarrow}{\longrightarrow} A^i \qquad (3)$$

where i as a plus sign (+) represents the cationic form, or a minus sign (−) the anionic form, of A. The protonation or deprotonation of a weak basic or acidic group on A will simply be reflected in the charge change that occurs. The scheme is nonstoichiometric because counter ions and charge-balance considerations have not been included.

When a particular molecular organization or emphasis of the solid state is needed, it will be denoted with the left subscript j. A wide variety of different solid states, denoted by ${}_jA$, are possible. For example, amorphous solids that have randomly packed molecules are denoted as ${}_\alpha A$ in this chapter. Crystalline solids, on the other hand, have regular packing arrangements and are denoted in a number of ways. Two types of crystalline phases, polymorphs and solvates, are possible for a given molecule depending on the crystallization conditions.

Polymorphs are crystals that have the same molecule formula but have different crystal structures. The Roman numerals I, II, III, . . . are used to denote polymorphs; the most stable polymorph under ambient conditions is usually designated with Roman numeral I. This solid-state form of A will be denoted as ${}_\text{I}A$ in this chapter.

Solvates, on the other hand, are crystals in which a solvent is incorporated into the crystal structure (polymorphs of solvates could exist). The solvent may be highly bound in the crystal or it may be more loosely bound in channels within the crystal. To simplify this discussion, only water of solvation will be considered. Hydrated solids are denoted by ${}_{nh}A$, where n is a fraction or an integer. For example, ${}_{h/2}A$ denotes a hemihydrate while ${}_{3h}A$ denotes a trihydrate.

In some situations, it will be useful to emphasize that a particular chemical reaction or physical change is occurring on the surface of a particle. For these purposes, the right subscript Σ will be used to emphasize the surface of the solid state. It should be noted that the right superscript i, used for charge designation, and the left subscript j, used for solid-state designation, are only general placeholders for more specific instances that will be detailed below; on the other hand, the right subscript Σ specifically denotes the surface of a solid particle and not a more general entity. For most situations, the full notation will not be used.

In actual APIs, crystal defective regions A_δ are present. These were formed during large-scale synthesis and milling operations that reduced the API's particle size. In Figure 38-8, defective regions as well as crystalline and amorphous regions are shown diagrammatically.

WATER: A MAJOR ENVIRONMENTAL VARIABLE

The presence or absence of moisture is one of the most important environmental factors that can affect solid-state stability. The surface of an API particle can gain or lose water depending on the relative humidity (RH). Figure 38-8 shows how water vapor can form regions of dissolved drug on the surface of the API particle. The amorphous region would be expected to dissolve the fastest, and the crystalline region the slowest; that is, the rank order of dissolution would be $A_\alpha > A_\delta > {}_\text{I}A$. In the Figure 38-8 diagram, this is indicated by the font size of the saturated dissolved form of A, a_s, associated with each of these regions. This surface coating results in chemical and physical instability.

Chemical Instability: Water as a Molecular Mobilizer

In general, chemical reactivity is slow in solids because of the spacial separation of different reactive components. For example, if a small amount of an impurity that can act as a catalyst is distributed heterogeneously in an API or a dosage form, the overall rate of reaction is limited because the reaction only occurs in microenvironmental regions. However, in dosage forms, most APIs are usually in contact with moisture-bearing excipients and are stress-tested at elevated temperatures and humidity. The presence of an adsorbed layer of moisture increases the catalytic reactivity of the impurity because water, acting as a molecular mobilizer, can transport different chemical species laterally over the surface of the API.[52] Equation 4 shows a chain of reactions from A to a degradant B,:

$$A \xrightarrow{(\text{H}_2\text{O})_\text{vapor}} a \xrightarrow{(\text{H}_2\text{O})_\text{vapor}\ \text{catalytic impurity}} b \xrightarrow{(\text{H}_2\text{O})_\text{vapor}} B \qquad (4)$$

where b is the solubilized form of B. Moisture also induces solid-state changes in A. (Further discussion of moisture- induced chemical instability will be treated in the section *Hydrate Stability: Importance of the Critical Relative Humidity.*)

Microenvironmental pH: Moisture-Induced Sensitivity of Acid/Bases

Acid–base reactivity in the solid-state change will be enhanced by moisture. Equation 5 shows a moisture-induced change of an anionic salt to its free acid on the surface of a drug particle:

$$A_\Sigma^- \xrightarrow{(\text{H}_2\text{O})_\text{vapor}} A_\Sigma^0 \qquad (5)$$

Conversely, Equation 6 shows a moisture-induced surface conversion of a cationic salt into its free base,

$$A_\Sigma^+ \xrightarrow{(\text{H}_2\text{O})_\text{vapor}} A_\Sigma^0 \qquad (6)$$

where $A^+ = \text{HA}^+$. Because the amount of solid drug is large compared to the amount of moisture, Equations 5 and 6 have been diagramed as irreversible reactions. Such solid-state changes can alter the physical properties of the API. For example, if particles of the sodium salt of an insoluble acid form a surface coating of the free acid as in Equation 5, the dissolution rate of the surface will be retarded. Testing methods are needed during the salt selection stage to anticipate this type of solid-state change (see under *Salt Selection*).

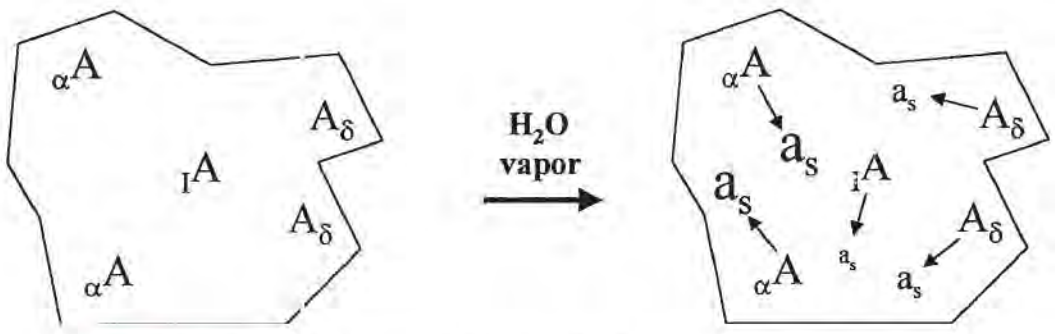


Figure 38-8. Surface of a milled API and dissolution of surface regions due to adsorbed moisture.

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:

$$_{II}A \xrightarrow{H_2O} {}_{I}A \tag{7}$$

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

$${}_{a}A \xrightarrow[\leftarrow]{(H_2O)_{vapor}} {}_{I}A \tag{8}$$

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

$$_{II}A \xrightarrow{H_2O} {}_{h}A \tag{9}$$

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

$$_{II}A^{+} \xrightarrow{H_2O} {}_{a}A^{+} \xrightarrow{H_2O} {}_{h/2}A^{+} \tag{10}$$

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 properties affect absorption and consistency, the two major development issues for an API. Salt selection, which determines the character of ${}_{j}A^{i}$, is the first critical solid-state decision for preformulation in the developmental arena.

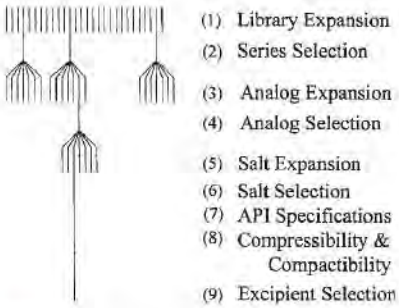


Figure 38-9. Typical API sequential decision-making: selection and expansion cycles.

Salt Expansion: Exploring the Molecular Possibilities of A^{I}

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 = Quartenary.
[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:

$$A^0H^+An^- \rightleftarrows A^0H^+ + An^- \text{ and } A^0H^+ \underset{\text{high pH}}{\overset{\text{low pH}}{\rightleftarrows}} A^0 + H^+ \qquad (11)$$

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 Brönsted-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

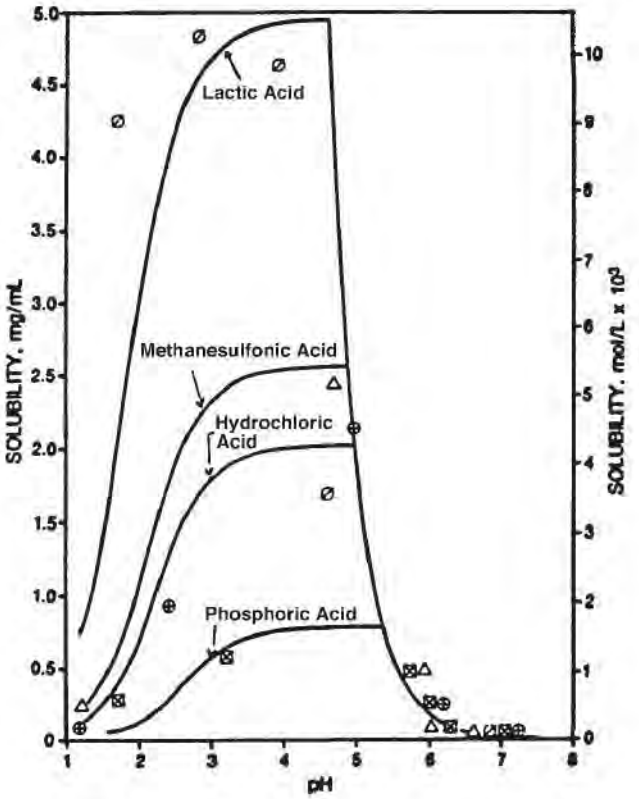


Figure 38-10. pH solubility profile of a weak base. (From Streng WH, et al. *J Pharm Sci* 1984;73:1679.)

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

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

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 possible[57] 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:

$$HAn \xrightarrow{\text{low dielectric solvents}} H^+ + An^- \qquad (13)$$

$$AH^+ \xrightarrow{\text{low dielectric solvents}} H^+ + A^0 \qquad (14)$$

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 reactive 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, $\Delta pK_a = pK_{a\,A}{}^0 - pK_{a\ \text{counter-acid, HA}n} > 0$, 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, $_jA$, 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:

$$A_{\text{solid}} \underset{\text{dissolution}}{\rightleftharpoons} a_{\text{GI tract}} \underset{\text{permeation}}{\rightleftharpoons} a_{\text{blood}} \qquad (15)$$

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.

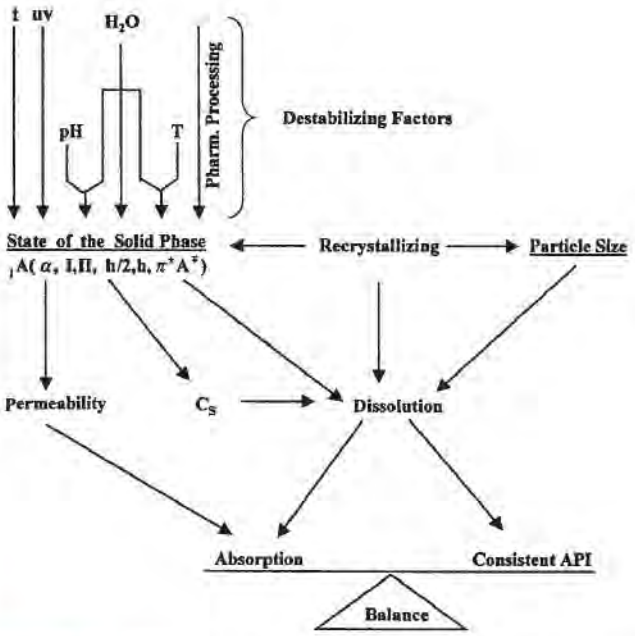


Figure 38-11. API salt selection decision: a balance between absorption and consistency.

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,

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

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 0[58]:

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

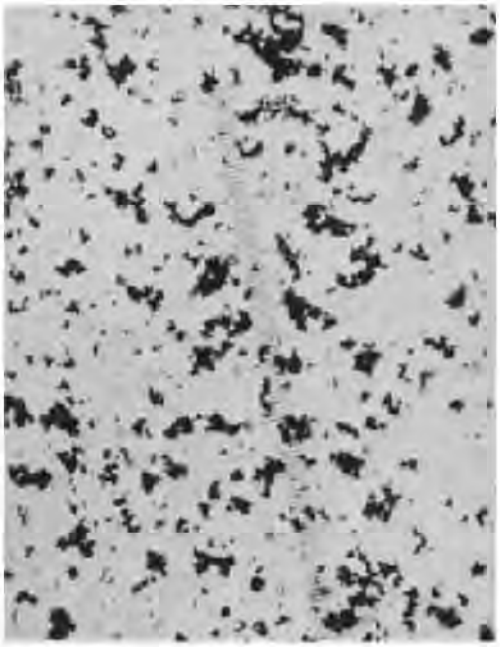
This initial rate of the Noyes–Whitney equation is termed sink conditions for the dissolution rate.

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

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

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 growth[59]



FORM I

INITIAL SUSPENSION

FORM I

SUSPENSION AFTER 6 HOURS.

Figure 38-12. Photomicrographs showing change in crystal size for a suspension of Form 1 of an experimental drug.

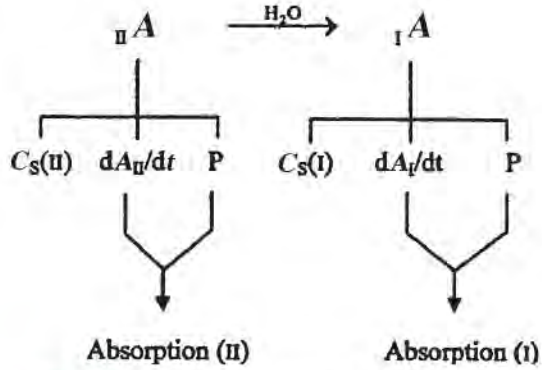


Figure 38-13. Absorption changes due to aqueous-phase transformations.

(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

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

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 Anhydrates 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, $_{0h}A$, 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 $_{0h}A$ (phase change). Note that initially the slope for $_{0h}A$ (phase change) approaches that of the very steep slope $_{0h}A$ (no phase change), and

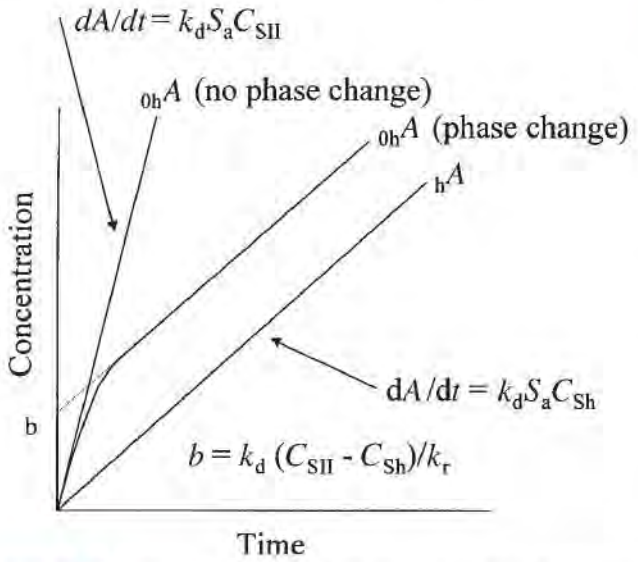


Figure 38-14. Biphasic dissolution of anhydrous to hydrous forms. (Data from Nogami H, Nagai T, Yotsuyanagi T. *Chem Pharm Bull* 1969;17:499.)

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 $_{0h}A_\Sigma$ 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, $\Sigma\uparrow$, and the corresponding dissolution enhancement.

$$A_\Sigma{}^0 \xrightarrow{\text{willing}} A_\Sigma{}^{0}\uparrow \xrightarrow{\text{faster}} a_S{}^0 \quad (21)$$

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 diagramed in Equation 22 where $a_{bulk}{}^0\uparrow$ indicates the buildup of the drug in the bulk solution.

$$A^0 \xrightarrow{\text{slow}} a_{bulk}{}^0\uparrow \quad (22)$$

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 ($a_{bulk}{}^+ = a_{bulk}{}^0 H^+$) acts as a sink to remove $a_{bulk}{}^0$ and promotes the dissolution of A^0 by driving the reaction to the right:

$$A^0 \xrightarrow{\text{fast}} a_{bulk}{}^0\downarrow \xrightarrow{\text{very fast}} a_{bulk}{}^+ \quad \text{(sink)} \quad (23)$$

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 show the species involved in plugging. The subscript Σ emphasizes that this is a surface phenomenon.

$$_{0h}A_\Sigma \xrightarrow{\text{slow}} a_{bulk} \xrightarrow{\text{recrystallization}} {}_hA_\Sigma \xrightarrow{\text{slower}} a_{bulk}\downarrow \quad \text{(plug)} \quad (24)$$

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

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

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 μg/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.

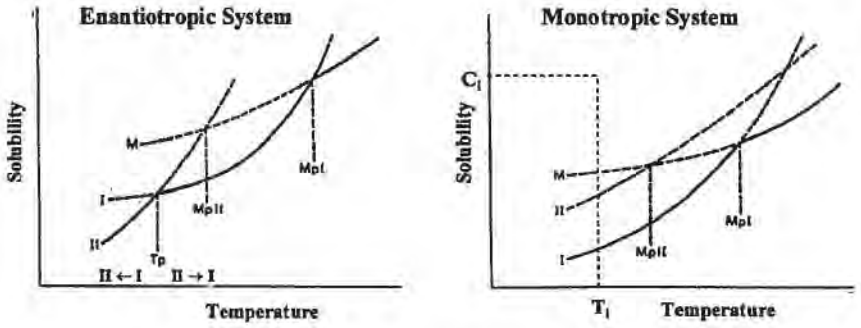


Figure 38-15. Thermal stability of polymorphic systems. (Data from Kuhnert-Bradnstatter M. *Thermomicroscopy in the Analysis of Pharmaceuticals.* New York: Pergamon, 1971; and Heleblian J, McCrone W. *J Pharm Sci* 1969;58:911.)

tiotropic 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,

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

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.

Enantiotropicity 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 variables, 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 interconvertability 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]

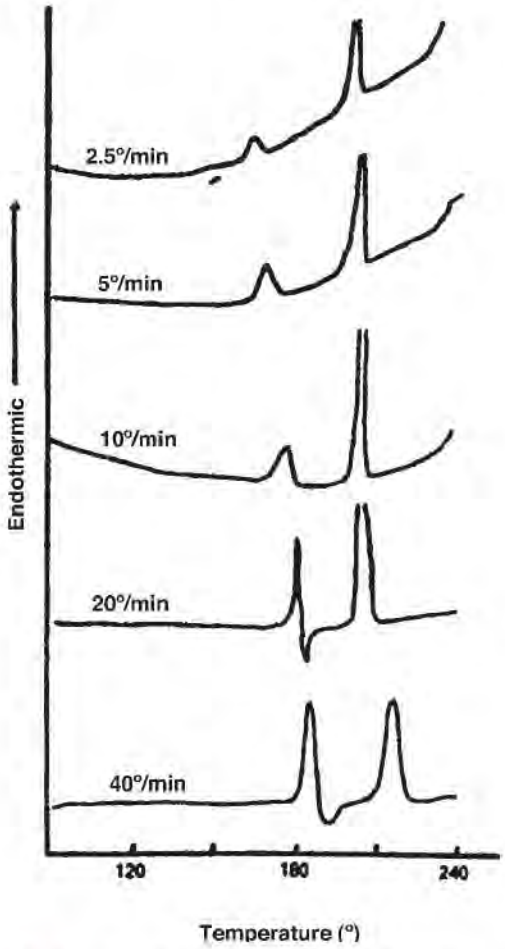


Figure 38-16. Detection of polymorphs by varying the DSC scanning rate.

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, a, 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, a, 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 an 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-*

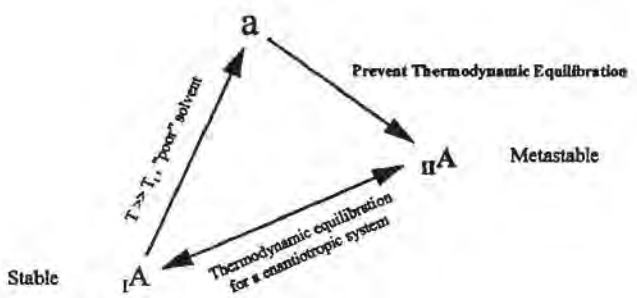
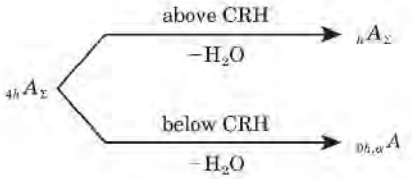


Figure 38-17. Formation of a metastable polymorph in a monotropic system.

drate 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]



(29)

The conversion of $_{4h}A$ to $_{h}A$ 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 $_{h}A$ crystal form.[74] Similarly, elevation of both temperature and RH were required to convert the $_{0h}A$ form of paroxetine HCl to the $_{0.5h}A$ form.[75] Water also promoted a solid-state transformation of the $_{\alpha}A$ form to the $_{0h}A$ 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 $_{II}A$ to $_{\alpha}A$ 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 $_{0.5h}A$ form of paroxetine HCl.[75] For the sodium salt of the tetrazole derivative shown in Equations 29 and 30, the denser $_{h}A$ structure is physically more stable than the $_{4h}A$ structure. The latter loses four water molecules from crystal channels at a significantly lower temperature than the one water molecule of the $_{h}A$ 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 $_{0h,\alpha}A_{\Sigma}$ means that any subsequent water vapor will encounter a more hygroscopic surface than $_{4h}A_{\Sigma}$ and thus a different hydration kinetic behavior. On the other hand, conversion of $_{4h}A$ to $_{h}A$ 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

SORPTION/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.

$$_{0h}A_{\Sigma} \xrightarrow[+H_2O]{\text{below CRH}} > {}_{>0h}A_{\Sigma} \quad \text{(partial oxidation protection)} \tag{30}$$

$$A \xrightarrow{\text{below CRH}} {}^{*}A \quad \text{(increase chemical reactivity)} \tag{31}$$

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 meclofenoxate HCl decomposition[79] 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.

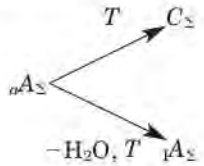
$$_{I}A_{\Sigma} \xrightarrow{+H_2O} {}_{I,>h}A_{\Sigma} \rightarrow {}_{\alpha}B_{\Sigma} \tag{32}$$

$$_{Ji}A_{\Sigma} \xrightarrow{-H_2O} {}_{<h}A_{\Sigma} \rightarrow {}_{a}A_{\Sigma} \tag{33}$$

TRANSFORMATION OF AMORPHOUS SURFACES—Because amorphous layers are more prone to be hygroscopic than crystalline solids, the chemical transformation of $_{I}A_{\Sigma}$ 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 meclofenoxate 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 a_{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.

$$\begin{array}{c} {}_{\alpha}B_{\Sigma} \\ \downarrow +H_2O \\ A_{\Sigma} \xrightarrow{b_t} a_{\Sigma} + b_{\Sigma} \\ \downarrow \\ b_{\Sigma} \end{array} \tag{34}$$

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 $_{h}A$ undergoes a solid phase transformation to a crystalline phase, $_{I}A$. 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.



(35)

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_Σ, which is assumed to be saturated[52]:

$$A_\Sigma \xrightarrow{\text{excess } H_2O} a_\Sigma \tag{36}$$

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 sulfate[82] and tromethamine.[83,84]

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.[85] 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.[86] Stronger bases like pelrinone (pK_a 4.71) can form stable and nonhygroscopic HCl salts.[87]

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,[88]

$${}_{III}A \xrightarrow{\text{grinding}} {}_{II}A \xrightarrow{\text{more grinding}} {}_{I}A \tag{37}$$

grinding causes a successive change to the ${}_{II}A$ polymorph (Form B) and finally to the ${}_{I}A$ polymorph (Form A).[89] Correspondingly, dissolution from the fastest to the slowest is in the order

$${}_{\text{ground II}}A > {}_{\text{ground I}}A > {}_{II}A > {}_{I}A \tag{38}$$

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

$${}_{3h}A \xrightarrow{\text{grinding}} {}_{\alpha,0h}A \tag{39}$$

Water in this situation plays an essential role in crystal formation. Its removal causes a collapse of the crystal lattice.[90] Other pharmaceutical processing operations and their impact on crystals have been reviewed.[91]

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 of 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.

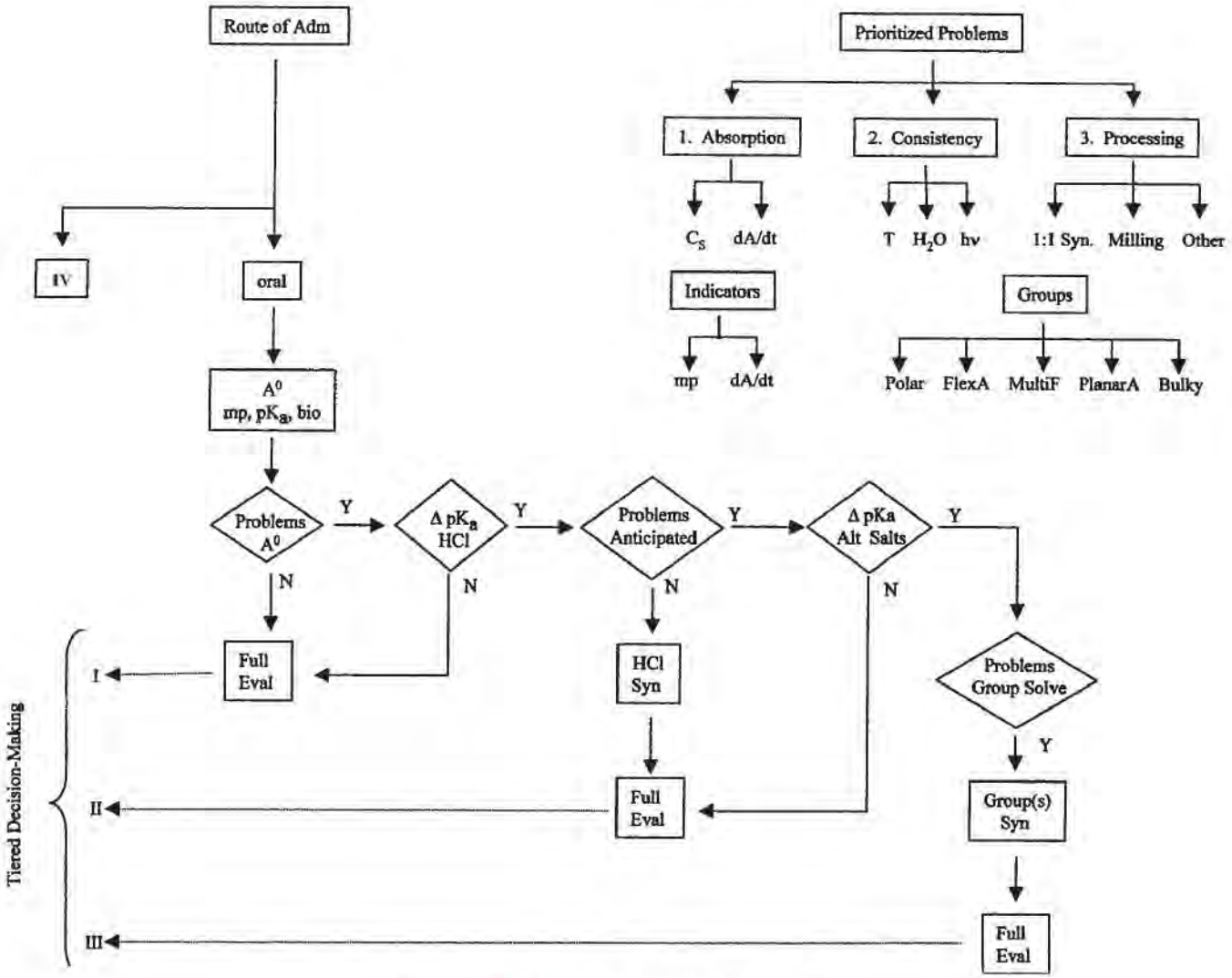


Figure 38-18. Absorption-dominated decision-tree.

The decision-tree considers the free base, the HCl salt, as well as other options. Although this approach uses statistical probabilities for molecular form consideration, ideally, a high-throughput, automated methodology would be available that could determine exhaustively which salts can form crystals and under which conditions. Feasible salts would then be synthesized and placed under accelerated stability and stressing conditions. This would allow for the maximum amount of exposure to the sample before a decision has to be made. Degradant evaluation need not be carried out on these stressed samples immediately; other issues may eliminate a particular candidate and make this unnecessary. However, evaluation for crystallinity should be carried out early to ensure that this does not impact physical or chemical stability. Physical property screens and absorption-dominated prioritization would then force a pharmaceutical evaluation to be made regarding the possibility of overcoming consistency and processing problems.[94] By using functional groupings (see Table 38-5), salt forms would be considered that could address specific problems.[57]

EXCIPIENT SELECTION: FORMULATION COMPATIBILITIES

Excipients serve many roles and are the backbone of a formulation. They may be needed to stabilize the API by providing antioxidant, heavy-metal chelating, or light-protection properties. They also may be used to enhance bioavailability and to control the release from dosage forms. For solid dosage forms, they provide suitable properties for dispensing the API in accurate dosage units that have reproducible release properties. Diluents provide a flowable bulk, binders hold powders together, lubricants provide punch-releasing properties, and disintegrants help to disperse dosage forms in the GI tract. On the other hand, judicious choices must be made to prevent incompatibilities between the API and excipients.

Screens to detect drug-excipient incompatibilities recently have been developed using elevated temperature and added water to accelerate potential interactions in ternary and more complex powder blends.[95] Such methods have been shown to be capable of rapidly detecting chemical incompatibilities and giving good correlations with results using powder blends of drug and excipients at elevated temperatures and humidity.

Processing incompatibilities can be more difficult to troubleshoot than chemical incompatibilities. For example, tablet performance has been shown to vary for ketorolac tromethamine, depending upon the kind of starch that was used. Cornstarch showed a decreased disintegration time and dissolution rate as a function of blending time whereas pregelatinized starch showed no such dependency. The difference between these two excipients was attributed to the formation of drug/cornstarch agglomerates with magnesium stearate.[96]

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 International 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 Classificaion 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

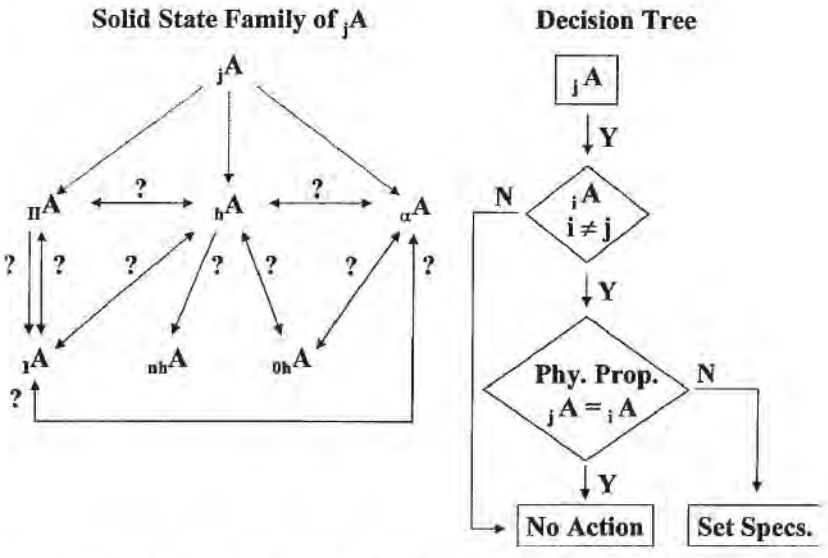


Figure 38-19. Solid-state forms and specification setting. (Data from Byrn S et al. *Pharm Res* 1995;9:84; and Byrn S et al. *Gold Sheet* 1996;30(6):1.)

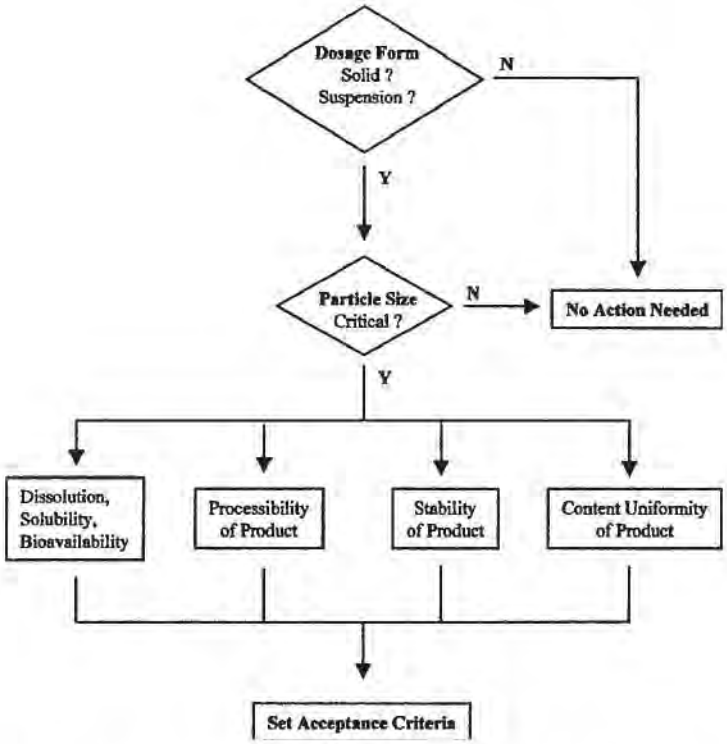


Figure 38-20. Decision-tree for drug substance particle-size distribution. (From Bym S et al. Specifications for new drug substances and products: Chemical Substances, ICH4, Fourth International Conference on Harmonization. Brussels, July 1997.)

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 contemplates the possibilities of 100 nanolaboratories on a single chip.

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 *in vitro* dissolution rate is similar to *in vivo* 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.

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-

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 marketplace. The patient is waiting!

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CHAPTER 45

Oral Solid Dosage Forms

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Drug substances most frequently are administered orally by means of solid dosage forms such as tablets and capsules. Large-scale production methods used for their preparation, as described later in the chapter, require the presence of other materials in addition to the active ingredients. Additives also may be included in the formulations to facilitate handling, enhance the physical appearance, improve stability, and aid in the delivery of the drug to the bloodstream after administration. These supposedly inert ingredients, as well as the production methods employed, have been shown in many cases to influence the absorption or bioavailability of the drug substances.[1] Therefore, care must be taken in the selection and evaluation of additives and preparation methods to ensure that the drug-delivery goals and therapeutic efficacy of the active ingredient(s) will not be diminished.

In a number of cases it has been shown that the drug substance's solubility and other physicochemical characteristics have influenced its physiological availability from a solid dosage form. These characteristics include its particle size, whether it is amorphous or crystalline, whether it is solvated or nonsolvated, and its crystalline, or polymorphic form. After clinically effective formulations are obtained, such variations among dosage units of a given batch, as well as batch-to-batch differences, should be reduced to a minimum through proper in-process controls and good manufacturing practices. The recognition of the importance of performance qualification, and validation for both equipment and processes has enhanced assurance in the reproducibility of solid dosage formulations greatly. It is in these areas that significant progress has been made with the realization that large-scale production of a satisfactory tablet or capsule depends not only on the availability of a clinically effective formulation but also on the raw materials, facilities, personnel, documentation, validated processes and equipment, packaging, and the controls used during and after preparation (Fig 45-1).

TABLETS

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and have been traditionally prepared by either compression, or molding methods. Recently, punching of laminated sheets, electronic deposition methods, and three-dimensional printing methods have been used to make tablets. Tablets have been in widespread use since the latter part of the 19th century, and their popularity continues. The term *compressed tablet* is believed to have been used first by John Wyeth and Brother of Philadelphia. During this same period, molded tablets were introduced to be used as *hypodermic* tablets for the extemporaneous preparation of solutions for injection. Tablets remain popular as a dosage form because of the advantages afforded both to the manufacturer (eg, simplicity and economy of preparation, stability, and convenience in packaging, shipping, and dispensing) and the patient (eg, accuracy of dosage, compactness, portability, blandness of taste, and ease of administration).

Although the basic mechanical approach for most tablet manufacture has remained the same, tablet technology has undergone great improvement and experimentation. Efforts are being made continually to understand more clearly the physical characteristics of powder compaction and the factors affecting the availability of the drug substance from the dosage form after oral administration. Tableting equipment continues to improve in both production speed and the uniformity of tablets compressed. Recent advances in tablet technology have been reviewed.[2–13]

Although tablets frequently are discoid in shape, they also may be round, oval, oblong, cylindrical, or triangular. Other geometric shapes, such as diamonds and pentagons, and hexagons have also been used. They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration. Most commercial tablets can be divided into two general classes by whether they are made by compression or molding. Compressed tablets usually are prepared by large-scale production methods, while molded tablets generally involve small-scale operations. The various tablet types and abbreviations used in referring to them are listed below.

COMPRESSED TABLETS (CT)—These tablets are formed by compression and in their simplest form, contain no special coating. They are made from powdered, crystalline, or granular materials, alone or in combination with binders, disintegrants, controlled-release polymers, lubricants, diluents, and in many cases colorants. The vast majority of tablets commercialized today are compressed tablets, either in an uncoated or coated state.

Sugar-Coated Tablets (SCT)—These are compressed tablets surrounded by a sugar coating. Such coatings may be colored and are beneficial in covering up drug substances possessing objectionable tastes or odors and in protecting materials sensitive to oxidation. These coatings were once quite common, and generally lost commercial appeal due to the high cost of process validation. Recently, they have made a comeback due to patient popularity and technical advances.

Film-Coated Tablets (FCT)—These are compressed tablets that are covered with a thin layer or film of a water-soluble material. A number of polymeric substances with film-forming properties may be used. Film coating imparts the same general characteristics as sugar coating,

Figure 45-1. Tablet press operators checking batch record in conformance with Current Good Manufacturing Practices (courtesy, Lilly).

with the added advantage of a greatly reduced time period required for the coating operation. Advances in material science and polymer chemistry has made these coatings the first-choice of formulators.

Enteric-Coated Tablets (ECT)—These are compressed tablets coated with substances that resist solution in gastric fluid but disintegrate in the intestine. Enteric coatings can be used for tablets containing drug substances that are inactivated or destroyed in the stomach, for those that irritate the mucosa, or as a means of delayed release of the medication.

Multiple Compressed Tablets (MCT)—These are compressed tablets made by more than one compression cycle. This process is best used when separation of active ingredients is needed for stability purposes, or if the mixing process is inadequate to guarantee uniform distribution of two or more active ingredients.

Layered Tablets—Such tablets are prepared by compressing additional tablet granulation on a previously compressed granulation. The operation may be repeated to produce multilayered tablets of two or three, or more layers. Special tablet presses are required to make layered tablets such as the Versa press *(Stokes/Pennwalt)*.

Press-Coated Tablets—Such tablets, also referred to as dry-coated, are prepared by feeding previously compressed tablets into a special tableting machine and compressing another granulation layer around the preformed tablets. They have all the advantages of compressed tablets (ie, slotting, monogramming, speed of disintegration) while retaining the attributes of sugar-coated tablets in masking the taste of the drug substance in the core tablets. An example of a press-coated tablet press is the *Manesty* Drycota. Press-coated tablets also can be used to separate incompatible drug substances; in addition, they can provide a means of giving an enteric coating to the core tablets. Both types of multiple-compressed tablets have been used widely in the design of prolonged-action dosage forms.

Controlled-Release Tablets (CRT)—Compressed tablets can be formulated to release the drug slowly over a prolonged period of time. Hence, these dosage forms have been referred to as *prolonged-release* or *sustained-release* dosage forms as well. These tablets (as well as capsule versions) can be categorized into three types: (1) those that respond to some physiological condition to release the drug, such as enteric coatings; (2) those that release the drug in a relatively steady, controlled manner; and (3) those that combine combinations of mechanisms to release *pulses* of drug, such as repeat-action tablets. The performance of these systems is described in more detail in Chapter 47. Other names for these types of tablets can be: *Extended Release, Sustained Release, Prolonged Release, Delayed Release*, and in the case of pulsatile tablets, *Repeat Action, Pulsatile Release* or *Pulse Release*.

Tablets for Solution (CTS)—Compressed tablets to be used for preparing solutions or imparting given characteristics to solutions must be labeled to indicate that they are not to be swallowed. Examples of these tablets are Halazone Tablets for Solution and Potassium Permanganate Tablets for Solution.

Effervescent Tablets—In addition to the drug substance, these contain sodium bicarbonate and an organic acid such as tartaric or citric. In the presence of water, these additives react, liberating carbon dioxide that acts as a distintegrator and produces effervescence. Except for small quantities of lubricants present, effervescent tablets are soluble.

Compressed Suppositories or Inserts—Occasionally, vaginal suppositories, such as Metronidazole tablets, are prepared by compression. Tablets for this use usually contain lactose as the diluent. In this case, as well as for any tablet intended for administration other than by swallowing, the label must indicate the manner in which it is to be used.

Buccal and Sublingual Tablets—These are small, flat, oval tablets. Tablets intended for buccal (the space between the lip and gum in the mouth) administration by inserting into the buccal pouch may dissolve or erode slowly; therefore, they are formulated and compressed with sufficient pressure to give a hard tablet. Progesterone tablets may be administered in this way. Some newer approaches have employed materials that act as bioadhesives to increase absorption of the drug.

Some other approaches use tablets that melt at body temperatures. The matrix of the tablet is solidified while the drug is in solution. After melting, the drug is automatically in solution and available for absorption, thus eliminating dissolution as a rate-limiting step in the absorption of poorly soluble compounds. Sublingual tablets, such as those containing nitroglycerin, isoproterenol hydrochloride, or erythrityl tetranitrate, are placed under the tongue. Sublingual tablets dissolve rapidly, and the drug substances are absorbed readily by this form of administration.

MOLDED TABLETS OR TABLET TRITURATES (TT)—Tablet triturates usually are made from moist material, using a triturate mold that gives them the shape of cut sections of a cylinder. Such tablets must be completely and rapidly soluble. The problem arising from compression of these tablets is the failure to find a lubricant that is completely water-soluble.

Dispensing Tablets (DT)—These tablets provide a convenient quantity of potent drug that can be incorporated readily into powders and liquids, thus circumventing the necessity to weigh small quantities. These tablets are supplied primarily as a convenience for extemporaneous compounding and should never be dispensed as a dosage form.

Hypodermic Tablets (HT)—Hypodermic tablets are soft, readily soluble tablets and originally were used for the preparation of solutions to be injected. Since stable parenteral solutions are now available for most drug substances, there is no justification for the use of hypodermic tablets for injection. Their use in this manner should be discouraged, since the resulting solutions are not sterile. Large quantities of these tablets continue to be made, but for oral administration. No hypodermic tablets ever have been recognized by the official compendia.

Compressed Tablets (CT)

For medicinal substances, with or without diluents, to be made into solid dosage forms with pressure, using available equipment, it is necessary that the material, either in crystalline or powdered form, possess a number of physical characteristics. These characteristics include the ability to flow freely, cohesiveness, and lubrication. The ingredients such as disintegrants designed to break the tablet up in gastrointestinal (GI) fluids and controlled-release polymers designed to slow drug release ideally should possess these characteristics or not interfere with the desirable performance traits of the other excipients. Since most materials have none or only some of these properties, methods of tablet formulation and preparation have been developed to impart these desirable characteristics to the material that is to be compressed into tablets.

The basic mechanical unit in all tablet-compression equipment includes a lower punch that fits into a die from the bottom and an upper punch, with a head of the same shape and dimensions, which enters the die cavity from the top after the tableting material fills the die cavity (Fig 45-2). The tablet is formed by pressure applied on the punches and subsequently is ejected from the die. The weight of the tablet is determined by the volume of the material that fills the die cavity. Therefore, the ability of the granulation to flow freely into the die is important in ensuring a uniform fill, as well as the continuous movement of the granulation from the source of supply or feed hopper. If the tablet granulation does not possess cohesive properties, the tablet after compression will crumble and fall apart on handling. As the punches must move freely within the

Figure 45-2. Basic mechanical unit for tablet compression: lower punch, die, and upper punch (courtesy, Vector/Colton).

die and the tablet must be ejected readily from the punch faces, the material must have a degree of lubrication to minimize friction and allow the removal of the compressed tablets.

There are three general methods typically used for commercial tablet preparation: the wet-granulation method, the dry-granulation method, and direct compression. The method of preparation and the added ingredients are selected to give the tablet formulation the desirable physical characteristics allowing the rapid compression of tablets. After compression, the tablets must have a number of additional attributes such as appearance, hardness, disintegration ability, appropriate dissolution characteristics, and uniformity, which also are influenced both by the method of preparation and by the added materials present in the formulation. In the preparation of compressed tablets, the formulator also must be cognizant of the effect that the ingredients and methods of preparation may have on the availability of the active ingredients and, hence, the therapeutic efficacy of the dosage form. In response to a request by physicians to change a dicumarol tablet so that it might be broken more easily, a Canadian company reformulated to make a large tablet with a score. Subsequent use of the tablet, containing the same amount of drug substance as the previous tablet, resulted in complaints that larger-than-usual doses were needed to produce the same therapeutic response. On the other hand, literature reports indicate that the reformulation of a commercial digoxin tablet resulted in a tablet that, although containing the same quantity of drug substance, gave the desired clinical response at half its original dose. Methods and principles that can be used to assess the effects of excipients and additives on drug absorption have been reviewed.[2,14,15]

TABLET INGREDIENTS

In addition to the active or therapeutic ingredient, tablets contain a number of inert materials. The latter are known as additives or *excipients*. They may be classified according to the part they play in the finished tablet. The first group contains those that help to impart satisfactory processing and compression characteristics to the formulation. These include diluents, binders, glidants, and lubricants. The second group of added substances helps to give additional desirable physical characteristics to the finished tablet. Included in this group are disintegrants, surfactants, colors, and, in the case of chewable tablets, flavors, and sweetening agents, and in the case of controlled-release tablets, polymers or hydrophobic materials, such as waxes or other solubility-retarding materials. In some cases, anti-oxidants or other materials can be added to improve stability and shelf-life.

Although the term *inert* has been applied to these added materials, it has become apparent that there is an important relationship between the properties of the excipients and the dosage forms containing them. Preformulation studies demonstrate their influence on stability, bioavailability, and the processes by which the dosage forms are prepared. The need for acquiring more information and use standards for excipients has been recognized in a joint venture of the Academy of Pharmaceutical Sciences and the Council of the Pharmaceutical Society of Great Britain. The result is called the *Handbook of Pharmaceutical Excipients*. This reference now is distributed widely throughout the world.[16]

Diluents

Frequently, the single dose of the active ingredient is small, and an inert substance is added to increase the bulk to make the tablet a practical size for compression. Compressed tablets of dexamethasone contain 0.75 mg steroid per tablet; hence, it is obvious that another material must be added to make tableting possible. Diluents used for this purpose include dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such tablets commonly are called *chewable tablets*. Upon chewing, properly prepared tablets will disintegrate smoothly at a satisfactory rate, have a pleasant taste and feel, and leave no unpleasant aftertaste in the mouth. Diluents used as excipients for direct compression formulas have been subjected to prior processing to give them flowability and compressibility. These are discussed under *Direct Compression*.

Most formulators of immediate-release tablets tend to use consistently only one or two diluents selected from the above group in their tablet formulations. Usually, these have been selected on the basis of experience and cost factors. However, in the formulation of new therapeutic agents, the compatibility of the diluents with the drug must be considered; eg, calcium salts used as diluents for the broad-spectrum antibiotic tetracycline have been shown to interfere with the drug's absorption from the GI tract. When drug substances have low water solubility, it is recommended that water-soluble diluents be used to avoid possible bioavailability problems. Highly adsorbent substances (eg, bentonite and kaolin) are to be avoided in making tablets of drugs used clinically in small dosage, such as the cardiac glycosides, alkaloids, and the synthetic estrogens. These drug substances may be adsorbed after administration. The combination of amine bases with lactose, or amine salts with lactose in the presence of an alkaline lubricant results in tablets that discolor on aging.

Microcrystalline cellulose (Avicel) usually is used as an excipient in direct-compression formulas. However, its presence in 5–15% concentrations in wet granulations has been shown to be beneficial in the granulation and drying processes in minimizing case-hardening of the tablets and in reducing tablet mottling.

Many ingredients are used for several different purposes, even within the same formulation (eg, cornstarch can be used in paste form as a binder). When added in drug or suspension form, it is a good disintegrant. Even though these two uses are to achieve opposite goals, some tablet formulas use cornstarch in both ways. In some controlled-release formulas, the polymer hydroxypropyl methylcellulose (HPMC) is used both as an aid to prolong the release from the tablet as well as a film-former in the tablet coating. Therefore, most excipients used in formulating tablets and capsules have many uses, and a thorough understanding of their properties and limitations is necessary to use them rationally.

Binders

Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators. They impart a cohesiveness to the tablet formulation that ensures the tablet remaining intact after compression, as well as improving the free-flowing qualities by the formulation of granules of desired hardness and size. Materials commonly used as binders include

starch, gelatin, and sugars such as sucrose, glucose, dextrose, molasses, and lactose. Natural and synthetic gums that have been used include acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, Veegum, and larch arabogalactan. Other agents that may be considered binders under certain circumstances are polyethylene glycol, ethylcellulose, waxes, water, and alcohol.

The quantity of binder used has considerable influence on the characteristics of the compressed tablets. The use of too much binder or too strong a binder will make a hard tablet that will not disintegrate easily and will cause excessive wear of punches and dies. Differences in binders used for CT Tolbutamide resulted in differences in hypoglycemic effects observed clinically. Materials that have no cohesive qualities of their own will require a stronger binder than those with these qualities. Alcohol and water are not binders in the true sense of the word, but because of their solvent action on some ingredients such as lactose, starch, and celluloses, they change the powdered material to granules, and the residual moisture retained enables the materials to adhere together when compressed.

Binders are used both as a solution and in a dry form, depending on the other ingredients in the formulation and the method of preparation. However, several *pregelatinized* starches available are intended to be added in the dry form so that water alone can be used as the granulating solution. The same amount of binder in solution will be more effective than if it were dispersed in a dry form and moistened with the solvent. By the latter procedure, the binding agent is not as effective in reaching and wetting each of the particles within the mass of powders. Each of the particles in a powder blend has a coating of adsorbed air on its surface, and it is this film that must be penetrated before the powders can be wetted by the binder solution. After wetting, a certain period of time is necessary to dissolve the binder completely and make it completely available for use. Since powders differ with respect to the ease with which they can be wetted and their rate of solubilization, it is preferable to incorporate the binding agent in solution. By this technique it often is possible to gain effective binding with a lower concentration of binder.

The direct-compression method for preparing tablets requires a material that is not only free-flowing but also sufficiently cohesive to act as a binder. This use has been described for a number of materials including microcrystalline cellulose, microcrystalline dextrose, amylose, and polyvinylpyrrolidone. It has been postulated that microcrystalline cellulose is a special form of cellulose fibril in which the individual crystallites are held together largely by hydrogen bonding. The disintegration of tablets containing the cellulose occurs by breaking the intercrystallite bonds by the disintegrating medium.

STARCH PASTE—Cornstarch is used widely as a binder. The concentration may vary from 10% to 20%. It usually is prepared as it is to be used, by dispersing cornstarch in sufficient cold purified water to make a 5–10% *w/w* suspension and warming in a water bath with continuous stirring until a translucent paste forms. It has been observed that during paste formation, not all of the starch is hydrolyzed. Starch paste then is not only useful as a binder, but also as a method to incorporate some disintegrant inside the granules.

GELATIN SOLUTION—Gelatin generally is used as a 10–20% solution; gelatin solutions should be prepared freshly as needed and used while warm or they will solidify. The gelatin is added to cold purified water and allowed to stand until it is hydrated. It then is warmed in a water bath to dissolve the gelatin, and the solution is made up to the final volume on a weight basis to give the concentration desired.

CELLULOSIC SOLUTIONS—Various cellulosics have been used as binders in solution form. Hydroxypropyl methylcellulose (HPMC) has been used widely in this regard. Typical of a number of cellulosics, HPMC is more soluble in cold water than hot. It also is more dispersable in hot water than cold. Hence, to obtain a good, smooth gel that is free from lumps or *fisheyes*, it is necessary to add the HPMC in hot, almost boiling water and, under agitation, cool the mixture down as quickly as possible, as low as possible. Other water-soluble cellulosics such as hydroxyethylcellulose (HEC) and hydroxypropylcellulose (HPC) have been used successfully in solution as binders.

Not all cellulosics are soluble in water. Ethylcellulose can be used effectively when dissolved in alcohol or as a dry binder that then is wetted with alcohol. It is used as a binder for materials that are moisture-sensitive.

POLYVINYLPYRROLIDONE—PVP can be used as an aqueous or alcoholic solution, and this versatility has increased its popularity. Concentrations range from 2% and vary considerably.

It will be noted that binder solutions usually are made up to weight rather than volume. This is to enable the formulator to determine the weight of the solids that have been added to the tablet granulation in the binding solution. This becomes part of the total weight of the granulation and must be taken into consideration in determining the weight of the compressed tablet, which will contain the stated amount of the therapeutic agent.

As can be seen by the list of binders in this chapter, most modern binders used in solution are polymeric. Because of this, the flow or spreadability of these solutions becomes important when selecting the appropriate granulating equipment. The rheology of polymeric solutions is a fascinating subject in and of itself and should be considered for these materials.

Lubricants

Lubricants have a number of functions in tablet manufacture. They prevent adhesion of the tablet material to the surface of the dies and punches, reduce interparticle friction, facilitate the ejection of the tablets from the die cavity, and may improve the rate of flow of the tablet granulation. Commonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid, glyceryl behanate, hydrogenated vegetable oils, and polyethylene glycol (PEG). Most lubricants, with the exception of talc, are used in concentrations below 1%. When used alone, talc may require concentrations as high as 5%. Lubricants are in most cases hydrophobic materials. Poor selection or excessive amounts can result in *waterproofing* the tablets, resulting in poor tablet disintegration and/or delayed dissolution of the drug substance.

The addition of the proper lubricant is highly desirable if the material to be tableted tends to stick to the punches and dies. Immediately after compression, most tablets have the tendency to expand and will bind and stick to the side of the die. The choice of the proper lubricant will overcome this effectively.

The method of adding a lubricant to a granulation is important if the material is to perform its function satisfactorily. The lubricant should be divided finely by passing it through a 60- to 100-mesh nylon cloth onto the granulation. In production this is called *bolting* the lubricant. After adding the lubricant, the granulation is tumbled or mixed gently to distribute the lubricant without coating the particles too well or breaking them down to finer particles. Some research has concluded that the order of mixing of lubricants and other excipients can have a profound effect on the performance of the final dosage form. Thus, attention to the mixing process itself is just as important as the selection of lubricant materials.

These process variables can be seen in the prolonged blending of a lubricant in a granulation. Overblending materially can affect the hardness, disintegration time, and dissolution performance of the resultant tablets.

The quantity of lubricant varies, being as low as 0.1% and, in some cases, as high as 5%. Lubricants have been added to the granulating agents in the form of suspensions or emulsions. This technique serves to reduce the number of operational procedures and thus reduce the processing time.

In selecting a lubricant, proper attention must be given to its compatibility with the drug agent. Perhaps the most widely in-

vestigated drug is acetylsalicylic acid. Different talcs varied significantly the stability of aspirin. Talc with a high calcium content and a high loss on ignition was associated with increased aspirin decomposition. From a stability standpoint, the relative acceptability of tablet lubricants for combination with aspirin was found to decrease in the following order: hydrogenated vegetable oil, stearic acid, talc, and aluminum stearate.

The primary problem in the preparation of a water-soluble tablet is the selection of a satisfactory lubricant. Soluble lubricants reported to be effective include sodium benzoate, a mixture of sodium benzoate and sodium acetate, sodium chloride, leucine, and polyethylene glycol/Carbowax 4000. However, it has been suggested that formulations used to prepare water-soluble tablets may represent a number of compromises between compression efficiency and water solubility. While magnesium stearate is one of the most widely used lubricants, its hydrophobic properties can retard disintegration and dissolution. To overcome these waterproofing characteristics, sodium lauryl sulfate sometimes is included. One compound found to have the lubricating properties of magnesium stearate without its disadvantages is magnesium lauryl sulfate. Its safety for use in pharmaceuticals has not been established.

Glidants

A glidant is a substance that improves the flow characteristics of a powder mixture. These materials always are added in the dry state just prior to compression (ie, during the lubrication step). Colloidal silicon dioxide Cab-o-sil *(Cabot)* is the most commonly used glidant and generally is used in low concentrations of 1% or less. Talc (asbestos-free) also is used and may serve the dual purpose of lubricant/glidant.

It is especially important to optimize the order of addition and the mixing process for these materials, to maximize their effect and to make sure that their influence on the lubricant(s) is minimized.

Disintegrants

A disintegrant is a substance or a mixture of substances added to a tablet to facilitate its breakup or disintegration after administration. The active ingredient must be released from the tablet matrix as efficiently as possible to allow rapid dissolution. Materials serving as disintegrants have been classified chemically as starches, clays, celluloses, algins, gums, and cross-linked polymers.

The oldest and still the most popular disintegrants are corn and potato starch that have been well dried and powdered. Starch has a great affinity for water and swells when moistened, thus facilitating the rupture of the tablet matrix. However, others have suggested that its disintegrating action in tablets is due to capillary action rather than swelling; the spherical shape of the starch grains increases the porosity of the tablet, thus promoting capillary action. Starch, 5%, is suggested, but if more rapid disintegration is desired, this amount may be increased to 10% or 15%. Although it might be expected that disintegration time would decrease as the percentage of starch in the tablet increased, this does not appear to be the case for tolbutamide tablets. In this instance, there appears to be a critical starch concentration for different granulations of the chemical. When their disintegration effect is desired, starches are added to the powder blends in the dry state.

A group of materials known as *super disintegrants* have gained in popularity as disintegrating agents. The name comes from the low levels (2–4%) at which they are completely effective. Croscarmellose, crospovidone, and sodium starch glycolate represent examples of a cross-linked cellulose, a cross-linked polymer, and a cross-linked starch, respectively.

The development of these disintegrants fostered new theories about the various mechanisms by which disintegrants work. Sodium starch glycolate swells 7- to 12-fold in less than 30 sec. Croscarmellose swells 4- to 8-fold in less than 10 sec. The starch swells equally in all three dimensions, while the cellulose swells only in two dimensions, leaving fiber length essentially the same. Since croscarmellose is the more efficient disintegrating agent, it is postulated that the rate, force, and extent of swelling play an important role in those disintegrants that work by swelling. Cross-linked PVP swells little but returns to its original boundaries quickly after compression. Wicking, or capillary action, also is postulated to be a major factor in the ability of cross-linked PVP to function.[17–19]

In addition to the starches, a large variety of materials have been used and are reported to be effective as disintegrants. This group includes Veegum HV, methylcellulose, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp, and carboxymethylcellulose.[20] Sodium lauryl sulfate in combination with starch also has been demonstrated to be an effective disintegrant. In some cases the apparent effectiveness of surfactants in improving tablet disintegration is postulated as due to an increase in the rate of wetting.

The disintegrating agent usually is mixed with the active ingredients and diluents prior to granulation. In some cases it may be advantageous to divide the starch into two portions: one part is added to the powdered formula prior to granulation, and the remainder is mixed with the lubricant and added prior to compression. Incorporated in this manner, the starch serves a double purpose; the portion added to the lubricant rapidly breaks down the tablet to granules, and the starch mixed with the active ingredients disintegrates the granules into smaller particles. Veegum has been shown to be more effective as a disintegrator in sulfathiazole tablets when most of the quantity is added after granulation and only a small amount before granulation. Likewise, the montmorillonite clays were found to be good tablet disintegrants when added to prepared granulations as powder. They are much less effective as disintegrants when incorporated within the granules.

Factors other than the presence of disintegrants can affect the disintegration time of compressed tablets significantly. The binder, tablet hardness, and the lubricant have been shown to influence the disintegration time. Thus, when the formulator is faced with a problem concerning the disintegration of a compressed tablet, the answer may not lie in the selection and quantity of the disintegrating agent alone.

The evolution of carbon dioxide is also an effective way to cause the disintegration of compressed tablets. Tablets containing a mixture of sodium bicarbonate and an acidulant such as tartaric or citric acid will effervesce when added to water. Sufficient acid is added to produce a neutral or slightly acidic reaction when disintegration in water is rapid and complete. One drawback to the use of the effervescent type of disintegrator is that such tablets must be kept in a dry atmosphere at all times during manufacture, storage, and packaging. Soluble, effervescent tablets provide a popular form for dispensing aspirin and noncaloric sweetening agents.

Coloring Agents

Colors in compressed tablets serve functions other than making the dosage form more esthetic in appearance. Color helps the manufacturer to control the product during its preparation, as well as serving as a means of identification to the user. The wide diversity in the use of colors in solid dosage forms makes it possible to use color as an important category in the identification code developed by the AMA to establish the identity of an unknown compressed tablet in situations arising from poisoning.

All colorants used in pharmaceuticals must be approved and certified by the FDA. For several decades colorants have been subjected to rigid toxicity standards, and as a result, a number of colorants have been removed from an approved list of Food, Drug and Cosmetic Act (FD&C) colors, or *delisted*. Several have

Table 45-1. Colors Approved for Use in the US in Oral Dosage Forms[a,b]

COLOR	OTHER NAMES	COLOR INDEX (CI 1971)	USE RESTRICTION (US)
FD&C Red 40	Allura red	16035	FDA certification on each lot of dye
D&C Red 33	Acid fuchsin D Naphtalone red B	17200	ADI 0–0.76 mg
D&C Red 36			ADI 0–1.0 mg
Canthaxanthinin	Food orange 8	40850	None
D&C Red 22	Eosin Y	45380	FDA certification on each lot of dye
D&C Red 28	Phloxine B	45410	FDA certification on each lot of dye
D&C Red 3	Erythrosine	45430	FDA certification on each lot of dye
Cochineal extract	Natural red 4 Carmine	75470	None
Iron oxide—red	—	77491	ADI 0–5 mg elemental iron
FD&C Yellow 6	Sunset yellow FCF Yellow orange 5	15985	None
FD&C Yellow 5	Tartrazine	19140	Label declaration and FDA certification on each lot of dye
D&C Yellow 10	Quinoline yellow WS	47005	FDA certification on each lot of dye
Beta-carotene	—	40800	
Iron oxide—yellow	—	77492	ADI 0–5 mg elemental iron
FD&C BLue 1	Brilliant blue FCF	42090	FDA certification on each lot of dye
FD&C Blue 2	Indigotine Indigo carmine	73015	None
FD&C Green 3	Fast green FCF	42035	FDA certification on each lot of dye
Iron oxide—black	—	77499	ADI 0–5 mg elemental iron
Caramel	Burnt sugar	—	None
Titanium dioxide	—	77891	None

[a] Abbreviations: ADI, acceptable daily intake (per kg body weight); CI, color index numbers of 1971 (US); D&C, Drug and Cosmetic Dyes (US); FD&C, Food, Drug and Cosmetic Dyes (US); FDA, Food and Drug Administration (US).
[b] As of February, 1988 and subject to revision.

been listed as well. The colorants currently approved in the US are listed in Table 45-1. Each country has its own list of approved colorants, and formulators must consider this in designing products for the international market.[21]

Any of the approved, certified, water-soluble FD&C dyes, mixtures of the same, or their corresponding lakes may be used to color tablets. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal resulting in an insoluble form of the dye. In some instances multiple dyes are used to give a purposefully heterogeneous coloring in the form of speckling to compressed tablets. The dyes available do not meet all the criteria required for the ideal pharmaceutical colorants. The photosensitivity of several of the commonly used colorants and their lakes has been investigated, as well as the protection afforded by a number of glasses used in packaging tablets.

Another approach for improving the photostability of dyes has been in the use of ultraviolet-absorbing chemicals in the tablet formulations with the dyes. The Di-Pac line *(Amstar)* is a series of commercially available colored, direct-compression sugars.

The most common method of adding color to a tablet formulation is to dissolve the dye in the binding solution prior to the granulating process. Another approach is to adsorb the dye on starch or calcium sulfate from its aqueous solution; the resultant powder is dried and blended with the other ingredients. If the insoluble lakes are used, they may be blended with the other dry ingredients. Frequently during drying, colors in wet granulations migrate, resulting in an uneven distribution of the color in the granulation. After compression, the tablets will have a mottled appearance due to the uneven distribution of the color. Migration of colors may be reduced by drying the granulation slowly at low temperatures and stirring the granulation while it is drying. The affinity of several water-soluble, anionic, certified dyes for natural starches has been demonstrated; in these cases this affinity should aid in preventing color migration.

Other additives have been shown to act as dye-migration inhibitors. Tragacanth (1%), acacia (3%), attapulgite (5%), and talc (7%) were effective in inhibiting the migration of FD&C Blue No 1 in lactose. In using dye lakes, the problem of color migration is avoided since the lakes are insoluble. Prevention of mottling can be helped also by the use of lubricants and other additives that have been colored similarly to the granulation prior to their use. The problem of mottling becomes more pronounced as the concentration of colorants increases. Color mottling is an undesirable characteristic common to many commercial tablets.

Flavoring Agents

In addition to the sweetness that may be afforded by the diluent of the chewable tablet, eg, mannitol or lactose, artificial sweetening agents may be included. Formerly, the cyclamates, either alone or in combination with saccharin, were used widely. With the banning of the cyclamates and the indefinite status of saccharin, new natural sweeteners are being sought. Aspartame *(Pfizer)*, has found applications in pharmaceutical formulations. Sweeteners other than the sugars have the advantage of reducing the bulk volume, considering the quantity of sucrose required to produce the same degree of sweetness. Being present in small quantities, they do not affect markedly the physical characteristics of the tablet granulation.

POWDER COMPACTION

Compressed tablets became a commercially viable and efficient dosage form with the invention of tablet machines. In 1843 William Brockendon, a British inventor, author, artist, and watchmaker, received British Patent #9977 for *Shaping Pills, Lozenges, and Black Lead by Pressure in Dies*.[22] In over 150 years of tablet manufacture, the basic process has not changed. Surprisingly, improvements have been made only with regards to speed of manufacture and quality control.

The process of compaction has several identifiable phases. As can be seen in Figure 45-3, when powders undergo compression (a reduction in volume), the first process to occur is a consolidation of the powders. During this consolidation phase, the powder particles adopt a more efficient packing order. The second phase of the compaction process is elastic, or reversible de-

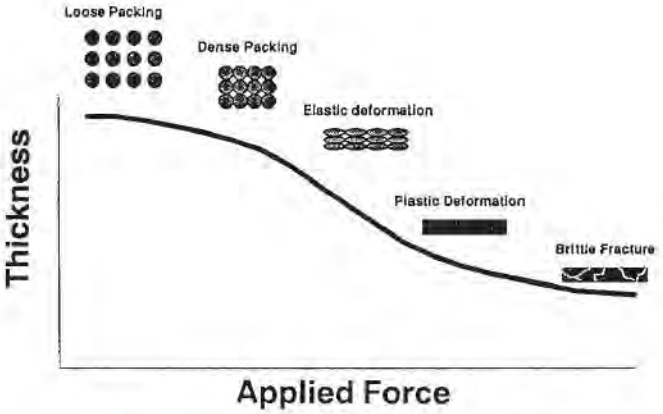


Figure 45-3. The stages of powder compaction.

formation. If the force were to be removed during this phase, the powder would recover completely to the efficiently packed state. For most pharmaceutical powders, this phase is very short in duration and very difficult to identify on most instrumented tablet presses. The third phase of compaction is plastic, or irreversible, deformation of the powder bed. It is this phase of the compaction process that is the most critical in tablet formation. If too much force is applied to the powder, brittle fracture occurs. If the force was applied too quickly, fracture and de-bonding during stress relaxation can occur.

In 1950, Stewart reported on the importance of plastic flow and suggested that if a material has significant plastic flow under compression, it will be more likely to form a compact.[23] David and Augsburger evaluated stress-relaxation data, using the Maxwell model of viscoelastic behavior in an attempt to quantify the rate of plastic deformation of some direct compression excipients.[24] Jones has used the term *contact time* to describe the total time for which a moving punch applies a detectable force to the die contents during the compression and decompression event, excluding ejection.[25]

Rees and Rue evaluated three parameters: stress relation during compaction, effect of contact time on tablet density, and rate of application of diametrical compression on tablet deformation.[26]

Jones[25] outlined numerous techniques to evaluate the compactability of powders. Because of the completeness of his review, these parameters are discussed below.

Tablet Strength—Compression Pressure Profile

Most formulators use tablet *hardness*, or tensile strength, as a measure of the cohesiveness of a tablet. With even the simplest of instrumented tablet presses, it is possible to plot tensile strength versus the force applied to the tablet. Figure 45-4 illustrates such a plot. These plots can be useful in identifying forces that can cause fracture and can lead to a quick, tangible assessment of the compatibility of the formulation. However, there are many limitations to this method, as these plots cannot predict *lamination* or *capping*. In addition, the cohesiveness of a tablet can change upon storage, in either a positive or negative direction.

Tablet Friability

This test is discussed later in the chapter, and there have been many suggestions about how they should be performed. Many formulators believe this is an important indicator of cohesiveness but is of limited value in predicting failure in the field.

Changes in Bed Density during Compression

As applied stress (force) increases, elastic and plastic deformation of the particles occurs, which results in plastic flow and a reduction in inter- and intraparticulate void spaces. This lowers the overall compact density.

For highly cohesive systems, the reduction in void space may yield a compact of sufficient strength for insertion into a capsules shell. However, the inherent cohesiveness for most drugs and excipients is not suitable alone for tablet manufacture.

The Heckel equation is given below; K can be considered equal to the reciprocal of the mean yield pressure, and A is a function of the original compact volume and is related to the densification and particle rearrangement prior to bonding.

$$\text{Log}\,[1/(1 - D)] = KP + A$$

where D is the relative density at pressure P, and K and A are constants.

Hersey and Rees[28] have classified Heckel plots into two categories. Figure 45-5 shows both types of Heckel plots. Type 2 differs from Type 1 in that above a certain pressure a single linear relationship occurs irrespective of the initial bed density.

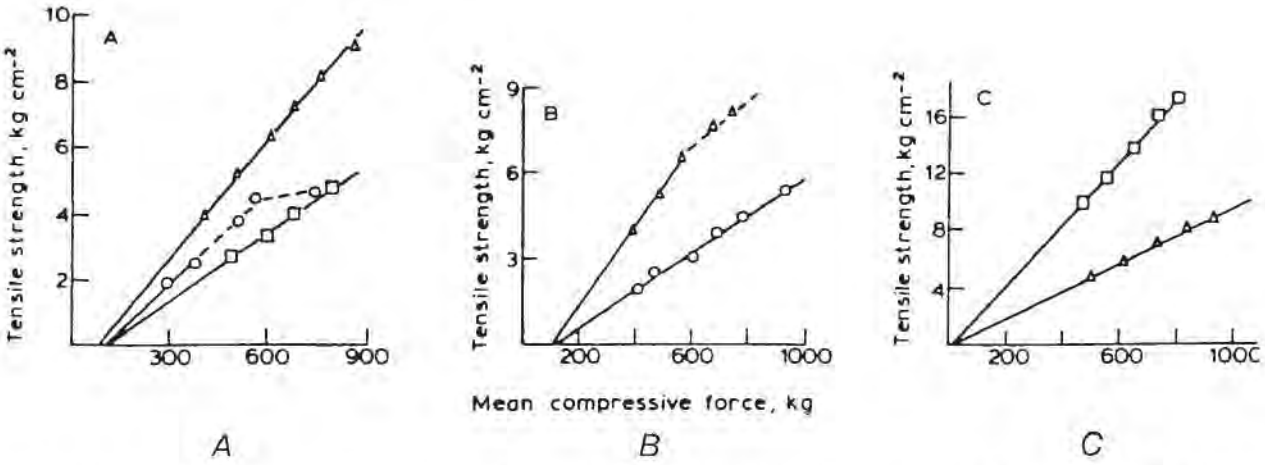


Figure 45-4. Tensile strength of compacts prepared from different crystal forms. *A:* Barbitone (104–152 μm)—○, Form I; □, Form II; △, Form III. *B:* Sulfathiazole (104–152 μm)—○, Form I; △, Form II. *C:* Aspirin (250–353 μm)—△, Form I; □, Form IV. (From Summers MP, Enever RP, Carless JE. *J Pharm Sci* 1977; 66:1172.)

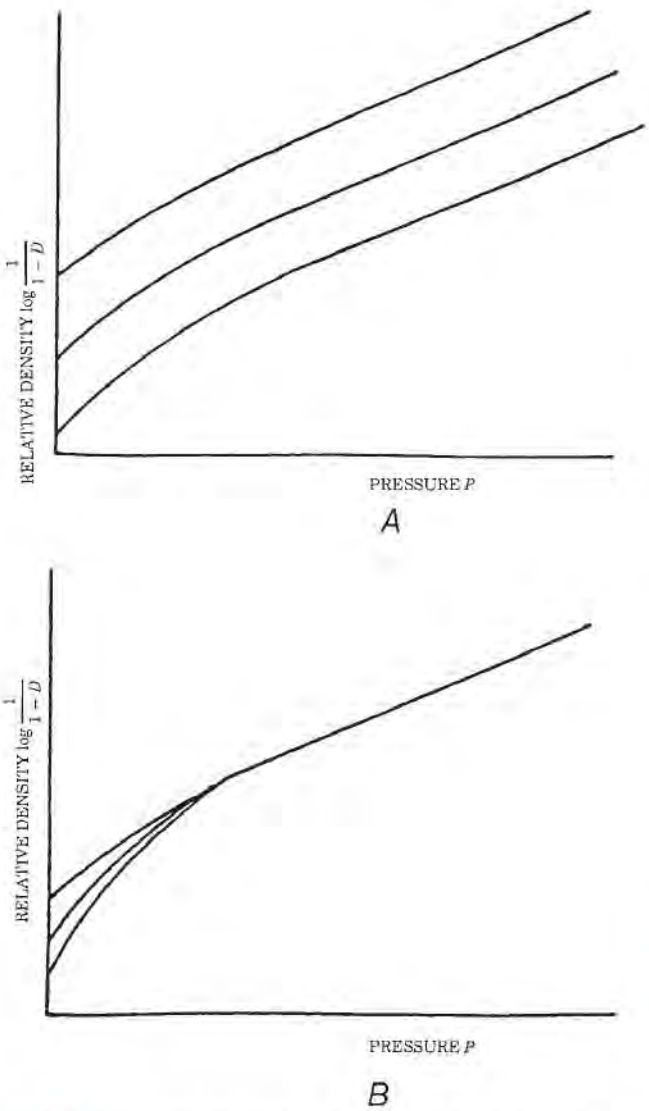


Figure 45-5. Heckel plots. *A:* Type I. *B:* Type II. (From Jones TM. *Acta Pharm Tech* 1978.)

This is independent of particle size and is probable due to fragmentation of particles and their subsequent compaction by plastic deformation. For Type 1 materials, no such fracture occurs, but adjacent particles simply deform plastically.

The pressure at which the plots transition to a linear portion is approximately equal to the minimum pressure required to form a coherent compact.

Changes in Surface Area During Compression

Bulk powders change their state of packing during compaction, and individual particles fracture and/or plastically deform. During this process, the surface area of the powders and the compact in whole, changes. Conventional nitrogen absorption techniques can estimate these changes. Although this can be tedious, these measurements can give a means of examining lamination tendency.

Stress Relaxation

The experimental technique consists of holding the compression process at a point of maximum compression and observing the compression force over various periods of time. By increasing the duration of this period (dwell time), plastic flow is maximized, and tablet strength increases.

Stress Transmissions during Compression

If the stresses in the upper punch, lower punch, and die wall are monitored, as in Figure 45-6, a general plot can be constructed showing the relationship between these forces. The elastic limit is reached at point *A*. At point *B*, the applied force is released, and the transmitted force on the wall of the die falls rapidly. The upper punch ceases to contact the powder/compact at point *C*, where the transmitted force falls rapidly to a residual force, point *D*. The force needed to eject the tablet from the die must be greater than the residual force holding it to the sides of the die. Therefore, residual forces tend to be proportional to ejection forces. In addition, these plots can give a good assessment of the elastic component of the compaction process of a powder.

Work and Compaction

Force-displacement (*F-D*) curves are useful in determining the *work* involved in forming a compact. Curves, such as shown in Figure 45-7,[29] represent the work of the compression process, but all compacts expand somewhat during decompression, and this force is transferred back to the punch. Therefore, by performing a second compression of the compact, the second result can be subtracted from the first for a *corrected F-D curve*. The corrected curve represents the work associated with plastic deformation during powder compaction, as well as a determination of the work of friction of the die wall and the work of elastic deformation.

GRANULATION METHODS

Wet Granulation

The most widely used and most general method of tablet preparation is the wet-granulation method. Its popularity is due to the greater probability that the granulation will meet all the physical requirements for the compression of good tablets. Its chief disadvantages are the number of separate steps involved, as well as the time and labor necessary to carry out the procedure, especially on a large scale. The steps in the wet method are weighing, mixing, granulation, screening the damp mass, drying, dry screening, lubrication, and compression. The equipment involved depends on the quantity or size of the batch. The active ingredient, diluent, and disintegrant are mixed or blended well. For small batches the ingredients may be mixed in stainless steel bowls or mortars. Small-scale blending also

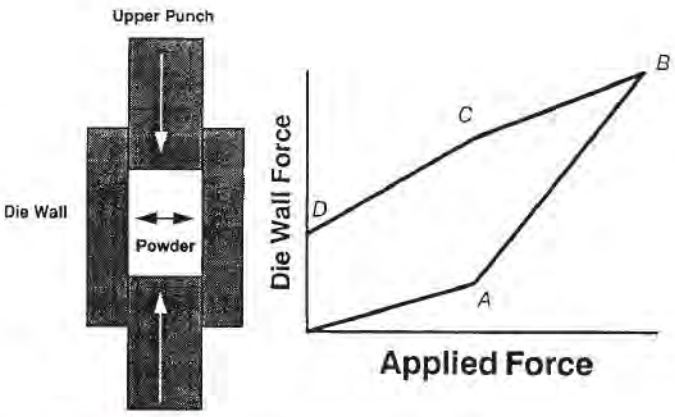


Figure 45-6. Transmitted stresses during tablet compaction.

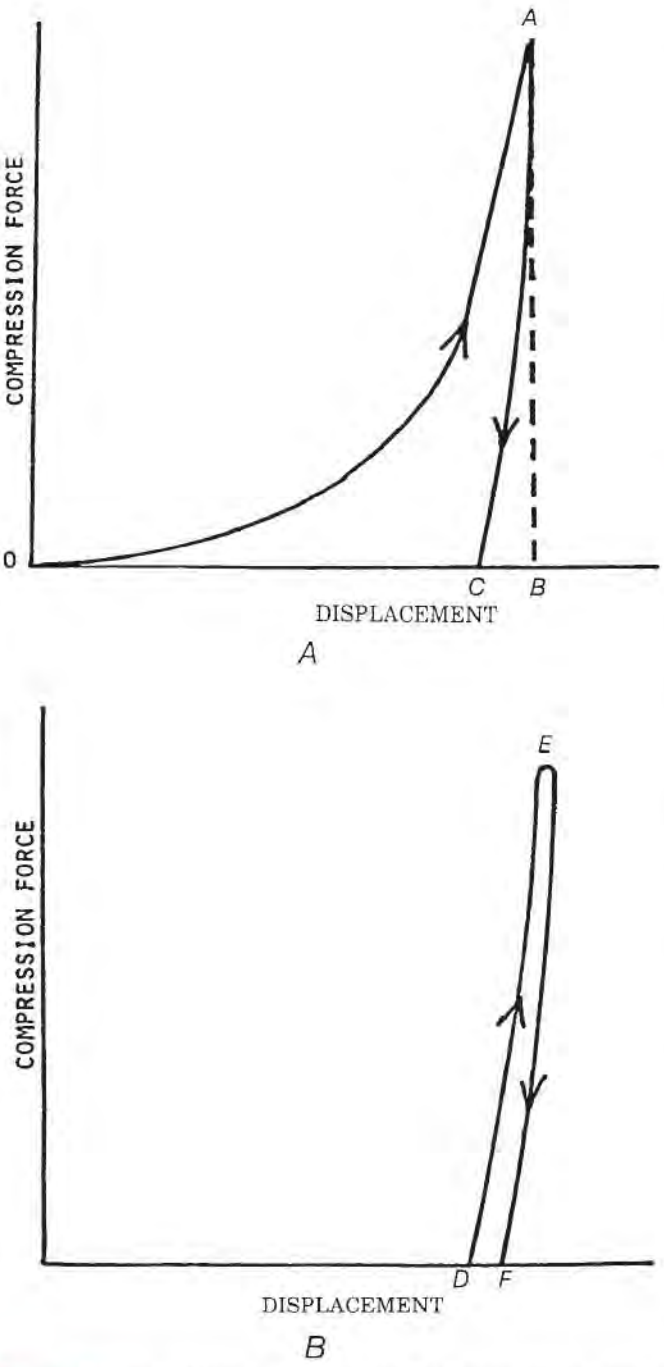


Figure 45-7. Typical forces. *A:* Displacement (F–D) curve; *B:* displacement (F–D), second compression. (From Jones TM. *Acta Pharm Tech* 1978.)

can be carried out on a large piece of paper by holding the opposite edges and tumbling the material back and forth. The powder blend may be sifted through a screen of suitable fineness to remove or break up lumps. This screening also affords additional mixing. The screen selected always should be of the same type of wire or cloth that will not affect the potency of the ingredients through interaction. For example, the stability of ascorbic acid is affected deleteriously by even small amounts of copper, thus care must be taken to avoid contact with copper or copper-containing alloys.

For larger quantities of powder, the Patterson-Kelley twin-shell blender and the double-cone blender offer a means of precision blending and mixing in short periods of time (Fig 45-8). Twin-shell blenders are available in many sizes from laboratory models to large production models. Planetary mixers (eg,

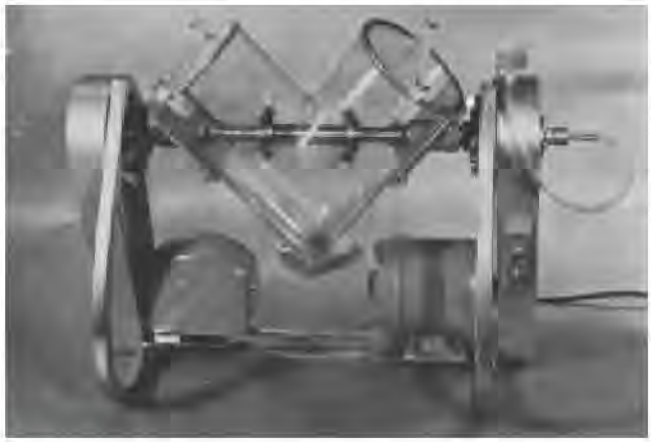


Figure 45-8. Twin-shell blender for solids or liquid-solids blending (courtesy, Patterson-Kelley).

the Glen mixer and the Hobart mixer) have served this function in the pharmaceutical industry for many years (Fig 45-9). On a large scale, ribbon blenders also are employed frequently and may be adapted for continuous-production procedures. Mass mixers of the sigma-blade type have been used widely in the pharmaceutical industry.

Highly popular are the high-speed, high-shear mixers such as the Diosna, Fielder, Lodige/Littleford, and Baker-Perkins. For these mixers a full range of sizes are available. The processing of granulations in these machines is generally faster than in conventional granulators. However, control over the process is critical, and scale-up issues may become extremely important.[30] Fluid-bed granulation (discussed below) also is gaining wide acceptance in the industry. For both of these types of processing, slight modifications to the following procedures are required.

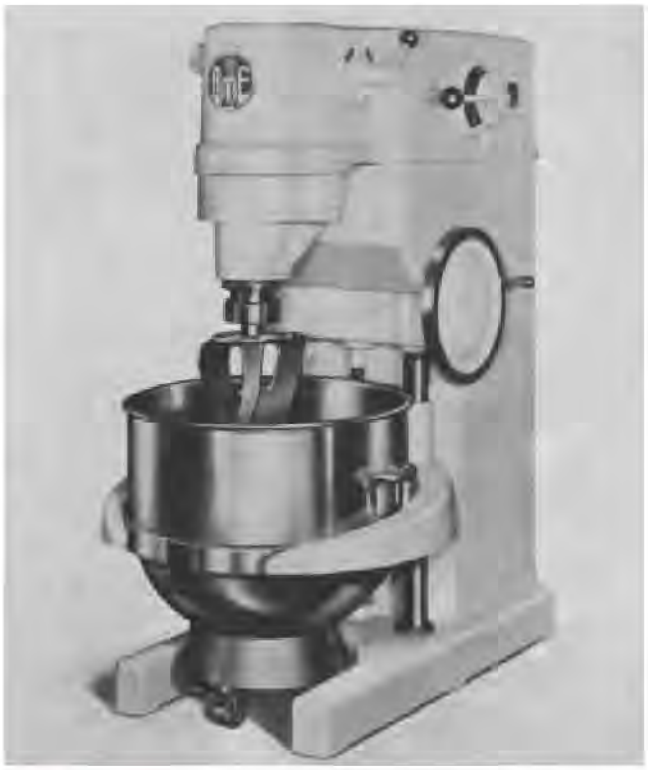


Figure 45-9. The Glen powder mixer (courtesy, Am Machine).

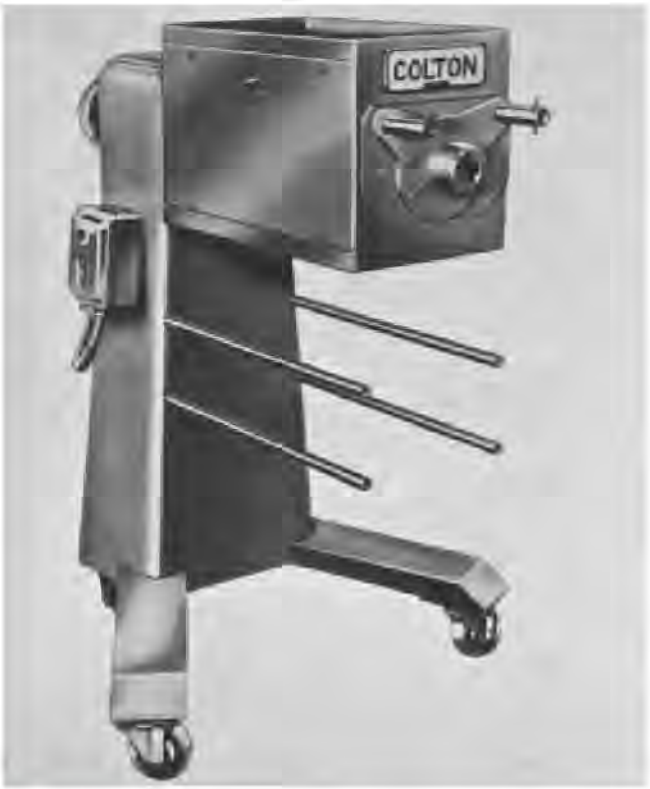


Figure 45-10. Rotary granulator and sifter (courtesy, Vector/Colton).

Solutions of the binding agent are added to the mixed powders with stirring. The powder mass is wetted with the binding solution until the mass has the consistency of damp snow or brown sugar. If the granulation is over-wetted, the granules will be hard, requiring considerable pressure to form the tablets, and the resultant tablets may have a mottled appearance. If the powder mixture is not wetted sufficiently, the resulting granules will be too soft, breaking down during lubrication and causing difficulty during compression.

The wet granulation is forced through a 6- or 8-mesh screen. Small batches can be forced through by hand using a manual screen. For larger quantities, one of several comminuting mills suitable for wet screening can be used. These include the Stokes oscillator, Colton rotary granulator, Fitzpatrick comminuting mill, or Stokes tornado mill. See Figure 45-10. In comminuting mills the granulation is forced through the sieving device by rotating hammers, knives, or oscillating bars. Most high-speed mixers are equipped with a chopper blade that operates independently of the main mixing blades and can replace the wet milling step, ie, can obviate the need for a separate operation.

For tablet formulations in which continuous production is justified, extruders such as the Reitz extruder have been adapted for the wet-granulation process. The extruder consists of a screw mixer with a chamber where the powder is mixed with the binding agent, and the wet mass gradually is forced through a perforated screen, forming threads of the wet granulation. The granulation then is dried by conventional methods. A semiautomatic, continuous process using the Reitz extruder has been described for the preparation of the antacid tablet Gelusil *(Warner-Lambert / Pfizer)*.

Moist material from the wet milling step traditionally was placed on large sheets of paper on shallow wire trays and placed in drying cabinets with a circulating air current and thermostatic heat control. See Figure 45-11. While tray drying was the most widely used method of drying tablet granulations in the past, fluid-bed drying is now considered the standard. In drying tablet granulation by fluidization, the material is suspended and agitated in a warm air stream while the granulation is maintained in motion. Drying tests comparing the fluidized bed and a tray dryer for a number of tablet granulations indicated that the former was 15 times faster than the conventional method of tray drying. In addition to the decreased drying time, the fluidization method is claimed to have other advantages such as better control of drying temperatures, decreased handling costs, and the opportunity to blend lubricants and other materials into the dry granulation directly in the fluidized bed. See Figure 45-12.[31]

The application of microwave drying and infrared drying to tablet granulations has been reported as successful for most granulations tried. These methods readily lend themselves to continuous granulation operations. The study of drying methods for tablet granulations led to the development of the Rovac dryer system by Ciba/Novartis pharmacists and engineers. The dryer is similar in appearance to the cone blender except for the heating jacket and vacuum connections. By excluding oxygen and using the lower drying temperatures made possible by drying in a vacuum, opportunities for degradation of the ingredients during the drying cycle are minimized. A greater uniformity of residual moisture content is achieved because of the moving bed, controlled temperature, and controlled time period of the drying cycle. Particle-size distribution can be controlled by varying the speed of rotation and drying temperature as well as by comminuting the granulation to the desired granule size after drying.

In drying granulations it is desirable to maintain a residual amount of moisture in the granulation. This is necessary to maintain the various granulation ingredients, such as gums, in a hydrated state. Also, the residual moisture contributes to the reduction of the static electric charges on the particles. In the selection of any drying process, aneffort is made to obtain a uniform moisture content. In addition to the importance of moisture content of the granulation in its handling during the manufacturing steps, the stability of the products containing moisture-sensitive active ingredients may be related to the moisture content of the products.

Previously it was indicated that water-soluble colorants can migrate toward the surface of the granulation during the drying process, resulting in mottled tablets after compression. This is also true for water-soluble drug substances, resulting in tablets unsatisfactory as to content uniformity. Migration can be reduced by drying the granulation slowly at low temperatures or using a granulation in which the major diluent is present as granules of large particle size. The presence of microcrystalline cellulose in wet granulations also reduces migration tendencies.

After drying, the granulation is reduced in particle size by passing it through a smaller-mesh screen. Following dry screening, the granule size tends to be more uniform. For dry granulations the screen size to be selected depends on the diameter of the punch. The following sizes are suggested:

Tablets up to $\frac{3}{16}$ inch diameter, use 20-mesh
Tablets $\frac{7}{32}$ to $\frac{1}{8}$ inch, use 16-mesh
Tablets $\frac{11}{32}$ to $\frac{13}{32}$ inch, use 14-mesh
Tablets $\frac{7}{16}$ inch and larger, use 12-mesh

For small amounts of granulation, hand screens may be used and the material passed through with the aid of a stainless steel spatula. With larger quantities, any of the comminuting mills

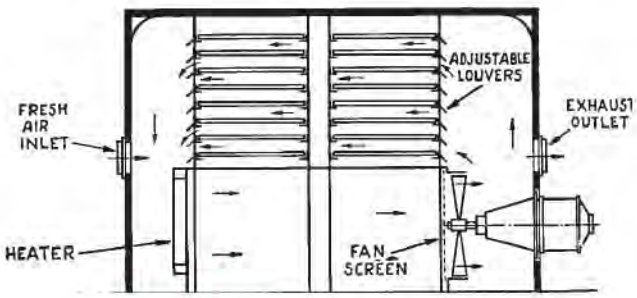


Figure 45-11. Cross-section of tray dryer.

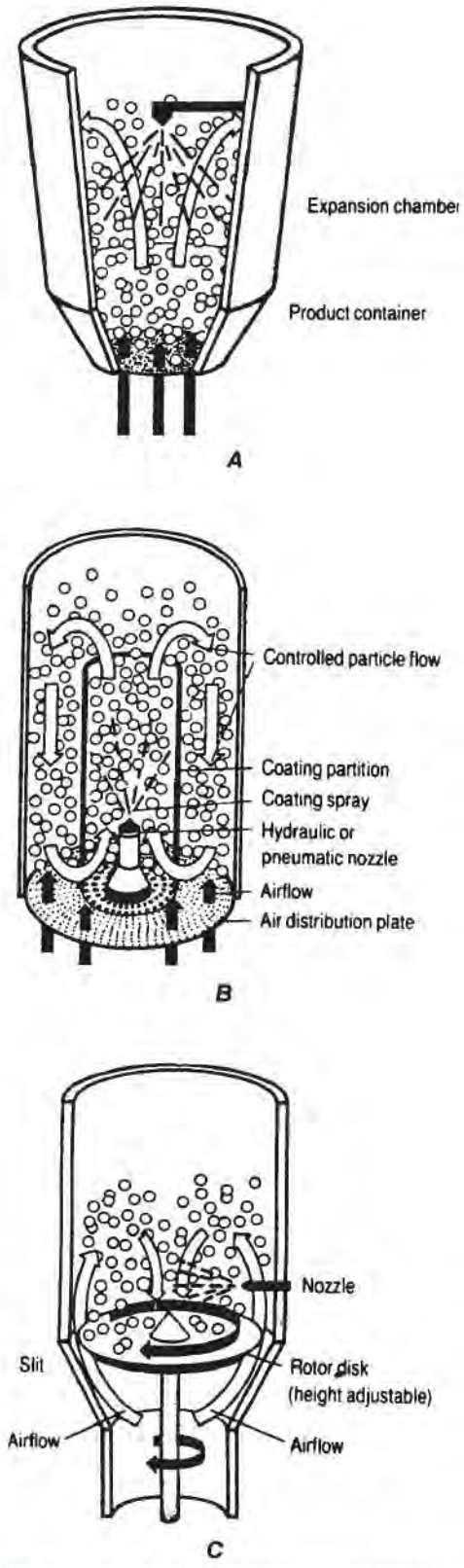


Figure 45-12. Three versions of fluidized-bed granulation and drying. *A:* Top-spray method used in conventional fluid-bed granulation coaters; *B:* bottom-spray method used in Wurster air- suspension columns; *C:* tangential-spray method used in rotary fluid-bed coaters/granulators. (Courtesy, Aster Publ, adapted from Mehta AM. *Pharm Technol* 1988; 12:46.)

with screens corresponding to those just mentioned may be used. Note that the smaller the tablet, the finer the dry granulation to enable more uniform filling of the die cavity; large granules give an irregular fill to a comparatively small die cavity. With compressed tablets of sodium bicarbonate, lactose, and magnesium trisilicate, a relationship has been demonstrated between the particle size of the granulated material and the disintegration time and capping of the resultant tablets. For a sulfathiazole granulation, however, the particle-size distribution did not appear to influence hardness or disintegration.

After dry granulation, the lubricant is added as a fine powder. It usually is screened onto the granulation through 60- or 100-mesh nylon cloth to eliminate small lumps as well as to increase the covering power of the lubricant. As it is desirable for each granule to be covered with the lubricant, the lubricant is blended with the granulation very gently, preferably in a blender using a tumbling action. Gentle action is desired to maintain the uniform granule size resulting from the granulation step. It has been claimed that too much fine powder is not desirable because fine powder may not feed into the die evenly; consequently, variations in weight and density result. Fine powders, commonly designated as *fines*, also blow out around the upper punch and down past the lower punch, making it necessary to clean the machine frequently. Fines, however, at a level of 10–20%, traditionally are sought by the tablet formulator. The presence of some fines is necessary for the proper filling of the die cavity. Now, even higher concentrations of fines are used successfully in tablet manufacture. Most investigators agree that no general limits exist for the amount of fines that can be present in a granulation; it must be determined for each specific formula.

Many formulators once believed (and some still believe) that overblending resulted in an increased amount of fines and, hence, caused air entrapment in the formula. The capping and laminating of tablets associated with overblending lubricants was thought to be caused by these air pockets. Most scientists now recognize that a more plausible explanation has to do with the function of the lubricants themselves. Since the very nature of a lubricant tends to make surfaces less susceptible to adhesion, overblending prevents the intergranular bonding that takes place during compaction.

Fluid-Bed Granulation

A new method for granulating evolved from the fluid-bed drying technology described earlier. The concept was to spray a granulating solution onto the suspended particles, which then would be dried rapidly in the suspending air. The main benefit from this system is the rapid granulation and drying of a batch. The two main firms that developed this technology are *Glatt* and *Aeromatic (now NIRO)*. The design of these systems is basically the same with both companies (see Fig 45-12). In this method, particles of an inert material or the active drug are suspended in a vertical column with a rising air stream; while the particles are suspended, the common granulating materials in solution are sprayed into the column. There is a gradual particle buildup under a controlled set of conditions resulting in a tablet granulation that is ready for compression after the addition of the lubricant. An obvious advantage exists, since granulating and drying can take place in a single piece of equipment. It should be noted, however, that many of the mixers discussed previously can be supplied with a steam jacket and vacuum and can provide the same advantage.

In these systems a granulating solution or solvent is sprayed into or onto the bed of suspended particles. The rate of addition of the binder, temperature in the bed of particles, temperature of the air, volume, and moisture of the air all play an important role in the quality and performance of the final product. Many scientists feel that this method is an extension of the wet-granulation method, as it incorporates many of its concepts. However anyone who has developed a formulation in a fluid-bed

system knows that the many operating parameters involved make it somewhat more complex.[31] In addition to its use for the preparation of tablet granulations, this technique also has been proposed for the coating of solid particles as a means of improving the flow properties of small particles. Researchers have observed that, in general, fluid-bed granulation yields a less dense particle than conventional methods, and this can affect subsequent compression behavior. A large-scale fluid-bed granulation process has been described for Tylenol *(McNeil)*. Methods for the preparation of compressed tablets have been reviewed in the literature.[32]

The *Merck* facility at Elkton, VA was the first completely automated tablet production facility in the world. The entire tablet-manufacturing process based on a wet-granulation method was computer-controlled. By means of a computer, the system weighed the ingredients, blended, granulated, dried, and lubricated to prepare a uniform granulation of specified particle size and particle-size distribution. The computer directed the compression of the material into tablets with exacting specifications for thickness, weight, and hardness. After compression, the tablets were coated with a water-based film coating. The computer controlled and monitored all flow of material. The plant represented the first totally automated pharmaceutical manufacturing facility. However, due to shifting market trends and the burdens of process validation and changes to processes, totally automated processes are generally not used today. Instead, many production operations focus on computer-controlled and monitored unit operations, such as seen in various tableting machines and granulators today. See Figure 45-13.

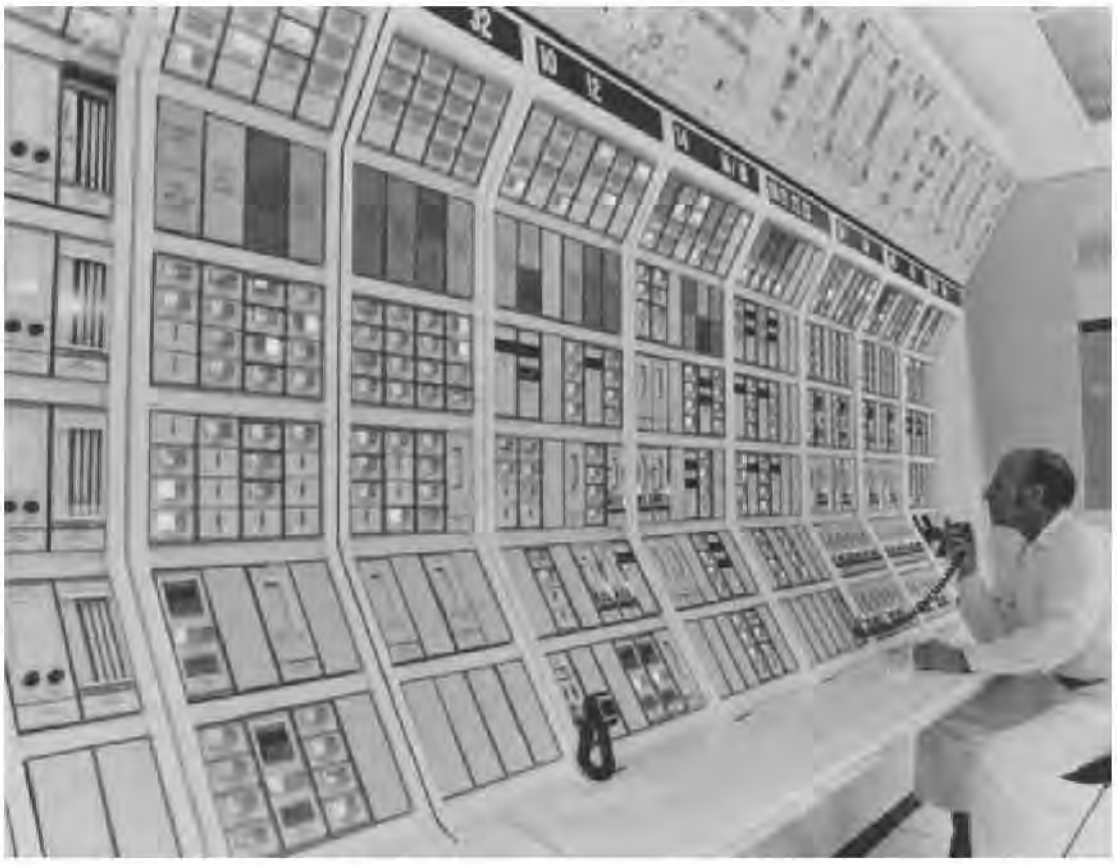
Equipment suppliers work closely with individual pharmaceutical companies in designing specialized and unique systems.

Dry Granulation

When tablet ingredients are sensitive to moisture or are unable to withstand elevated temperatures during drying, and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules. This method is referred to as dry granulation, precompression, or double-compression. It eliminates a number of steps but still includes weighing, mixing, slugging, dry screening, lubrication, and compression. The active ingredient, diluent (if required), and part of the lubricant are blended. One of the constituents, either the active ingredient or the diluent, must have cohesive properties. Powdered material contains a considerable amount of air; under pressure this air is expelled, and a fairly dense piece is formed. The more time allowed for this air to escape, the better the tablet or slug.

When slugging is used, large tablets are made as slugs because fine powders flow better into large cavities. Also, producing large slugs decreases production time; 7/8 to 1 in are the most practical sizes for slugs. Sometimes, to obtain the pressure that is desired the slug sizes are reduced to 3/4 in. The punches should be flat-faced. The compressed slugs are comminuted through the desirable mesh screen either by hand or, for larger quantities, through the Fitzpatrick or similar comminuting mill. The lubricant remaining is added to the granulation and blended gently, and the material is compressed into tablets. Aspirin is a good example of where slugging is satisfactory. Other materials such as aspirin combinations, acetaminophen, thiamine hydrochloride, ascorbic acid, magnesium hydroxide, and other antacid compounds may be treated similarly.

Results comparable to those accomplished by the slugging process also are obtained with compacting mills. In the com-



A

Figure 45-13. Fixed automated processes in the 1980s have given way to flexible micro-processor controlled unit operations. **a.** Computer control room for the first large-scale computer-controlled tablet manufacturing facility (courtesy, Merck).

B

Figure 45-13. *(continued)* **b.** Computer-controlled/monitored coating.

paction method the powder to be densified passes between high-pressure rollers that compress the powder and remove the air. The densified material is reduced to a uniform granule size and compressed into tablets after the addition of a lubricant. Excessive pressures that may be required to obtain cohesion of certain materials may result in a prolonged dissolution rate. Compaction mills available include the Chilsonator *(Fitzpatrick),* Roller Compactor *(Vector),* and the Compactor Mill *(Allis-Chalmers).*

Direct Compression

As its name implies, direct compression consists of compressing tablets directly from powdered material without modifying the physical nature of the material itself. Formerly, direct compression as a method of tablet manufacture was reserved for a small group of crystalline chemicals having all the physical characteristics required for the formation of a good tablet. This group includes chemicals such as potassium salts (chlorate, chloride, bromide, iodide, nitrate, permanganate), ammonium chloride, and methenamine. These materials possess cohesive and flow properties that make direct compression possible.

Since the pharmaceutical industry constantly is making efforts to increase the efficiency of tableting operations and reduce costs by using the smallest amount of floor space and labor as possible for a given operation, increasing attention is being given to this method of tablet preparation. Approaches being used to make this method more universally applicable include the introduction of formulation additives capable of im-

C

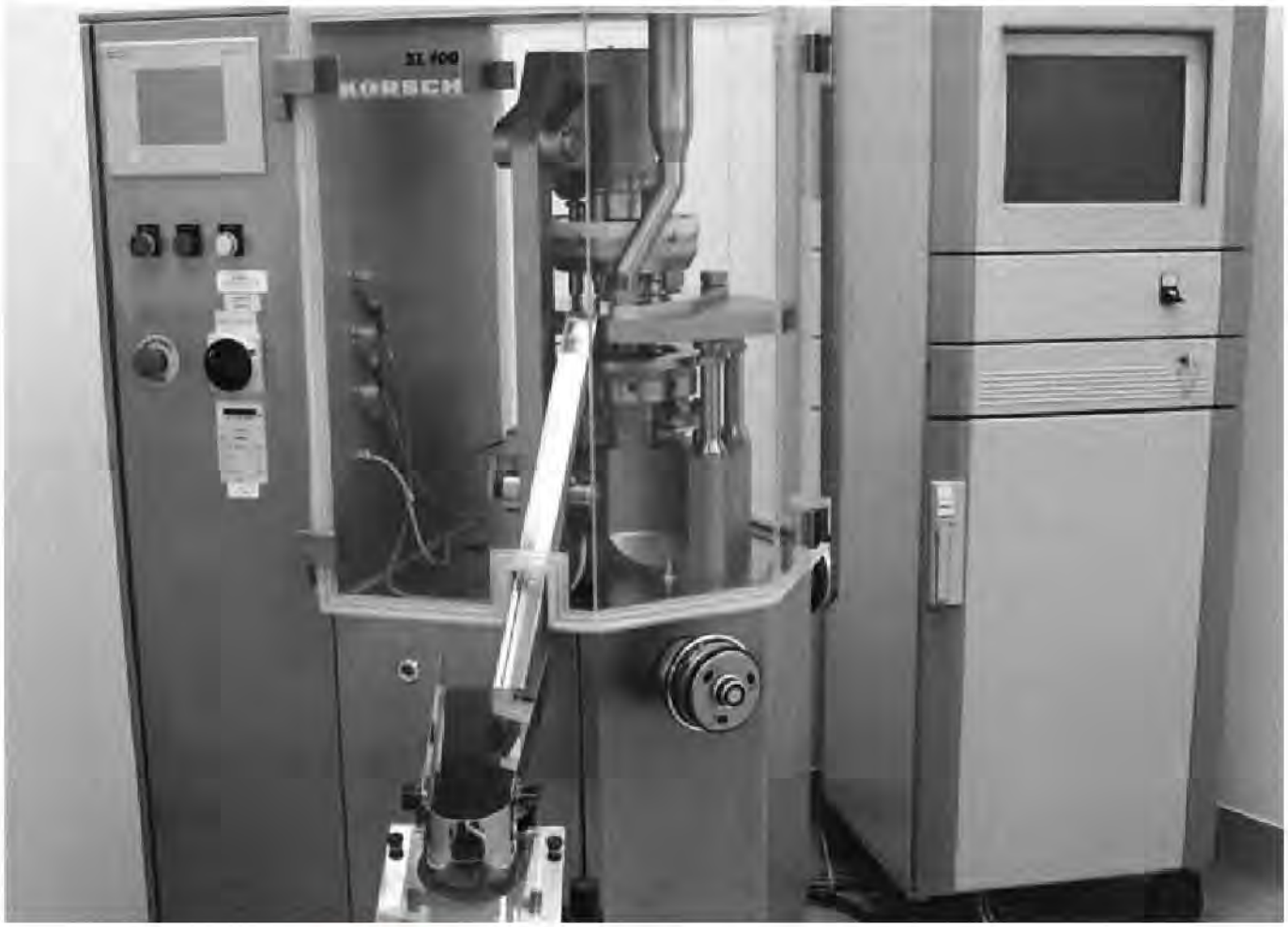
Figure 45-13. *(continued)* **c.** Computer-controlled/monitored granulation.

parting the characteristics required for compression and the use of force-feeding devices to improve the flow of powder blends.

For tablets in which the drug itself constitutes a major portion of the total tablet weight, it is necessary that the drug possess those physical characteristics required for the formulation to be compressed directly. Direct compression for tablets containing 25% or less of drug substances frequently can be used by formulating with a suitable diluent that acts as a carrier or vehicle for the drug.[32–34]

Direct-compression vehicles or carriers must have good flow and compressible characteristics. These properties are imparted to them by a preprocessing step such as wet granulation, slugging, spray drying, spheronization, or crystallization. These vehicles include processed forms of most of the common diluents including dicalcium phosphate dihydrate, tricalcium phosphate, calcium sulfate, anhydrous lactose, spray-dried lactose, pregelatinized starch, compressible sugar, mannitol, and microcrystalline cellulose. These commercially available direct-compression vehicles may contain small quantities of other ingredients (eg, starch) as processing aids. Dicalcium phosphate dihydrate (Di-Tab, *Stauffer*) in its unmilled form has good flow properties and compressibility. It is a white, crystalline agglomerate insoluble in water and alcohol. The chemical is odorless, tasteless, and nonhygroscopic. Since it has no inherent lubricating or disintegrating properties, other additives must be present to prepare a satisfactory formulation.

Compressible sugar consists mainly of sucrose that is processed to have properties suitable for direct compression. It also may contain small quantities of dextrin, starch, or invert sugar. It is a white crystalline powder with a sweet taste and complete water solubility. It requires the incorporation of a suitable lu-



D

Figure 45-13. *(continued)* **d.** Computer-controlled/monitored tableting.

bricant at normal levels for lubricity. The sugar is used widely for chewable vitamin tablets because of its natural sweetness. One commercial source is Di-Pac *(Amstar)* prepared by the cocrystallization of 97% sucrose and 3% dextrins. Some forms of lactose meet the requirements for a direct-compression vehicle. Hydrous lactose does not flow, and its use is limited to tablet formulations prepared by the wet-granulation method. Both anhydrous lactose and spray-dried lactose have good flowability and compressibility and can be used in direct compression provided a suitable disintegrant and lubricant are present. Mannitol is a popular diluent for chewable tablets because of its pleasant taste and mouth feel resulting from its negative heat of solution. In its granular form *(ICI Americas)* it has good flow and compressible qualities. It has a low moisture content and is not hygroscopic.

The excipient that has been studied extensively as a direct compression vehicle is microcrystalline cellulose (Avicel, *FMC*). This nonfibrous form of cellulose is obtained by spray-drying washed, acid-treated cellulose and is available in several grades that range in average particle size from 20 to 100 μm. It is water-insoluble, but the material has the ability to draw fluid into a tablet by capillary action; it swells on contact and thus acts as a disintegrating agent. The material flows well and has a degree of self-lubricating qualities, thus requiring a lower level of lubricant than other excipients.

Forced-flow feeders are mechanical devices, available from pharmaceutical equipment manufacturers, designed to deaerate light and bulky material. Mechanically, they maintain a steady flow of powder moving into the die cavities under moderate pressure. By increasing the density of the powder, higher uniformity in tablet weights is obtained. See Figure 45-14.

Recently, many companies have reversed their optimism for some direct-compression systems. Some formulations made by direct compression were not as *forgiving* as the older wet-granulated products were. As raw material variations occurred, especially with the drug, many companies found themselves with poorly compactable formulations. Interest in direct compression also is stimulating basic research on the flowability of powders with and without additives.

Related Granulation Processes

SPHERONIZATION—Spheronization, a form of pelletization, refers to the formation of spherical particles from wet granulations. Since the particles are round, they have good flow properties when dried. They can be formulated to contain sufficient binder to impart cohesiveness for tableting. Spheronization equipment such as the Marumerizer *(Luwa)* and the CF-Granulator *(Vector)* are commercially available for small-scale manufacture, on up to commercial sized equipment. A wet granulation containing the drug substance, diluent (if required), and binder, is passed first through an extruding machine to form rod-shaped cylindrical segments ranging in diameter from 0.5 to 12 mm. The segment diameter and the size of the final spherical particle depend on the extruder screen size. After extrusion the segments are placed into the Marumerizer where they are shaped into spheres by centrifugal and frictional forces on a rotating plate (see Fig 45-15). The

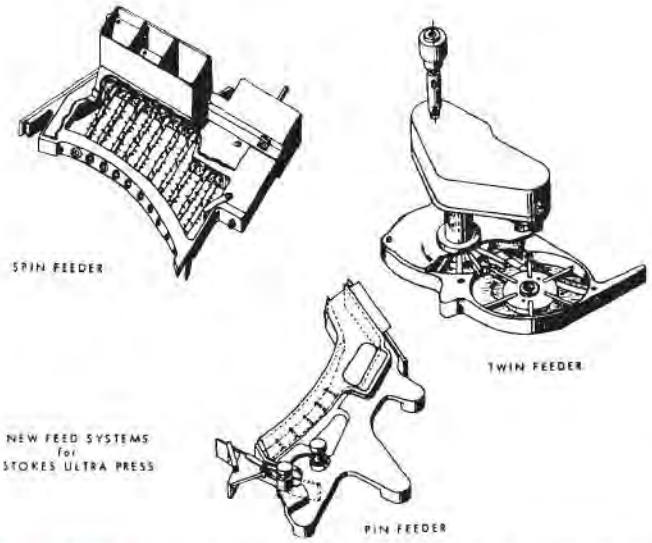


Figure 45-14. Feeding devices designed to promote flow of granulations for high-speed machines (courtesy, Stokes/Pennwalt).

pellets then are dried by conventional methods, mixed with suitable lubricants, and compressed into tablets or used as capsule-fill material. Microcrystalline cellulose has been shown to be an effective diluent and binder in granulations to be spheronized.[35–38] The advantages of the process include the production of granules, regular in shape, size, and surface characteristics; low friability resulting in fewer fines and less dust; and the ability to regulate the size of the spheres within a narrow particle-size distribution.

Spheres also can be produced by fluid-bed granulation techniques and by other specialized equipment such as the CF-Granulator *(Vector)*. These processes, however, must begin with crystals or nonpareil seeds followed by buildup. Exact results, such as sphere density, are different for the various methods and could be important in product performance. These processes can be run as batches or continuously.

SPRAY-DRYING—A number of tableting additives suitable for direct compression have been prepared by the drying process known as spray-drying. The method consists of bringing together a highly dispersed liquid and a sufficient volume of hot air to produce evaporation and drying of the liquid droplets. The feed liquid may be a solution, slurry, emulsion, gel, or paste, provided it is pumpable and capable of being atomized. As shown in Figure 45-16, the feed is sprayed into a current of warm filtered air. The air supplies the heat for evaporation and

Figure 45-15. The inside of a QJ-400 Marumerizer (courtesy, Luwa).

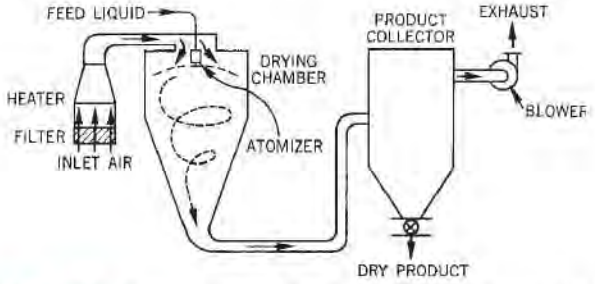


Figure 45-16. Typical spray-drying system (courtesy, Bowen Eng).

conveys the dried product to the collector; the air is then exhausted with the moisture. As the liquid droplets present a large surface area to the warm air, local heat and transfer coefficients are high.

The spray-dried powder particles are homogeneous, approximately spherical in shape, nearly uniform in size, and frequently hollow. The latter characteristic results in low bulk density with a rapid rate of solution. Being uniform in size and spherical, the particles possess good flowability. The design and operation of the spray-dryer can vary many characteristics of the final product, such as particle size and size distribution, bulk and particle densities, porosity, moisture content, flowability, and friability. Among the spray-dried materials available for direct compression formulas are lactose, mannitol, and flour. Another application of the process in tableting is spray-drying the combination of tablet additives as the diluent, disintegrant, and binder. The spray-dried material then is blended with the active ingredient or drug, lubricated, and compressed directly into tablets.

Since atomization of the feed results in a high surface area, the moisture evaporates rapidly. The evaporation keeps the product cool and as a result the method is applicable for drying heat-sensitive materials. Among heat-sensitive pharmaceuticals successfully spray-dried are the amino acids; antibiotics as aureomycin, bacitracin, penicillin, and streptomycin; ascorbic acid; cascara extracts; liver extracts; pepsin and similar enzymes; protein hydrolysates; and thiamine.[39]

Frequently, spray-drying is more economical than other processes, since it produces a dry powder directly from a liquid and eliminates other processing steps as crystallization, precipitation, filtering or drying, particle-size reduction, and particle classifying. By the elimination of these steps, labor, equipment costs, space requirements and possible contamination of the product are reduced. Intrinsic factor concentrate obtained from hog mucosa previously was prepared by *Lederle / American Home Products*, using a salt-precipitation process followed by a freeze-drying. By using spray-drying it was possible to manufacture a high-grade material by a continuous process. The spherical particles of the product facilitated its subsequent blending with vitamin B_{12}. Similar efficiencies have been found in processes producing magnesium trisilicate and dihydroxyaluminum sodium carbonate; both chemicals are used widely in antacid preparations.

Encapsulation of chemicals also can be achieved using spray-drying equipment. The process is useful in coating one material on another to protect the interior substance or to control the rate of its release. The substance to be coated can be either liquid or solid but must be insoluble in a solution of the coating material. The oil-soluble vitamins, A and D, can be coated with a variety of materials such as acacia gum to prevent their deterioration. Flavoring oils and synthetic flavors are coated to give the so-called dry flavors.

SPRAY-CONGEALING—Also called spray-chilling, spray-congealing is a technique similar to spray-drying. It consists of melting solids and reducing them to beads or powder by spraying the molten feed into a stream of air or other gas. The same basic equipment is used as with spray-drying, although

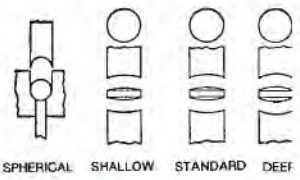


Figure 45-17. Concave punches.

no source of heat is required. Either ambient or cooled air is used, depending on the freezing point of the product. For example, monoglycerides and similar materials are spray-congealed with air at 50°F. A closed-loop system with refrigeration cools and recycles the air. Using this process, drugs can be dissolved or suspended in a molten wax and spray-congealed; the resultant material then can be adapted for a prolonged-release form of the drug.

Among the carbohydrates used in compressed tablets, mannitol is the only one that possesses high heat stability. Mannitol melts at 167° and, either alone or in combination with other carbohydrates, can be fused and spray-congealed. Selected drugs have been shown to be soluble in these fused mixtures, and the resultant spray-congealed material possesses excellent flow and compression characteristics.

TABLET MACHINES

As mentioned previously, the basic mechanical unit in tablet compression involves the operation of two steel punches within a steel die cavity. The tablet is formed by the pressure exerted on the granulation by the punches within the die cavity, or cell. The tablet assumes the size and shape of the punches and die used. See Figures 45-17 and 45-18. While round tablets are used more generally, oval, capsule-form, square, triangular, or other irregular shapes may be used. Likewise, the curvature of the faces of the punches determines the curvature of the tablets. The diameters generally found to be satisfactory and frequently referred to as standard are as follows: 3/16, 7/32, 1/4, 9/32, 5/16, 11/32, 7/16, 1/2, 9/16, 5/8, 11/16, and 3/4 in. Punch faces with ridges are used for compressed tablets scored for breaking into halves or fourths, although it has been indicated that variation among tablet halves is significantly greater than among intact tablets. However, a patented formulation[40] for a tablet scored to form a groove that is one-third to two-thirds the depth of the total tablet thickness is claimed to give equal parts containing substantially equal amounts of the drug substance. Tablets, engraved or embossed with symbols or initials, require punches with faces embossed or engraved with the corresponding designs. See Figures 45-19 and 45-20. The use of the tablet sometimes determines its shape; effervescent tablets are usually large, round, and flat, while vitamin tablets frequently are prepared in capsule-shaped forms. Tablets prepared using deep-cup punches appear to be round and when coated take on the appearance of pills. Veterinary tablets often have a bolus shape and are much larger than those used in medical practice.

The quality-control program for punches and dies, frequently referred to as tooling, instituted by large pharmaceuti-

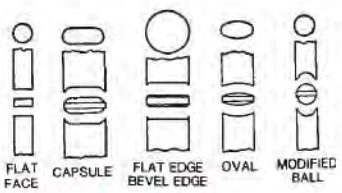


Figure 45-18. Specially shaped punches.

Figure 45-19. Collection of punches (courtesy, Stokes/Pennwalt).

cal companies, emphasizes the importance of their care in modern pharmaceutical production. To produce physically perfect compressed tablets, an efficient punch-and-die program must be set up. Provisions for inspection of tooling, parameters for cost-per-product determination, product identification, and tooling specifications must all be considered. A committee of the Industrial and Pharmaceutical Technology Section of the APhA Academy of Pharmaceutical Sciences established a set of dimensional specifications and tolerances for standard punches and dies.[41]

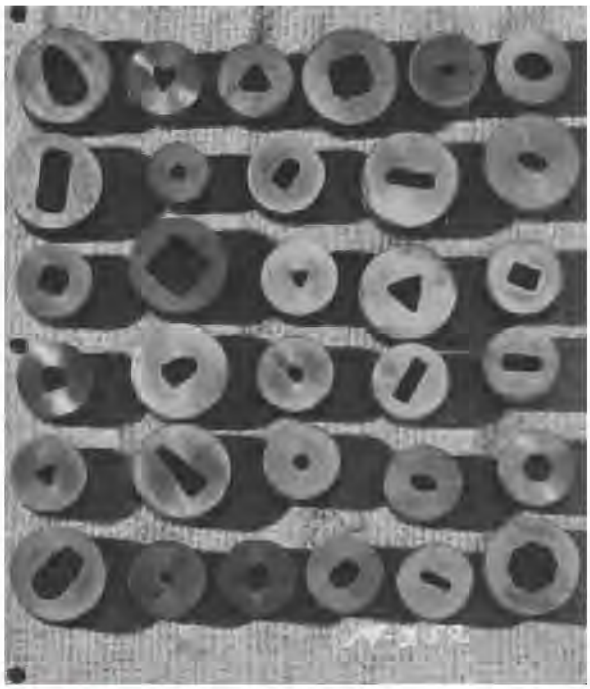


Figure 45-20. Collection of dies (courtesy, Stokes/Pennwalt).

Regardless of the size of the tableting operation, the attention that must be given to the proper care of punches and dies should be noted. They must be highly polished and kept free from rust and imperfections. In cases in which the material pits or abrades the dies, chromium-plated dies have been used. Dropping the punches on hard surfaces will chip their fine edges. When the punches are in the machine, the upper and lower punches should not be allowed to contact each other; otherwise, a curling or flattening of the edges will result that is one of the causes of capping. This is especially necessary to observe in the case of deep-cup punches.

When the punches are removed from the machine, they should be washed thoroughly in warm soapy water and dried well with a clean cloth. A coating of grease or oil should be rubbed over all parts of the dies and punches to protect them from the atmosphere. They should be stored carefully in boxes or paper tubes.

Single-Punch Machines

The simplest tableting machines available are those having the single-punch design. A number of models are available as outlined in Table 45-2. While most of these are power-driven, several hand-operated models are available. Compression is accomplished on a single-punch machine as shown in Figure 45-21. The feed shoe filled with the granulation is positioned over the die cavity, which then fills. The feed shoe retracts and scrapes all excess granulation away from the die cavity. The upper punch lowers to compress the granulation within the die cavity. The upper punch retracts, and the lower punch rises to eject the tablet. As the feed shoe returns to fill the die cavity, it pushes the compressed tablet from the die platform. The weight of the tablet is determined by the volume of the die cavity; the lower punch is adjustable to increase or decrease the volume of granulation, thus increasing or decreasing the weight of the tablet.

For tablets having diameters larger than 1/2 inch, sturdier models are required. This is also true for tablets requiring a high degree of hardness, as in the case of compressed lozenges. The heavier models are capable of much higher pressures and are suitable for slugging.

OPERATION OF SINGLE-PUNCH MACHINES—In installing punches and dies in a single-punch machine, insert the lower punch first by lining up the notched groove on the punch with the lower punch setscrew and slipping it into the smaller bore in the die table; the setscrew is not tightened yet. The lower punch is differentiated from the upper punch in that it has a collar around the punch head. Slip the die over the punch head so that the notched groove (with the widest area at the top) lines up with the die setscrew. Tighten the lower punch setscrew after seating the lower punch by pressing on the punch with the thumb. Tighten the die setscrew, making certain that the surface of the die is flush with the die table. Insert the upper punch, again lining up the grooved notch with the upper punch setscrew. To be certain that the upper punch is seated securely, turn the machine over by hand with a block of soft wood or wad of cloth between the upper and lower punches. When the punch is seated, tighten the upper punch setscrew. Adjust the pressure so that the upper and lower punches will not come in contact with each other when the machine is turned over. Adjust the lower punch so that it is flush with the die table at the ejection point. Install the feed shoe and hopper.

After adding a small amount of granulation to the hopper, turn the machine over by hand and adjust the pressure until a tablet is formed. Adjust the tablet weight until the desired weight is obtained. The pressure will have to be altered concurrently with the weight adjustments. It should be remembered that as the fill is increased the lower punch moves farther away from the upper punch, and more pressure will have to be applied to obtain comparable hardness. Conversely, when the fill is decreased, the pressure will have to be decreased. When all the adjustments have been made, fill the hopper with granulation and turn on the motor. Hardness and weight should be checked immediately, and suitable adjustments made if necessary. Periodic checks should be made on the tablet hardness and weight during the running of the batch, at 15- to 30-min intervals.

When the batch has been run off, turn off the power and remove loose dust and granulation with the vacuum cleaner. Release the pressure from the punches. Remove the feed hopper and the feed shoe. Remove the upper punch, the lower punch, and the die. Clean all surfaces of the tablet machine, and dry well with clean cloth. Cover surfaces with thin coating of grease or oil prior to storage.

As tablets are ejected from the machine after compression, they usually are accompanied by powder and uncompressed granulation. To remove this loose dust, the tablets are passed over a screen, which may be vibrating, and cleaned with a vacuum line.

Table 45-2. Single-Punch Tablet Machines

MACHINE MODEL	MAXIMUM TABLET DIAMETER (INCHES)	PRESS SPEED (TABLETS/MIN)	DEPTH OF FILL (INCHES)
Stokes-Pennwalt equipment[a]			
511-5	½	40–75	7/16
206-4	1¾	10–40	1 1/16
530-1	2	12–48	1⅜
525-2	3	16–48	2
Manesty equipment (Thomas Eng)			
Hand machine	½	100	7/16
Model F3	⅞	85	11/16
Model 35T[a]	3	36	2¼

[a] Widely used for veterinary boluses.

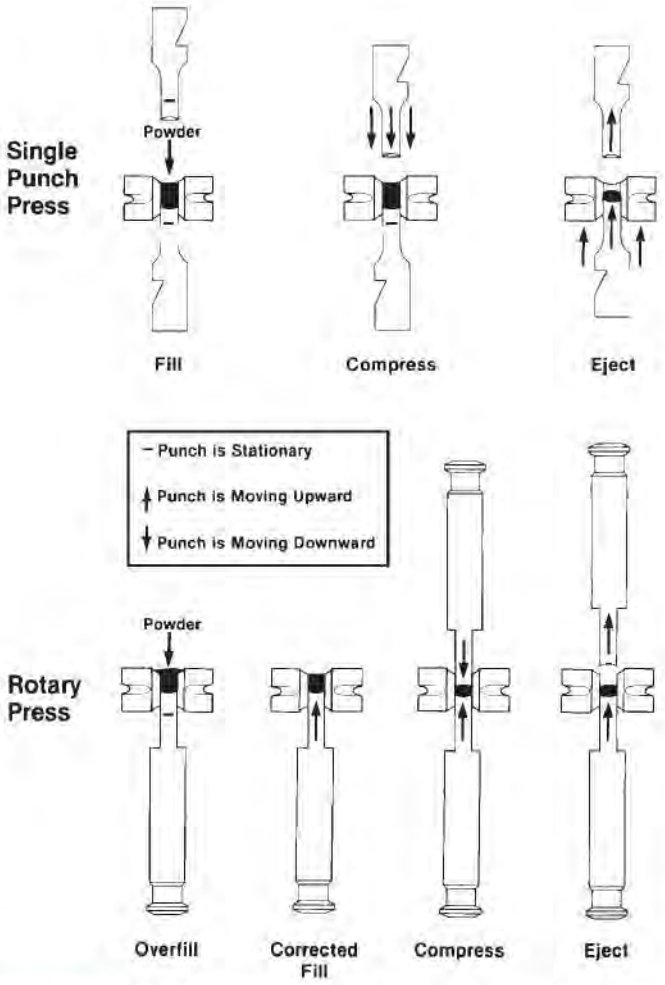


Figure 45-21. The steps associated with single-punch and rotary tablet machines.

Rotary Tablet Machines

For increased production, rotary machines offer great advantages. A head carrying a number of sets of punches and dies revolves continuously while the tablet granulation runs from the

hopper, through a feed frame and into the dies placed in a large, steel plate revolving under it. This method promotes a uniform fill of the die and therefore an accurate weight for the tablet. Compression takes place as the upper and lower punches pass between a pair of rollers, as can be seen in Figure 45-21. This action produces a slow squeezing effect on the material in the die cavity from the top and bottom and so gives a chance for the entrapped air to escape. The lower punch lifts up and ejects the tablet. Adjustments for tablet weight and hardness can be made without the use of tools while the machine is in operation. Figure 45-22 shows a high speed press. Figure 45-23 shows the tooling in a 16-station rotary press in the positions of a complete cycle to produce 1 tablet per set of tooling. One of the factors that contributes to the variation in tablet weight and hardness during compression is the internal flow of the granulation within the feed hopper.

On most rotary machine models there is an excess pressure release that cushions each compression and relieves the machine of all shocks and undue strain. The punches and dies can be removed readily for inspection, cleaning, and inserting different sets to produce a great variety of sizes and shapes. Many older presses have been modernized with protective shields to prevent physical injury and to comply with OSHA standards (Fig 45-24). It is possible to equip the machine with as few punches and dies as the job requires and thus economize on installation costs. For types of rotary machines available, see Table 45-3.

OPERATION OF ROTARY MACHINES—Before inserting punches and dies, make certain that the pressure has been released from the pressure wheel. The die holes should be cleaned thoroughly, making certain that the die seat is completely free of any foreign materials. Back off all die locks, and loosely insert dies into the die holes, then tap each die securely into place with a fiber of soft metal rod through the upper punch holes. After all the dies have been tapped into place, tighten each die lockscrew progressively and securely. As each screw is tightened the die is checked to see that it does not project above the die table. Insert the lower punches through the hole made available by removing the punch head. Turn the machine by hand until the punch bore coincides with the plug hole. Insert each lower punch in its place progressively. Insert the upper punches by dropping them into place in the head. Each punch (upper and lower) should be coated with a thin film of mineral oil before insertion into the machine. Adjust the ejection cam so that the lower punch is flush with the die table at the ejection point.

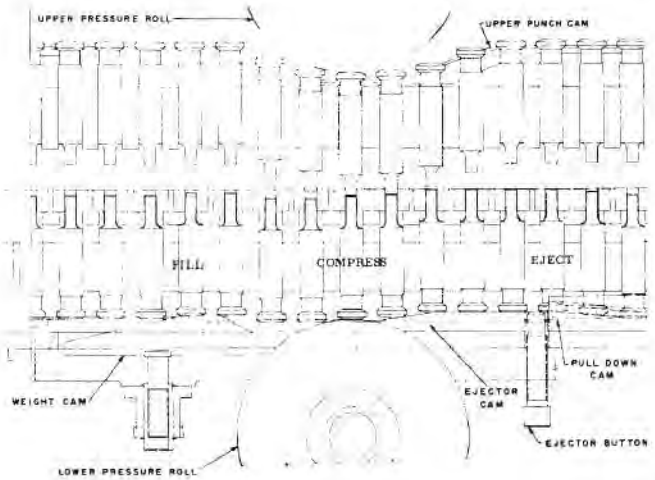


Figure 45-23. Tooling for a 16-station rotary press showing positions of the cycle required to produce one tablet per set of tooling (courtesy, Vector/Colton).

After insertion of the punches and dies, adjust the machine for the tablet weight and hardness. The feed frame should be attached to the machine along with the feed hopper. Add a small amount of the granulation through the hopper and turn over the machine by hand. Increase the pressure by rotating the pressure wheel until a tablet is formed. Check the weight of the tablet and adjust the fill to provide the desired tablet weight. Most likely more than one adjustment of the fill will be necessary before obtaining the acceptable weight. When the fill is decreased, the pressure must be decreased to provide the same hardness in the tablet. Conversely, when the fill is increased, the pressure must be increased to obtain comparable hardness.

Fill the hopper with the granulation and turn on the power. Check tablet weight and hardness immediately after the mechanical operation begins, and make suitable adjustments, if necessary. Check these properties routinely and regularly at 15- to 30-min intervals while the machine is in operation. When the batch has been run, turn off the power. Remove the hopper and feed frame from the machine. Remove loose granulation and dust with a vacuum line. Remove all pressure from the wheel. Remove the punches and dies in the reverse order of that used in setting up the machine. First, remove the upper punches individually,

Figure 45-22. Model 747 High Speed Press, double-sided rotary compacting press designed to produce at speeds over 10,000/min (courtesy, Stokes/Pennwalt).

Figure 45-24. Research technicians use an instrumented tablet press to develop processes at Schering-Plough.

Table 45-3. High-Speed Rotary Tablet Machines

MACHINE MODEL	TOOL SETS	MAXIMUM TABLET DIAMETER (INCHES)	PRESS SPEED (TABLETS/MIN)	DEPTH OF FILL (INCHES)
Vector-Colton equipment				
2216	16	5/8	1180	3/4
240	16	7/8	640	13/16
250	12	1 1/4	480	1 1/8
260	25	1 3/16	1450	1 3/4
	31	1	1800	1 3/4
	33	13/16	1910	1 3/8
	43	5/8	2500	1 3/8
270	25	1 3/8	450	2 1/4
Stokes/Pennwalt equipment				
Manesty equipment (Thomas Eng)				
B3B	16	5/8	350–700	11/16
	23	7/16	500–1000	11/16
BB3B	27	5/8	760–1520	11/16
	33	7/16	924–1848	11/16
	35	5/8	1490–2980	11/16
	45	7/16	1913–3826	11/16
D3B	16	1	260–520	15/16
Key equipment				
DC-16	16	13/16	210–510	13/16
BBC	27	5/8	1025–2100	11/16
	35	5/8	1325–2725	11/16
	45	7/16	1700–3500	11/16
Cadpress	37	13/16	850–3500	13/16
	45	5/8	2000–6000	11/16
	55	7/16	2500–7500	11/16
Fette equipment (Raymond Auto)				
		(mm)		(mm)
Perfecta 1000	28	16	2100	18
	33	13	2475	18
Perfecta 2000	29	25	2175	22
	36	16	3600	18
	43	13	4300	18
Courtoy equipment (AC Compact)				
R-100	24	25	285–2260	20
	30	19	356–2850	20
	36	13	550–440	16
Kikusui equipment				
Hercules	18	37	180–540	16
	21	26	210–630	16
	29	25	290–870	16
Virgo	19	16	418–1330	16
	24	11	528–1680	16
Killian equipment				
TX21	21	28	231–1386	20
TX25	25	22	275–2166	20
TX30	30	16	330–3150	20
TX21D	21	25	231–1826	20
TX30A	30	16	330–3150	16
TX40A	40	13	440–4200	16
Korsch equipment				
PH 250/20	20	25	240–1640	22
PH 250/25	25	16	270–2700	18
PH 250/30	30	13	315–3233	18
Elizabeth-Hata equipment				
AP-15-SSU	15	17	300–1050	8–18
AP-18-SSU	18	13	360–1260	8–18
AP-22-SSU	22	11	440–1540	8–18
AP-32-SSU	32	17	640–2240	8–18
AP-38-MSU	38	13	760–2660	8–18
AP-45-MSU	32	11	900–3150	8–18
Vector-Colton equipment				
2247	33	5/8	3480	3/4
	41	7/16	4300	3/4
	49	7/16	5150	3/4
Magna	66	23/32	10,560	3/4
	74	1/2	11,840	3/4
	90	7/16	14,400	3/4
Stokes/Pennwalt equation				
552-2	35	5/8	800–3200	11/16
328-4	45	3/4	1600–4500	1 1/8
610	65	7/16	3500–10,000	11/16
747	65	7/16	3000–10,000	11/16
	53	5/8	2900–8100	11/16
	41	15/16	2150–6150	11/16
Direct Triple Compression Type				
580-1	45	7/16	525–2100	11/16
580-2	35	5/8	400–1600	11/16
610	65	7/16	3500–10,000	11/16
	53	5/8	2900–8100	11/16
Manesty equipment (Thomas Eng)				
Betapress	16	5/8	600–1500	11/16
	23	7/16	860–2160	11/16
Express	20	1	800–2000	13/16
	25	5/8	1000–2500	11/16
	30	7/16	1200–3000	11/16
Unipress	20	1	970–2420	13/16
	27	5/8	1300–3270	11/16
	34	7/16	1640–4120	11/16
Novapress	37	1	760–3700	13/16
	45	5/8	900–4500	11/16
	61	7/16	1220–6100	11/16
BB3B	35	5/8	1490–2980	11/16
BB4	27	5/8	900–2700	11/16
	35	3/8	1167–3500	11/16
	45	7/16	1500–4500	11/16
Rotapress				
Mark IIA	37	1	710–3550	13/16
	45	5/8	1640–8200	11/16
	61	7/16	2200–11,100	11/16
Mark IV	45	1	2090–6000	13/16
	55	5/8	2550–7330	11/16
	75	7/16	3500–10,000	11/16
Fette tool systems				
		(mm)		(mm)
PT 2080	29	25	435–2900	18
	36	16	540–4100	18
	43	16	645–4900	18
PT 2090IC	22	34	1760	18
	29	25	2900	18
	36	16	4140	18
	43	13	5160	18
	47	11	6110	18
PT 3090IC	37	34	5920	18
	49	25	7840	18
	61	16	9760	18
P 3100	37	25	5618	22
	45	16	8100	18
	55	13	9900	18
Courtoy equipment (AC Compact)				
R-200	43	25	750–5833	20
	55	19	916–8500	20
	65	13	1083–10,000	16
Kikusui equipment				
Libra	36	16	900–2520	16
	45	11	1125–3150	16
	49	8	1225–3430	16
Gemini	55	16	2200–7700	16
	67	11	2680–9380	16
	73	8	2920–10,200	16
Elizabeth-Hata equipment				
AP-45-LDU	45	17	1800–6300	8–18
AP-55-LDU	55	13	2200–7700	8–18
AP-65-LDU	65	11	2600–9100	8–18
AP-71-LDU	71	11	2840–9940	8–18
51-XLDU	51	17	2040–7140	8–18
65-XLDU	61	13	2440–8540	8–18

then the lower punches, and finally the dies. Wash each punch and die in alcohol and brush with a soft brush to remove adhering material. Dry them with a clean cloth, and cover them with a thin coating of grease or oil before storing.

High-Speed Rotary Tablet Machines

The rotary tablet machine has evolved gradually into models capable of compressing tablets at high production rates. See Figures 45-22, 45-25, and 45-26. This has been accomplished by increasing the number of stations, ie, sets of punches and dies, in each revolution of the machine head, improving feeding devices, and on some models installing dual compression points. In Figure 45-26, the drawing shows a rotary machine with dual compression points. Rotary machines with dual compression points are referred to as double rotary machines, and those with one compression point, single rotary. In the diagram, half of the tablets are produced 180° from the tablet chute. They travel outside the perimeter and discharge with the second tablet production. While these models are mechanically capable of operating at the production rates shown in Table 45-3, the actual speed still depends on the physical characteristics of the tablet granulation and the rate that is consistent with compressed tablets having satisfactory physical characteristics. The main difficulty in rapid machine operation is ensuring adequate filling of the dies. With rapid filling, dwell time of the die cavity beneath the feed frame is insufficient to ensure the requirements of uniform flow and packing of the dies. Various methods of force-feeding the granulation into the dies have been devised to refill the dies in the very short dwell time permitted on the high-speed machine. These devices are illustrated in Figure 45-14. Presses with triple compression points (see Table 45-3) permit the partial compaction of material before final compaction. This provides for partial deaeration and particle orientation of material before final compression. This helps in the direct compacting of materials and reduces laminating and capping due to entrapped air.

Figure 45-25. Rotapress Mark IIA. Designed for improvements in sound reduction, operator safety, cleanliness, and operational convenience; note the control panel on front of machine (courtesy, Thomas/Manesty).

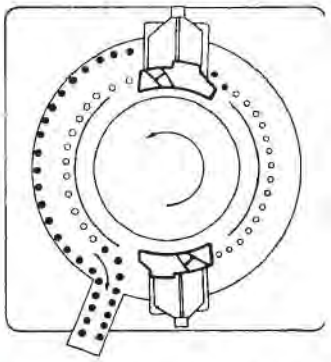


Figure 45-26. The movement of tablets on die table of a double rotary press (courtesy, Vector/Colton).

Multilayer Rotary Tablet Machines

The rotary tablet machines also have been developed into models capable of producing multiple-layer tablets; the machines are able to make 1-, 2-, or 3-layer tablets (Versa Press, *Stokes/Pennwalt*). Stratified tablets offer a number of advantages. Incompatible drugs can be formed into a single tablet by separating the layers containing them with a layer of inert material. It has permitted the formulation of time-delay medication and offers a wide variety of possibilities in developing color combinations that give the products identity.

Originally, the tablets were prepared by a single-compression method. The dies were filled with the different granulations in successive layers, and the tablet was formed by a single compression stroke. The separation lines of the tablets prepared by this method tended to be irregular. In the machines now available for multilayer production the granulation receives a precompression stroke after the first and second fill, which lightly compacts the granulation and maintains a well-defined surface of separation between each layer. The operator is able to eject either precompressed layer with the machine running at any desired speed for periodic weight and analysis checks.

Other multiple-compression presses can receive previously compressed tablets and compress another granulation around the preformed tablet. An example of a press with this capability is the Manesty Drycota *(Thomas/Manesty)*. Pressure-coated tablets can be used to separate incompatible drug substances and also to give an enteric coating to the core tablets.

Capping and Splitting of Tablets

The splitting or capping of tablets is one of great concern and annoyance in tablet making. It is quite difficult to detect while the tablets are being processed but can be detected easily by vigorously shaking a few in the cupped hands. A slightly chipped tablet does not necessarily mean that the tablet will cap or split.

There are many factors that may cause a tablet to cap or split:

Excess *fines* or powder, which traps air in the tablet mixture.

Deep markings on tablet punches. Many designs or *scores* on punches are too broad and deep. Hairline markings are just as appropriate as deep, heavy markings.

Figure 45-27. Courtoy R-100 with computer-controlled operation.

Worn and imperfect punches. Punches should be smooth and buffed. Nicked punches often cause capping. The development of fine feather edges on tablets indicates wear on punches.

Worn dies. Dies should be replaced or reversed. Dies that are chrome-plated or have tungsten carbide inserts wear longer and give better results than ordinary steel dies.

Too much pressure. By reducing the pressure on the machines the condition may be corrected.

Unsuitable formula. It may be necessary to change the formula.

Moist and soft granulation. This type of granulation will not flow freely into the dies, thus giving uneven weights and soft or capped tablets.

Figure 45-28. Direct weighing of tablets produced gives actual weight feedback for the controller of the Courtoy R-100 (seen in the bottom left of Fig 45-27).

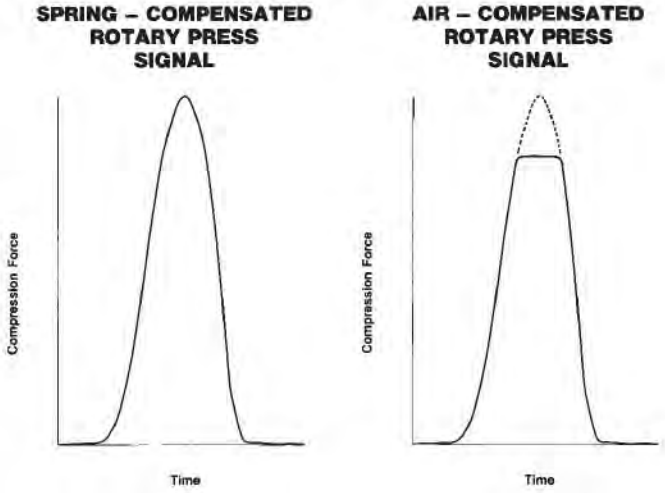


Figure 45-29. Force-time curves for two types of tablet press.

Poorly machined punches. Uneven punches are detrimental to the tablet machine itself and will not produce tablets of accurate weight. One punch out of alignment may cause one tablet to split or cap on every revolution.

Instrumented Tablet Presses

Compressional and ejectional forces involved in tablet compression can be studied by attaching strain gauges to the punches and other press components involved in compression. The electrical output of the gauges has been monitored by telemetry or use of a dual-beam oscilloscope equipped with camera.[42,43] Instrumentation permits a study of the compaction characteristics of granulations, their flowabilities, and the effect of formulation additives, such as lubricants, as well as differences in tablet press design, as shown in Figures 45-27 to 45-30. Physical characteristics of tablets, such as hardness, friability, disintegration time, and dissolution rate, are influenced not only by the nature of the formulation but by the compressional force as well.

As can be seen in Figures 45-29 and 45-30, the rate and duration of compaction forces can be quantified. The rate of force application has a profound effect on powder consolidation within the die and, hence, efficiency of packing and powder compaction. The rate of release of force, or *decompression* has

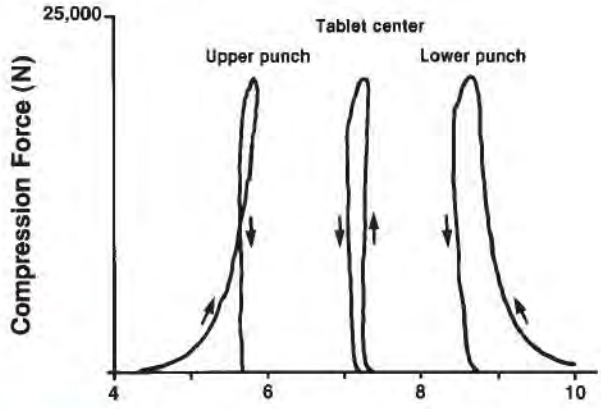


Figure 45-30. Plot showing the upper and lower punch forces as functions of the position of the punch face within the die. A biaxial force/displacement curve also shown is a plot of the position of the tablet center as a function of the compression force.

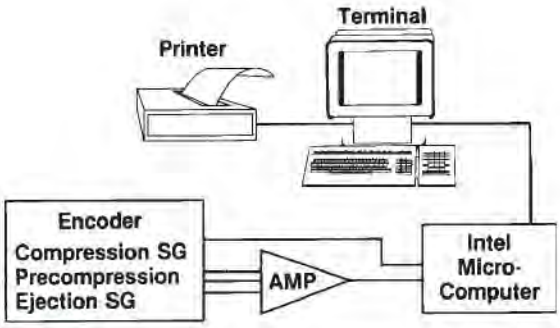


Figure 45-31. Schematic of an instrumentation system using a microcomputer as developed by Schering-Plough.

a direct effect on the ability of the tablet to withstand relaxation. A prominent hypothesis, fostered by Hiestand[44,45] and later Luenberger[46], suggested that capping and laminating of tablets is caused by too-rapid stress relaxation or decompression. This explains why slowing a tablet press and using tapered dies is useful in such situations. Most prominent pharmaceutical scientists have embraced this theory and largely have discounted air entrapment as a cause of capping and laminating.

Figure 45-30 presents an interesting set of plots. Walter and Augsburger reported that as compaction force rises, the steel tooling actually compresses in accommodation to the forces applied. The forces used to produce a tablet are considerable and should be monitored and understood.[47] Therefore, definition of the compressional force and duration of force (dwell time) giving a satisfactory tablet for a formulation provides an in-process control for obtaining both tablet-to-tablet and lot-to-lot uniformity (see Figs 45-24 and 45-31).

Instrumentation has led to the development of on-line, automatic, electromechanical tablet weight-control systems capable of continuously monitoring the weights of tablets as they are produced. Units are available commercially (Thomas Tablet Sentinel *(Thomas Eng);* Fette Compression Force Monitor *(Raymond Auto);* Vali-Tab *(Stokes/Pennwalt))* and are applicable to single or rotary tablet machines. Most commercial presses today can be delivered with some sort of instrumentation attached. When tablet weights vary from preset limits, the monitor automatically will adjust the weight control mechanism to reestablish weights within acceptable limits. If the difficulty continues, the unit will activate an audible warning signal or an optional shut-down relay on the press (see Figs 45-27 and 45-28). Most production-model tablet presses come equipped with complete instrumentation (optional) and with options for statistical analysis and print out of compression/ejection signals. The techniques and applications of press instrumentation have been reviewed.[48,49]

Contamination Control

While good manufacturing practices used by the pharmaceutical industry for many years have stressed the importance of cleanliness of equipment and facilities for the manufacture of drug products, the penicillin contamination problem resulted in renewed emphasis on this aspect of manufacturing. Penicillin, as either an airborne dust or residual quantities remaining in equipment, is believed to have contaminated unrelated products in sufficient concentrations to cause allergic reactions in individuals hypersensitive to penicillin who received these products. This resulted in the industry spending millions of dollars to change or modify buildings, manufacturing processes, equipment, and standard operating procedures to eliminate penicillin contamination.

With this problem has come renewed emphasis on the dust problem, material handling, and equipment cleaning in dealing with drugs, especially potent chemicals. Any process using chemicals in powder form can be a dusty operation; the preparation of compressed tablets and encapsulation fall in this category. In the design of tablet presses attention is being given to the control and elimination of dust generated in the tableting process. In the Perfecta press shown in Figure 45-32, the pressing compartment is completely sealed off from the outside environment, making cross-contamination nearly impossible. The pressing compartment can be kept dust-free by the air supply and vacuum equipment developed for the machine. It removes airborne dust and granular particles that have not been compressed, thus keeping the circular pressing compartment and the upper and lower punch guides free of dust.

Drug manufacturers have the responsibility to make certain that microorganisms present in finished products are unlikely to cause harm to the patient and will not be deleterious to the product. An outbreak of *Salmonella* infections in Scandinavian countries was traced to thyroid tablets that had been prepared from contaminated thyroid powder. This concern eventually led to the establishment of microbial limits for raw materials of animal or botanical origin, especially those that readily support microbial growth and are not rendered sterile during subsequent processing. Harmful microorganisms when present in oral products include *Salmonella* spp, *Escherichia coli,* certain *Pseudomonas* spp such as *P aeruginosa,* and *Staphylococcus aureus*. The compendia have microbial limits on raw materials such as aluminum hydroxide gel, cornstarch, thyroid, acacia, and gelatin.

These represent examples of the industry's efforts to conform with the intent of current good manufacturing practice as defined by the FDA.

Figure 45-32. Fette Perfecta 3000 high-speed tablet press with pressing compartment completely sealed off from outside environment, making cross-contamination impossible (courtesy, Raymond Auto).

Tablet Formulations

WET GRANULATION

CT Acetaminophen, 300 mg

INGREDIENTS	IN EACH	IN 10,000
Acetaminophen	300 mg	3000 g
Polyvinylpyrrolidone	22.5 mg	225 g
Lactose 61.75 mg 617.5 g		
Alcohol SD3A—200 proof	4.5 mL	45 L
Stearic acid	9 mg	90 g
Talc	13.5 mg	135 g
Cornstarch	43.25 mg	432.5 g

Blend acetaminophen, polyvinylpyrrolidone, and lactose together; pass through a 40-mesh screen. Add the alcohol slowly, and knead well. Screen the wet mass through a 4-mesh screen. Dry the granulation at 50° overnight. Screen the dried granulation through a 20-mesh screen. Bolt the stearic acid, talc, and cornstarch through a 60-mesh screen prior to mixing by tumbling with the granulation. Compress, using 7/16-inch standard concave punch. Ten tablets should weigh 4.5 g (courtesy, *Abbott*).

CT Ascorbic Acid USP, 50 mg

INGREDIENTS	IN EACH	IN 7000
Ascorbic acid USP (powder No. 80)[a]	55 mg	385 g
Lactose	21 mg	147 g
Starch (potato)	13 mg	91 g
Ethylcellulose N 100 (80–105 cps)	16 mg	112 g
Starch (potato)	7 mg	49 g
Talc	6.5 mg	45.5 g
Calcium stearate (impalpable powder)1 mg		7 g
Weight of granulation		836.5 g

[a] Includes 10% in excess of label claim.

Granulate the first three ingredients with ethylcellulose (5%) dissolved in anhydrous ethyl alcohol, adding additional anhydrous alcohol to obtain good, wet granules. Wet-screen through a #8 stainless steel screen and dry at room temperature in an air-conditioned area. Dry-screen through a #20 stainless steel screen and incorporate the remaining three ingredients. Mix thoroughly and compress. Use a flat, beveled, ¼-inch punch. Twenty tablets should weigh 2.39 g.

Chewable Antacid Tablets

INGREDIENTS	IN EACH	IN 10,000
Magnesium trisilicate	500 mg	5000 g
Aluminum hydroxide, dried gel	250 mg	2500 g
Mannitol	300 mg	3000 g
Sodium saccharin	2 mg	20 g
Starch paste, 5%	qs	qs
Oil of peppermint	1 mg	10 g
Magnesium stearate	10 mg	100 g
Cornstarch	10 mg	100 g

Mix the magnesium trisilicate and aluminum hydroxide with the mannitol. Dissolve the sodium saccharin in a small quantity of purified water, then combine this with the starch paste. Granulate the powder blend with the starch paste. Dry at 140°F and screen through 16-mesh screen. Add the flavoring oil, magnesium stearate, and corn starch; mix well. Age the granulation for at least 24 hr and compress, using a ⅜-inch, flat-face, bevel-edge punch (courtesy, *Atlas*).

CT Hexavitamin

INGREDIENTS	IN EACH	IN 7000
Ascorbic acid USP (powder)[a]	82.5 mg	577.5 g
Thiamine mononitrate USP (powder)[a]	2.4 mg	16.8 g
Riboflavin[a]	3.3 mg	23.1 g
Nicotinamide USP (powder)[a]	22 mg	154 g
Starch	13.9 mg	97.4 g
Lactose	5.9 mg	41.2 g
Zein	6.4 mg	45 g
Vitamin A acetate	6250 U	
Vitamin D_2[a] (use Pfizer crystalets medium granules containing 500,000 U vitamin A acetate and 50,000 U vitamin D_2/g)	625 U	87.5 g
Magnesium stearate		7.5 g
Weight of granulation		1050 g

[a] Includes the following in excess of label claim: ascorbic acid 10%, thiamine mononitrate 20%, riboflavin 10%, nicotinamide 10%, and vitamin A acetate–vitamin D_2 crystalets 25%.

Thoroughly mix the first six ingredients and granulate with zein (10% in ethyl alcohol, adding additional alcohol if necessary to obtain good, wet granules). Wet-screen through a #8 stainless steel screen and dry at 110 to 120°F. Dry-screen through a #20 stainless steel screen and add the vitamin crystalets. Mix thoroughly, lubricate, and compress. Ten tablets should weigh 1.50 g. Coat with syrup.

CT Theobromine-Phenobarbital

INGREDIENTS	IN EACH	IN 7000
Theobromine	325 mg	2275 g
Phenobarbital	33 mg	231 g
Starch	39 mg	273 g
Talc	8 mg	56 g
Acacia (powder)	8 mg	56 g
Stearic acid	0.7 mg	4.9 g
Weight of granulation		2895.9 g

Prepare a paste with the acacia and an equal weight of starch. Use this paste for granulating the theobromine and phenobarbital. Dry and put through a 12-mesh screen, add the remainder of the material, mix thoroughly, and compress into tablets, using a 13/32-inch concave punch. Ten tablets should weigh 4.13 g.

FLUID-BED GRANULATION

CT Ascorbic Acid USP, 50 mg

INGREDIENTS	IN EACH	IN 10,000
Ascorbic acid USP (powder no 80)[a]	55 mg	550 g
Lactose	21 mg	210 g
Starch (potato)	13 mg	130 g
Ethylcellulose N100 (80–105 cps)	16 mg	160 g
Starch (potato)	7 mg	70 g
Talc	6.5 mg	65 g
Calcium stearate	1 mg	10 g
Weight of granulation		1195.0 g

[a] Includes 10% in excess of claim.

Add the first three ingredients to the granulator. Mix for 5 to 15 min or until well mixed. Dissolve the ethylcellulose in anhydrous ethanol and spray this solution and any additional ethanol into the fluidized mixture. Cease spraying when good granules are produced. Dry to approximately 3% moisture. Remove the granules and place them in a suitable blender. Sequentially add the remaining three ingredients with mixing steps in between each addition. Compress, using a flat, beveled, 1/4-inch punch. Twenty tablets should weigh 2.39 g.

Sustained-Release (SR) Procainamide Tablets

INGREDIENTS	IN EACH	IN 10,000
Procainamide	500 mg	5000 g
HPMC 2208, USP	300 mg	3000 g
Carnauba wax	60 mg	600 g
HPMC 2910, USP	30 mg	300 g
Magnesium stearate	4 mg	40 g
Stearic acid	11 mg	110 g
Talc	5 mg	50 g
Weight of granulation		9100 g

Place the first three ingredients in the granulator and mix for 5 to 15 min. Dissolve the HPMC in water (mix in hot water, then cool down) and spray into the fluidized mixture. Dry to approximately 5% moisture. Sequentially add the last three ingredients, with mixing steps in between each addition. Compress, using capsule-shaped tooling. Ten tablets should weigh 9.1 g.

DRY GRANULATION

CT Acetylsalicylic Acid

INGREDIENTS	IN EACH	IN 7000
Acetylsalicylic Acid (crystals 20-mesh)	0.325 g	2275 g
Starch		226.8 g
Weight of granulation		2501.8 g

Dry the starch to a moisture content of 10%. Thoroughly mix this with the acetylsalicylic acid. Compress into slugs. Grind the slugs to 14- to 16-mesh size. Recompress into tablets, using a ½-inch punch. Ten tablets should weigh 3.575 g.

CT Sodium Phenobarbital

INGREDIENTS	IN EACH	IN 7000
Phenobarbital sodium	65 mg	455 g
Lactose (granular, 12-mesh)	26 mg	182 g
Starch	20 mg	140 g
Talc	20 mg	140 g
Magnesium stearate	0.3 mg	2.1 g
Weight of granulation		919.1 g

Mix all the ingredients thoroughly. Compress into slugs. Grind and screen to 14- to 16-mesh granules. Recompress into tablets, using a ⅝-inch concave punch. Ten tablets should weigh 1.3 g.

CT Vitamin B Complex

INGREDIENTS	IN EACH	IN 10,000
Thiamine mononitrate[a]	0.733 mg	7.33 g
Riboflavin[a]	0.733 mg	7.33 g
Pyridoxine hydrochloride	0.333 mg	3.33 g
Calcium pantothenate[a]	0.4 mg	4 g
Nicotinamide	5 mg	50 g
Lactose (powder)	75.2 mg	752 g
Starch	21.9 mg	219 g
Talc	20 mg	200 g
Stearic acid (powder)	0.701 mg	7.01 g
Weight of granulation		1250 g

[a] Includes 10% in excess of label claim.
Mix all the ingredients thoroughly. Compress into slugs. Grind and screen to 14- to 16-mesh granules. Recompress into tablets, using a ¼-inch concave punch. Ten tablets should weigh 1.25 g.
Sufficient tartaric acid should be used in these tablets to adjust the pH to 4.5.

DIRECT COMPRESSION

APC Tablets

INGREDIENTS	IN EACH	IN 10,000
Aspirin (40-mesh crystal)	224 mg	2240 g
Phenacetin	160 mg	1600 g
Caffeine (anhyd USP gran)	32 mg	320 g
Compressible sugar (Di-Pac[a])	93.4 mg	934 g
Sterotex	7.8 mg	78 g
Silica gel (Syloid 244[b])	2.8 mg	28 g

[a] *Amstar.*
[b] *Davison Chem.*
Blend ingredients in a twin-shell blender for 15 min and compress on a ⅜-inch standard concave punch (courtesy, *Amstar*).

CT Ascorbic Acid USP, 250 mg

INGREDIENTS	IN EACH	IN 10,000
Ascorbic Acid USP (Merck, fine crystals)	255 mg	2550 g
Microcrystalline cellulose[a]	159 mg	1590 g
Stearic acid	9 mg	90 g
Colloidal silica[b]	2 mg	20 g
Weight of granulation		4250 g

[a] Avicel-PH-101.
[b] Cab-O-Sil.
Blend all ingredients in a suitable blender. Compress, using ⅛-inch standard concave punch. Ten tablets should weigh 4.25 g (courtesy, *FMC*).

Breath Freshener Tablets

INGREDIENTS	IN EACH	IN 10,000
Wintergreen oil	0.6 mg	6 g
Menthol	0.85 mg	8.5 g
Peppermint oil	0.3 mg	3 g
Silica gel (Syloid 244[a])	1 mg	10 g
Sodium saccharin	0.3 mg	3 g
Sodium bicarbonate	14 mg	140 g
Mannitol USP (granular)	180.95 mg	1809.5 g
Calcium stearate	2 mg	20 g

[a] *Davison* Chem.
Mix the flavor oils and menthol until liquid. Adsorb onto the silica gel. Add the remaining ingredients. Blend and compress on ¾-inch, flat-face bevel-edge punch to a thickness of 3.1 mm (courtesy, *Atlas*).

Chewable Antacid Tablets

INGREDIENTS	IN EACH	IN 10,000
Aluminum hydroxide and magnesium carbonate, codried gel[a]	325 mg	3250 g
Mannitol USP (granular)	675 mg	6750 g
Microcrystalline cellulose[b]	75 mg	750 g
Corn starch	30 mg	300 g
Calcium stearate	22 mg	220 g
Flavor	qs	qs

[a] *Reheis F-MA-11.*
[b] *Avicel*
Blend all ingredients in a suitable blender. Compress, using a 5/8-inch, flat-face, bevel-edge punch (courtesy, *Atlas*).

Chewable Multivitamin Tablets

INGREDIENTS	IN EACH	IN 10,000
Vitamin A USP (dry, stabilized form)	5000 USP units	50 million units
Vitamin D dry, stabilized form)	400 USP units	4 million units
Ascorbic Acid USP	60.0 mg	600 g
Thiamine Hydrochloride USP	1 mg	10 g
Riboflavin USP	1.5 mg	15 g
Pyridoxine Hydrochloride USP	1 mg	10 g
Cyanocobalamin USP	2 μg	20 mg
Calcium Pantothenate USP	3 mg	30 g
Niacinamide USP	10 mg	100 g
Mannitol USP (granular)	236.2 mg	2362 g
Cornstarch	16.6 mg	166 g
Sodium saccharin	1.1 mg	11 g
Magnesium stearate	6.6 mg	66 g
Talc USP	10 mg	100 g
Flavor	qs	qs

Blend all ingredients in a suitable blender. Compress, using a ⅜-inch, flat-face, bevel-edge punch (courtesy, *Atlas*).

CT Ferrous Sulfate

INGREDIENTS	IN EACH	IN 7000
Ferrous Sulfate USP (crystalline)	0.325 g	2275 g
Talc		0.975 g
Sterotex		1.95 g
Weight of granulation		2277.93 g

Grind to 12- to 14-mesh, lubricate, and compress. Coat immediately to avoid oxidation to the ferric state with 0.410 gr of tolu balsam (dissolved in alcohol) and 0.060 gr of salol and chalk. Use a deep, concave, 11/32-inch punch. Ten tablets should weigh 3.25 g.

CT Methenamine

INGREDIENTS	IN EACH	IN 7000
Methenamine (12- to 14-mesh crystals)	0.325 g	2275 g
Weight of granulation		2275 g

Compress directly, using a 11/32-inch punch. Ten tablets should weigh 3.25 g.

CT Phenobarbital USP, 30 mg

INGREDIENTS	IN EACH	IN 10,000
Phenobarbital	30.59 mg	305.9 g
Microcrystalline cellulose[a]	30.59 mg	305.9 g
Spray-dried lactose	69.16 mg	691.6 g
Colloidal silica[b]	1.33 mg	13.3 g
Stearic acid	1.33 mg	13.3 g
Weight of granulation		1330 g

[a] Avicel-PH-101.
[b] QUSO F-22.
Screen the phenobarbital to break up lumps and blend with the microcrystalline cellulose. Add spray-dried lactose and blend. Finally, add the stearic acid and colloidal silica; blend to obtain a homogeneous mixture. Compress, using a ⅜-inch, shallow, concave punch. Ten tablets should weigh 1.33 g (courtesy, *FMC*).

Molded Tablets or Tablet Triturates (TT)

Tablet triturates are small, discoid masses of molded powders weighing 30 to 250 mg each. The base consists of lactose, β-lactose, mannitol, dextrose, or other rapidly soluble materials. It is desirable in making tablet triturates to prepare a solid dosage form that is rapidly soluble; as a result they are generally softer than compressed tablets.

Figure 45-33. Hand-molding tablet triturates (courtesy, Merck).

This type of dosage form is selected for a number of drugs because of its rapidly dissolving characteristic. Nitroglycerin in many concentrations is prepared in tablet triturate form since the molded tablet rapidly dissolves when administered by placing under the tongue. Potent alkaloids and highly toxic drugs used in small doses are prepared as tablet triturates that can serve as dispensing tablets to be used as the source of the drug in compounding other formulations or solutions. Narcotics in the form of hypodermic tablets originally were made as tablet triturates because they rapidly dissolve in sterile water for injection prior to administration. Today with stable injections of narcotics available, there is no longer any justification for their use in this manner. Although many hypodermic tablets currently are made, they are used primarily for oral administration.

Tablet triturates are made by forcing a moistened blend of the drug and diluent into a mold, extruding the formed mass, which is allowed to dry. This method is essentially the same as it was when introduced by Fuller in 1878. Hand molds may vary in size, but the method of operation is essentially the same. Molds consist of two plates made from polystyrene plastic, hard rubber, nickel-plated brass, or stainless steel. The mold plate contains 50 to 500 carefully polished perforations. The other plate is fitted with a corresponding number of projecting pegs or punches that fit the perforations in the mold plate. The mold plate is placed on a flat surface, the moistened mass is forced into the perforations, and the excess is scraped from the top surface. The mold plate is placed over the plate with the corresponding pegs and lowered. As the plates come together, the pegs force the tablet triturates from the molds. They remain on the tops of the pegs until dry, and they can be handled (see Fig 45-33). In some hand molds, as shown in Figure 45-34, the pegs are forced down onto the plate holding the moist trituration.

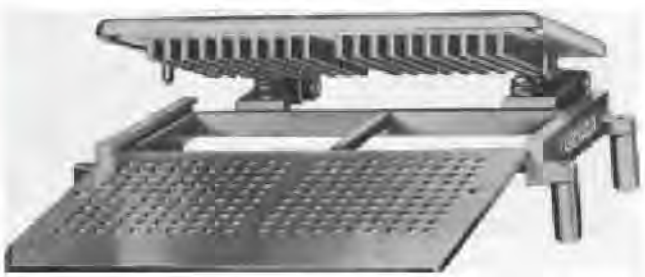


Figure 45-34. Tablet triturate mold (courtesy, Vector/Colton).

FORMULATION

In developing a formula it is essential to know the blank weight of the mold that is to be used. To determine this, the weight of the diluent that exactly fills all the openings in the mold is determined by experiment. This amount of diluent is weighed and placed aside. The total amount of the drug required is determined by multiplying the number of perforations in the plate used in the previous experiment by the amount of drug desired in each tablet. The comparative bulk of this medication is compared with that of an equal volume of diluent and that quantity of diluent is removed and weighed. The drug and the remaining diluent are mixed by trituration, and the resulting triturate is moistened and forced into the openings of the mold. If the perforations are not filled completely, more diluent is added, its weight noted, and the formula written from the results of the experiments.

It is also permissible in the development of the formula to weigh the quantity of medication needed for the number of tablets represented by the number of perforations in the mold, triturate with a weighed portion (more than 1/2) of the diluent, moisten the mixture, and press it into the perforations of the mold. An additional quantity of the diluent is moistened immediately and also forced into the perforations in the plate until they are filled completely. All excess diluent is removed, the trial tablets are forced from the mold, then triturated until uniform, moistened again, if necessary, and remolded. When these tablets are dried thoroughly and weighed, the difference between their total weight and the weight of medication taken will indicate the amount of diluent required and accordingly supply the formula for future use for that particular tablet triturate.

PREPARATION

The mixed powders are moistened with a proper mixture of alcohol and water, although other solvents or moistening agents such as acetone, petroleum benzin, and various combinations of these may be used in specific cases; the agent of choice depends on the solvent action that it will exert on the powder mixture. Often the moistening agent is 50% alcohol, but this concentration may be increased or decreased depending on the constituents of the formula. Care must be used in adding the solvent mixture to the powder. If too much is used, the mass will be soggy and will require a long time to dry, and the finished tablet will be hard and slowly soluble; if the mass is too wet, shrinkage will occur in the molded tablets; finally, a condition known as creeping will be noticed. Creeping is the concentration of the medication on the surface of the tablet caused by capillarity and rapid evaporation of the solvent from the surface. Because molded tablets by their very nature are quite friable, an inaccurate strength in each tablet may result from creeping if powder is lost from the tablet's surface. On the other hand, if an insufficient amount of moistening agent is used, the mass will not have the proper cohesion to make a firm tablet. The correct amount of moistening agent can be determined initially only by experiment.

HAND-MOLDING TABLET TRITURATES

In preparing hand-molded tablets place the mold plate on a glass plate. The properly moistened material is pressed into the perforations of the mold with a broad spatula, exerting uniform pressure over each opening. The excess material is removed by passing the spatula at an oblique angle, with strong hand pressure, over the mold to give a clean, flat surface. The material thus removed should be placed with the remainder of the unmolded material.

The mold with the filled perforations should be reversed and moved to another clean part of the plate where the pressing operation with the spatula is repeated. It may be necessary to add more material to fill the perforations completely and uniformly. The mold should be allowed to stand in a position so that part of the moistening agent will evaporate equally from both faces. While the first plate is drying, another mold can be prepared. As soon as the second mold has been completed, the first mold should be sufficiently surface-dried so that the pegs will press the tablets from the mold with a minimum of sticking.

To remove the tablets from the mold, place the mold over the peg plate so that the pegs and the perforations are in juxtaposition. The tablets are released from the mold by hand pressure, which forces the pegs through the perforations. The ejected tablets are spread evenly in single layers on silk trays and dried in a clean, dust-free chamber with warm, circulating air. If only a small quantity of tablet triturates is made and no warm-air oven is available, the tablet triturates may be dried to constant weight at room temperature.

MACHINE-MOLDING TABLET TRITURATES

Tablet triturates also can be made using mechanical equipment. The automatic tablet triturate machine illustrated in Figure 45-35 makes tablet triturates at a rate of 2500/min. For machine-molding, the powder mass need not be as moist as for plate-molding, since the time interval between forming the tablets and pressing them is considerably shorter. The moistened mass passes through the funnel of the hopper to the feed plates below. In this feed plate are four holes having the same diameter as the mouth of the funnel. The material fills one hole at a time and, when filled, revolves to a position just over the mold plate. When in position the weighted pressure foot lowers and imprisons the powder. At the same time a spreader in the sole of the pressure foot rubs it into the mold cavities and evens it off so that the triturates are smooth on the surface and are of uniform density. When this operation is completed, the mold passes to the next position, where it registers with a nest of punches or pegs that eject the tablets from the mold plate onto a conveyor belt. The conveyor belt sometimes is extended to a length of 8 or 10 ft. under a battery of infrared drying lamps to hasten the setting of the tablets for more rapid handling. This method of drying can be used only if the drug is chemically stable to these drying conditions.

Figure 45-35. Automatic tablet triturate machine (courtesy, Vector-Colton).

COMPRESSED TABLET TRITURATES

Frequently, tablet triturates are prepared on compression tablet machines using flat-face punches. When solubility and a clear solution are required, water-soluble lubricants must be used to prevent sticking to the punches. The granulations are prepared as directed for ordinary compressed tablets; lactose generally is used as the diluent. Generally, tablet triturates prepared by this method are not as satisfactory as the molded type regarding their solubility and solution characteristics.

TABLET CHARACTERISTICS

Compressed tablets may be characterized or described by a number of specifications. These include the diameter size, shape, thickness, weight, hardness, disintegration time, and dissolution characteristics. The diameter and shape depend on the die and the punches selected for the compression of the tablet. Generally, tablets are discoid in shape, although they may be oval, oblong, round, cylindrical, or triangular. Their upper and lower surfaces may be flat, round, concave, or convex to various degrees. The concave punches (used to prepare convex tablets) are referred to as shallow, standard, and deep cup, depending on the degree of concavity (see Figs 45-17 to 45-20). The tablets may be scored in halves or quadrants to facilitate breaking if a smaller dose is desired. The top or lower surface may be embossed or engraved with a symbol or letters that serve as an additional means of identifying the source of the tablets. These characteristics along with the color of the tablets tend to make them distinctive and identifiable with the active ingredient that they contain.

The remaining specifications assure the manufacturer that the tablets do not vary from one production lot to another. In the case of new tablet formulations their therapeutic efficacy is demonstrated through clinical trials, and it is the manufacturer's aim to reproduce the same tablet with the exact characteristics of the tablets that were used in the clinical evaluation of the dosage form. Therefore, from the control viewpoint these specifications are important for reasons other than physical appearance.

Tablet Hardness

The resistance of the tablet to chipping, abrasion, or breakage under conditions of storage, transportation, and handling before usage depends on its hardness. In the past, a rule of thumb described a tablet to be of proper hardness if it was firm enough to break with a sharp snap when it was held between the 2nd and 3rd fingers and using the thumb as the fulcrum, yet didn't break when it fell on the floor. For obvious reasons and control purposes a number of attempts have been made to quantitate the degree of hardness.

A small and portable hardness tester was manufactured and introduced in the mid-1930s by *Monsanto*. It now is distributed by the Stokes Div *(Pennwalt)* and may be designated as either the Monsanto or Stokes hardness tester. The instrument measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet. The force is measured in kilograms and when used in production, a hardness of 4 kg is considered to be minimum for a satisfactory tablet.

The Strong-Cobb hardness tester introduced in 1950 also measures the diametrically applied force required to break the tablet. In this instrument the force is produced by a manually operated air pump. As the pressure is increased, a plunger is forced against the tablet placed on anvil. The final breaking point is indicated on a dial calibrated into 30 arbitrary units. The hardness values of the Stokes and Strong-Cobb instruments are not equivalent. Values obtained with the Strong-Cobb tester have been found to be 1.6 times those of the Stokes tester.

Another instrument is the Pfizer hardness tester, which operates on the same mechanical principle as ordinary pliers. The force required to break the tablet is recorded on a dial and may be expressed in either kilograms or pounds of force. In an experimental comparison of testers the Pfizer and the Stokes testers were found to check each other fairly well. Again the Strong-Cobb tester was found to give values 1.4 to 1.7 times the absolute values on the other instruments.

The most widely used apparatus to measure tablet hardness or crushing strength is the Schleuniger apparatus, also known as the Heberlein, distributed by *Vector*. This and other, newer, electrically operated test equipment eliminate the operator variability inherent in the measurements described above. Newer equipment is also available with printers to provide a record of test results. See Figure 45-36.

Manufacturers, such as *Key, Van Kel, Erweka,* and others, make similar hardness testers.

Hardness (or more appropriately, crushing strength) determinations are made throughout the tablet runs to determine the need for pressure adjustments on the tableting machine. If the tablet is too hard, it may not disintegrate in the required period of time or meet the dissolution specification; if it is too soft, it will not withstand the handling during subsequent processing such as coating or packaging and shipping operations.

A tablet property related to hardness is *friability,* and the measurement is made by use of the Roche friabilator. Rather than a measure of the force required to crush a tablet, the instrument is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling, and shipping. A number of tablets are weighed and placed in the tumbling apparatus where they are exposed to rolling and repeated shocks resulting from freefalls within the apparatus. After a given number of rotations the tablets are weighed, and the loss in weight indicates the ability of the tablets to withstand this type of wear (Fig 45-37).

Recent research has proposed that there are at least three measurable hardness parameters that can give a clue to the compatibility and intrinsic strength of powdered materials. These include bonding strength, internal strain, and brittleness. Hiestand proposed indices to quantify these parameters, and they are listed in Table 45-4 for a number of materials.

The higher the bonding index, the stronger a tablet is likely to be. The higher the strain index, the weaker the tablet. Since the two parameters are opposite in their effect on the tablet, it is possible for a material (such as Avicel) to have a relatively high strain index, but yet have superior compaction properties because of an extraordinary bonding potential. The higher the brittleness index, the more friable the tablet is likely to be. For

Figure 45-36. The Schleuniger or Heberlein tablet hardness tester shown with calibration blocks (courtesy, Vector).

Figure 45-37. The Roche friabilator (courtesy, Hoffmann-LaRoche).

a more detailed discussion of this subject, the reader is directed to References 22, 37, 38.

A similar approach is taken by many manufacturers when they evaluate a new product in the new market package by sending the package to distant points and back using various methods of transportation. This is called a *shipping test*. The condition of the product on its return indicates its ability to withstand transportation handling.

Tablet Thickness

The thickness of the tablet from production-run to production-run is controlled carefully. Thickness can vary with no change in weight because of difference in the density of the granulation and the pressure applied to the tablets, as well as the speed of tablet compression. Not only is the tablet thickness important in reproducing tablets identical in appearance but also to ensure that every production lot will be usable with selected packaging components. If the tablets are thicker than specified, a given number no longer may be contained in the volume of a given size bottle. Tablet thickness also becomes an important characteristic in counting tablets using filling equipment. Some filling equipment uses the uniform thickness of the tablets as a counting mechanism. A column containing a known number of tablets is measured for height; filling is accomplished by continually dropping columns of tablets of the same height into bottles. If thickness varies throughout the lot, the result will be variation in count. Other pieces of filling equipment can malfunction because of variation in tablet thickness, since tablets above specified thickness may cause wedging of tablets in previously adjusted depths of the counting slots. Tablet thickness is determined with a caliper or thickness gauge that measures the thickness in millimeters. Plus or minus 5% may be allowed, depending on the size of the tablet.

Table 45-4. Hiestand Compaction Indices for a Number of Materials

MATERIAL	BONDING INDEX	STRAIN INDEX	BRITTLENESS INDEX
Aspirin	1.5	1.11	0.16
Dicalcium phosphate	1.3	1.13	0.15
Lactose anhydrous	0.8	1.40	0.27
Avicel pH 102	4.3	2.20	0.04
Corn starch	0.4	2.48	0.26
Sucrose NF	1.0	1.45	0.35
Erythromycin dihydrate	1.9	2.13	0.98

Uniformity of Dosage Forms

TABLET WEIGHT—The volumetric fill of the die cavity determines the weight of the compressed tablet. In setting up the tablet machine the fill is adjusted to give the desired tablet weight. The weight of the tablet is the quantity of the granulation that contains the labeled amount of the therapeutic ingredient. After the tablet machine is in operation the weights of the tablets are checked routinely, either manually or electronically, to ensure that proper-weight tablets are being made. This has become rather routine in most manufacturing operations with newer, electronically controlled tablet presses. The USP has provided tolerances for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50 mg or more of the drug substance or when the latter comprises 50% or more, by weight, of the dosage form. Twenty tablets are weighed individually, and the average weight is calculated. The variation from the average weight in the weights of not more than two of the tablets must not differ by more than the percentage listed below; no tablet differs by more than double that percentage. Tablets that are coated are exempt from these requirements but must conform to the test for content uniformity if it is applicable.

AVERAGE WEIGHT	PERCENT DIFFERENCE
130 mg or less	10
More than 130 mg through 324 mg	7.5
More than 324 mg	5

CONTENT UNIFORMITY—To ensure that every tablet contains the amount of drug substance intended, with little variation among tablets within a batch, the USP includes the content uniformity test for certain tablets. Due to the increased awareness of physiological availability, the content uniformity test has been extended to monographs on all coated and uncoated tablets and all capsules intended for oral administration where the range of sizes of the dosage form available includes a 50 mg or smaller size, in which case the test is applicable to all sizes (50 mg and larger and smaller) of that tablet or capsule. The official compendia can be consulted for the details of the test. Tablet monographs with a content uniformity requirement do not have a weight variation requirement.

Tablet Disintegration

It is recognized generally that the *in vitro* tablet disintegration test does not necessarily bear a relationship to the *in vivo* action of a solid dosage form. To be absorbed, a drug substance must be in solution, and the disintegration test is a measure only of the time required under a given set of conditions for a group of tablets to disintegrate into particles. Generally, this test is useful as a quality-assurance tool for conventional (non-sustained-release) dosage forms. In the present disintegration test the particles are those that will pass through a 10-mesh screen. In a comparison of disintegration times and dissolution rates or initial absorption rates of several brands of aspirin tablets, it was found that the faster-absorbed tablets had the longer disintegration time. Regardless of the lack of significance as to *in vivo* action of the tablets, the test provides a means of control in ensuring that a given tablet formula is the same as regards disintegration from one production batch to another. The disintegration test is used as a control for tablets intended to be administered by mouth, except for tablets intended to be chewed before being swallowed or tablets designed to release the drug substance over a period of time.

Exact specifications are given for the test apparatus, inasmuch as a change in the apparatus can cause a change in the results of the test. The apparatus consists of a basket rack holding six plastic tubes, open at the top and bottom; the bottom of the tubes is covered with 10-mesh screen. See Figure 45-38. The basket rack is immersed in a bath of suitable liquid, held at 37°C,

Figure 45-38. Vanderkamp tablet disintegration tester (courtesy, VanKel).

preferably in a 1-L beaker. The rack moves up and down in the fluid at a specified rate. The volume of the fluid is such that on the upward stroke the wire mesh remains at least 2.5 cm below the surface of the fluid and descends to not less than 2.5 cm from the bottom on the downward stroke. Tablets are placed in each of the six cylinders along with a plastic disc over the tablet unless otherwise directed in the monograph. The endpoint of the test is indicated when any residue remaining is a soft mass with no palpably soft core. The plastic discs help to force any soft mass that forms through the screen.

For compressed, uncoated tablets the testing fluid is usually water at 37°, but in some cases the monographs direct that Simulated Gastric Fluid TS be used. If one or two tablets fail to disintegrate, the test is to be repeated using 12 tablets. Of the 18 tablets then tested, 16 must have disintegrated within the given period of time. The conditions of the test are varied somewhat for coated tablets, buccal tablets, and sublingual tablets. Disintegration times are included in the individual tablet monograph. For most uncoated tablets the period is 30 min, although the time for some uncoated tablets varies greatly from this. For coated tablets up to 2 hr may be required, while for sublingual tablets, such as CT Isoproterenol Hydrochloride, the disintegration time is 3 min. For the exact conditions of the test, consult the USP.

Dissolution Test

For certain tablets the monographs direct compliance with limits on dissolution rather than disintegration. Since drug absorption and physiological availability depend on having the drug substance in the dissolved state, suitable dissolution characteristics are an important property of a satisfactory tablet. Like the disintegration test, the dissolution test for measuring the amount of time required for a given percentage of the drug substance in a tablet to go into solution under a specified set of conditions is an *in vitro* test. It is intended to provide a step toward the evaluation of the physiological availability of the drug substance, but as described currently, it is not designed to measure the safety or efficacy of the tablet being tested. Both the safety and effectiveness of a specific dosage form must be demonstrated initially by means of appropriate *in vivo* studies and clinical evaluation. Like the disintegration test, the dissolution test does provide a means of control in ensuring that a given tablet formulation is the same as regards dissolution as the batch of tablets shown initially to be clinically effective. It also provides an *in vitro* control procedure to eliminate variations among production batches. Refer to Chapter 35 for a complete discussion of dissolution testing.

Validation

In this era of increasing regulatory control of the pharmaceutical industry, manufacturing procedures cannot be discussed without the mention of some process-validation activity. By way of documentation, product testing, and perhaps in-process testing as well, manufacturers can demonstrate that their formulas and processes perform in the manner expected and that they do so reproducibly.

Although the justification for requiring validation is found in the regulations relating to *Current Good Manufacturing Practices for Finished Pharmaceuticals* as well as other sources, there is still much room for interpretation, and the process varies from one company to another. General areas of agreement appear to be that

The validation activity must begin in R&D and continue through product introduction.
Documentation is the key.
In general, three batches represent an adequate sample for validation.

The FDA has rejected historical data or *retrospective validation*. They require that new products be validated from beginning to end, a process called *prospective validation*.

CAPSULES

Capsules are solid dosage forms in which the drug substance is enclosed in either a hard or soft, soluble container or shell of a suitable form of gelatin. The soft gelatin capsule was invented by Mothes, a French pharmacist, in 1833. During the following year DuBlanc obtained a patent for his soft gelatin capsules. In 1848 Murdock patented the two-piece hard gelatin capsule. Although development work has been done on the preparation of capsules from methylcellulose, starch and calcium alginate, gelatin, because of its unique properties, remains the primary composition material for the manufacture of capsules. The gelatin used in the manufacture of capsules is obtained from collagenous material by hydrolysis. There are two types of gelatin, Type A, derived mainly from pork skins by acid processing, and Type B, obtained from bones and animal skins by alkaline processing. Blends are used to obtain gelatin solutions with the viscosity and bloom strength characteristics desirable for capsule manufacture.[50]

The encapsulation of medicinal agents remains a popular method for administering drugs. Capsules are tasteless, easily administered, and easily filled either extemporaneously or in large quantities commercially. In prescription practice the use of hard gelatin capsules permits a choice in prescribing a single drug or a combination of drugs at the exact dosage level considered best for the individual patient. This flexibility is an advantage over tablets. Some patients find it easier to swallow capsules than tablets, therefore preferring to take this form when possible. This preference has prompted pharmaceutical manufacturers to market the product in capsule

form, even though the product already has been produced in tablet form. While the industry prepares approximately 75% of its solid dosage forms as compressed tablets, 23% as hard gelatin capsules, and 2% as soft elastic capsules, market surveys have indicated a consumer preference of 44.2% for soft elastic capsules, 39.6% for tablets, and 19.4% for hard gelatin capsules.[51]

HARD GELATIN CAPSULES

The hard gelatin capsule, also referred to as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely surrounding the drug formulation. The classic capsule shape is illustrated in Figure 45-39. These capsules are filled by introducing the powdered material into the longer end or body of the capsule and then slipping on the cap. Hard gelatin capsules are made largely from gelatin, FD&C colorants, and sometimes an opacifying agent such as titanium dioxide; the USP permits the gelatin for this purpose to contain 0.15% sulfur dioxide to prevent decomposition during manufacture. Hard gelatin capsules contain 12–16% water, but the water content can vary depending on the storage conditions. When the humidity is low, the capsules become brittle; if stored at high humidities, the capsules become flaccid and lose their shape. Storage in high-temperature areas also can affect the quality of hard gelatin capsules. Gelatin capsules do not protect hygroscopic materials from atmospheric water vapor, as moisture can diffuse through the gelatin wall.

Companies having equipment for preparing empty hard gelatin capsules include *Lilly, Parke-Davis, Scherer,* and *SmithKline*. The latter's production is mainly for its own use; the others are suppliers to the industry. With this equipment, stainless steel pins, set in plates, are dipped into the gelatin solution, which must be maintained at a uniform temperature and an exact degree of fluidity. If the gelatin solution varies in viscosity, it correspondingly will decrease or increase the thickness of the capsule wall. This is important since a slight variation is sufficient to make either a loose or a tight joint. When the pins have been withdrawn from the gelatin solution, they are rotated while being dried in kilns through which a strong blast of filtered air with controlled humidity is forced. Each capsule is stripped, trimmed to uniform length and joined, the entire process being mechanical. Capsule-making equipment is illustrated in Figures 45-40 and 45-41. These show the stainless steel pins being dipped into the gelatin solutions and then being rotated through the drying kiln.

Capsules are supplied in a variety of sizes. The hard, empty capsules (Fig 45-39) are numbered from 000, the largest size that can be swallowed, to 5, which is the smallest. Larger sizes are available for use in veterinary medicine. The approximate capacity for capsules from 000 to 5 ranges from 600 to 30 mg, although this will vary because of the different densities of powdered drug materials.

Commercially filled capsules have the conventional oblong shape illustrated, with the exception of capsule products by *Lilly* and *SmithKline,* which are of distinctive shape. For Lilly products, capsules are used in which the end of the base is tapered to give the capsule a bullet-like shape; products encapsulated in this form are called *Pulvules*. The *SmithKline* capsules differ in that both ends of the cap and body are angular, rather than round.

Figure 45-40. Manufacture of hard gelatin capsules by dipping stainless steel pins into gelatin solutions (courtesy, Lilly).

After hard gelatin capsules are filled and the cap applied, there are a number of methods used to ensure that the capsules will not come apart if subjected to vibration or rough handling, as in high-speed counting and packaging equipment. The capsules can be spot-welded by means of a heated metal pin pressed against the cap, fusing it to the body, or they may be banded with molten gelatin laid around the joint in a strip and dried. Colored gelatin bands around capsules have been used for many years as a trademark by *Parke-Davis* for their line of capsule products, *Kapseals*. Another approach was used in the *Snap-Fit* and *Coni-Snap* capsules. A pair of matched locking rings are formed into the cap and body portions of the capsule. Prior to filling, these capsules are slightly longer than regular capsules of the same size. When the locking rings are engaged after filling, their length is equivalent to that of the conventional capsule.

Following several tampering incidents, many pharmaceutical companies now use any number of locking and sealing technologies to manufacture and distribute these very useful dosage forms safely. Unfortunately, tamper-resistant packaging has become standard for capsule products.

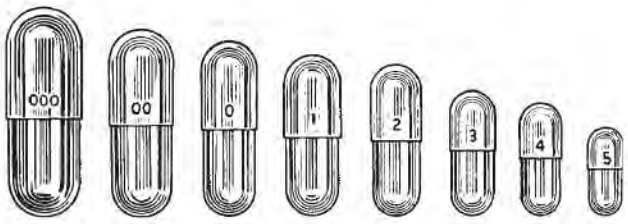


Figure 45-39. Hard gelatin capsules showing relative sizes (courtesy, Parke-Davis).

Figure 45-41. Formed capsules being dried by rotating through a drying kiln (courtesy, Lilly).

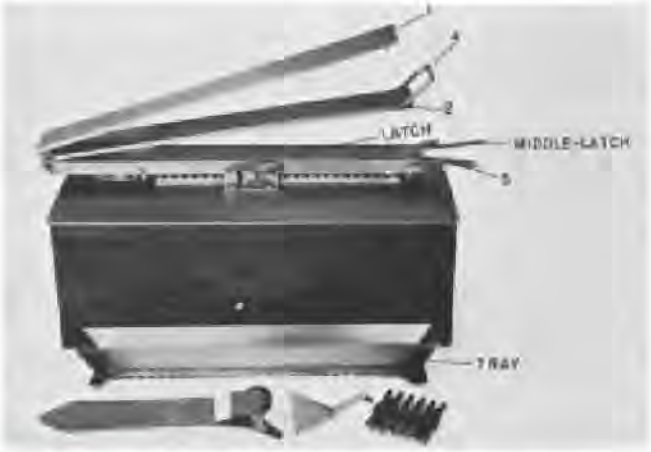


Figure 45-42. Hand-operated capsule machine (courtesy, Chemi-Pharm).

It is usually necessary for the pharmacist to determine the size of the capsule needed for a given prescription through experimentation. The experienced pharmacist, having calculated the weight of material to be held by a single capsule, often will select the correct size immediately. If the material is powdered, the base of the capsule is filled and the top is replaced. If the material in the capsule proves to be too heavy after weighing, a smaller size must be taken and the test repeated. If the filled capsule is light, it is possible that more can be forced into it by increasing the pressure or, if necessary, some of the material may be placed in the cap. This is not desirable as it tends to decrease the accuracy of subdivision and it is much better to select another size, whose base will hold exactly the correct quantity. In prescription filling it is wise to check the weight of each filled capsule.

In addition to the transparent, colorless, hard gelatin capsule, capsules are also available in various transparent colors such as pink, green, reddish brown, blue, yellow, and black. If they are used, it is important to note the color as well as the capsule size on the prescription so that in the case of renewal the refilled prescription will duplicate the original. Colored capsules have been used chiefly by manufacturers to give a specialty product a distinctive appearance. Titanium dioxide is added to the gelatin to form white capsules or to make an opaque, colored capsule. In addition to color contrasts, many commercial products in capsules are given further identification by markings, which may be the company's name, a symbol on the outer shell of the capsule, or banding. Some manufacturers mark capsules with special numbers based on a coded system to permit exact identification by the pharmacist or physician.

Extemporaneous Filling Methods

When filling capsules on prescription, the usual procedure is to mix the ingredients by trituration, reducing them to a fine and uniform powder. The principles and methods for the uniform distribution of an active medicinal agent in a powder mixture are discussed in Chapter 37. Granular powders do not pack readily in capsules, and crystalline materials, especially those that consist of a mass of filament-like crystals such as the quinine salts, are not fitted easily into capsules unless powdered. Eutectic mixtures that tend to liquefy may be dispensed in capsules if a suitable absorbent such as magnesium carbonate is used. Potent drugs given in small doses usually are mixed with an inert diluent such as lactose before filling into capsules. When incompatible materials are prescribed together, it is sometimes possible to place one in a smaller capsule and then enclose it with the second drug in a larger capsule.

Usually, the powder is placed on paper and flattened with a spatula so that the layer of powder is not greater than about ⅓ the length of the capsule that is being filled. This helps to keep both the hands and capsules clean. The cap is removed from the selected capsule and held in the left hand; the body is pressed repeatedly into the powder until it is filled. The cap is replaced and the capsule is weighed. In filling the capsule the spatula is helpful in pushing the last quantity of the material into the capsule. If each capsule has not been weighed, there is likely to be an excess or a shortage of material when the specified number of capsules have been packed. This condition is adjusted before dispensing the prescription.

A number of manual filling machines and automatic capsule machines are available for increasing the speed of the capsule-filling operation. Figure 45-42 illustrates a capsule-filling machine that was known formerly as the Sharp & Dohme machine. This equipment is now available through *ChemiPharm*. Many community pharmacists find this a useful piece of apparatus, and some pharmaceutical manufacturers use it for small-scale production of specialty items. The machine fills 24 capsules at a time with the possible production of 2000 per day. Entire capsules are placed in the machine by hand; the lower plate carries a clamp that holds the capsule bases and makes it possible to remove and replace the caps mechanically. The plate holding the capsule bases is perforated for three sizes of capsules. The powder is packed in the bases; the degree of accuracy depends on the selection of capsule size and the amount of pressure applied in packing. The hand-operated machine (Model 300, *ChemiPharm*) illustrated in Figure 45-43 has a production capacity of 2000 capsules per hour. The machine is made for a single capsule size and cannot be changed over for other sizes. A different machine is required for any additional capsule size. Its principle of operation is similar to that of the Sharp & Dohme machine.

Machine Filling Methods

Large-scale filling equipment for capsules operates on the same principle as the manual machines described above, namely the filling of the base of the capsule. Compared with tablets,

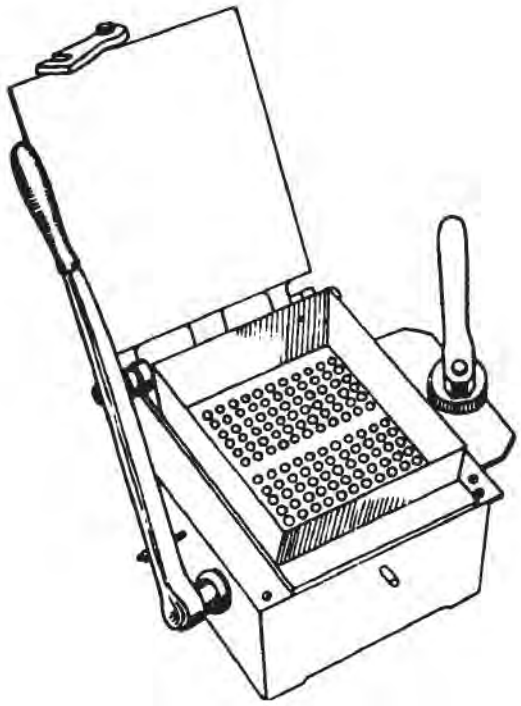


Figure 45-43. Hand-operated capsule machine, Model 300 (courtesy, ChemiPharm).

Table 45-5. Capsule Fill Chart

CAPSULE FILL WEIGHTS (MG) BASED ON SIZE AND DENSITY

	CAPSULE VOLUME (mL)									
	0.95	0.78	0.68	0.54	0.5	0.37	0.3	0.25	0.21	0.13
POWDER DENSITY	CAPSULE SIZE									
(g/ml)	00	0el	0	1el	1	2	3	4el	4	5
0.3	285	234	204	162	150	111	90	75	63	39
0.4	380	312	272	216	200	148	120	100	84	52
0.5	475	390	340	270	250	185	150	125	105	65
0.6	570	468	408	324	300	222	180	150	126	78
0.7	665	546	476	378	350	259	210	175	147	91
0.8	760	624	544	432	400	296	240	200	168	104
0.9	855	702	612	486	450	333	270	225	189	117
1.0	950	780	680	540	500	370	300	250	210	130
1.1	1045	858	748	594	550	407	330	275	231	143
1.2	1140	936	816	648	600	444	360	300	252	156
1.3	1235	1014	884	702	650	481	390	325	273	169
1.4	1330	1092	952	756	700	518	420	350	294	182
1.5	1425	1170	1020	810	750	555	450	375	315	195

powders for filling into hard gelatin capsules require a minimum of formulation efforts. The powders usually contain diluents such as lactose, mannitol, calcium carbonate, or magnesium carbonate. Since the flow of material is of great importance in the rapid and accurate filling of the capsule bodies, lubricants such as the stearates also are used frequently.

Because of the absence of numerous additives and manufacturing processing, the capsule form is used frequently to administer new drug substances for evaluation in initial clinical trials. However, it is now realized that the additives present in the capsule formulation, like the compressed tablet, can influence the release of the drug substance from the capsule. Tablets and capsules of a combination product containing triamterene and hydrochlorothiazide in a 2:1 ratio were compared clinically. The tablet caused approximately twice as much excretion of hydrochlorothiazide and three times as much triamterene as the capsule.[52]

Most equipment operates on the principle by which the base of the capsule is filled and the excess is scraped off. Therefore, the active ingredient is mixed with sufficient volume of a diluent, usually lactose or mannitol, to give the desired amount of the drug in the capsule when the base is filled with the powder mixture. The manner of operation of the machine can influence the volume of powder that will be filled into the base of the capsule; therefore, the weights of the capsules must be checked routinely as they are filled. See Table 45-5.

Semiautomatic capsule-filling machines manufactured by *Parke-Davis* and *Lilly* are illustrated in Figures 45-44 and 45-45. The Type 8 capsule-filling machine performs mechanically under the same principle as the hand filling of capsules. This includes separation of the cap from the body, filling the body half, and rejoining the cap and body halves.

Empty capsules are taken from the bottom of the capsule hopper into the magazine. The magazine gauge releases one

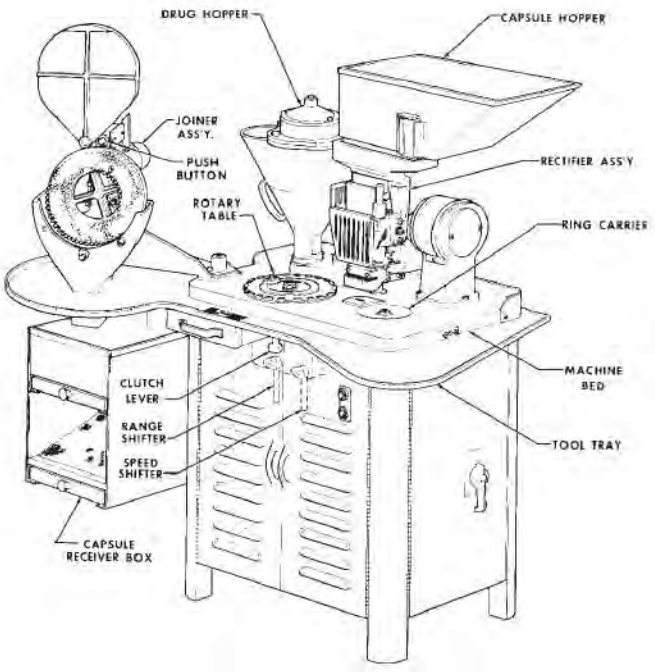


Figure 45-44. Schematic of Type 8 capsule-filling machine (courtesy, Parke-Davis).

Figure 45-45. Type 8 capsule-filling machine (courtesy, Lilly).

capsule from each tube at the bottom of each stroke of the machine. Leaving the magazine, the capsules drop onto the tracks of the raceway and are pushed forward to the rectifying area with a push blade. The rectifier block descends, turning the capsules in each track, cap up, and drops them into each row of holes in the capsule-holding ring assembly.

As the capsules fall into the holding ring, the cap half has a seat on the counter bore in each hole for the top ring. The body half is pulled by vacuum down into the bottom ring. When all rows in the ring assembly are full, the top ring, filled with caps only, is removed and set aside for later assembly. The body halves now are located in the bottom ring, ready for filling.

The ring holding the body halves is rotated at one of eight speeds on the rotary table. The drug hopper is swung over the rotating ring, and the auger forces drug powder into the open body cavities. When the ring has made a complete revolution and the body halves have been filled, the hopper is swung aside. The cap-holding ring is placed over the body-holding ring and the assembly is ready for joining. The capsule-holding ring assembly is placed on the joiner and the joiner plate is swung down into position to hold the capsules in the ring. The peg ring pins are entered in the holes of the body holding ring and tapped in place by the air cylinder pushing the body halves back into the cap halves.

The holding-ring assembly is now pushed by hand back onto the peg ring away from the joiner plate, thus pushing the capsules out of the holding-ring assembly. The joined capsules then fall through the joiner chute into the capsule receiver box. The capsule receiver box screens the excess powder from the capsules and delivers them to any convenient container.

Many companies use the Type 8 capsule-filling equipment for small-scale manufacture and clinical supplies for investigational use because of its ease of operation, low cost, and extreme flexibility. A Type 8 capsule filling machine will produce approximately 200,000 capsules per day. This, of course, depends upon the operator and the type of material being filled. For this machine, a mathematical model has been developed that describes the effect of selected physical powder properties as well as mechanical operating conditions on the capsule-filling operation. While the Type 8 capsule-filling machine has been in existence for many years, recent modifications have been made to this machine to improve the capsule-filling operations.

There are several pieces of equipment available that are classified as automatic capsule-filling machines. These are automatic in the sense that one operator can handle more than one machine. In this category are the Italian-made Zanasi *(United Machinery)* and MG-2 *(Supermatic)* models, plus the West German–made Hoefliger & Karg models *(Bosch)*.

Automatic capsule machines are capable of filling either powder or granulated products into hard gelatin capsules. With accessory equipment these machines also can fill pellets or place a tablet into the capsule with the powder or pellets. The capsules are fed at random into a large hopper. They are oriented as required and transferred into holders where the two halves are separated by suction. The top-half and bottom-half of the capsules are in separate holders, which at this stage take diverting directions.

A set of filling heads collects the product from the hopper, compresses it into a soft slug, and inserts this into the bottom half of the capsule. After filling, each top-half is returned to the corresponding bottom-half. The filled capsules are ejected, and an air blast at this point separates possible empty capsules from the filled. The machines can be equipped to handle all sizes of capsules. Depending upon the make and model, speeds from 9000 to 150,000 units per hour can be obtained (see Figs 45-46 to 45-48).

All capsules, whether they have been filled by hand or by machine, will require cleaning. Small quantities of capsules may be wiped individually with cloth. Larger quantities are rotated or shaken with crystalline sodium chloride. The capsules then are rolled on a cloth-covered surface.

Figure 45-46. MG-2, automatic capsule-filling machine (courtesy, Supermatic).

Uniformity of Dosage Units

The uniformity of dosage forms can be demonstrated by either of two methods, weight variation or content uniformity. Weight variation may be applied when the product is a liquid-filled, soft, elastic capsule or when the hard gelatin capsule contains 50 mg or more of a single active ingredient comprising 50% or more, by weight, of the dosage form. See the official compendia for details.

Disintegration tests usually are not required for capsules unless they have been treated to resist solution in gastric fluid (enteric-coated). In this case they must meet the requirements for disintegration of enteric-coated tablets. For certain capsule dosage forms a dissolution requirement is part of the monograph. Procedures used are similar to those employed in the case of compressed tablets.

Figure 45-47. Zanasi automatic filling machine, Model AZ-60. The set of filling heads shown at the left collects the powder from the hopper, compresses it into a soft slug, and inserts it into the bottom half of the capsule (courtesy, United Machinery).

Figure 45-48. Hoefliger & Karg automatic capsule-filling machine, Model GFK 1200 (courtesy, Amaco).

SOFT ELASTIC CAPSULES

The soft elastic capsule (SEC) is a soft, globular, gelatin shell somewhat thicker than that of hard gelatin capsules. The gelation is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of fungi. Commonly used preservatives are methyl- and propylparabens and sorbic acid. When the suspending vehicle or solvent can be an oil, soft gelatin capsules provide a convenient and highly acceptable dosage form. Large-scale production methods generally are required for the preparation and filling of soft gelatin capsules.

Formerly, empty soft gelatin capsules were available to the pharmacist for the extemporaneous compounding of solutions or suspensions in oils. Commercially filled soft gelatin capsules come in a wide choice of sizes and shapes; they may be round, oval, oblong, tubular, or suppository-shaped. Some sugar-coated tablets are quite similar in appearance to soft gelatin capsules. The essential differences are that the soft gelatin capsule has a seam at the point of closure of the two halves, and the contents can be liquid, paste, or powder. The sugar-coated tablet will not have a seam but will have a compressed core.

Oral SEC dosage forms generally are made so that the heat seam of the gelatin shell opens to release its liquid medication into the stomach less than 5 min after ingestion. Its use is being studied for those drugs poorly soluble in water having bioavailability problems. When used as suppositories, it is the moisture present in the body cavity that causes the capsule to come apart at its heat-sealed seam and to release its contents.

Plate Process

In this method a set of molds is used. A warm sheet of prepared gelatin is laid over the lower plate, and the liquid is poured on it. A second sheet of gelatin is carefully put in place, and this is followed by the top plate of the mold. The set is placed under the press where pressure is applied to form the capsules, which are washed off with a volatile solvent to remove any traces of oil from the exterior. This process has been adapted and is used for encapsulation by *Upjohn*. The sheets of gelatin may have the same color or different colors.

Rotary-Die Process

In 1933 the rotary-die process for elastic capsules was perfected by Robert P Scherer.[53] This process made it possible to improve the standards of accuracy and uniformity of elastic gelatin capsules and globules.

The rotary-die machine is a self-contained unit capable of continuously and automatically producing finished capsules from a supply of gelatin mass and filling material, which may be any liquid, semiliquid, or paste that will not dissolve gelatin. Two continuous gelatin ribbons, which the machine forms, are brought into convergence between a pair of revolving dies and an injection wedge. Accurate filling under pressure and sealing of the capsule wall occur as dual and coincident operations; each is delicately timed against the other. Sealing also severs the completed capsule from the net. The principle of operation is shown in Figure 45-49. See also Figure 45-50.

Figure 45-49. Rotary-die elastic capsule filler.

Figure 45-50. Scherer soft elastic capsule machine (courtesy, Scherer).

By this process the content of each capsule is measured individually by a single stroke of a pump so accurately constructed that plunger travel of 0.025 inch will deliver 1 <minim> (apoth). The Scherer machine contains banks of pumps so arranged that many capsules may be formed and filled simultaneously. All pumps are engineered to extremely small mechanical tolerances and to an extremely high degree of precision and similarity. All operations are controlled on a weight basis by actual periodic checks with a group of analytical balances. Individual net-fill weights of capsules resulting from large-scale production vary no more than ±1 to 3% from theory, depending upon the materials used.

The rotary-die process makes it possible to encapsulate heavy materials such as ointments and pastes. In this manner solids can be milled with a vehicle and filled into capsules. When it is desirable to have a high degree of accuracy and a hermetically sealed product, this form of enclosure is suited ideally.

The modern and well-equipped capsule plant is completely air conditioned, a practical necessity for fine capsule production. Its facilities and operations include the availability of carbon dioxide at every exposed point of operation for the protection of oxidizable substances before encapsulation. Special ingredients also have been used in the capsule shell to exclude light wavelengths that are destructive to certain drugs.

Norton Capsule Machine

This machine produces capsules completely automatically by leading two films of gelatin between a set of vertical dies. These dies as they close, open, and close are in effect a continual vertical plate forming row after row of pockets across the gelatin film. These are filled with medicament and, as they progress through the dies, are sealed, shaped, and cut out of the film as capsules, which drop into a cooled solvent bath.

Accogel Capsule Machine

Another means of soft gelatin encapsulation uses the Accogel machine and process which were developed at *Lederle*. The Accogel, or Stern machine, uses a system of rotary dies but is unique in that it is the only machine that successfully can fill dry powder into a soft gelatin capsule. The machine is available to the entire pharmaceutical industry by a lease arrangement and is used in many countries of the world. It is extremely versatile, not only producing capsules with dry powder but also encapsulating liquids and combinations of liquids and powders. By means of an attachment, slugs or compressed tablets may be enclosed in a gelatin film. The capsules can be made in a variety of colors, shapes, and sizes.

Microencapsulation

As a technology, microencapsulation is placed in the section on capsules only because of the relationship in terminology to mechanical encapsulation described above. The topic is also discussed in Chapter 47 (Extended-release and Targeted Drug Delivery Systems) of this text. Essentially, microencapsulation is a process or technique by which thin coatings can be applied reproducibly to small particles of solids, droplets of liquids, or dispersions, thus forming microcapsules. It can be differentiated readily from other coating methods in the size of the particles involved; these range from several tenths of a micrometer to 5000 μm in size.

A number of microencapsulation processes have been disclosed in the literature.[54] Some are based on chemical processes and involve a chemical or phase change; others are mechanical and require special equipment to produce the physical change in the systems required.

A number of coating materials have been used successfully; examples of these include gelatin, polyvinyl alcohol, ethylcellulose, cellulose acetate phthalate, and styrene maleic anhydride. The film thickness can be varied considerably, depending on the surface area of the material to be coated and other physical characteristics of the system. The microcapsules may consist of a single particle or clusters of particles. After isolation from the liquid manufacturing vehicle and drying, the material appears as a free-flowing powder. The powder is suitable for formulation as compressed tablets, hard gelatin capsules, suspensions, and other dosage forms.

The process provides answers for problems such as masking the taste of bitter drugs, a means of formulating prolonged-action dosage forms, a means of separating incompatible materials, a method of protecting chemicals against moisture or oxidation, and a means of modifying a material's physical characteristics for ease of handling in formulation and manufacture.

Among the processes applied to pharmaceutical problems is that developed by the National Cash Register Co (NCR). The NCR process is a chemical operation based on phase separation or coacervation techniques. In colloidal chemistry, coacervation refers to the separation of a liquid precipitate, or phase, when solutions of two hydrophilic colloids are mixed under suitable conditions.

The NCR process, using phase separation or coacervation techniques, consists of three steps:

1. Formation of three immiscible phases: a liquid manufacturing phase, a core material phase, and a coating material phase.
2. Deposition of the liquid polymer coating on the core material.
3. Rigidizing the coating, usually by thermal, cross-linking, or desolvation techniques, to form a microcapsule.

In Step 2, the deposition of the liquid polymer around the core material occurs only if the polymer is absorbed at the interface formed between the core material and the liquid vehicle phase. In many cases physical or chemical changes in the coating polymer solution can be induced so that phase separation (coacervation) of the polymer will occur. Droplets of concentrated polymer solution will form and coalesce to yield a two-phase, liquid-liquid system. In cases in which the coating material is an immiscible polymer or insoluble liquid polymer, it may be added directly. Also monomers can be dissolved in the liquid vehicle phase and, subsequently, polymerized at the interface.

Equipment required for microencapsulation by this method is relatively simple; it consists mainly of jacketed tanks with variable-speed agitators. Figure 45-51 shows a typical flow diagram of a production installation.

Other Oral Solid Dosage Forms

PILLS

Pills are small, round, solid, dosage forms containing a medicinal agent and are intended for oral administration. Pills were formerly the most extensively used oral dosage form, but they have been replaced largely by compressed tablets and capsules. Substances that are bitter or unpleasant to the taste, if not corrosive or deliquescent, can be administered in this form if the dose is not too large.

Formerly, pills were made extemporaneously by the community pharmacist whose skill at pill-making became an art. However, the few pills that are now used in pharmacy are prepared on a large scale with mechanical equipment. The pill formulas of the NF were introduced largely for the purpose of establishing standards of strength for the well-known and currently used pills. Hexylresorcinol Pills consist of hexylresorcinol crystals covered with a rupture-resistant coating that is dispersible in the digestive tract. It should be noted that the official hexylresorcinol pills are prepared not by traditional methods but by a patented process, the gelatin coating being sufficiently tough that it cannot be broken readily, even when chewed. Therefore,

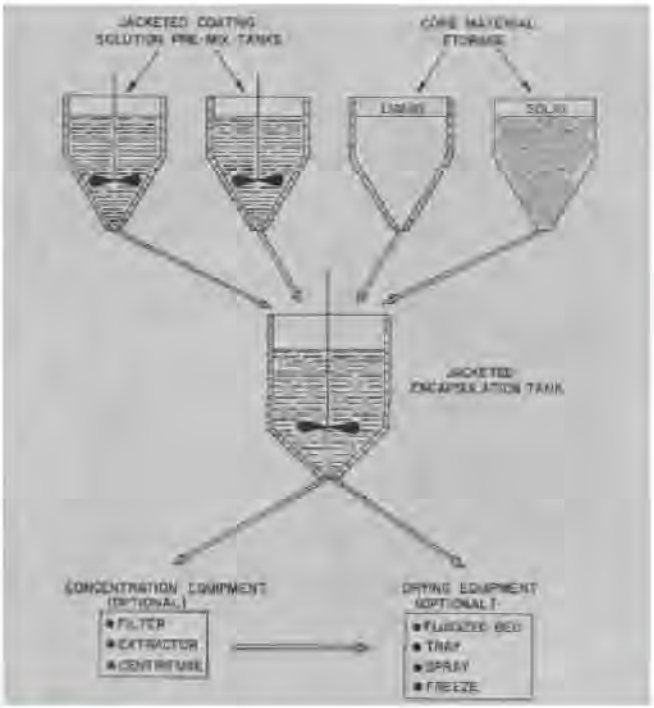


Figure 45-51. Production installation for the microencapsulation process (courtesy, NCR).

the general method for the preparation of pills does not apply to hexylresorcinol pills.

Previous editions of this text should be consulted for methods of pill preparation.

TROCHES

These forms of oral medication, also known as *lozenges* or *pastilles,* are discoid-shaped solids containing the medicinal agent in a suitably flavored base. The base may be a hard sugar candy, glycerinated gelatin, or the combination of sugar with sufficient mucilage to give it form. Troches are placed in the mouth, where they slowly dissolve, liberating the active ingredient. The drug involved can be an antiseptic, local anesthetic, antibiotic, antihistaminic, antitussive, analgesic, or a decongestant.

Formerly, troches were prepared extemporaneously by the pharmacist. The mass is formed by adding water slowly to a mixture of the powdered drug, powdered sugar, and a gum until a pliable mass is formed. Powdered acacia in 7% concentration gives sufficient adhesiveness to the mass. The mass is rolled out and the troche pieces cut out using a cutter, or else the mass is rolled into a cylinder and divided. Each piece is shaped and allowed to dry before dispensing.

If the active ingredient is heat-stable, it may be prepared in a hard candy base. Syrup is concentrated to the point at which it becomes a pliable mass, the active ingredient is added, and the mixture is kneaded while warm to form a homogeneous mass. The mass is worked gradually into a pipe form having the diameter desired for the candy piece, and the lozenges are cut from the pipe and allowed to cool. This is an entirely mechanical operation with equipment designed for this purpose.

If the active ingredient is heat-labile, it may be made into a lozenge preparation by compression. The granulation is prepared in a manner similar to that used for any compressed tablet. The lozenge is made using heavy compression equipment to give a tablet that is harder than usual, as it is desirable for the troche to dissolve or disintegrate slowly in the mouth. In the formulation of the lozenge the ingredients are chosen that will promote its slow-dissolving characteristics. Compression is gaining in popularity as a means of making troches and candy pieces because of the increased speeds of compression equipment. In cases in which holes are to be placed in troches or candy pieces, core-rod tooling is used (Fig 45-52). Core-rod tooling includes a rod centered on the lower punch around which the troche is compressed in the die cavity. The upper punch has an opening in its center for the core rod to enter during compression. It is evident that maximum accuracy is needed to provide alignment as the narrow punches are inserted into the die.

CACHETS

Related to capsules, inasmuch as they provide an edible container for the oral administration of solid drugs, cachets formerly were used in pharmacy. They varied in size from ¾ to ⅛ inch in diameter and consisted of two concave pieces of wafer made of flour and water. After one section was filled with the prescribed quantity of the medicinal agent, they were sealed tightly by moistening the margins and pressing them firmly together. When moistened with water, their character was changed entirely; they became soft, elastic, and slippery. Hence, they could be swallowed easily by floating them on water.

PELLETS

The term pellet is sometimes applied to small, sterile cylinders about 3.2 mm in diameter by 8 mm in length, which are formed by compression from medicated masses.[55] Whenever prolonged and continuous absorption of testosterone, estradiol, or desoxycorticosterone is desired, pellets of these potent hormones may be used by implantation.

MEDICATED CHEWING GUM

Chewing gum has been a widely popular form of confection that has its roots in ancient times. Only recently has its use as a drug delivery system become mainstream. Worldwide, there are commercially available chewing gums for use in smoking cessation, pain relief, and motion sickness. Chewing gum can also offer an advantage for localized delivery of drugs in the mouth, and is now being evaluated for these uses.[56–60]

Gums can be manufactured by a variety of mixing processes that incorporate several components into a sheet of product,

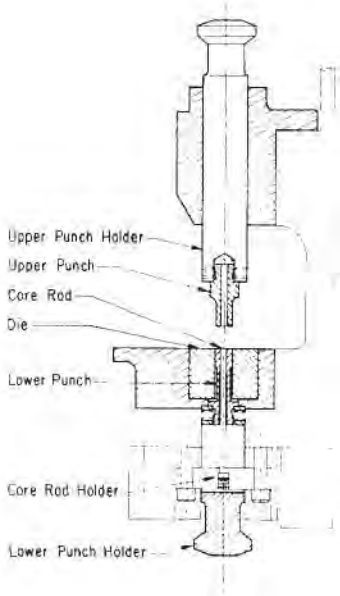


Figure 45-52. Core-rod tooling for compressing troches or candy pieces with hole in center (courtesy, Vector/Colton).

Table 45-6. Formula of a Medicated Chewing Gum

COMPONENT	CONENTRATION (%W/W)
Drug	0–40
Gum Base	20–45
Sweeteners	30–60
Softeners	0–10
Flavor(s)	1–5
Color(s)	0–1

whereby the units are stamped or cut from the rolled out sheet. A typical formulation for a chewing gum might be considered in Table 45-6.

Chewing gums can be made by compression and other processes, but the predominant method in use today is mixing, rolling and stamping of the finished units. After the finished units are completed, they can be film or sugar coated for better mouth feel or taste improvement.

RAPIDLY DISSOLVING TABLETS

Recently, a number of fast-dissolving tablets have been produced to rapidly deliver drugs for a variety of applications. One of the first solid dosage forms, Zydis (RP Scherer) used lyophilized technology to prepare the powder to dissolve quickly on the tongue. Since then, numerous technologies have been developed to give quick dissolution of the active in the mouth. Other technologies such as Lyoc (Farmalyoc), WOW-Tab (Yamanouchi), Flash-Dose (Biovail), Orasolv (CIMA) and DuraSolv (CIMA) have been used in commercialized products. There are some comparable benefits to one technology over the others, but the objective is still the same. These products have had some acceptance, and will have a place in formularies for years to come.

The challenges these dosage forms have had is durability during shipping, and changes to the drug substance that can occur during the lyophilization or manufacturing process. In addition, these products are best suited for drugs where there is a demonstrable benefit from very fast onset of activity of the drug. To date, there have been few clinical studies to show the significance of benefit of these products over standard immediate-release products.

TABLETS MADE BY ELECTROSTATIC DEPOSITION

The most common example of electrostatic deposition takes place every day in the office photocopy machine. The basic principle of electrostatic deposition is well-founded in basic physics: opposite charges attract. Deposition of material occurs when a pattern of charges is established on the substrate where the deposition is desired, and very fine particles with an opposite charge is placed near the substrate. The Sarnoff Research Laboratories developed an electro-static method of depositing and thereby coating solid surfaces with powder in a dry form. This technology was initially developed for phosphorus coating for cathode ray tubes, and was first applied to the manufacture of tablets by Delsys Corporation, now merged with Elan Corporation.[61–65]

Figure 45-53 illustrates this process. A substrate is chosen as the base for the deposit of particles. The charging is done us-

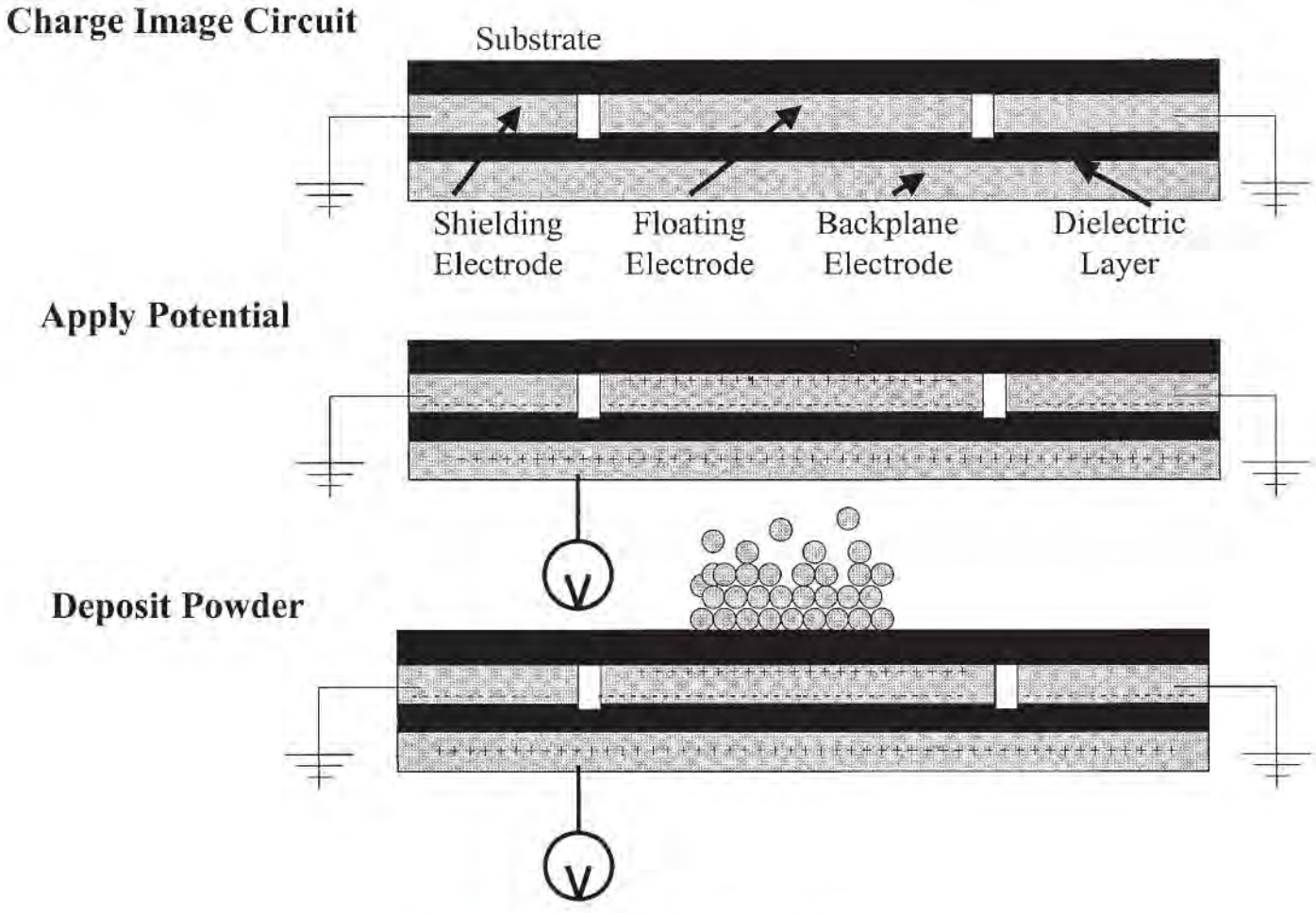


Figure 45-53. Electrostatic powder deposition process.

ing a three-layer structure that has a conducting backplane electrode, an insulating layer and a patterned conducting top electrode. Application of a positive voltage to the backplane electrode establishes a positive surface charge in the electrode. Charges that mirror the backplane charges are induced in the conductive top electrodes. In the floating electrodes, negative mirror charges induced by the backplane electrode leave uncompensated positive charges in the top surface of the floating electrode. By controlling the amount and strength of these positive charges, the rate of deposition and porosity of the resulting solid can be controlled.

The electrostatic process has several potential applications. First, the uniformity of ultra low dose drugs could be precisely achieved. Drugs with significant stability or incompatibility problems could be easily addressed without separate operations. Because little or no excipients are used in this process, the cost, storage and movement of materials in the modern manufacturing facility may be reduced significantly. In addition, it may be possible to have a final formulation designed and finalized much earlier in the development process. Currently, there are no commercial tablets using this technology, but one can imagine the considerable issues associated with the scale-up, validation and implementation of this technology.

THREE-DIMENSIONAL PRINTING OF TABLETS

Another technology that has been adapted for the manufacture of tablets is three-dimensional printing, called 3DP by Therics Corporation, the company to first apply this technology to pharmaceuticals. The technology is quite similar to ink-jet printer technology. It was improved by engineers at the Massachusetts Institute of Technology, and later at Therics.

Figures 45-54 and 45-55 illustrate three-dimensional printing.[66] In Figure 45-54, the basic system is shown. Powder is spread into a tray and binder droplets are precisely sprayed onto a substrate to form virtually any shape or design. A piston holding the unit changes position for each pass of the dispensing module, allowing for a build-up of the tablet. The process is repeated over and over until the desired shape is obtained. Using a tray that can accommodate many hundreds of powder wells, and hundreds of dispensing modules would be required to make this unit suitable for commercial manufacture. To this date, there are no commercial tablets made from this technology. However, it's versatility and complete freedom for design of novel solid dosage forms make this technology fascinating. Figure 45-55 illustrates this point showing a design on the computer screen, with a tablet completed next to it. In the cutaway section can be seen many programmed walls and empty compartments "constructed" within the confines of the tablet.

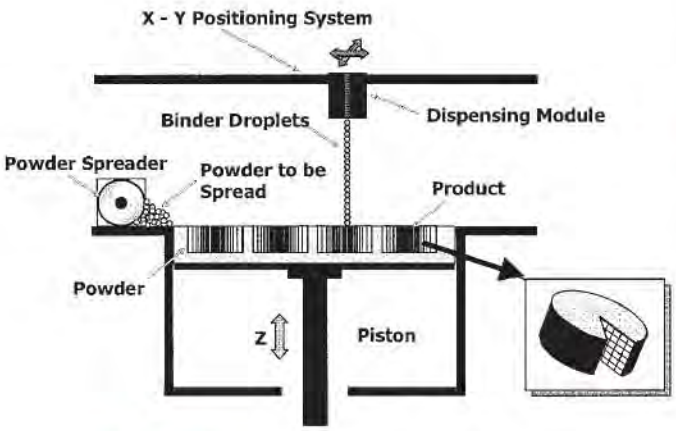


Figure 45-54. Three-dimensional printing process.

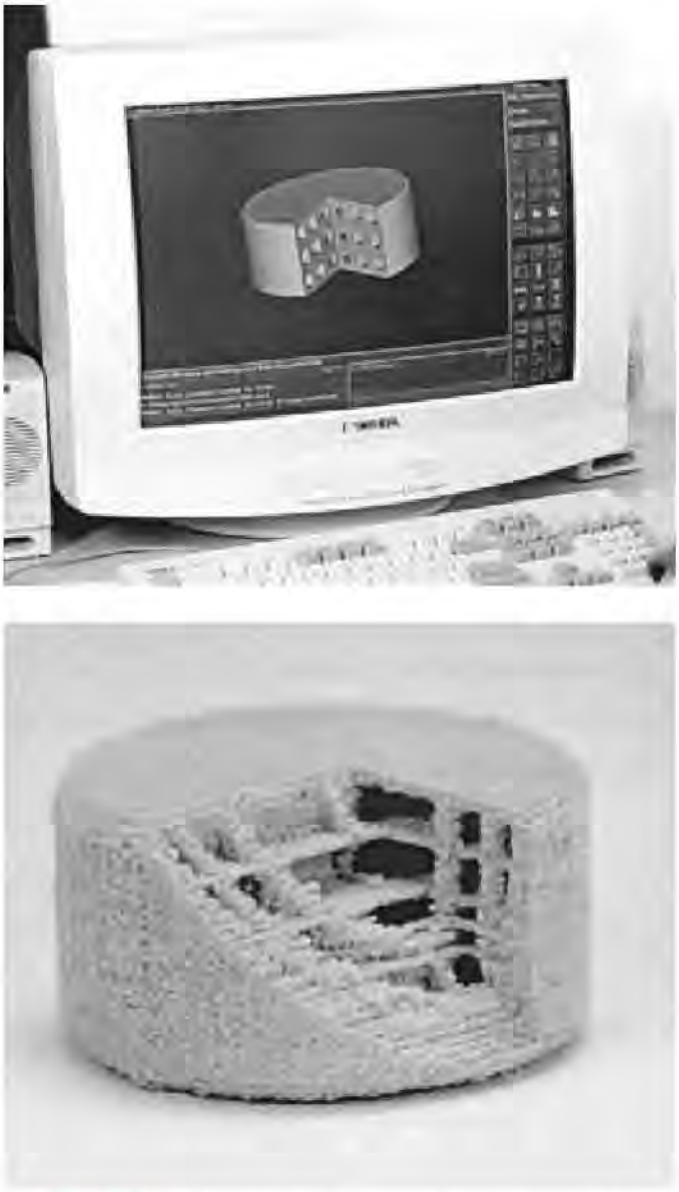


Figure 45-55. Design versatility of three-dimensional printing.

Three-dimensional printing technology has all of the advantages of electrostatic powder deposition, but has many more practical applications.

WEB-COATED SYSTEMS

In the early 1980s, Roche laboratories developed a system whereby sheets of a substrate were coated with drug and binder solution.[62] A number of sheets were then laminated, or glued together to form a complex, multi-layered sheet containing drug and various binder/excipient systems. The final laminate sheet was then punched to produce many dosage forms. This system was quite flexible, and was capable of producing various types of controlled-release, and combination products. However, due to it's impracticality, it was abandoned by Roche in the mid-1980s. It remains an important development, and is instructive from a historical perspective.

HOT-MELT EXTRUSION

Hot-melt extrusion technology has been extensively used as a processing technique in the plastics industry and is currently being investigated in the pharmaceutical arena as a novel tableting method. The process involves the active, suitable polymeric carrier, and other excipients being mixed in the molten state and then extruded through a die. The final product may take the form of a film, pipe, tube, or granule, depending on the shape of the die. A matrix is formed due to the melted polymer acting as a thermal binder. In addition to being anhydrous, this technology offers the advantage of tableting poorly compressible materials and manufacturing sustained-release tablets. The thermal stability of each material must be sufficient to withstand the production process.

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Current Good Manufacturing Practices

APPENDIX A

CFR Title 21 Food and Drugs

PART 211 CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

SUBPART A GENERAL PROVISIONS

211.3 (Definitions) The scope of the regulations are explained for human prescription and OTC drug products including drugs used to produce medicated animal feed. Reference is made to Part 210.3 of the chapter that gives definitions for all significant terms used in the regulations.

SUBPART B ORGANIZATION AND PERSONNEL

211.22 (Responsibilities of QC unit) Highlighted here is the assignment to the QC unit of total responsibility for ensuring that adequate systems and procedures exist and are followed to ensure product quality.

211.25 (Personnel qualifications) Personnel, either supervisory or operational, must be qualified by training and experience to perform their assigned tasks.

211.28 (Personnel responsibilities) The obligations of personnel engaged in the manufacture of drug products concerning their personal hygiene, clothing, and medical status are defined.

211.34 (Consultants) The qualifications of consultants must be sufficient for the project to which they are assigned.

SUBPART C BUILDINGS AND FACILITIES

Buildings and facilities can be considered acceptable only if they are suitable for their intended purpose and can be maintained. Construction concepts, such as air handling systems, lighting, eating facilities, and plumbing systems including water, sewage and toilet facilities, are outlined.

211.42 (Design and construction features)

211.44 (Lighting)

211.46 (Ventilation, air filtration, air heating and cooling)

211.48 (Plumbing)

211.50 (Sewage and refuse)

211.52 (Washing and toilet facilities)

211.56 (Sanitation)

211.58 (Maintenance)

SUBPART D EQUIPMENT

Equipment must be designed, constructed, of adequate size, suitably located, and able to be maintained and cleaned to be considered suitable for its intended use. Reference is made to the use of automatic equipment, data processors, and computers, highlighting the need for input/output verification and for proper calibration of recorders, counters, and other electrical or mechanical devices.

211.63 (Equipment design, size, and location)

211.65 (Equipment construction)

211.67 (Equipment cleaning and maintenance)

211.68 (Automatic, mechanical, and electronic equipment)

211.72 (Filters) Special note is made that the only filters to be used are those that do not release fibers into products.

SUBPART E CONTROL OF COMPONENTS AND DRUG PRODUCT CONTAINERS AND CLOSURES

211.80 (General requirements) Written procedures must be available that describe the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components (raw materials) and drug products.

211.82 (Receipt and storage of untested components, drug product containers, and closures)

211.84 (Testing and approval or rejection of components, drug product containers, and closures)

211.86 (Use of approved components, drug product containers, and closures) These shall be rotated so that the oldest approved stock is used first.

211.87 (Retesting of approved components, drug product containers, and closures) Materials that are subject to deterioration during storage should be retested at an appropriate time based on stability profiles.

211.89 (Rejected components, drug product containers, and closures) These shall be identified and controlled to prevent their use in manufacturing.

211.94 (Drug product containers and closures) Containers and closures (product contact materials) must protect the product and must be nonreactive with or additive to the product, suitable for their intended use, and controlled using written procedures.

SUBPART F PRODUCTION AND PROCESS CONTROLS

211.100 (Written procedures; deviations) Written standard operating procedures (SOPs) for each production process and control procedure are necessary. Any deviation from an SOP must be investigated, recorded, and approved prior to final product acceptance.

211.101 (Charge-in of components) The procedures used to formulate a batch shall be written and followed.

211.103 (Calculation of yield) Actual yields and theoretical yields shall be determined. All products are to be formulated to provide not less than 100% of the required amount of active ingredient. Records are to be maintained of each component and the quantity, which is incorporated into a batch.

211.105 (Equipment identification) Equipment shall be properly identified.

211.110 (Sampling and testing of in-process materials and drug products) Significant in-process steps are to be identified and appropriate sampling, testing, and approvals obtained before proceeding further in the production cycle. Rejected material must be controlled.

211.111 (Time limitations on production) If required, time limitations will be placed on in-process steps.

211.113 (Control of microbiological contamination) Appropriate procedures are to be prepared for the control and prevention of microbiological contamination. The sterilization process must be validated.

211.115 (Reprocessing) Reprocessing of product is allowed providing there are written procedures covering the methods and QC unit review to be used.

SUBPART G PACKAGING AND LABELING CONTROL

211.122 (Materials examination and usage criteria) Labeling and packaging materials are to be received, identified, stored, sampled, and tested following detailed written procedures.

211.125 (Labeling issuance) Strict control shall be exercised over labeling for use in drug product labeling operations

211.130 (Packaging and labeling operations) There shall be written procedures designed to ensure that correct labels, labeling, and packaging materials are used for drug products. Special controls must be exercised over labeling to ensure that only the correct labels are issued to packaging for a specific product and that the quantities used are reconciled with the quantity issued.

211.132 (Tamper-resistant packaging requirements for over-the-counter (OTC) human drug products) Provides details of tamper-resistant packaging.

211.134 (Drug product inspection) Packaged and labeled products shall be inspected for correct labels.

211.137 (Expiration dating) Following appropriate stability studies at prescribed temperature conditions, products on the market shall bear an expiration date to ensure that they are used within their expected shelf life.

SUBPART H HOLDING AND DISTRIBUTION

211.142 (Warehousing procedures) Describes the requirements for warehousing holding product under appropriate conditions of light, temperature, and humidity.

211.150 (Distribution procedures) Written procedures describing product distribution shall be prepared

SUBPART I LABORATORY CONTROLS

211.160 (General requirements) Describes the general requirements for laboratory control mechanisms.

211.165 (Testing and release for distribution) Concerns written procedures in the form of specifications, standards, sampling plans, and test procedures that are used in a laboratory for controlling components and finished drug products. Acceptance criteria for sampling and approval shall be adequate to support release of product for distribution.

211.166 (Stability testing) There shall be a written testing program designed to assess the stability characteristics of drug products. The results of this testing shall be used in assigning appropriate storage conditions and expiration dates.

211.167 (Special testing requirements) Special testing requirements are given for sterile and/or pyrogen-free ophthalmic ointment and controlled-release dosage form products.

211.170 (Reserve samples) Reserve sample quantity and retention times are described.

211.173 (Laboratory animals) Animals used in any testing shall be maintained and controlled in a manner suitable for use.

211.176 (Penicillin contamination) Drug products cannot be marketed if, when tested by a prescribed procedure, found to contain any detectable levels of penicillin.

SUBPART J RECORDS AND REPORTS

211.180 (General requirements) Describes record retention time and availability for inspection.

211.182 (Equipment cleaning and use log) A written record of major equipment cleaning, maintenance, and use shall be included in major equipment logs.

211.184 (Component, drug product container, closure, and labeling records) Deals with the issues of the receipt, testing, and storage of components, drug product containers, and closures. Details the various records and documents that should be generated during the manufacture of drug products and that are to be available for review.

211.186 (Master production and control records) A master production record must be prepared for each drug product, describing all aspects of its manufacture, packaging, and control. Individual batch records are derived from this approved master.

211.188 (Batch production and control records) Calls for batch production and control records with information about the production and control of each batch

211.192 (Production record review) All drug product batch records shall be reviewed and approved by the QC unit (QA/QC) before the batch is released.

211.194 (Laboratory records) Complete records of any laboratory testing shall be maintained to include raw data, test procedures and results, equipment calibration, and stability testing.

211.196 (Distribution records) Distribution records include warehouse shipping logs, invoices, bills of lading, and all documents associated with distribution. These records should provide all the information necessary to trace lot distribution to facilitate product retrieval if necessary.

211.198 (Complaint files) Records of complaints received from consumers and professionals are to be maintained along with the report of their investigation and response.

SUBPART K RETURNED AND SALVAGED DRUG PRODUCTS

211.204 (Returned drug products) Records are to be maintained of drug products returned from distribution channels and the reason for their return. These data can be used as part of the total lot accountability, should the need arise, to trace its distribution and/or for its recall.

211.208 (Drug product salvaging) Drug products that have been stored improperly are not to be salvaged.

CHAPTER 52

Stability of Pharmaceutical Products

Patrick B O'Donnell, PhD
Allan D Bokser, PhD

Stability of a pharmaceutical product may be defined as the capability of a particular formulation, in a specific container/closure system, to remain within its physical, chemical, microbiological, therapeutic, and toxicological specifications. Assurances that the packaged product will be stable for its anticipated shelf life must come from an accumulation of valid data on the drug in its commercial package. These stability data involve selected parameters that, taken together, form the stability profile. Pharmaceutical products are expected to meet their specifications for identity, purity, quality, and strength throughout their defined storage period at specific storage conditions.

The stability of a pharmaceutical product is investigated throughout the various stages of the development process. The stability of a drug substance is first assessed in the preformulation stage. At this stage, pharmaceutical scientists determine the drug substance and its related salts stability/compatibility with various solvents, buffered solutions, and excipients considered for formulation development. Optimization of a stable formulation of a pharmaceutical product is built upon the information obtained from the preformulation stage and continues during the formulation development stages.

Typically, the first formulation development stage is the preparation of a "first in human" formulation which is often a non-elegant formulation optimized for short-term dose-ranging clinical studies. The second major formulation development stage occurs to support Phase II and early Phase III clinical studies. The pharmaceutical product developed at this stage is usually the prototype for the commercial product. Therefore, the pharmaceutical product will be formulated based in part on the stability information obtain from the previous formulations and must meet stability requirements for longer-term clinical studies. The final formulation development stage is for the commercial pharmaceutical product. In addition to building on the clinical requirements of the drug, the commercial pharmaceutical product must also incorporate the commercial or the final market image of the product, which includes the container closure system. The stability of this product must be demonstrated to the appropriate regulatory agencies in order to assign an expiration date for the product.

Once a pharmaceutical product has gained regulatory approval and is marketed, the pharmacist must understand the proper storage and handling of the drug. In some cases, a pharmacist may need to prepare stable compounded preparations from this product. It is the responsibility of the pharmacist, via the information of the manufacturer, to instruct the patient in the proper storage and handling of the drug product. The impact of a drug product with a poor stability profile could delay approval, affect the safety and efficacy of the drug, and/or cause product recall.

Much has been written about the development of a stable pharmaceutical product. Comprehensive treatments of all aspects of pharmaceutical product stability has been published by Lintner,[1] Connors et al,[2] and more recently Carstensen[3]. This chapter will outline the appropriate steps from preformulation to drug approval to assure that the pharmaceutical product developed is stable. Requirements for compounded products will also be discussed.

The USP defines the stability of a pharmaceutical product as "extent to which a product retains, within specified limits, and throughout its period of storage and use (ie, its shelf-life), the same properties and characteristics that it possessed at the time of its manufacture." There are five types of stability that must be considered for each drug.

Type of Stability	Conditions Maintained Throughout the Shelf-Life of the Drug Product
Chemical	Each active ingredient retains its chemical integrity and labeled potency, within the specified limits.
Physical	The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability are retained.
Microbiological	Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents that are present retain effectiveness within the specified limits.
Therapeutic	The therapeutic effect remains unchanged.
Toxicological	No significant increase in toxicity occurs.

Stability of a drug also can be defined as the time from the date of manufacture and packaging of the formulation until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously. Although there are exceptions, 90% of labeled potency generally is recognized as the minimum acceptable potency level. Expiration dating is defined, therefore, as the time in which a drug product in a specific packaging configuration will remain stable when stored under recommended conditions.

An expiration date, which is expressed traditionally in terms of month and year, denotes the last day of the month. The expiration date should appear on the immediate container and the outer retail package. However, when single-dose containers are packaged in individual cartons, the expiration date may be

placed on the individual carton instead of the immediate product container. If a dry product is to be reconstituted at the time of dispensing, expiration dates are assigned to both the dry mixture and the reconstituted product. Tamper-resistant packaging is to be used where applicable.

One type of time-related stability failure is a decrease in therapeutic activity of the preparation to below labeled content. A second type of stability failure is the appearance of a toxic substance, formed as a degradation product upon storage of the formulation. The numbers of published cases reflecting this second type are few. However, it is possible, though remote, for both types of stability failures to occur simultaneously within the same pharmaceutical product. Thus, the use of stability studies with the resulting application of expiration dating to pharmaceuticals is an attempt to predict the approximate time at which the probability of occurrence of a stability failure may reach an intolerable level. This estimate is subject to the usual Type 1 or alpha error (setting the expiration too early so that the product will be destroyed or recalled from the market appreciably earlier than actually is necessary) and the Type 2 or beta error (setting the date too late so that the failure occurs in an unacceptably large proportion of cases). Thus, it is obligatory that the manufacturer clearly and succinctly define the method for determining the degree of change in a formulation and the statistical approach to be used in making the shelf-life prediction. An intrinsic part of the statistical methodology must be the statements of value for the two types of error. For the safety of the patient a Type 1 error can be accepted, but not a Type 2 error.

REGULATORY REQUIREMENTS

Stability study requirements and expiration dating are covered in the Current Good Manufacturing Practices (cGMPs),[4] the USP,[5] and the FDA guidelines.[6]

GOOD MANUFACTURING PRACTICES—The GMPs[4] state that there shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used to determine appropriate storage conditions and expiration dating. The latter is to ensure that the pharmaceutical product meets applicable standards of identity, strength, quality, and purity at time of use. These regulations, which apply to both human and veterinary drugs, are updated periodically in light of current knowledge and technology.

COMPENDIA—The compendia also contain extensive stability and expiration dating information. Included are a discussion of stability considerations in dispensing practices and the responsibilities of both the pharmaceutical manufacturer and the dispensing pharmacist. It now is required that product labeling of official articles provide recommended storage conditions and an expiration date assigned to the specific formulation and package. Official storage conditions as defined by the USP 26[5] are as follows: *Cold* is any temperature not exceeding 8°C, and *refrigerator* is a cold place where the temperature is maintained thermostatically between 2 and 8°C. A *freezer* is a cold place maintained between −25 and −10°C. *Cool* is defined as any temperature between 8 and 15°C, and *room temperature* is that temperature prevailing in a working area. *Controlled room temperature* is that temperature maintained thermostatically between 20 and 25°C. *Warm* is any temperature between 30 and 40°C, while *excessive heat* is any heat above 40°C. Should freezing subject a product to a loss of potency or to destructive alteration of the dosage form, the container label should bear appropriate instructions to protect the product from freezing. When no specific storage instructions are given in a USP monograph, it is understood that the product's storage conditions shall include protection from moisture, freezing, and excessive heat.

As is noted above in USP 26, the definition of controlled room temperature was a "temperature maintained thermostatically between 20 and 25°C (68 and 77°F)." This definition was established to harmonize with international drug standards efforts. The usual or customary temperature range is identified as 20 to 25°C, with the possibility of encountering excursions in the 15 to 30°C range and with the introduction the mean kinetic temperature (MKT).

The mean kinetic temperature is calculated using the following equation:

$$T_k = \left[\frac{\Delta H/R}{-In\left(\frac{e^{-\Delta H/RT_1} + e^{-\Delta H/RT_2} + \ldots + e^{-\Delta H/RT_{n-1}} + e^{-\Delta H/RT_n}}{n} \right)} \right]$$

in which T_k is the mean kinetic temperature; ΔH is the heat of activation, 83.144kJ·mole^{-1}; R is the universal gas constant, 8.3144×10^{-3} kJ· mole^{-1}· degree^{-1}; T_1 is the value for the temperature (in degrees Kelvin [°K]) recorded during the first time period, T_2 is the value for the temperature recorded during the second time period, eg, second week; T_{n-1} is the value of the second to last time period, and T_n is the value for the temperature recorded during the nth time period. Typically, the time period is in days or weeks. The mean kinetic temperature determines the thermal exposure of a material. This allows an acceptable estimation to assess if a temperature excursion (or series of excursions) adversely affected a material.

FDA Guidelines provide recommendations for:

1. The design of stability studies to establish appropriate expiration dating periods and product storage requirements
2. The submission of stability information for investigational new drugs, biologicals, new drug applications, and biological product license applications

Thus, the guidelines represent a framework for the experimental design and data analysis as well as the type of documentation needed to meet regulatory requirements in the drug-development process.

Table 52-1. Stability Protocols

CONDITIONS	MINIMUM TIME PERIOD AT SUBMISSION
Long-term testing 25°C ± 2°C/60% ± 5% RH	12 mo
Accelerated testing 40°C ± 2°C/75% ± 5% RH	6 mo
Alternate testing[a] 30°C ± 2°C/65% ± 5% RH	12 mo

[a]Required if *significant change* occurs during 6-mo storage under conditions of accelerated testing.

Example Stability Pull Schedule for a Solid Oral Dose for Zone I and II

STORAGE CONDITIONS	DURATIONS (MONTHS)								
	0	1	3	6	9	12	18	24	36
25°C/60% RH	R*		X	X	X	X, Y	X	X	X
30°C/65% RH			O	O	O	O			
40°C/75% RH		X	X	X, Y					

*From Release testing if testing is within 30 days of stability set down.

R = Release Tests
- Appearance (visual)
- Identity
- Assay (HPLC)
- Impurities (HPLC)
- Dissolution (USP <711>)
- Moisture Content (Karl Fischer)
- Uniformity of Dosage Unit

X = Tests at Every Stability Pull
- Appearance (visual)
- Assay (HPLC)
- Impurities (HPLC)
- Dissolution (USP <711>)

O = Pull and test only after 40°C/75% is out of specification
- Appearance (visual)
- Assay (HPLC)
- Impurities (HPLC)
- Dissolution (USP <711>)

Y = Additional tests periodically performed
- Moisture Content (Karl Fischer)

FDA Guidelines, however, has been reevaluated and revised significantly in the last few years, with the aim of harmonizing the technical requirements for the registration of pharmaceuticals worldwide. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brought together regulatory authorities and experts from the pharmaceutical industry from three regions of the world; Europe, Japan, and the US. The first conference (ICH1) took place in November 1991 in Brussels, and the second conference (ICH2) in Orlando, FL, in October 1993. These conferences provided an open forum for discussion and resulted in the creation of an extensive set of guidelines dealing with the many aspects of safety, quality, and efficacy of medicinal products. The ICH Harmonized Tripartite Guideline provides a general indication on the requirements for *Stability Testing of New Drug Substances and Products*. The main thrust of the stability guideline centers around criteria for setting up stability protocols, shown in Table 52-1 and the example Stability Pull Schedule.

The guidelines were published in a draft form in the *Federal Register*, April 16, 1993. The final guidelines were published in 1994, with implementation of the guidelines occurring with Registration Applications after January 1, 1998. Revision 1 of the guidance was published in August 2001. Online computer can now access a complete listing of FDA publications and guidances. To view the publications, go to http://www.fda.gov/cder/guidance/index.htm.

PRODUCT STABILITY

Many factors affect the stability of a pharmaceutical product and include the stability of the active ingredient(s), the potential interaction between active and inactive ingredients, the manufacturing process, the dosage form, the container-liner-closure system, and the environmental conditions encountered during shipment, storage and handling, and length of time between manufacture and usage.

Classically, pharmaceutical product stability evaluations have been separated into studies of chemical (including biochemical) and physical stability of formulations. Realistically, there is no absolute division between these two arbitrary divisions. Physical factors, such as heat, light, and moisture, may initiate or accelerate chemical reactions, while every time a measurement is made on a chemical compound. Physical dimensions are included in the study.

In this treatment, physical and chemical stability are discussed along with those dosage form properties that can be measured and are useful in predicting shelf life. The effect of various physical and chemical phenomena of pharmaceuticals also is treated.

Knowledge of the physical stability of a formulation is very important for three primary reasons. First, a pharmaceutical product must appear fresh, elegant, and professional, for as long as it remains on the shelf. Any changes in physical appearance such as color fading or haziness can cause the patient or consumer to lose confidence in the product. Second, since some products are dispensed in multiple-dose containers, uniformity of dose content of the active ingredient over time must be ensured. A cloudy solution or a broken emulsion can lead to a non-uniform dosage pattern. Third, the active ingredient must be available to the patient throughout the expected shelf life of the preparation. A breakdown in the physical system can lead to non-availability or "dose dumping" of the medication to the patient. In the case of metered-dose inhaler pulmonary aerosols, particle aggregation may result in inadequate lung deposition of the medication.

The chemical causes of drug deterioration have been classified as incompatibility, oxidation, reduction, hydrolysis, racemization, and other mechanisms. In the latter category, decarboxylation, deterioration of hydrogen peroxide and hypochlorites, and the formation of precipitates have been included.

PHARMACEUTICAL DOSAGE FORMS

As the various pharmaceutical dosage forms present unique stability problems, they are discussed separately in the following section.

TABLETS—Stable tablets retain their original size, shape, weight, and color under normal handling and storage conditions throughout their shelf life. In addition, the *in vitro* availability of the active ingredients should not change appreciably with time.

Excessive powder or solid particles at the bottom of the container, cracks or chips on the face of a tablet, or appearance of crystals on the surface of tablets or on container walls are indications of physical instability of uncoated tablets. Hence, the effect of mild, uniform, and reproducible shaking and tumbling of tablets should be studied. The recommended test for such studies is the determination of tablet friability as described in the USP. Tablet Friability <1216> describes the recommended apparatus and the test procedure. After visual observation of the tablets for chips, cracks, and splits, the intact tablets are sorted and weighed to determine the amount of material worn away by abrasion. In general a maximum weight loss of not more than 1% of the weight of the tablets being tested is considered acceptable for most products. The results of these tests are comparative rather than absolute and should be correlated with actual stress experience. Packaged tablets also should be subjected to cross-country shipping tests as well as to various *drop tests*.

Tablet hardness (or resistance to crushing or fracturing) can be assessed by commercially available hardness testers. As results will vary with the specific make of the test apparatus used, direct comparison of results obtained on different instruments may not necessarily be made. Thus, the same instrument should be used consistently throughout a particular study.

Color stability of tablets can be followed by an appropriate colorimeter or reflectometer with heat, sunlight, and intense artificial light employed to accelerate the color deterioration. Caution must be used in interpreting the elevated temperature data, as the mechanism for degradation at that temperature may differ from that at a lower temperature. It is not always proper to assume that the same changes will occur at elevated temperatures as will be evidenced later at room temperature. Cracks, mottling, or tackiness of the coating indicates evidence of instability of coated tablets.

For tablets containing the more insoluble active ingredients, the results of dissolution tests are more meaningful than disintegration results for making bioavailability predictions. Dissolution-rate tests should be run in an appropriate medium such as artificial gastric and/or intestinal fluid at 37°. When no significant change (such as a change in the polymorphic form of the crystal) has occurred, an unaltered dissolution-rate profile of a tablet formulation usually indicates constant *in vivo* availability.

Uniformity of weight, odor, texture, drug and moisture contents, and humidity effect also are studied during a tablet stability test.

GELATIN CAPSULES—Hard gelatin capsules are the type used by pharmaceutical manufacturers in the production of the majority of their capsule products. The pharmacist in the extemporaneous compounding of prescriptions may also use hard gelatin capsules. Soft gelatin capsules are prepared from shells of gelatin to which glycerin or a polyhydric alcohol such as sorbitol has been added to render the gelatin elastic or plastic-like. Gelatin is stable in air when dry but is subject to microbial decomposition when it becomes moist or when it is maintained in aqueous solution. Normally hard gelatin capsules contain between 13% and 16% moisture. If stored in a high humidity environment capsule shells may soften, stick together, or become distorted and lose their shape. On the other hand, in an environment of extreme dryness gelatin capsules may harden and crack under slight pressure. Gelatin capsules should be protected from sources of microbial contamination.

Encapsulated products, like all other dosage forms, must be packaged properly.

Because moisture may be absorbed or released by gelatin capsules depending on the environmental conditions, capsules offer little physical protection to hygroscopic or deliquescent materials enclosed within a capsule when stored in an area of high humidity. It is not uncommon to find capsules packaged in containers along with a packet of desiccant material as a precautionary measure.

Both hard and soft gelatin capsules exposed to excessive heat and moisture may exhibit delayed or incomplete dissolution due to cross-linking of the gelatin in the capsule shell. The cross-linking of gelatin capsules is an irreversible chemical reaction. Cross-linking may also occur in capsules that are exposed to aldehydes and peroxides. Although cross-linked capsules may fail dissolution due to pellicle formation, digestive enzymes will dissolve the capsules. For hard or soft gelatin capsules that do not conform to the dissolution specification, the dissolution test may be repeated with the addition of enzymes. Where water or a medium with a pH less than 6.8 is specified as the medium in the individual monograph, the same medium specified may be used with the addition of purified pepsin that results in an activity of 750,000 units or less per 1000 mL. For media with a pH of 6.8 or greater, pancreatin can be added to produce not more than 1750 USP units of protease activity per 1000 mL.

SUSPENSIONS—A stable suspension can be redispersed homogeneously with moderate shaking and can be poured easily throughout its shelf life, with neither the particle-size distribution, the crystal form, nor the physiological availability of the suspended active ingredient changing appreciably with time.

Most stable pharmaceutical suspensions are flocculated; that is, the suspended particles are bonded together physically to form a loose, semi rigid structure. The particles are said to uphold each other while exerting no significant force on the liquid. Sedimented particles of a flocculated suspension can be redispersed easily at any time with only moderate shaking.

In nonflocculated suspensions, the particles remain as individuals unaffected by neighboring particles and are affected only by the suspension vehicle. These particles, which are smaller and lighter, settle slowly, but once they have settled, often form a hard, difficult-to-disperse sediment. Nonflocculated suspensions can be made acceptable by decreasing the particle size of the suspended material or by increasing the density and viscosity of the vehicle, thus reducing the possibility of settling.

When studying the stability of a suspension, first determine with a differential manometer if the suspension is flocculated. If the suspension is flocculated, the liquid will travel the same distance in the two side arms. With nonflocculated suspensions, the hydrostatic pressures in the two arms are unequal; hence, the liquids will be at different levels.

The history of settling of the particles of a suspension may be followed by a Brookfield viscometer fitted with a Helipath attachment. This instrument consists of a rotating T-bar spindle that descends slowly into the suspension as it rotates. The dial reading on the viscometer is a measure of the resistance that the spindle encounters at various levels of the sedimented suspension. This test must be run only on fresh, undisturbed samples.

An electronic particle counter and sizer, such as a Coulter counter, or a microscope may be used to determine changes in particle-size distribution. Crystal form alterations may be detected by microscopic, near-IR or Raman examination and, when suspected, must be confirmed by x-ray powder diffraction.

All suspensions should be subjected to cycling temperature conditions to determine the tendency for crystal growth to occur within the suspension. Shipping tests, ie, transporting bottles across the country by rail or truck are also used to study the stability of suspensions.

SOLUTIONS—A stable solution retains its original clarity, color, and odor throughout its shelf life. Retention of clarity of a solution is a main concern of a physical stability program. As visual observation alone under ordinary light is a poor test of clarity, a microscope light should be projected through a diaphragm into the solution. Undissolved particles will scatter the light, and the solution will appear hazy. While the Coulter counter also can be used, light-scattering instruments are the most sensitive means of following solution clarity.

Solutions should remain clear over a relatively wide temperature range such as 4 to 47°C. At the lower range an ingredient may precipitate due to its lower solubility at that temperature, while at the higher temperature the flaking of particles from the glass containers or rubber closures may destroy homogeneity. Thus, solutions should be subjected to cycling temperature conditions.

The stability program for solutions also should include a study of pH changes, especially when the active ingredients are soluble salts of insoluble acids or bases. Among other tests are observations for changes in odor, appearance, color, taste, light-stability, redispersibility, suspendibility, pourability, viscosity, isotonicity, gas evolution, microbial stability, specific gravity, surface tension, and pyrogen content, in the case of parenteral products.

When solutions are filtered, the filter medium may absorb some of the ingredients from the solution. Thus, the same type of filter should be used for preparing the stability samples as will be used to prepare the production-size batches.

For dry-packaged formulations reconstituted prior to use, the visual appearance should be observed on both the original dry material and on the reconstituted preparation. The color and odor of the cake, the color and odor of the solution, the moisture content of the cake, and the rate of reconstitution should be followed as a part of its stability profile.

EMULSIONS—A stable emulsion can be redispersed homogeneously to its original state with moderate shaking and can be poured at any stage of its shelf life. Although most of the important pharmaceutical emulsions are of the oil in water (O/W) type, many stability test methods can be applied to either an O/W or water in oil (W/O) emulsion.

Two simple tests are used to screen emulsion formulations. First, heating to 50 to 70°C and observing its gross physical stability either visually or by turbidimetric measurements can determine the stability of an emulsion. Usually the emulsion that is the most stable to heat is the one most stable at room temperature. However, this may not be true always, because an emulsion at 60°C may not be the same as it is at room temperature. Second, the stability of the emulsion can be estimated by the *coalescence time* test. Although this is only a rough quantitative test, it is useful for detecting gross differences in emulsion stability at room temperature.

Emulsions also should be subjected to refrigeration temperatures. An emulsion stable at room temperature has been found to be unstable at 4°C. It was reasoned that an oil-soluble emulsifier precipitated at the lower temperature and disrupted the system. An emulsion chilled to the extent that the aqueous base crystallizes is damaged irreversibly.

The ultracentrifuge also is used to determine emulsion stability. When the amount of separated oil is plotted against the time of centrifugation, a plateau curve is obtained. A linear graph results when the oil flotation (creaming) rate is plotted versus the square of the number of centrifuge revolutions per minute. The flotation rate is represented by the slope of the line resulting when the log distance of emulsion-water boundary from the rotor center is plotted against time for each revolution per minute.

For stability studies, two batches of an emulsion should be made at one time on two different sizes of equipment. One should be a bench-size lot and the other a larger, preferably production-size, batch. Different types of homogenizers produce different results, and different sizes of the same kind of homogenizer can yield emulsions with different characteristics.

OINTMENTS—Ointments have been defined as high-viscosity suspensions of active ingredients in a non-reacting

vehicle. A stable ointment is one that retains its homogeneity throughout its shelf-life period. The main stability problems observed in ointments are *bleeding* and changes in consistency due to aging or changes in temperature. When fluid components such as mineral oil separate at the top of an ointment, the phenomenon is known as *bleeding* and can be observed visually. Unfortunately, as there is no known way to accelerate this event, the tendency to *bleed* cannot be predicted.

An ointment that is too soft is messy to use, while one that is very stiff is difficult to extrude and apply. Hence, it is important to be able to define quantitatively the consistency of an ointment. This may be done with a penetrometer, an apparatus that allows a pointed weight to penetrate into the sample under a measurable force. The depth of the penetration is a measure of the consistency of an ointment. Consistency also can be measured by the Helipath attachment to a high-viscosity viscometer or by a Burrell Severs rheometer. In the latter instrument, the ointment is loaded into a cylinder and extruded with a measured force. The amount extruded is a measure of the consistency of the ointment.

Ointments have a considerable degree of structure that requires a minimum of 48 hours to develop after preparation. As rheological data on a freshly made ointment may be erroneous, such tests should be performed only after the ointment has achieved equilibrium. Slight changes in temperature (1 or 2°C) can affect the consistency of an ointment greatly; hence, rheological studies on ointments must be performed only at constant and controlled temperatures.

Among the other tests performed during the stability study of an ointment are a check of visual appearance, color, odor, viscosity, softening range, consistency, homogeneity, particle-size distribution, and sterility. Undissolved components of an ointment may change in crystal form or in size with time. Microscopic examination or an x-ray diffraction measurement may be used to monitor these parameters.

In some instances it is necessary to use an ointment base that is less than ideal, to achieve the required stability. For example, drugs that hydrolyze rapidly are more stable in a hydrocarbon base than in a base containing water, even though they may be more effective in the latter.

TRANSDERMAL PATCHES—A typical transdermal patch consists of a protective backing, a matrix containing active drug, an adhesive that allows the patch to adhere to the skin, and a release liner to protect the skin adhering adhesive. Therefore, the transdermal patch must deliver drug as labeled, adhere properly to both the backing and to the patient's skin. In addition, the transdermal patch must be pharmaceutically elegant through the shelf life of the product. For a transdermal patch, this means that the release line peels easily with minimal transfer of adhesive onto the release liner and that the adhesive does not ooze from the sides of the patch. Therefore, the typical stability related tests for transdermal patches are, appearance, assay, impurities, drug release USP<724> and, backing peel force.

METERED-DOSE AEROSOLS DRUG PRODUCTS—A metered dose inhalation product consists of an aerosol can containing a propellant, a drug and a mouthpiece used to present an aerosolized drug to the patient. There are many drug contact components in a metered-dose inhalation product. Therefore, the drug may be in contact with materials that could allow plasticizer leach into the drug. The typical stability related tests for metered-dose aerosols include appearance, assay, impurities, plume geometry, emitted dose, particle size distribution of the emitted dose, and number of doses per unit. In addition, stability studies on leachables may be required. Shelf life of metered-dose aerosols drug products may also be dependent on the orientation that the drug product is stored. Typically most canisters type product are tested at least in the upright orientation.

DRY-POWDERED INHALATION PRODUCTS—A dry-powdered inhalation product consists of drug with excipients delivered in a dry powdered form. The delivery system for a dry-powdered inhalation product may be a separate device or integrated with the active. A dry-powdered dosage must reproducibly deliver a specific amount of drug at a particle size that can be deposited into the lungs. Particles too large will get trapped in the throats and particles too small will just be carried out of the lungs on the next expiration. The typical stability related tests for dry powder inhalation products include appearance, assay, impurities, emitted dose, particle size distribution of the emitted dose, and water content.

NASAL INHALATION PRODUCTS—A nasal inhalation product consists of drug with excipients delivered from a delivery system. The delivery system for a nasal inhalation product may be a separate device or integrated with the active. A nasal inhalation product must reproducibly deliver a specific amount of drug at a particle size and plume that can be deposited into the nasal membrane. Particles too large will not be absorbed into nasal membrane or run out of the nose; and poor spray pattern will deposit the drug ineffective in the nasal cavity. The typical stability related tests for nasal inhalation products include appearance, assay, impurities, spray content uniformity, particle (droplet) size distribution of the emitted dose, spray pattern or /and plume geometry, leachables, weight loss and preservative content. Sterility and microbial testing may be required periodically for stability testing.

INCOMPATIBILITY

Typically, physicochemical stability is assessed at the preformulation stage of development. A drug substance candidate is treated with acid, base, heat, light, and oxidative conditions to assess its inherit chemical stability. Binary mixtures of the drug substance with individual excipients are also investigated at the preformulation stage. These tests are performed to determine the drug substance sensitivity to degrade or react with common pharmaceutical excipients. The most common reactions observed for drug substances from these tests include: hydrolysis, epimerization (racemization), decarboxylation, dehydration, oxidation, polymerization, photochemical decomposition, and addition. All drug substances have the potential to degrade by at least one of the reactions mentioned above. With an understanding of the stability/reactivity of a drug substance in the preformulation stage, it is possible to formulate the drug product to minimize drug decomposition. Numerous examples are described in other sections of this book, and the literature is replete with illustrations.

While undesirable reactions between two or more drugs are said to result in a *physical, chemical,* or *therapeutic* incompatibility, physical incompatibility is somewhat of a misnomer. It has been defined as a physical or chemical interaction between two or more ingredients that leads to a visibly recognizable change. The latter may be in the form of a gross precipitate, haze, or color change.

On the other hand, a chemical incompatibility is classified as a reaction in which a visible change is not necessarily observed. Since there is no visible evidence of deterioration, this type of incompatibility requires trained, knowledgeable personnel to recognize it.

A therapeutic incompatibility has been defined as an undesirable pharmacological interaction between two or more ingredients that leads to

1. Potentiation of the therapeutic effects of the ingredients
2. Destruction of the effectiveness of one or more of the ingredients
3. Occurrence of a toxic manifestation within the patient.

REACTION KINETICS

An understanding of reaction kinetics is important in determining the shelf life of a product.

CHEMICAL REACTIONS

The most frequently encountered chemical reactions, which may occur within a pharmaceutical product, are described below.

OXIDATION-REDUCTION—Oxidation is a prime cause of product instability, and often, but not always, the addition of oxygen or the removal of hydrogen is involved. When molecular oxygen is involved, the reaction is known as auto-oxidation because it occurs spontaneously, though slowly, at room temperature.

Oxidation, or the loss of electrons from an atom, frequently involves free radicals and subsequent chain reactions. Only a very small amount of oxygen is required to initiate a chain reaction. In practice, it is easy to remove most of the oxygen from a container, but very difficult to remove it all. Hence, nitrogen and carbon dioxide frequently are used to displace the headspace air in pharmaceutical containers to help minimize deterioration by oxidation.

As an oxidation reaction is complicated, it is difficult to perform a kinetic study on oxidative processes within a general stability program. The redox potential, which is constant and relatively easy to determine, can, however, provide valuable predictive information. In many oxidative reactions, the rate is proportional to the concentration of the oxidizing species but may be independent of the concentration of the oxygen present. The rate is influenced by temperature, radiation, and the presence of a catalyst. An increase in temperature leads to an acceleration in the rate of oxidation. If the storage temperature of a preparation can be reduced to 0 to 5°C, usually it can be assumed that the rate of oxidation will be at least halved.

The molecular structures most likely to oxidize are those with a hydroxyl group directly bonded to an aromatic ring (eg, phenol derivatives such as catecholamines and morphine), conjugated dienes (eg, vitamin A and unsaturated free fatty acids), heterocyclic aromatic rings, nitroso and nitrite derivatives, and aldehydes (eg, flavorings). Products of oxidation usually lack therapeutic activity. Visual identification of oxidation, for example, the change from colorless epinephrine to its amber colored products, may not be visible in some dilutions or to some eyes.

Oxidation is catalyzed by pH values that are higher than optimum, polyvalent heavy metal ions (eg, copper and iron), and exposure to oxygen and UV illumination. The latter two causes of oxidation justify the use of antioxidant chemicals, nitrogen atmospheres during ampul and vial filling, opaque external packaging, and transparent amber glass or plastic containers.

Trace amounts of heavy metals such as cupric, chromic, ferrous, or ferric ions may catalyze oxidation reactions. As little as 0.2 mg of copper ion per liter considerably reduces the stability of penicillin. Similar examples include the deterioration of epinephrine, phenylephrine, lincomycin, isoprenaline, and procaine hydrochloride. Adding chelating agents to water to sequester heavy metals and working in special manufacturing equipment (eg, glass) are some means used to reduce the influence of heavy metals on a formulation. Parenteral formulations should not come in contact with heavy metal ions during their manufacture, packaging, or storage.

Hydronium and hydroxyl ions catalyze oxidative reactions. The rate of decomposition for epinephrine, for example, is more rapid in a neutral or alkaline solution with maximum stability (minimum oxidative decomposition) at pH 3.4. There is a pH range for maximum stability for any antibiotic and vitamin preparation, which usually can be achieved by adding an acid, alkali, or buffer.

Oxidation may be inhibited by the use of antioxidants, called negative catalysts. They are very effective in stabilizing pharmaceutical products undergoing a free-radical-mediated chain reaction. These substances, which are easily oxidizable, act by possessing lower oxidation potentials than the active ingredient. Thus, they undergo preferential degradation or act as chain inhibitors of free radicals by providing an electron and receiving the excess energy possessed by the activated molecule.

The ideal antioxidant should be stable and effective over a wide pH range, soluble in its oxidized form, colorless, nontoxic, nonvolatile, nonirritating, effective in low concentrations, thermostable, and compatible with the container-closure system and formulation ingredients.

The commonly used antioxidants for aqueous systems include sodium sulfite, sodium metabisulfite, sodium bisulfite, sodium thiosulfate, and ascorbic acid. For oil systems, ascorbyl palmitate, hydroquinone, propyl gallate, nordihydroguaiaretic acid, butylated hydroxytoluene, butylated hydroxyanisole, and alpha-tocopherol are employed.

Synergists, which increase the activity of antioxidants, are generally organic compounds that complex small amounts of heavy metal ions. These include the ethylenediamine tetraacetic acid (EDTA) derivatives, dihydroethylglycine, and citric, tartaric, gluconic, and saccharic acids. EDTA has been used to stabilize ascorbic acid, oxytetracycline, penicillin, epinephrine, and prednisolone.

Reduction reactions are much less common than oxidative processes in pharmaceutical practice. Examples include the reduction of gold, silver, or mercury salts by light to form the corresponding free metal.

HYDROLYSIS—Drugs containing esters (eg, cocaine, physostigmine, aspirin, tetracaine, procaine and methyldopa), amides (eg, dibucaine), imides (eg, amobarbital), imines (eg, diazepam) and lactam (eg, penicillins, cephalosporins) functional groups are among those prone to hydrolysis.

Hydrolysis reactions are often pH dependent and are catalyzed by either hydronium ion or hydroxide ions (specific-acid or specific-base catalysis, respectively). Hydrolysis reactions can also be catalyzed by either a Brønsted acid or a Brønsted base (general-acid or general-base catalysis, respectively). Sources of Brønsted acid or base include buffers and some excipients. Sometimes, it is necessary to compromise between the optimum pH for stability and that for pharmacological activity. For example, several local anesthetics are most stable at a distinctly acid pH, whereas for maximum activity they should be neutral or slightly alkaline. Small amounts of acids, alkalines, or buffers are used to adjust the pH of a formulation. Buffers are used when small changes in pH are likely to cause major degradation of the active ingredient.

Obviously, the amount of water present can have a profound effect on the rate of a hydrolysis reaction. When the reaction takes place fairly rapidly in water, other solvents sometimes can be substituted. For example, barbiturates are much more stable at room temperature in propylene glycol–water than in water alone.

Modification of chemical structure may be used to retard hydrolysis. In general, as it is only the fraction of the drug in solution that hydrolyzes, a compound may be stabilized by reducing its solubility. This can be done by adding various substituents to the alkyl or acyl chain of aliphatic or aromatic esters or to the ring of an aromatic ester. In some cases less-soluble salts or esters of the parent compound have been found to aid product stability. Steric and polar complexation have also been employed to alter the rate of hydrolysis. Caffeine reduces the rate of hydrolysis and thus promotes stability by complexation with local anesthetics such as benzocaine, procaine, or tetracaine.

Esters and β-lactams are the chemical bonds that are most likely to hydrolyze in the presence of water. For example, the acetyl ester in aspirin is hydrolyzed to acetic acid and salicylic acid in the presence of moisture, but in a dry environment the hydrolysis of aspirin is negligible. The aspirin hydrolysis rate increases in direct proportion to the water vapor pressure in an environment.

The amide bond also hydrolyzes, though generally at a slower rate than comparable esters. For example, procaine (an ester) will hydrolyze upon autoclaving, but procainamide will not. The amide or peptide bond in peptides and proteins varies

in the labiality to hydrolysis. The lactam and azomethine (or imine) bonds in benzodiazepines are also labile to hydrolysis. The major chemical accelerators or catalysts of hydrolysis are adverse pH and specific chemicals (eg, dextrose and copper in the case of ampicillin hydrolysis).

The rate of hydrolysis depends on the temperature and the pH of the solution. A much-quoted estimation is that for each 10°C rise in storage temperature, the rate of reaction doubles or triples. As this is an empiricism, it is not always applicable.

When hydrolysis occurs, the concentration of the active ingredient decreases while the concentration of the decomposition products increases. The effect of this change on the rate of the reaction depends on the order of the reaction. With zero-order reactions the rate of decomposition is independent of concentration of the ingredient. Although dilute solutions decompose at the same absolute rate as more concentrated solutions, the more dilute the solution, the greater the proportion of active ingredient destroyed in a given time; ie, the percentage of decomposition is greater in more dilute solutions. Increasing the concentration of an active ingredient that is hydrolyzing by zero-order kinetics will slow the percentage decomposition.

With first-order reactions, which occur frequently in the hydrolysis of drugs, the rate of change is directly proportional to the concentration of the reactive substance. Thus, changes in the concentration of the active ingredient have no influence on the percentage decomposition.

The degradation of many drugs in solution accelerates or decelerates exponentially as the pH is decreased or increased over a specific range of pH values. Improper pH ranks with exposure to elevated temperature as a factor most likely to cause a clinically significant loss of drug, resulting from hydrolysis and oxidation reactions. A drug solution or suspension, for example, may be stable for days, weeks, or even years in its original formulation, but when mixed with another liquid that changes the pH, it degrades in minutes or days. It is possible that a pH change of only one unit (eg, from 4 to 3 or 8 to 9) could decrease drug stability by a factor of ten or greater.

A pH-buffer system, which is usually a weak acid or base and its salt, is a common excipient used in liquid preparations to maintain the pH in a range that minimizes the drug degradation rate. The pH of drug solutions may also be either buffered or adjusted to achieve drug solubility. For example, pH in relation to pKa controls the fractions of the usually more soluble ionized and less soluble nonionized species of weak organic electrolytes.

INTERIONIC (ION N+ −ION N−) COMPATIBILITY— The compatibility or solubility of oppositely charged ions depends mainly on the number of charges per ion and the molecular size of the ions. In general, polyvalent ions of opposite charge are more likely to be incompatible. Thus, an incompatibility is likely to occur upon the addition of a large ion with a charge opposite to that of the drug.

As many hydrolytic reactions are catalyzed by both hydronium and hydroxyl ions, pH is an important factor in determining the rate of a reaction. The pH range of minimum decomposition (or maximum stability) depends on the ion having the greatest effect on the reaction. If the minimum occurs at about pH 7, the two ions are of equal effect. A shift of the minimum toward the acid side indicates that the hydroxyl ion has the stronger catalytic effect and *vice versa* in the case of a shift toward the alkaline side. In general, hydroxyl ions have the stronger effect. Thus, the minimum is often found between pH 3 and 4. The influence of pH on the physical stability of two-phase systems, especially emulsions, is also important. For example, intravenous fat emulsion is destabilized by acidic pH.

DECARBOXYLATION— Pyrolytic solid-state degradation through decarboxylation usually is not encountered in pharmacy, as relatively high heats of activation (25 to 30 kcal) are required for the reaction. However, solid *p*-aminosalicylic acid undergoes pyrolytic degradation to *m*-aminophenol and carbon dioxide. The reaction, which follows first-order kinetics, is highly pH-dependent and is catalyzed by hydronium ions. The decarboxylation of *p*-aminobenzoic acid occurs only at extremely low pH values and at high temperatures.

Some dissolved carboxylic acids, such as *p*-aminosalicylic acid, lose carbon dioxide from the carboxyl group when heated. The resulting product has reduced pharmacological potency. β-Keto decarboxylation can occur in some solid antibiotics that have a carbonyl group on the β-carbon of a carboxylic acid or a carboxylate anion. Such decarboxylations will occur in the following antibiotics: carbenicillin sodium, carbenicillin free acid, ticarcillin sodium, and ticarcillin free acid.

RACEMIZATION— Racemization, or the action or process of changing from an optically active compound into a racemic compound or an optically inactive mixture of corresponding *R* (*rectus*) and *S* (*sinister*) forms, is a major consideration in pharmaceutical stability. Optical activity of a compound may be monitored by polarimetry and reported in terms of specific rotation. Chiral HPLC has been used in addition to polarimetry to confirm the enantiomeric purity of a sample.

In general, racemization follows first-order kinetics and depends on temperature, solvent, catalyst, and the presence or absence of light. Racemization appears to depend on the functional group bound to the asymmetric carbon atom, with aromatic groups tending to accelerate the process.

EPIMERIZATION— Members of the tetracycline family are most likely to incur epimerization. This reaction occurs rapidly when the dissolved drug is exposed to a pH of an intermediate range (higher than 3), and it results in the steric rearrangement of the dimethylamino group. The epimer of tetracycline, epitetracycline, has little or no antibacterial activity.

PHOTOCHEMICAL REACTIONS

Photolytic degradation can be an important limiting factor in the stability of pharmaceuticals. A drug can be affected chemically by radiation of a particular wavelength only if it absorbs radiation at that wavelength and the energy exceeds a threshold. Ultraviolet radiation, which has a high energy level, is the cause of many degradation reactions. Exposure to, primarily, UV illumination may cause oxidation (photo-oxidation) and scission (photolysis) of covalent bonds. Nifedipine, nitroprusside, riboflavin, and phenothiazines are very labile to photo-oxidation. In susceptible compounds, photochemical energy creates free radical intermediates, which can perpetuate chain reactions.

If the absorbing molecule reacts, the reaction is said to be photochemical in nature. When the absorbing molecules do not participate directly in the reaction, but pass their energy to other reacting molecules, the absorbing substance is said to be a photosensitizer.

As many variables may be involved in a photochemical reaction, the kinetics can be quite complex. The intensity and wavelength of the light and the size, shape, composition, and color of the container may affect the velocity of the reaction.

The photodegradation of chlorpromazine through a semiquinone free-radical intermediate follows zero-order kinetics. On the other hand, alcoholic solutions of hydrocortisone, prednisolone, and methylprednisolone degrade by reactions following first-order kinetics.

Colored-glass containers most commonly are used to protect light-sensitive formulations. Yellow-green glass gives the best protection in the ultraviolet region, while amber confers considerable protection from ultraviolet radiation but little from infrared. Riboflavin is best protected by a stabilizer that has a hydroxyl group attached to or near the aromatic ring. The photodegradation of sulfacetamide solutions may be inhibited by an antioxidant such as sodium thiosulfate or metabisulfite.

A systematic approach to photostability testing is recommended covering, as appropriate, studies such as tests on the drug substance, tests on the exposed drug product outside of the immediate pack; and if necessary, tests on the drug product

in the immediate pack. ICH Q1B discusses the minimum requirements for assessing photostability. Drug substance is first assessed by exposing sample powder having a depth of not more than 3 mm to an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter. If the drug substance shows sensitivity to photodegrations, then the drug product will need to be tested as well. The testing of drug product uses the same light exposure that was used to test drug substance. The drug product should be tested directly exposed to light and in its container closure system.

ULTRASONIC ENERGY

Ultrasonic energy, which consists of vibrations and waves with frequencies greater than 20,000 Hz, promotes the formation of free radicals and alters drug molecules. Changes in prednisolone, prednisone acetate, or deoxycorticosterone acetate suspensions in an ultrasonic field have been observed spectrometrically in the side chain at C-17 and in the oxo group of the A ring. With sodium alginate, in an ultrasonic field, it has been reported that above a minimum power output, degradation increased linearly with increased power.

IONIZING RADIATION

Ionizing radiation, particularly gamma rays, has been used for the sterilization of certain pharmaceutical products. At the usual sterilizing dose, 2.5 mRad, it seldom causes appreciable chemical degradation. In general, formulations that are in the solid or frozen state are more resistant to degradation from ionizing radiation than those in liquid form. For example, many of the vitamins are little affected by irradiation in the solid state but are decomposed appreciably in solution. On the other hand, both the liquid- and solid-state forms of atropine sulfate are affected seriously by radiation.

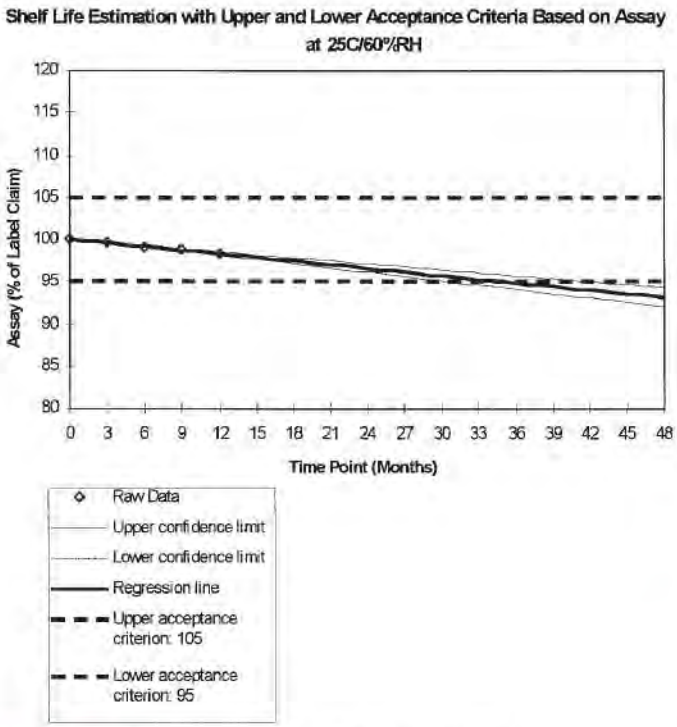

Figure 52-1. Typical two-sided shelf-life estimation plot.

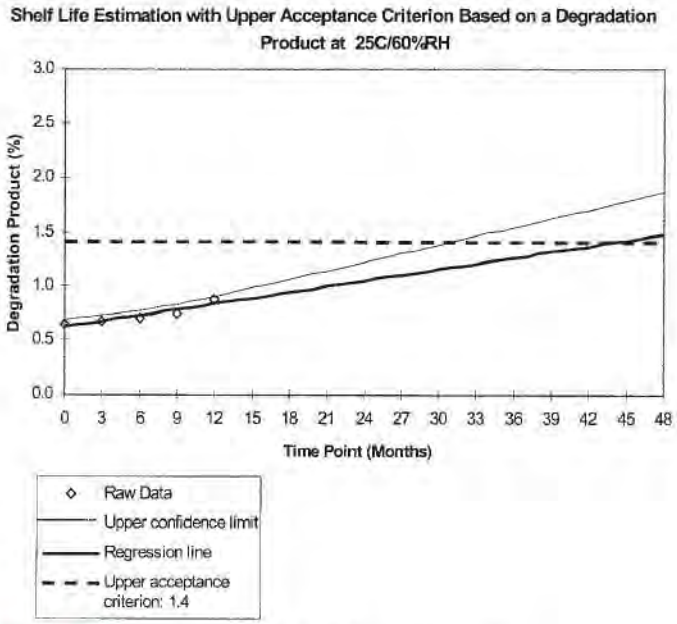

Figure 52-2. Typical one-sided shelf-life estimation plot.

PREDICTING SHELF LIFE

ICH Recommended Evaluation

The shelf life of a commercial drug product must be determined in the commercial container closure at the defined storage conditions. ICH requires at least 12 months stability data at the time of NDA submission. Most products require at least 24 months to be commercially viable. The ICH Q1E recommends how the 12 months data may be used to predict long-term stability. Figures 52-1 and 52-2 show trending graphs with double-sided and single-sided 95% confidence limits plots, respectively.

Figure 52-1 shows a plot of 12 months of assay (potency) results versus time. The acceptance criteria for this test have a lower and an upper limit of 95% and 105%, respectively. The extrapolated line from this data set intersects the lower acceptance limit at about 35 months. However, there is always statistical uncertainty when extrapolating a data set. The 95% confidence limit is used to take this uncertainty into account. The lower 95% confidence intersects the lower acceptance limit at about 29 months. Therefore, this product would be assessed an expiration date of 29 months.

Figure 52-2 shows a plot of 12 months of degradation product results. In this case, the acceptance criterion is an upper limit of not more than 1.4%. The extrapolated line from this data set intersects the acceptance limit at about 44 months. The upper 95% confidence limit curve intersects the acceptance limit at about 30 months. Therefore, this product would be assessed an expiration date of 30 months. The expiration of a product is the time where the confidence line intersects with the acceptance limit. Trend analysis of data need only be performed on test data that shows a change related to time.

Approximations in Assessing Product Stability—Estimation of Temperature Effect

In early development, a shelf life prediction of a clinical material, especially a Phase I material, may be based on a very limited amount of sample and limited amount of time to make the evaluation. One way to estimate long-term storage for a material is by extrapolating data from studies performed at elevated conditions. An understanding of potential activation energy is needed to estimate long-term stability. Many may have heard

of the estimate that for every 10°C decrease in storage temperature the shelf-life doubles. This is only true, however, if the activation energy of the reaction(s) that causes degradation is 15 kcal/moles. The activation energy, E_a, for many chemical processes related to the degradation of a drug substance/product is typically within the range of 10 to 25 kcal/moles.

The equation below shows a way of calculating the $Q_{\Delta T}$ value that may be used to estimate the affect of temperature on shelf life.

$$Q_{\Delta T} = \exp\left[\frac{E_a}{R}\left(\frac{\Delta T}{T + \Delta T(T)}\right)\right] \quad (1)$$

where, $Q_{\Delta T}$ is a factor (multiplier/divisor) used to estimate the change in the reaction rate constant with change in temperature, ΔT. E_a is the activation energy established for a reaction

An approximation for the change in reaction rate constants due to the temperature effects are shown in the table below.

Ea (kcal/mole)	Q_5 (25 to 30°C)	Q_{10} (25 to 35°C)	Q_{15} (25 to 40°C)
10	1.32	1.73	2.24
15	1.52	2.27	3.36
20	1.75	2.99	5.04
25	2.01	3.93	7.55

Therefore, the old rule of thumb that a reaction rate doubles with every 10°C is only true if the reaction has an activation energy between 10 to 15 kcal/mole (Q_{10} = 1.73 and 2.27, respectively). Q_{15} is useful for understanding the relationship of ICH accelerated temperature of 40°C has with controlled room temperature at 25°C. Materials made and packaged for clinical studies are usually tested at an accelerated condition in order to predict that the packaged material will be stable for the duration of the clinical study. A material stable for one month at accelerated temperature (40°C) supports that the material stored at room temperature should be stable for at least 3 months. This true only when the activation energy of the degradation process is about 15 kcal/mole (Q_{15} factor = 3.36) [In other words, a reaction at 40°C should be 3.36 times faster than the same reaction at 25°C; or the reaction will take 3.36 times longer at 25°C than at 40°C)].

The technique of estimating the shelf life of a formulation from its accumulated stability data has evolved from examining the data and making an educated guess through plotting the time-temperature points on appropriate graph paper and crudely extrapolating a regression line to the application of rigorous physical-chemical laws, statistical concepts, and computers to obtain meaningful, reliable estimates.

A simple means of estimating shelf life from a set of computer-prepared tables has been described by Lintner et al.[6] This system was developed to select the best prototype formulation on the basis of short-term stability data and predict both estimated and minimum shelf-life values for the formulation. It is a middle-ground approach between the empirical methods and the modern, rigorous statistical concepts. All calculations can be made readily by hand, and the estimated values can be obtained easily from appropriate tables. The system assumes that

1. Shelf-life predictions can be made satisfactorily for lower temperatures using the classical Arrhenius model from data obtained at higher temperatures.
2. The energy of activation of the degradation reaction is between 10 and 20 kcal/mol (this is a safe assumption, as Kennon[8] has noted that rarely are drugs with energies of activation below 10 kcal/mol used in pharmacy, and for values as high as 20 kcal/mol, the error in the shelf-life prediction will be on the conservative side).
3. The rate of decomposition will not increase beyond that already observed.
4. The standard deviation of the replicated assays is known or can be estimated from the analytical data.

This concept further assumes that the degradation reaction follows zero- or pseudo-zero-order kinetics. For data corresponding to a zero-, first-, or second-order degradation pattern, it is impossible to distinguish one order from another with usual analytical procedures, when the total degraded material is not large. In addition, shelf-life calculations assuming zero-order kinetics are more conservative than those for higher orders.

This middle-ground system is useful in creating the experimental design for the stability study. The formulator has the opportunity to study various combinations of parameters to try to optimize the physical-statistical model. One can check the effect of improving the assay standard deviation, running additional replicates, using different time points, and assuming various degradation rates and energies of activation on the stability of the test formulation.

McMinn and Lintner later developed and reported on an information-processing system for handling product stability data.[9] This system saves the time of formulators in analyzing and interpreting their product stability data, in addition to minimizing the amount of clerical help needed to handle an ever-increasing assay load. For products such as those of vitamins, for example, where large overages are required, the statistical portions of this advanced technique aid the manufacturer to tailor the formula composition to obtain the desired and most economical expiration dating.

This system stores both physical and chemical data and retrieves the information in three different formats (one of which was designed specifically for submitting to regulatory agencies). It analyzes single-temperature data statistically by analysis of covariance and regression or multiple-temperature data by weighted or unweighted analysis using the Arrhenius relationship; provides estimates of the shelf life of the preparation with the appropriate confidence intervals; preprints the assay request cards that are used to record the results of the respective assay procedures and to enter the data into the system; and produces a 5-yr master-stability schedule as well as periodic 14-day schedules of upcoming assays.

As mentioned above, a portion of the advanced system analyzes the stability data obtained at a single temperature by analysis of covariance and regression. This analysis is based on the linear (zero-order) model

$$Y_{ij} = \beta_i X_{ij} + \alpha_i + \varepsilon_{ij} \quad (2)$$

where Y_{ij} is the percentage of label of the jth stability assay of the ith lot, X_{ij} is the time in months at which Y_{ij} was observed, β_i and α_i are the slope and intercept, respectively, of the regression line of the ith lot, and ε_{ij} is a random error associated with Y_{ij}. The random errors are assumed to be identically and independently distributed normal variables with a zero mean and a common variance, σ^2.

A summary of the regression analysis for each individual lot and for the combination of these lots, plus a summary of the analyses of covariance and deviation from regression is prepared by the computer.

Because the computer combines, or pools, the stability data from the individual lots, irrespective of the statistical integrity of this step, the pooled data are examined for validity by the F test. The mean square of the regression coefficient (slope) is divided by the mean square of the deviation within lots, and similarly, the adjusted mean (y intercept) is divided by the common mean square to give the respective F ratios. The latter values then are compared with the critical 5% F values. When the calculated F values are smaller than the critical F values, the data may be combined, and the pooled data analyzed.

A printout for the combined lots as well as for each individual lot provides the estimated rate of degradation and its standard error in percentage per month for each ingredient. The *Student t* value is calculated from these estimates and tested for significance from zero. When the t value is significant, the printout contains an estimate of the shelf life with the appropriate confidence interval. When the t value is not significantly different from zero, estimates of the minimum and projected shelf-life values are made. In addition, coordinates of the calculated least-squares regression line with ap-

propriate confidence limits for the mean and individual predicted assays are printed.

Plots of the resulting least-squares line containing the individual data points also are printed by the computer. For the calculation of X_0, $\hat{Y}$ equals $\overline{Y} + \hat{\beta}(X_0 - \overline{X..})$, where $\hat{\beta}$ is the least-squares estimate of the slope, and $\overline{X..}$ is the mean time of assay.

The sample variance for this estimate, $S^2(Y)$ is equal to

$$S_{y \cdot x}{}^2 \left[\frac{1}{N} + \left[\frac{(X_0 - \overline{X..})^2}{\sum (X_{ij} - \overline{X..})^2} \right] \right] \quad (3)$$

where N is the number of assays. The 95% confidence interval is equal to $Y \pm t_{0.05S(\hat{Y})}$.

For cases in which the slope of the best fitting line is positive and significantly different from zero (resulting, eg, from solvent evaporation), the statement "no degradation has been detected and hence no shelf-life estimate is made" is printed. When the computed line has a positive slope but not significantly different from zero, only the minimum shelf-life value is calculated.

Traditionally, extensive stability data are collected at the recommended storage temperatures (usually refrigerator and/or room temperature) to be placed on the label of the package. However, elevated-temperature data are very valuable in determining the shelf life of a product. In practice, multiple levels of thermal stress are applied to the formulation so that appropriate shelf-life estimates can be made for normally expected marketing conditions. In cases in which data from accelerated studies are used to project a tentative expiration date that is beyond the date supported by actual shelf-life studies, testing must continue until the tentative expiration date is verified.

The effect of temperature variation on the rate of a reaction can be expressed by an integrated form of the Arrhenius equation

$$k = se^{-E_A/RT} \quad (4)$$

where, k is the rate constant, E_A is the energy of activation in kcal/mole, R is the universal gas constant of 1.987 cal/deg mole, T is the temperature in degrees in Kelvin, and S is a constant that is related to the specific reaction.

$$\log \frac{k_2}{k_1} = \frac{E_a}{2.303R}\left(\frac{T_2 - T_1}{T_2 * T_1}\right) \quad (5)$$

where, k_1 is the rate constant at temperature T_1 and k_2 is the rate constant at temperature T_2.

A weighted modification of this model has been incorporated into the previously described computerized system. Each printout contains a statement concerning the acceptability of the Arrhenius assumption with its appropriate probability level, the slope and intercept for the Arrhenius line, the estimated apparent energy of activation with its 95% confidence limits, plus the estimated shelf-life values at selected temperatures.

The analysis of first-order stability data is based on the linear model

$$Y_{ij} = \alpha_i + \beta_i X_{ij} + \varepsilon_{ij} \quad (6)$$

where Y_{ij} is the natural logarithm of the assay value for the jth observation of the ith temperature, X_{ij} is the elapsed time in months for the assay sample for the ith temperature, β_i and α_i are the slope and intercept, respectively, and ε_{ij} is a random error associated with Y_{ij}. The errors are assumed to be distributed identically and independently, normally with a zero mean and variance σ^2.

For orders other than first, Y_{ij} represents the concentration raised to the power of 1 minus the order.

The estimated rate constant (ie, the negative slope) is

$$-b_i = -\sum_j (Y_{ij} - Y_i)(X_{ij} - X_i) / \sum_j (X_{ij} - X_i)^2 \quad (7)$$

The standard error of the estimated rate constant is

$$S_{-b_i} = \frac{S(X/Y)}{[\sum (X_{ij} - X_i)^2]^{1/2}} \quad (8)$$

where $S(Y/X)$, the residual standard error, is equal to

$$S(X/Y) = \left\{ \frac{1}{N-2} \left[\sum_{j=1}^{12} (Y_{ij} - Y_i)^2 - \frac{[\sum (X_{ij} - X_i)(Y_{ij} - Yi)^2]}{\sum (X_{ij} - X_i)^2} \right] \right\}^{1/2} \quad (9)$$

According to the Arrhenius relationship, faster degradation occurs at the higher temperatures; hence, assays for the high-temperature data usually are run more often but for a shorter period of time. The effect of simple least-squares analysis of this type of data is to force the Arrhenius equation through the low temperature data and essentially ignore the high-temperature information. Thus, much more credence is placed in the point estimates of the low temperature than is warranted. In addition, the usual confidence limits on extrapolated degradation rates at refrigerator or room temperature cannot be made validly. For these reasons, Bentley[10] presented a method based on a weighted least-squares analysis to replace the unweighted approximation. He also developed a statistical test for the validity of the Arrhenius assumption, which is computed easily from the results of the unweighted method.

To make shelf-life estimates from elevated temperature data, two storage temperatures are obviously the minimum. As the accuracy of the extrapolation is enhanced by using additional temperatures, a minimum of four different temperatures is recommended for most product stability studies. With the current use of computers to do the bulk of stability calculations, including weighted least-squares analysis, the temperatures and storage conditions need not be selected for arithmetic convenience.

It is not necessary to determine the mechanism of the degradation reaction. In most cases, it is necessary only to follow some property of degradation and to linearize this function. Either the amount of intact drug or the amount of a formed degradation product may be followed. It usually is impractical to determine the exact order of the reaction. With assay errors in the range of 2 to 5%, at least 50% decomposition must occur before the reaction order can be determined. As the loss with pharmaceuticals generally is less, zero-order kinetics should be assumed, unless the reaction order is known from previous work. In any case, replication of stability assays is advisable.

The batches of drugs used for a stability study should be representative of production run material or at least material of a known degree of purity. The quality of the excipients also should be known, as their impurities or even their moisture content can affect product stability deleteriously. Likewise, the samples of the formulation taken for the stability study must be representative of the lot.

Specific, stability-indicating assay methods must be used, to make meaningful shelf-life estimates. The reliability and specificity of the test method on the intact molecule and on the degradation products must be demonstrated.

ADDITION OF OVERAGE

The problem of declining potency in an unstable preparation can be ameliorated by the addition of an excess or overage of the active ingredient. Overages, then, are added to pharmaceutical formulations to keep the content of the active ingredient within the limits compatible with therapeutic requirements, for a predetermined period of time.

The amount of the overage depends upon the specific ingredient and the galenical dosage form. The International Pharmaceutical Federation has recommended that overages be limited to a maximum of 30% over the labeled potency of an ingredient.

PHARMACEUTICAL CONTAINERS

The official standards for containers apply to articles packaged by either the pharmaceutical manufacturer or the dispensing

pharmacist unless otherwise indicated in a compendial monograph. In general, repackaging of pharmaceuticals is inadvisable. However, if repackaging is necessary, the manufacturer of the product should be consulted for potential stability problems.

A pharmaceutical container has been defined as a device that holds the drug and is, or may be, in direct contact with the preparation. The immediate container is described as that which is in direct contact with the drug at all times. The liner and closure traditionally have been considered to be part of the container system. The container should not interact physically or chemically with the formulation so as to alter the strength, quality, or purity of its contents beyond permissible limits.

The choice of containers and closures can have a profound effect on the stability of many pharmaceuticals. Now that a large variety of glass, plastics, rubber closures, tubes, tube liners, etc are available, the possibilities for interaction between the packaging components and the formulation ingredients are immense. Some of the packaging elements themselves are subject to physical and chemical changes that may be time-temperature dependent.

Frequently, it is necessary to use a well-closed or a tight container to protect a pharmaceutical product. A *well-closed container* is used to protect the contents from extraneous solids or a loss in potency of the active ingredient under normal commercial conditions. A *tight container* protects the contents from contamination by extraneous materials, loss of contents, efflorescence, deliquescence, or evaporation and is capable of tight re-closure. When the packaging and storage of an official article in a well-closed or tight container is specified, water-permeation tests should be performed on the selected container.

In a stability program, the appearance of the container, with special emphasis on the inner walls, the migration of ingredients onto/into the plastic or into the rubber closure, the migration of plasticizer or components from the rubber closure into the formulation, the possibility of two-way moisture penetration through the container walls, the integrity of the tac-seal, and the back-off torque of the cap, must be studied.

GLASS—Traditionally, glass has been the most widely used container for pharmaceutical products to ensure inertness, visibility, strength, rigidity, moisture protection, ease of re-closure, and economy of packaging. While glass has some disadvantages, such as the leaching of alkali and insoluble flakes into the formulation, these can be offset by the choice of an appropriate glass. As the composition of glass may be varied by the amounts and types of sand and silica added and the heat treatment conditions used, the proper container for any formulation can be selected.

According to USP 26, glass containers suitable for packaging pharmacopeial preparations may be classified as either Type I, Type II, Type III, or type NP. Containers of Type I borosilicate glass are generally used for preparations that are intended for parenteral administration, although Type II treated soda-lime glass may be used where stability data demonstrates its suitability. Containers of Type III and Type NP are intended for packaging articles intended for oral or topical use.

New, unused glass containers are tested for resistance to attack by high-purity water by use of a sulfuric acid titration to determine the amount of released alkali. Both glass and plastic containers are used to protect light-sensitive formulations from degradation. The amount of transmitted light is measured using a spectrometer of suitable sensitivity and accuracy.

Glass is generally available in flint, amber, blue, emerald green, and certain light-resistant green and opal colors. The blue-, green-, and flint-colored glasses, which transmit ultraviolet and violet light rays, do not meet the official specifications for light-resistant containers.

Colored glass usually is not used for injectable preparations, since it is difficult to detect the presence of discoloration and particulate matter in the formulations. Light-sensitive drugs for parenteral use usually are sealed in flint ampuls and placed in a box. Multiple-dose vials should be stored in a dark place.

Manufacturers of prescription drug products should include sufficient information on their product labels to inform the pharmacist of the type of dispensing container needed to maintain the identity, strength, quality, and purity of the product. This brief description of the proper container, e.g., light- resistant, well-closed, or tight, may be omitted for those products dispensed in the manufacturer's original container.

PLASTICS—Plastic containers have become very popular for storing pharmaceutical products. Polyethylene, polystyrene, polyvinyl chloride, and polypropylene are used to prepare plastic containers of various densities to fit specific formulation needs.

Factors such as plastic composition, processing and cleaning procedures, contacting media, inks, adhesives, absorption, adsorption, and permeability of preservatives also affect the suitability of a plastic for pharmaceutical use. Hence, biological test procedures are used to determine the suitability of a plastic for packaging products intended for parenteral use and for polymers intended for use in implants and medical devices. Systemic injection and intracutaneous and implantation tests are employed. In addition, tests for nonvolatile residue, residue on ignition, heavy metals, and buffering capacity were designed to determine the physical and chemical properties of plastics and their extracts.

The high-density polyethylene (HDPE) containers, which are used for packaging capsules and tablets, possess characteristic thermal properties, a distinctive infrared absorption spectrum, and a density between 0.941 and 0.965 g/cm^3. In addition, these containers are tested for light transmission, water-vapor permeation, extractable substances, nonvolatile residue, and heavy metals. When a stability study has been performed to establish the expiration date for a dosage form in an acceptable high-density polyethylene container, any other high-density polyethylene container may be substituted provided that it, too, meets compendial standards and that the stability program is expanded to include the alternative container.

Materials from the plastic itself can leach into the formulation, and materials from the latter can be absorbed onto, into, or through the container wall. The barrels of some plastic syringes bind various pharmaceutical preservatives. However, changing the composition of the syringe barrel from nylon to polyethylene or polystyrene has eliminated the binding in some cases.

A major disadvantage of plastic containers is the two-way permeation or *breathing* through the container walls. Volatile oils and flavoring and perfume agents are permeable through plastics to varying degrees. Components of emulsions and creams have been reported to migrate through the walls of some plastics, causing either a deleterious change in the formulation or collapse of the container. Loss of moisture from a formulation is common. Gases, such as oxygen or carbon dioxide in the air, have been known to migrate through container walls and affect a preparation.

Solid dosage forms, such as penicillin tablets, when stored in some plastics, are affected deleteriously by moisture penetration from the atmosphere into the container.

Single unit does packaging in the form of blister packages are often used to package capsule and tablet dosage forms. A typical blister package is comprised of a polymeric film that is molded to have a cavity into which the dosage form is placed. The polymer film is then heat bonded to a paper backed foil liner.

As with plastic bottles, the blister package will allow a certain amount of moisture vapor permeation to occur, and this must be a consideration when selecting the type of film used for the package. The choice of packaging materials used depends on the degree to which the product needs to be protected from light, heat and moisture. Each material has different resistance to each of these elements and will affect the shelf life and storage conditions of the packaged pharmaceutical.

Polyvinylchloride (PVC) offers the least resistance to moisture vapor permeation. Polyvinylidenechloride (PVdC) has characteristics similar to PVC but offers superior resistance to moisture vapor permeation. Aclar, which is a polychlorotrifluo-

roethylene (PVC-CTFE) film has the lowest water vapor permeability and thus offers the best protection from moisture.

METALS—The pharmaceutical industry was, and to a degree still is, a tin stronghold. However, as the price of tin constantly varies, more-collapsible aluminum tubes are being used. Lead tubes tend to have pinholes and are little used in the industry.

A variety of internal linings and closure fold seals are available for both tin and aluminum tubes. Tin tubes can be coated with wax or with vinyl linings. Aluminum tubes are available with epoxy or phenolic resin, wax, vinyl, or a combination of epoxy or phenolic resin with wax. As aluminum is able to withstand the high temperatures required to cure epoxy and phenolic resins adequately, tubes made from this metal presently offer the widest range of lining possibilities.

Closure fold seals may consist of unmodified vinyl resin or plasticized cellulose and resin, with or without added color.

Collapsible tubes are available in many combinations of diameters, lengths, openings, and caps. Custom-use tips for ophthalmic, nasal, mastitis, and rectal applications also are available. Only a limited number of internal liners and closure seals are available for tubes fitted with these special-use tips.

Lined tubes from different manufacturers are not necessarily interchangeable. While some converted resin liners may be composed of the same base resin, the actual liner may have been modified to achieve better adhesion, flow properties, drying qualities, or flexibility. These modifications may have been necessitated by the method of applying the liner, the curing procedure, or, finally, the nature of the liner itself.

CLOSURES

The closures for the formulations also must be studied as a portion of the overall stability program. While the closure must form an effective seal for the container, the closure must not react chemically or physically with the product. It must not absorb materials from the formulation or leach its ingredients into the contents.

The integrity of the seal between the closure and container depends on the geometry of the two, the materials used in their construction, the composition of the cap liner, and the tightness with which the cap has been applied. Torque is a measure of the circular force, measured in inch-pounds, which must be applied to open or close a container. When pharmaceutical products are set up on a stability study, the formulation must be in the proposed market package. Thus, they should be capped with essentially the same torque to be used in the manufacturing step.

Rubber is a common component of stoppers, cap liners, and parts of dropper assemblies. Sorption of the active ingredient, preservative, or other formulation ingredients into the rubber and the extraction of one or more components of the rubber into the formulation are common problems.

The application of an epoxy lining to the rubber closure reduces the amount of leached extractives but essentially has no effect on the sorption of the preservative from the solution. Teflon-coated rubber stoppers may prevent most of the sorption and leaching.

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Glossary

A

AA	atomic absorption, Alcoholics Anonymous
AACP	American Association of Colleges of Pharmacy
AAFP	American Academy of Family Practice
AAGR	average annual growth
AAP	American Academy of Pediatrics
AAPCC	American Association of Poison Control Centers
AAPS	American Association of Pharmaceutical Scientists
AARP	American Association of Retired Persons
ABAT	American Board of Applied Toxicology
ABC	ATP binding casette
ABG	arterial blood gas
ABMS	American Board of Medical Specialties
ACA	American College of Apothecaries
ACD	acid-citrate-dextrose
ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
ACCP	American College of Clinical Pharmacy, American College of Clinical Pharmacists
ACF	Administration for Children and Families
Ach	acetylcholine
ACh	acetylcholinesterase
ACHC	Accreditation Committee for Health Care
ACIP	American Committee on Immunization Practices, Immunization Practices Advisory Committee
ACP	American College of Physicians, acyl carrier protein
ACPE	Accreditation Council for Pharmaceutical Education
ACTH	corticotropin (adrenocorticotropic hormone)
AD	Alzheimer's disease, Alzheimer's dementia
ADA	American Dental Association, American Dietetic Association, adenosine deaminase, American Diabetes Association
ADCC	antibody-dependent cell-mediated cytotoxicity
ADE	adverse drug event, adverse drug experience
ADEPT	antibody directed enzyme prodrug therapy
ADH	antidiuretic hormone
ADL	activity of daily living
ADME	absorption, distribution, metabolism, and excretion
ADP	adenosine diphosphate
ADR	adverse drug reaction
AEC	Atomic Energy Commission
AERS	Adverse Event Reporting System
AES	Auger electron spectrometry
AF	atrial fibrillation
AFMS	Air Force Medical Service
AFP	α-1-fetoprotein
A/G	albumin-globulin ratio
AGD	agar gel diffusion
AHA	American Hospital Association, American Heart Association
AHCPR	Agency for Health Care Policy Research
AHF	antihemophilic factor
AHFS	American Hospital Formulary System
AHG	antihemophilic globulin
AHRQ	Agency for Healthcare Research and Quality
AI	adequate intake, aortic insufficiency
AIDS	acquired immunodeficiency syndrome
AIMS	abnormal involuntary movement scale
AIRA	American International Reiki Association
AL	allergy unit
ALARA	as low as reasonably achievable
ALF	American Liver Foundation
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AMA	American Medical Association
AMC	Army Medical Center
AMCP	Academy of Managed Care Pharmacists
AMD	age-related macular degeneration
AMDA	American Medical Director's Association
AMI	acute myocardial infarction
AMTA	American Massage Therapy Association
ANA	antinuclear antibodies
ANC	acid neutralizing capacity
ANDA	abbreviated new drug application
ANF	atrial natriuretic factor
ANN	artificial neural network
ANOVA	analysis of variance
ANS	autonomic nervous system
AO	atomic orbital
AOA	American Osteopathic Association
AoA	Administration on Aging
APAP	acetaminophen
APC	antigen-presenting cell, ambulatory patient classification
APCI	atmospheric pressure chemical ionization
APHA	American Public Health Association
APhA	American Pharmacists Association
API	active pharmaceutical ingredient, atmospheric pressure ionization
APP	alternating pressure pad
APPM	Academy of Pharmacy Practice and Management
APRS	Academy of Pharmaceutical Research and Science
APSF	Anesthesia Patient Safety Foundation
APTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
ARDS	adult respiratory distress syndrome
ASA	acetylsalicylic acid, American Society for Anesthesia
ASCP	American Society of Consultant Pharmacists
ASHP	American Society of Health-System Pharmacists
ASNN	associate neural network
ASO	administrative service organization
ASP	Academy of Students of Pharmacy
ASPEN	American Society of Parenteral and Enteral Nutrition
ASRS	Aviation Safety and Reporting System
AST	aspartase aminotransferase
ATC	around-the-clock
ATCC	American *Type Culture* Collection
ATM	automated teller machine
ATN	acute tubular necrosis
ATP	adenosine triphosphate
ATPase	adenosine triphosphatase
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	area under the curve
AV	atrioventricular
AZT	zidovudine

B

BAC	blood alcohol concentration
BAL	British anti-Lewisite, bioequivalent allergy unit
BBB	blood-brain barrier
BCE	before the Christian era
BCG	Bacillus Calmette Guerin
BCMA	Bar Code Medication Administration System
BCNP	Board Certified Nuclear Pharmacist
BCPS	Board Certified Pharmacotherapy Specialist
BCS	Biopharmaceutical Classification System
BET	bacterial endotoxin test
bFGF	basic fibroblast growth factor
BI	biological indicator
BIA	bacteria inhibition assay
BJA	Basic Journal Abstracts
BM	bowel movement
BMD	Bureau of Medical Devices, bone mineral density
BMI	body mass index
BMJ	British Medical Journal
BMS	between mean square
BMT	bone marrow transplantation
BOC	Board for Arthotists/Prosthetist Certification
BOP	Bureau of Prisons
BP	British Pharmacopeia
BPC	bulk pharmaceutical chemical
BPH	benign prostatic hypertrophy
BPS	Board of Pharmaceutical Specialties
BRH	Bureau of Radiologic Health
BSA	bovine serum albumin
BSC	Biomedical Service Corps
BSE	breast self-examination, bovine spongiform encephalopathy
BSS	between sum-of-squares, balanced salt solution
BUN	blood urea nitrogen
BWFI	bacteriostatic water for injection

C

CAD	coronary artery disease
CADD	computer-assisted drug design
CAGE	cut down, annoyed, guilty, eye opener
CAM	cell adhesion molecule, complimentary/alternative medicine
cAMP	cyclic adenosine monophosphate, cyclic adenosine-3′,5′-monophosphate
CARF	Commission on Accreditation of Rehab Facilities
CARTI	community-acquired respiratory tract infection

CAS Chemical Abstracts Service, composite adherence score
CAT cellulose acetate trimellitate, computer-aided tomography
CBAC Chemical-Biological Activities
CBC complete blood count
CBA cost-benefit analysis
CBER Center for Biologics Evaluation and Research
CCB calcium channel blockers
CCD countercurrent distribution
CCP Council on Credentialing in Pharmacy
CCRF Commissioned Corps Readiness Force
CD circular dichroism
CDA chiral derivatizing agent
CDC Centers for Disease Control and Prevention
CDER Center for Drug Evaluation and Research
CDM certified disease management
CDRH Center for Devices and Radiologic Health
CD-ROM compact disk-read only memory
CE capillary electrophoresis
CEA carcinoembryonic antigen, cost-effectiveness analysis
CEC capillary electrochromatography
CEO chief executive officer
CEP counterelectrophoresis
CF complement fixation
CFC chlorofluorocarbon
CFR Code of Federal Regulations
CFSAN Center for Food Safety and Applied Nutrition
CFTR cystic fibrosis transmembrane regulator
CFU colony-forming unit
CGD chronic granulomatous disease
cGMP cyclic guanosine-3′,5′-monophosphate, current good manufacturing practice
CHAP Commission on Health Accreditation Programs
CHD coronary heart disease
CHF congestive heart failure
CHO Chinese hamster ovary
CI confidence interval, chemical ionization
CIMS chemical ionization mass spectrometry, chemical ionization mass spectroscopy
CIOMS Council for International Organization of Medical Sciences
CIP clean-in-place
CI-PDED chlorine-selective pulsed discharge emission detector
CK creatinine kinase
CLIA Clinical Laboratory Improvement Amendments
CLL chronic lymphoblastic leukemia
CLT Central Limit Theorem
CMC comprehensive medical chemistry, critical micelle concentration
CME cystoid macular edema
CMI cell-mediated immunity
CML chronic myeloid leukemia
CMN certificate of medical necessity
CMOP Consolidated Mail Outpatient Pharmacies
$CMRO_2$ cerebral metabolic rate for oxygen
CMS Centers for Medicare and Medicaid Services
CMV cytomegalovirus
CN Crigler-Najjar syndrome
CNS central nervous system
CO communication objective, carbon monoxide
COHgB carboxyhemoglobin
COMTA Commission on Massage Therapy Accreditation
CONSORT Consolidated Standards of Reporting Trials
COPD chronic obstructive pulmonary disease
COSTEP Commissioned Officer Student Training and Externship Program
COSY correlation spectroscopy
COX cyclo-oxygenase
CPC Council on Pharmacy and Chemistry, centrifugal partition chromatography
CPD citrate-phosphate-dextrose
CPG FDA's Compliance Policy Guide
CPI consumer price index
CPMP Committee for Proprietary Medicinal Products
CPOE computerized physician order entry, computerized prescriber order entry
CPPDE calcium pyrophosphate deposition disease
CPR cardiopulmonary resuscitation
CPS Compendium of Pharmaceutical Specialties
CPSC Consumer Product Safety Commission
CPT current procedural terms
CQI continuous quality improvement
CREST calcinosis, Reynaud's phenomenon, esophageal involvement, sclerodactyly, and telangiectasis
CRF chronic renal failure
CRH critical relative humidity, corticotropic releasing hormone
CRO contract research organization
CRP C-reactive protein
CRT controlled-release tablet
CSA Comprehensive Drug Abuse Prevention and Control Act of 1970, Controlled Substances Act
CSF cerebrospinal fluid, colony stimulating factor
CSH combat support hospitals
CSP chiral stationary phase, compounding sterile preparations
CT charge-transfer, compressed tablet, computerized tomography, computed tomography
CTL cytotoxic T-lymphocyte
CTS compressed tablet for solution
CTZ chemoreceptor trigger zone
CUA cost utility analysis
CV coefficient of variation
CVD cardiovascular disease
CVID common variable immunodeficiency
CW continuous wave

D

DEA Drug Enforcement Administration
DAEA diethylaminoethyl
D&C drug and cosmetic
DATA Drug Addiction Treatment Act
DBP diastolic blood pressure
DC direct current
DCBE double contrast barium exam
DCCT Diabetes Complications and Control Trial
DDMAC FDA's Drug Marketing Advertising and Communications
DEA Drug Enforcement Administration, Drug Enforcement Agency
DEET diethyltoluamide
DF degrees of freedom
DFV daily food value
DHHS Department of Health and Human Services
DI diabetes insipidus
DIC disseminated intravascular coagulation
DIP desquamative interstitial pneumonitis
DIP distal interphalangeal
DISCUS dyskinesia identification system-condensed use scale
DJD degenerative joint disease
DLBCL diffuse large B-cell lymphoma
DLVO Derjaguin-Landau-Verwey-Overbeek
DM dermatomyositis
DMAA Disease Management Association of America
DMSO dimethyl sulfoxide
DMT dimethyltryptamine
DNA deoxyribonucleic acid
DNR do not resuscitate
DOD Department of Defense
DOT directly observed treatment, Department of Transportation
DPCPTRA Drug Price Competition and Patent Term Restoration Act
DPPC dipalmitoylphosphatidylcholine
DPSV differential pulse stripping voltammetry
DRE drug response element, digital rectal examination
DRG diagnosis-related group
DRI dietary reference intake
DRP drug-related problem
DRR drug regimen review
DRV daily reference value
DS degree of substitution
DSC differential scanning calorimetry
DSHEA Dietary Supplement Health and Education Act
DSMB Drug Safety and Monitoring Board
DSM disease state management
DSMT diabetes self-management training
DT dispensing tablet
DTA differential thermal analysis
DTAP diphtheria and tetanus toxoids and acellular pertussis
DTAW drug therapy assessment worksheet
DTP diphtheria, tetaus and pertussis
DTPL drug therapy problem list
DTwP diphtheria and tetnus toxoids and whole-cell pertussis
DUE drug utilization evaluation, drug usage evaluation
DUR drug utilization review, drug use review
DV daily value
DVA Department of Veterans Affairs
DVD digital video disk
DVT deep venous thrombosis
DXA dual energy x-ray absorptimometry

E

E&M evaluation and management
EAR estimated average requirement

EBM	evidence-based medicine
EBV	Epstein-Barr virus
EC	ethics committee, effective concentration
ECD	electron capture detector
ECF	extracellular fluid
ECF-A	eosinophil chemotactic factor of anaphylaxis
ECG	electrocardiogram
ECL	enterochromaffin-like
ECT	enteric-coated tablet
ED	emergency department
EDA	electron donor-acceptor
ED_{50}	50% effective dose
EDI	electronic data interchange
EDRF	endothelium-derived relaxing factor
EDTA	ethylenediaminetetraacetic acid
EDV	end diastolic volume
EEG	electroencephalogram
EES	exfoliative erythroderma syndrome
EI	electron impact
EIA	enzyme immunoassay
EKG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
ELS	evaporative light scattering
ELSI	ethical, legal, and social implication
EM	electromagnetic, emergency medicine
EMIT	enzyme-mediated immunologic technique
EMS	error mean square
EN	enteral nutrition
ENTOMA	Entomological Society of America
ENZ-Aux	enzyme auxotroph bacterial assay
EOF	electro-osmotic flow
EP	European Pharmacopeia
EPA	Environmental Protection Agency
EPMA	electron probe microanalysis
EPS	extrapyramidal symptom
EPT	enzyme prodrug therapy
Eq	equivalent, equation
ERM	electrochemical relaxation measurements
ESCA	electron spectroscopy chemical analysis
ESI	electrospray ionization
E-Sign	Electronic Signatures in Global and National Commerce Act
ESR	electron spin resonance, erythrocyte sedimentation rate
ESRD	end stage renal disease
ET	enterostomal therapist
EU	endotoxin unit

F

FAA	Federal Aviation Administration
FAB	fast-atom bombardment
FAO	Food and Agriculture Organization
FBI	Federal Bureau of Investigation
FCT	film-coated tablet
F-D	force-displacement
FDA	Food and Drug Administration
FDAMA	FDA Modernization Act
FD&C	Food, Drug and Cosmetic
FDP	fibrinogen degradation products
FEF	forced expiratory flow
FEPCA	Federal Environmental Pesticide Control Act
FEV	forced expiratory volume
FFA	free fatty acid
FFT	fast Fourier transform
FH	field hospital, familial hypercholesterolemia
FHD	first human dose
FIA	flow injection analysis
FID	flame ionization detector, free induction decay
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FIR	far infrared
FLP	fragment length polymorphism
FMEA	failure mode and effects analysis
FOBT	fecal occult blood test
FODA	fiber-optic Doppler anemometer
FPD	flame photometric detector
FPIA	fluorescence polarization immunoassay
FRC	functional residual capacity
FSH	follicle-stimulating hormone
FT	Fourier transformation
FTA	fluorescent treponemal antibody
FTC	Federal Trade Commission
FT-IR	Fourier transform infrared spectrometry
FTMS	Fourier transform mass spectrometry
FT-NMR	Fourier transform nuclear magnetic resonance
FVC	forced vital capacity

G

GABA	gamma-aminobutyric acid
GAD	generalized anxiety disorder
GAO	General Accounting Office
GAP	good aseptic practice
GC	gas chromatography
G-cells	gastrin-producing cells
GCP	Good Clinical Practices, Good Compounding Practices
GC-MS	gas chromatography/mass spectrometry
GCP	Good Compounding Practices
G-CSF	granulocyte colony-stimulating factor
GDEPT	gene-directed EPT
GDP	gross domestic product
GERD	gastroesophageal reflux disease
GFR	glomerular filtration rate
GH	growth hormone
GI	gastrointestinal
GLC	gas-liquid chromatography
GLP	good laboratory practice
GLUT	glucose transporter
GMP	good manufacturing practice
Gn-RH	gonadotropin-releasing hormone
GN	glomerulonephritis
GNDF	glial cell line-derived neurotrophic factor
GPCR	guanine nucleotide-coupled receptor
GRAS	generally recognized as safe
GSC	gas-solid chromatography
G6P	glucose 6-phosphate
G6PD	glucose 6-phosphate dehydrogenase
GVHD	graft vs host disease
GYN	gynecology

H

HA	hemagglutination
HAA	hepatitis-associated antigen
HAART	highly active antiretroviral therapy
HACEK	haemophilus, actinobacillus, cardiobacterium, eikenella, kingella
HACCP	hazard analysis and critical control point
HBIG	hepatitis B immune globulin
HBP	high blood pressure
HbS	hemoglobin S
HBV	hepatitis B virus
HC	hydrocarbon
HCA	hierarchical cluster analysis
HCFA	Health Care Financing Administration
HCFC	hydrochlorofluorocarbons
HCG	human chorionic gonadotropin
HCM	health collaboration model
HCP	home care pharmaceutical
HCPCS	HCFA Common Procedure Coding System
HCPS	home-care pharmaceuticals
HCR	health care representative
HCTZ	hydrochlorothiazide
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDPE	high-density polyethylene
HEDIS	health employer data and information set
HEPA	high-efficiency particulate air
HepB	hepatitis B
HETP	height equivalent to a theoretical plate
HFA	hydrofluoroalkane
HFC	hydrofluorocarbons
HFMEA	health care failure modes and effects analysis
HGF	hyperglycemic factor
hGH	human growth hormone
HHS	Health and Human Services
Hib	*Haemophilus influenza* type b
HIC	hydrophobic interaction chromatography
HIMA	Health Industry Manufacturers Association
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLA-DR	human leukocyte antigen (locus) DR
HLB	hydrophile-lipophile balance
HLH	human luteinizing hormone
HME	home medical equipment
HMO	health maintenance organization
HOCA	high osmolality contrast agents
HOPE	Heart Outcomes Prevention Evaluation, Women's Health, Osteoporosis, Progestin, Estrogen Trial
HPDP	health promotion and disease prevention
HPA	hypothalamic-pituitary-adrenal
HPL	human placental lactogen
HPLC	high-performance liquid chromatography
HPLC/MS	high-performance liquid chromatography/mass spectrometry
HPRS	Homeopathic Pharmacopoeia Revision Service
HPUS	Homeopathic Pharmacopoeia of the United States
HPV	human papillomavirus
HRSA	Health Resource and Services Administration
HRT	hormone replacement therapy
HSA	human serum albumin
HSAB	hard and soft acid-base
HSV	herpes simplex virus
HT	hypodermic tablet
HTS	high-throughput screen
HUS	hemolytic-uremic syndrome
HVAC	heating, ventilating, and air conditioning
HWD	hot wire detector

I

I electric current
IBD inflammatory bowel disease
IBW ideal body weight
IC ion chromatography
ICD International Classification of Diseases
ICF intracellular fluid, intermediate care facility
ICH International Committee on Harmonization
ICP inductively coupled argon plasma, intercostals position
ICR ion cyclotron resonance
ICSH interstitial cell-stimulating hormone
ICU intensive care unit
ID intradermal
IDDM insulin dependent diabetes mellitus
IDIS Iowa Drug Information Service
IDU injection drug user
IEC institution ethics committee
IFN interferon
Ig immunoglobulin
IGIM immune globulin intramuscular
IGIV immune globulin intravenous
IGT impaired glucose tolerance
IHD ischemic heart disease
IHGFC International Human Genome Sequencing Consortium
IHI Institute for Healthcare Improvement
IHS Indian Health Service
IL interleukin
ILP inductive logic programming
IM intramuscular
IMA Individual Mobilization Augmentee
IN intranasal
INADEQUATE incredible natural abundance double quantum transition experiment
IND Investigational New Drug
INEPT insensitive nucleus enhancement by polarization transfer
INN International Nonproprietary Names
INR International Normalized Ratio
IOL intraocular lens
IOM Institute of Medicine
IOP intraocular pressure
IPA International Pharmaceutical Abstracts, isopropyl alcohol
IPE introductory practice experiences
IPM integrated pest management
IPV inactivated polio virus
IR infrared
IRB institutional review board
IRR Individual Ready Reserve
IS information sciences
ISE ion-sensitive electrode
ISF interstitial fluid
ISI Institute for Scientific Information
ISMP Institute for Safe Medication Practices
ISO International Standardization Organization
ISP internet service provider
ISPE International Society for Pharmaceutical Engineering
ISS ion-scattering spectroscopy
ITA intention to treat analysis
ITP idiopathic thrombocytopenic purpura, immune thrombocytopenia purpura
IUD intra-uterine device
IUPAC International Union of Pure and Applied Chemistry
IV intravenous
IVD *in-vitro* diagnostic
IVF intravascular fluid
IVIV *in vitro—in vivo*

J

JAMA Journal of the American Medical Association
JCAH Joint Commission on Accrediation of Hospitals
JCAHO Joint Commission on Accrediation of Healthcare Organizations
JNC Joint National Committee
JP Japanese Pharmacopeia

K

KS ketosteroid, Kaposi's sarcoma
kGy kilogray
KVO keeping the vein open

L

LAFW laminar airflow workbench
LAIV live attenuated influenza vaccine
LAL limulus amebocyte lysate
LC liquid chromatography
LC-FTIR liquid chromatography-Fourier transform infrared
LC-MS liquid chromatography
LCST lower critical solution temperature
LDL low-density lipoprotein
LDPE low-density polyethylene
LED light-emitting diode
LF laminar flow
LH luteinizing hormone
LLDPE linear low-density polyethylene
LLE liquid-liquid extraction
LOCA lower osmolality contrast agents
LPL lipoprotein lipase gene
L/S least square, lecithin to sphingomyelin ratio
LSD lysergic acid diethylamide
LT leukotriene
LTCF long term care facility
LTH luteotropin
LVEDP left ventricular end diastolic pressure
LVI large-volume injection
LVP large-volume parenteral

M

MAb monoclonal antibody
MAC maximum allowable cost, minimum alveolar concentration
MALDI matrix-assisted laser desorption ionization
MALT mucosa-associated lymphoid tissue
MAOI monoamine oxidase inhibitor
MAP maximum *a posteriori*
MAS magic angle spinning
MASH mobile army surgical hospital
MAT mean absorption time
MAUT multi-atribute utility theory
MBC minimum bactericidal concentration
MBNQ Malcolm Baldrige National Quality Program
MCH mean corpuscular hemoglobin
MCHC mean corpuscular hemoglobin concentration
MCO managed care organization
MCP metacarpophalangeal
MCT multiple compressed tablet
MCV mean corpuscular volume
MDI metered-dose inhaler
MDR multidrug resistance
MDS minimum data set
MEC minimum effective concentration
MECC micellar electrokinetic capillary chromatography
MedDRA Medical Dictionary for Drug Regulatory Affairs
MEKC micellar electrokinetic chromatography
MEMS medication event monitoring system
mEq milliequivalent
MER medication errors reporting
MERP medication error reduction program
MHHP Minnesota Hospital and Healthcare Partnership
MHC major histocompatibility complex
Mho reciprocal ohm
MI mitral insufficiency, myocardial infarction
MIA metabolite bacterial inhibition assay
MIC minimum inhibitory concentration
MIL-STD military standard
MKT mean kinetic temperature
MLV multilamellar vesicle
MMR measles, mumps, and rubella
MMWR Morbidity and Mortality Weekly Report
MNT medical nutrition therapy
MO molecular orbital
MPBR master production batch record
MPD minimum pyrogenic dose
MPJE Multistate Pharmacy Jurisprudence Exam
MQ-NMR multiple quantum technique nuclear magnetic resonance
MR mental retardation, mentally retarded
MRC medical research council
MRFIT Multiple Risk Factor Intervention Trial
MRI magnetic resonance imaging
MRIP Model Rules for Institutional Pharmacy
mRNA messenger RNA
MRS magnetic resonance spectroscopy
MRT mean residence time
MS mass spectrometry, mass spectroscopy, multiple sclerosis, mitral stenosis
MSC Medical Service Corps
MSD mass spectral detector
MS/MS mass spectrometry/mass spectrometry
MSPPA Model State Pharmacy Practice Act
MSUD maple syrup urine disease
MTC minimum toxic concentration
MTP metatarsophalangeal
MTT mean transit time
MTX methotrexate
MUE medication-use evaluation
MW molecular weight
MWQ minimum weighable quantity

N

NABP National Association of Boards of Pharmacy
NACDS National Association of Chain Drug Stores
NADPH nicotinamide-adenine-dinucleotide phosphate
NAG ASPEN's National Advisory Group
NAMS North American Menopause Society
NARD National Association of Retail Druggists
NASA National Aeronautics and Space Administration
NASHP National Academy for State Health Policy
NCBTMB National Certification Board for Therapeutic Massage and Bodywork

NCCAM	National Center for Complimentary and Alternative Medicine
NCCAOM	National Center for Complimentary and Alternative Oriental Medicine
NCCLS	National Committee for Clinical Laboratory Standards
NCC MERP	National Coordinating Council for Medication Error Reporting and Prevention
NCE	new chemical entity
NCEP	National Cholesterol Education Program
NCF-A	neutrophil chemotactic factor of anaphylaxis
NCHC	National Coalition on Health Care
NCI	negative-ion chemical ionization, National Cancer Institute
NCPA	National Community Pharmacists Association
NCPDP	National Council for Prescription Drug Programs
NCPIE	National Council on Patient Information and Education
NCPS	National Center for Patient Safety
NCQA	National Committee for Quality Assurance
NDA	New Drug Application
NDC	National Drug Code
NDMS	National Disaster Medical System
NEPM	non-parametric population modeling
NGC	National Guideline Clearinghouse
NHANES	National Health and Nutrition Examination Survey
NHGRI	National Human Genome Research Institute
NIDA	National Institute on Drug Abuse
NIDDM	non-insulin dependent diabetes mellitus
NIH	National Institutes of Health
NIMH	National Institute for Mental Health
NIOSH	National Institute for Occupational Safety and Health
NIR	near infrared
NISPC	National Institute for Standards in Pharmacist Credentialing
NIST	National Institute of Standards and Technology
NKC	natural killer cell
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NPD	nitrogen phosphorus detector
NPH	neutral protamine Hagedorn
NPLEX	Naturopathic Physician Licensing Examination
NPN	nonprotein nitrogen
NPR	National Public Radio
NPSF	National Patient Safety Foundation
NPSG	National Patient Safety Goals
NQF	National Quality Forum
NQMC	National Quality Measures Clearinghouse
NRC	Nuclear Regulatory Committee, Nuclear Regulatory Commission
NRT	nicotine-replacement therapy
NSABP	National Surgical Adjuvant Breast and Bowel Project
NSAID	nonsteroidal anti-inflammatory drug
NSF	National Science Foundation
NTI	narrow therapeutic index

O

OA	"open access," osteoarthritis
OAM	Office of Alternate Medicine
OASI	Old-Age and Survivors Insurance
OB	obstetrics
OBDIV	operational division
OBRA	Omnibus Budget Reconciliation Act
OCD	obsessive-compulsive disorder
OCP	oral contraceptive pill
OD	outside diameter
ODT	orally disintegrating tablet
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OLV	oligolamellar vesicles
OMD	Oriental medicine degree
OPV	oral polio vaccine
OR	operating room
ORD	optical rotatory dispersion
OSHA	Occupational Safety and Health Administration
OT	old tuberculin
OTC	over-the-counter, ornithine transcarbamylase
O/W	oil-in-water

P

PAD	premature atrial depolarization
PADE	potential adverse drug event
PAGE	polyacrylamide gel electrophoresis
P&P	policies and procedures
P&T	pharmacy and therapeutics
PANSS	positive and negative syndrome scale
PAO	peak acid output
PAW	pulmonary arterial wedge
Pb	phenobarbital
PBE	proton-balance equation
PBI	protein-bound iodine
PBM	pharmacy benefit management, pharmacy benefit manager
PBP	penicillin-binding protein
PBR	production batch record
PC	personal computer, percutaneous
PCA	patient-controlled analgesia, principal component analysis
PCCF	pharmacist care claim form
PCP	phencyclidine, *pneumocystis carinii* pneumonia
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PDA	Parenteral Drug Association, personal digital assistant
PDCA	Plan-Do-Check-Act
PDGF	platelet-derived growth factor
PDMA	Prescription Drug Marketing Act
PDR	Physicians' Desk Reference
PDSA	Plan-Do-Study Act
PDUFA	Prescription Drug User Fee Act
PE	pulmonary embolism
PEG	polyethylene glycol, percutaneous endoscopic gastrostomy
PEPI	Postmenopausal Estrogen/Progestin Interventions
PEPT1	plasma membrane peptide transporter
PET	positron emission tomography, positron emission test
PFG	pulsed field gradients
PFM	peak flow meter
PFR	peak flow rate
PGDB	Prevention Guidelines Database
PGE	prostaglandin E
PHI	personal health information, protected health information
PhRMA	Pharmaceutical Research and Manufacturers Association
PHS	US Public Health Service
PHSA	Public Health Service Act
PICVI	plasma impulse chemical vapor deposition
PID	photo-ionization detector, pelvic inflammatory disease
PIP	proximal interphalangeal
PIT	phase inversion temperature
PKC	protein kinase C
PKU	phenylketonuria
PL	Public Law
PLAN	Pharmacists' Learning Assictance Network
PLC	programmable logic controllers, phospholipase C
PLM	polarized light microscopy
PM	polymyositis
PMA	Pharmaceutical Manufacturers Association
PMMA	polymethylmethacrylate, (methacrylic acid)
PMN	polymorphonuclear leukocyte
PMS	post-marketing surveillance
PN	parenteral nutrition
PND	paroxysmal nocturnal dyspnea
PNI	psychoneuroimmunology
PNS	peripheral nervous system
PNSU	probability of nonsterile unit
PNU	protein nitrogen unit
POA	durable power of attorney
POC	point-of-care
POMR	problem-oriented medical record
POST	Polymer Science and Technology
PP	protein precipitation
PPA	phenylpropanolamine
PPAC	pharmacy practice activity classification
PPD	purified protein derivative
PPI	proton pump inhibitor, patient package insert
PPLO	pleuropneumonia-like organism
ppm	parts per million
PPO	preferred provider organization, poly(propylene oxide)
PPPA	Poison Prevention Packaging Act
PPS	professional pharmacy services
Prl	prolactin
PRN	as needed, Pharmacist Recovery Network
PRO	professional review organization
PSA	prostate specific antigen
PSC	Program Support Center, pluripotent stem cell
PSE	porto-systemic encephalopathy
PSIT	Pennsylvania Smell Identification Test
PSP	phenolsulfonthalein
PSST	pressure sore status tool
PST	pocket smell test
PSVT	paroxysmal supraventicular tachycardia
PT	prothrombin time
PTA	plasma thromboplastin antecedent
PTC	plasma thromboplastin component
PTCB	Pharmacy Technician Certification Board
PTFE	polytetrafluorethylene
PTH	parathyroid hormone
PT/INR	prothrombin time/international normalized ratio

PTSD	post-traumatic stress disorder
PTT	partial thromboplastin time
P2C2	professionals and patients for customized care
PUSH	pressure ulcer scale for healing
PVC	premature ventricular contraction
PVD	premature ventricular depolarization
PVP	polyvinylpyrrolidone
PWDT	pharmacist's workup of drug therapy

Q

Q	coulomb
QA	quality assurance
QALY	quality-adjusted life years
QC	quality control
QOL	quality of life

R

RA	rheumatoid arthritis
RAM	random access memory
R&D	research and development
RAP	resident assessment protocol
RBC	red blood cell
RBRVS	resource-based relative value scale
RCA	root cause analysis
RCC	renal cell carcinoma
RCT	randomized controlled trial
RDA	recommended daily allowance, recommended dietary allowance
rDNA	recombinant DNA
RDI	reference daily intake
REM	rapid eye movement
RES	reticuloendothelial system
RF	rheumatoid factor
RFLP	restriction fragment length polymorphism
RH	relative humidity
Rh	rhesus blood factor/group
rhGM	recombinant granulocyte-macrophage
RI	refractive index
RIA	radioimmunoassay
RIBA	recombinant immunoblot assay
RMP	risk management program
RNA	ribonucleic acid
RNAi	RNA interference
RNase	ribonuclease
RO	reverse osmosis
ROI	return on investment
rPA	recombinant plasminogen activator
RPC	reverse-phase chromatography
RPN	risk priority number
RPR	rapid plasma reagin
RPS	Remington's Pharmaceutical Sciences
RSD	relative standard deviation
RSE	reference standard endotoxin
RSV	respiratory syncytial virus
RV	residual volume
RVU	relative value unit
Rx	prescription

S

SA	sinoatrial
SAD	sunlight affective disorder
SADR	suspected adverse drug reaction
SAE	serious adverse event
SAL	sterility assurance level
SAMHSA	Substance Abuse and Mental Health Services
SAP	sterility assurance probability
SARA	Superfund Amendment and Reauthorization Act
SARS	severe acute respiratory syndrome
SBP	systolic blood pressure
SC	subcutaneous
SCD	soybean casein digest
SCID	severe combined immunodeficiency
SCOT	support-coated open tubular
SCT	sugar-coated tablet
SD	standard deviation
SDO	standards development organization
SDS	special delivery system
SEC	size-exclusion chromatography, soft elastic capsule
SERM	selective estrogen-receptor modulator
SFC	supercritical fluid chromatography
SI	International System of Units
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SIDS	sudden infant death syndrome
SIMS	secondary ion mass spectrometry
siRNA	small interfering RNA
SLE	systemic lupus erythematosus
SMBGP	self-monitoring blood glucose product
SMILES	Simplified Molecular Line Entry Specification
SMU EC	Safe Medication Use Expert Committee
SNDA	supplemental new drug application
SNP	single nucleotide polymorphism
SOAP	subjective, objective, assessment, and plan
SOP	standard operating procedure
SPE	solid phase extraction
SPF	sun protective factor
SRM	selected reaction monitoring
SSA	Social Security Act
SSRI	selective serotonin reuptake inhibitor
STA	slit-to-agar
STD	sexully transmitted disease
STH	somatotrophic hormone
STP	standard temperature and pressure
SUPAC	scale-up and post-approval changes
SUV	small unilamellar vesicles
SVI	small-volume injection
SVM	support vector machine
SVP	small-volume parenteral
SWI	sterile water for injection
SWOT	strengths, weaknesses, opportunities, and threats

T

T_3	triiodothyronine
T_4	thyroxine
TAP	total available pool
TB	tuberculosis
TBG	thyroxine-binding globulin
TBPA	thyroxine-binding prealbumin
TC	total cholesterol
TCD	thermal conductivity conductor
TCGF	T-cell growth factor
TCR	T-cell receptor
TD	toxicodynamic, tetanus and diphtheria
TDD	telecommunication device for the deaf
TDDS	transdermal drug-delivery system
TESS	toxic exposure and surveillance system
TG	triglyceride
TGA	thermogravimetric analysis
TH	T helper
TIA	transient ischemic attack
TIBC	total iron binding capacity
TIV	trivalent inactivated influenza vaccine
TK	toxicokinetic
TLC	thin-layer chromatography, therapeutic life-style change
TM	transcendental meditation
TMA	thermomechanical analysis
TMP-SMZ	trimethoprim-sulfamethoxazole
TNA	total nutrient admixture
TNF	tissue necrosis factor
TOC	total organic carbon
TOPS	Take Off Pounds Sensibly
tPA	tissue plasminogen activator
TPC	total pharmacy care
TPN	total parenteral nutrition
TPO	treatment, payment and health care operations
TPU	Troop Program Unit
TPQ	total product quality
TQM	total quality management
TRH	thyrotropin-releasing hormone
TRIP	turning research into practice
T.R.U.E.	thin-layer rapid use epicutaneous
TS	test solution
TSD	thermionic specific detector
TSH	thyroid-stimulating hormone
TT	tablet triturate
TTP	thrombotic thrombocytopenic purpura
TV	tidal volume
2D-NMR	two-dimensional nuclear magnetic resonance

U

UCC	Uniform Commercial Code
UCR	usual, customary and reasonable
UL	tolerable upper intake level
ULV	unilamellar vesicles, ultralow-volume
UPIN	unique provider identification number
URI	upper respiratory infection
URL	Uniform Resource Locater
USAF	United States Air Force
USAN	United States Adopted Names
U.S.C.	United States Code
USDA	United States Department of Agriculture
USNS	United States Naval Ship
USP	United States Pharmacopeia
USP DI	USP Drug Information
USP/NF	United States Pharmacopeia/National Formulary
USPSTF	United States Preventive Services Task Force
UTI	urinary tract infection
UV	ultraviolet

V

V	volt
VA	Veterans Affairs
VC	vital capacity
VDRL	Venereal Disease Research Laboratory
VEGF	vascular endothelial growth factor
VHA	Veterans Health Administration
VIP	vasoactive intestinal polypeptide
VIPPS	verified internet pharmacy practice sites
Vis	visible
VLCD	very low calorie diet
VLDL	very low-density lipoprotein
VOC	volatile organic compound
VTE	venous thromboembolism
VNTR	variable number of tandem repeats

v/v percent volume in volume
VWD von Willebrand's disease
VWF von Willebrand factor

W

W watt
WA wide awake
WAP wireless application protocol
WAS Wiskott-Aldrich syndrome
WAVE Women's Angiographic Vitamin and Estrogen
WBC white blood cell
WCOT wall-coated open tubular
WFI water for injection
WHA World Health Assembly
WHIMS Women's Health Initiative Memory Study
WHO World Health Organization
WIC Special Supplemental Program for Women, Infants, and Children
W/O water-in-oil
w/v percent weight in volume
w/w percent weight in weight

X

X-LA X-linked agammaglobulinemia
XML extensible markup language
XRD X-ray diffraction
XRPD X-ray powder diffraction

Y

Z

Z atomic number
ZE Zollinger-Ellison syndrome
ZSR zeta sedimentation ratio

Index

B

c

D

E

F

G

I