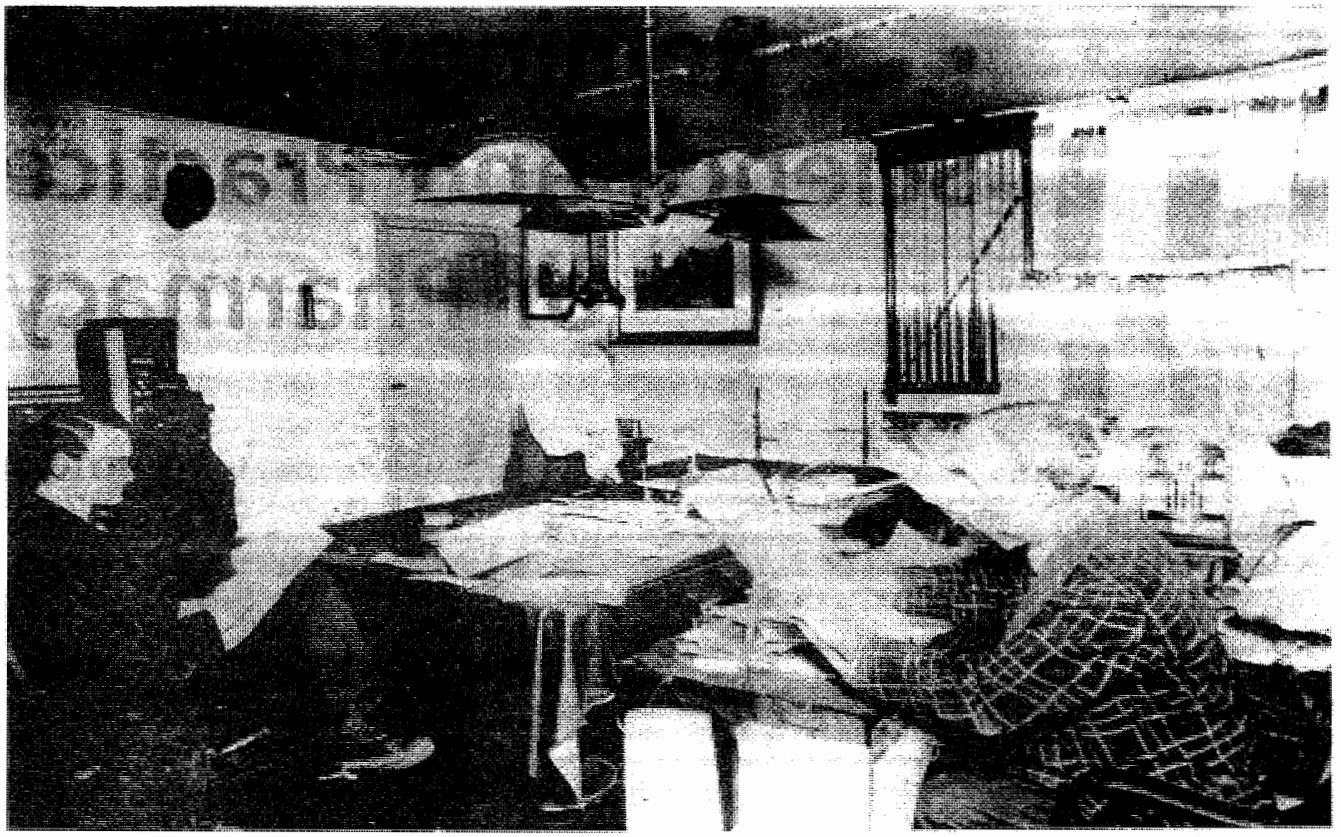

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Volume I

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Preface to the Twentieth Edition

At this writing, Remington, as it is commonly known in the profession, is at a point midway through the second decade of its second century. One hundred and fifteen years of service to students and practitioners, Remington is now poised on the brink of a new millenium. The 5 years that have elapsed since the publication of the previous edition have witnessed substantial and far-reaching changes in practically every field of human endeavor. Pharmacy—both the science and practice—perhaps has enjoyed more than its share. It is not so peculiar that a comment quite similar to the previous sentence has been incorporated in the first paragraph of practically every Preface of the previous 19 editions, including the first.

The impact of current information-exchange technology, with enormous quantities of data available at the touch of a key, engendered much consideration in the planning stages of this publication. At one time, a book of 2000 pages could be created using an all-inclusive approach: a tome with rather complete coverage of a field, in which one could find a wealth of information on practically every relevant subject. Without question, this approach is now beyond consideration. It was obvious that Remington 20 must address the newer concepts of information exchange. With modern technology, current information is processed and updated so rapidly that it may quickly become stale and, sometimes, of questionable value.

A wholesale transformation of the book was not envisioned, but rather a judicious and planned metamorphosis. Thus, a number of areas have been digested, reorganized, and pruned or amplified. Monographs for drugs have been culled, and most of the dosing and dosage form information has been deleted from individual drug monographs. This type of changeable information is impossible to keep current considering a 5-year publication cycle and the availability of the Internet. The general statements preceding individual classes of drugs have been expanded to provide comprehensive coverage of each class. Thus, useful information for the drug specialist is presented in an expanded format, rather than offered as overwhelming masses of data, which, if simply learned by rote, may easily be confused or forgotten.

The listing of names of manufacturers for each drug (official and/or generic) has been dropped. With the publication of the previous edition, it was evident that due to the dynamic situation in the drug industry, almost 25% of the pharmaceutical houses either had changed names or merged during the interval between completion of the manuscript and the publication date. Thus, this information often was either of little value or misleading.

One chapter (Calculus) has been deleted, and two chapters (Immunizing Agents and Diagnostic Skin Antigens [81] and Allergenic Extracts [82]) were consolidated into a single chapter [89] bearing the combined titles. Many chapters were trimmed in order to recover space for 10 new chapters, all within the realm of Pharmacy Practice. Several areas (such as Alternative Medicines and Treatment), which have enjoyed a resurgence of activity, have been expanded.

Essentially, the goal has been to reduce the clutter of excessive, easily attainable reference material and elaborate the area of pharmacy practice, without sacrificing the scientific concepts. The intention was to focus on the textbook features of the publication. This is a departure from the traditional role of a complete reference medium, to one that emphasizes teaching and learning principles while still retaining essential source material.

A number of previous authors have gone on to other interests and have transferred their tasks to new members of the team. This has exposed many areas to fresh ideas and alternative perspectives. The 143 authors/editors, of which 52 are first-time contributors, represent 34 universities, 17 pharmaceutical firms, 16 private practices, and 3 associated government agencies. Thus, practically every facet of the profession is encompassed.

Several members of the Editorial Board, who have served for a number of editions—Drs Hussar, Rippie, and Zink—have decided to relinquish their responsibilities. Their extensive contribution of time and effort is duly appreciated. A new member, Dr Nicholas Popovich, assumed the onus of a greatly expanded Part 8, Pharmacy Practice, and has completed the task superbly.

Mr John Hoover, associated with Remington for eight editions and currently as Managing Editor, has again done an exemplary job of coordination, especially at the early stages of manuscript preparation when all seems a clutter and disarray of paper (even in the "paperless" computer age!). Ms Bonnie Packer, our inveterate reader, critic, and editorial assistant, has untangled numerous word snarls, which are usually the product of overzealous authors and editors who have become immersed in their own disciplines and overlooked the fact that their words will also be read, and hopefully understood, by the novice.

It has been said that everything comes full circle or, in modern parlance, "What goes around comes around." In 1885, with the first edition of Remington, the publisher of this book was the well-established Philadelphia firm of JB Lippincott Co. This arrangement survived through eight editions, ending in 1936. With the intervention of the Second World War, the ninth edition did not appear until 1948 under the banner of the Mack Publishing Co, and this relationship has been sustained through the 19th edition in 1995. Mack has foregone the publishing role but will continue to print the book. The new publisher is, in reality, not so new, as the book is now in the hands of Lippincott Williams & Wilkins—the ring has been closed.

A volume of 2000 pages requires the cooperation of authors, editors, and the publisher and their associates in order to complete a tedious and time-consuming task. All who have contributed are to be commended for their efforts and time. However, having read the text at least twice in its entirety, the responsibility for errors, of any kind, ultimately resides with the editor. One can only work and strive to ensure that the book is free of flaws, blunders, and errors, but if this were the case, it probably would be a first.

Philadelphia, January 2000
ARG

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Preface to the First Edition

The rapid and substantial progress made in Pharmacy within the last decade has created a necessity for a work treating of the improved apparatus, the revised processes, and the recently introduced preparations of the age.

The vast advances made in theoretical and applied chemistry and physics have much to do with the development of pharmaceutical science, and these have been reflected in all the revised editions of the Pharmacopoeias which have been recently published.When the author was elected in 1874 to the chair of Theory and Practice of Pharmacy in the Philadelphia College of Pharmacy, the outlines of study which had been so carefully prepared for the classes by his eminent predecessors, Professor William Proctor, Jr, and Professor Edward Parrish, were found to be not strictly in accord, either in their arrangement of the subjects or in their method of treatment.Desiring to preserve the distinctive characteristics of each, an effort was at once made to frame a system which should embody their valuable features, embrace new subjects, and still retain that harmony of plan and proper sequence which are absolutely essential to the success of any system.

The strictly alphabetical classification of subjects which is now universally adopted by pharmacopoeias and dispensatories, although admirable in works of reference, presents an effectual stumbling block to the acquisition of pharmaceutical knowledge through systematic study; the vast accumulation of facts collected under each head arranged lexically, they necessarily have no connection with one another, and thus the saving of labor effected by considering similar groups together, and the value of the association of kindred subjects, are lost to the student.In the method of grouping the subjects which is herein adopted, the constant aim has been to arrange the latter in such a manner that the reader shall be gradually led from the consideration of elementary subjects to those which involve more advanced knowledge, whilst the groups themselves are so placed as to follow one another in a natural sequence.

The work is divided into six parts.Part I is devoted to detailed descriptions of apparatus and definitions and comments on general pharmaceutical processes.

The Official Preparations alone are considered in Part II. Due weight and prominence are thus given to the Pharmacopoeia, the National authority, which is now so thoroughly recognized.

In order to suit the convenience of pharmacists who prefer to *weigh solids* and *measure liquids*, the official formulas are expressed, in addition to parts by weight, in *avoirdupois weight* and *apothecaries' measure*.These equivalents are printed in *bold type* near the margin, and arranged so as to fit them for quick and accurate reference.

Part III treats of Inorganic Chemical Substances.Precedence is of course given to official preparation in these.The descriptions, solubilities, and tests for identity and impurities of each substance are systematically tabulated under its proper title.It is confidently believed that by this method of arrangement the valuable descriptive features of the Pharmacopoeia will be more prominently developed, ready reference facilitated, and close study of the details rendered easy. Each chemical operation is accompanied by equations, whilst the reaction is, in addition, explained in words.

The Carbon Compounds, or Organic Chemical Substances, are considered in Part IV.These are naturally grouped according to the physical and medical properties of their principal constituents, beginning with simple bodies like cellulin, gum, etc, and progressing to the most highly organized alkaloids, etc.

Part V is devoted to Extemporaneous Pharmacy.Care has been taken to treat of the practice which would be best adapted for the needs of the many pharmacists who conduct operations upon a moderate scale, rather than for those of the few who manage very large establishments.In this, as well as in other parts of the work, operations are illustrated which are conducted by manufacturing pharmacists.

Part VI contains a formulary of Pharmaceutical Preparations which have not been recognized by the Pharmacopoeia.The recipes selected are chiefly those which have been heretofore rather difficult of access to most pharmacists, yet such as are likely to be in request.Many private formulas are embraced in the collection; and such of the preparations of the old Pharmacopoeias as have not been included in the new edition, but are still in use, have been inserted.

In conclusion, the author ventures to express the hope that the work will prove an efficient help to the pharmaceutical student as well as to the pharmacist and the physician. Although the labor has been mainly performed amidst the harassing cares of active professional duties, and perfection is known to be unattainable, no pains have been spared to discover and correct errors and omissions in the text.The author's warmest acknowledgments, are tendered to Mr A B Taylor, Mr Joseph McCreery, and Mr George M Smith for their valuable assistance in revising the proof sheets, and to the latter especially for his work on the index.The outline illustrations, by Mr John Collins, were drawn either from the actual objects or from photographs taken by the author.

Philadelphia, October, 1885 JPR.

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CHAPTER 38

Preformulation

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PREFORMULATION CHALLENGES

Bridging Discovery and Development

Preformulation activities range from supporting discovery's identification of new active agents to characterizing physical properties necessary for the design of dosage forms. Critical information provided during preformulation can enhance the rapid and successful introduction of new therapeutic entities for humans. For example, the selection of compounds that have physical properties favorable for oral absorption early in discovery can facilitate the rapid progress of these compounds at all stages of development. Similarly, the adaptation of technologies that permit the rapid selection of a salt that is best suited for development can facilitate the manufacturing of the final market-image dosage form. The broad range of activities in preformulation requires a continuing dialog between scientists in many different disciplines, as shown in Figure 38-1.

Discovery to Development

The introduction of mechanism-based mass screening of small molecules in the late 1980s ushered in a new discovery era. Previously, animal tissue and whole animal screens had been used to find new chemical entities (NCE) that had therapeutic potential. Although the throughput was low, the final candidates for development had proven activity in animals. Today, recombinant enzymes and receptors are used in high-throughput *in vitro* screens that can evaluate quickly the hundreds of thousands of compounds that are found in chemical libraries. Active compounds (mass screen hits) then are evaluated, and some are used as the basis for further synthetic efforts. Because synthesis of new compounds can become rate limiting, combinatorial methods have been developed to synthesize rapidly new compounds using automated technologies. Today, even newer technologies are being used to increase speed and reduce material consumption. This is the attraction for using nanotechnologies in screening, synthesis, purification, and analysis.

All of these innovative changes have had a cascading impact on development. Unprecedented *in vitro* activity and specificity can now be found using recombinant proteins and automated mass screening, but aqueous solubility problems are masked by dimethyl sulfoxide, a universal solvent that is used to dissolve chemical libraries for testing. As a result, although many initially promising NCEs are extremely potent in the *in vitro* enzyme assays, they are inactive *in vivo* because of their unfavorable solubility and dissolution characteristics in the aqueous media of the body. This provides a demanding challenge for the preformulation scientist because, with mechanism-based therapy, testing in humans is often the only means of evaluating the efficacy of a new therapeutic strategy.

Integrating Discovery and Development

If unfavorable physical properties can be minimized before extensive *in vitro* optimization occurs, it may be possible to reduce the time required to discover *active and absorbable* NCEs that are poised for rapid development. Integrating discovery and development, however, will require that preformulation scientists develop a greater understanding of the molecular mechanisms of unfavorable physical properties such as aqueous insolubility. This knowledge then will provide a rational basis for making structural modifications that can enhance physical properties while *in vitro* activity also is being optimized. Figure 38-2 shows the potential time delay in discovering an orally active NCE when only activity is optimized, compared to the potential time savings when both activity and aqueous solubility are balanced for oral absorption.

Assume that a company has a chemical library of thousands of compounds that it wants to screen for a particular therapeutic target. It has isolated the appropriate receptor (protein) and has developed a high-throughput mass screen for its *in vitro* activity. In addition, for every compound that is screened for activity, it can determine aqueous solubility using a high-throughput method. Figure 38-2 shows a plot of activity versus solubility for the screened compounds. For simplicity, an ellipse is used to show regions that are possible for this hypothetical receptor. The inverse relationship shown by the ellipse, with the major axis decreasing from left to right, is based on anecdotal observations that compounds that have high *in vitro* activity often have poor aqueous solubility. A molecular explanation for why such a relationship might exist is given in the section *Aqueous Insolubility*, page 716. The two-phase discovery of an orally active NCE will now be discussed.

During Discovery Phase A, the company used *in vitro* activity as its only criterion for discovering the best compound to develop. Point 0 on the ellipse shows a compound that was chosen for further synthetic optimization on the basis of mass screening. This compound had the highest in vitro activity. During optimization, mass screens were used to provide feedback to direct the synthesis of more active analogs. Compound 1 was the most active NCE the discovery team found. However, this compound is also the most insoluble NCE on the ellipse. Enthusiasm for the compound diminished when *in vivo* animal testing showed inadequate blood levels. A lack of absorption due to poor aqueous solubility was suspected as the cause (other studies had shown that metabolism and permeability did not account for the low blood levels).

During Discovery Phase B, aqueous solubility and *in vitro* activity were optimized simultaneously. The NCE shown at

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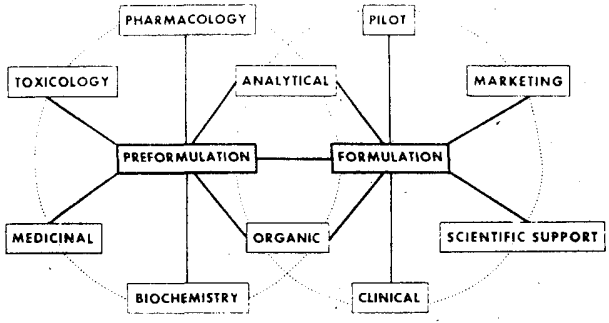

Figure 38-1. The wheels of product development.

Point 2 was eventually recommended for development. Although this compound is less active than Compound 1, it represented a better compromise between aqueous solubility and *in vitro* activity. Such compromises may be necessary if formulation techniques cannot be used to obtain good *in vivo* activity. The declaration of Compound 1 as a lead in the hope that formulation techniques might solve the absorption issue could slow development. For this reason, it is essential that preformulation provide the discovery process with rapid feedback regarding the feasibility of formulation solutions that may compensate for poor physical properties and subsequent absorption problems.

A strategy in which discovery and development work in concert is also shown in Figure 38-2. In this scenario, both aqueous solubility and *in vitro* activity were used simultaneously in the search to improve Compound 0. By using dual feedback, the company may have been able to progress more directly from Compound 0 to Compound 2. In addition, knowledge of the aqueous solubilities of all the mass screen hits also may have provided alternative starting points. Instead of picking Compound 0 as the only starting point for synthetic optimization, Compound 3, which was not as active but had much better aqueous solubility, could have been chosen. Dual activity and solubility feedback in the co-optimization of both Compounds 0 and 3 would have been used to guide further synthesis.

The potential time saved using the concerted strategy could be considerable. However, for the whole program to be in synchrony, it will require that preformulation scientists develop high-throughput screening methodologies for physical properties, analogous to discovery's biological screens; high-throughput screening methods can predict the feasibility of a formulation solution for poor absorption. Because technological breakthroughs in the discovery process have increased the number of NCEs that will be candidates for development, it is imperative that new candidates have the requisite physical properties that are needed for rapid development. Otherwise, development may become an unacceptable bottleneck.

Preformulation scientists will have to work proactively with discovery scientists to design active NCEs that are active *and* transportable through biological tissues such as the gastrointestinal (GI) tract or the endothelial cells of the blood–brain barrier. New insight into the molecular basis of physical properties and rapid high-throughput physical property screens are needed to accomplish this goal. The section on *Engineering in the Solid State*, page 714, will discuss briefly some of these areas. In the following sections, characteristics of the solid state are discussed. A fundamental understanding of this state of matter is essential for making timely preformulation decisions.

Critical API Decisions

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.

REQUIREMENTS OF THE SOLID STATE

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 38-1). Application of this notation to the effects of moisture, the major environmental factor influencing the solid state, will then be examined.

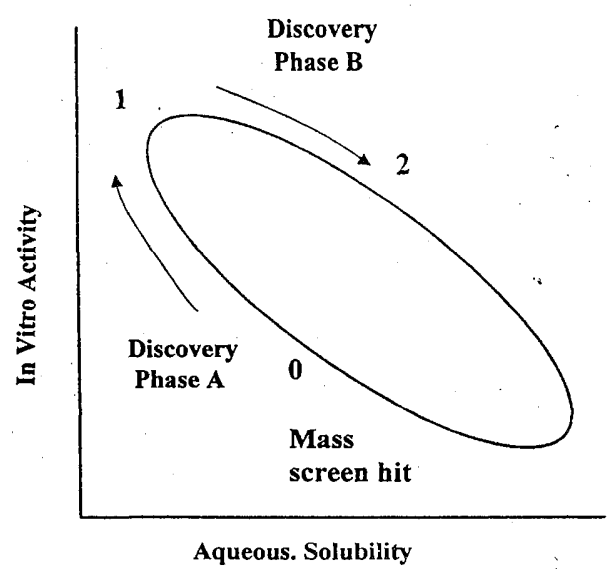

Figure 38-2. Search for an active and orally absorbable NCE.

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Table 38-1. 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
${}_jA^i_\Sigma$	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, ${}_jA^i_\Sigma$ 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

$$A \xrightarrow{H_2O} a. \tag{1}$$

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,

$$A \rightarrow B \tag{2}$$

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

$$A \rightleftarrows A^i \tag{3}$$

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 ${}_{\mathrm{I}}A$ 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 38-3, 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 38-3 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 $A_\alpha > A_\delta > {}_{\mathrm{I}}A$. In the Figure 38-3 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 in-

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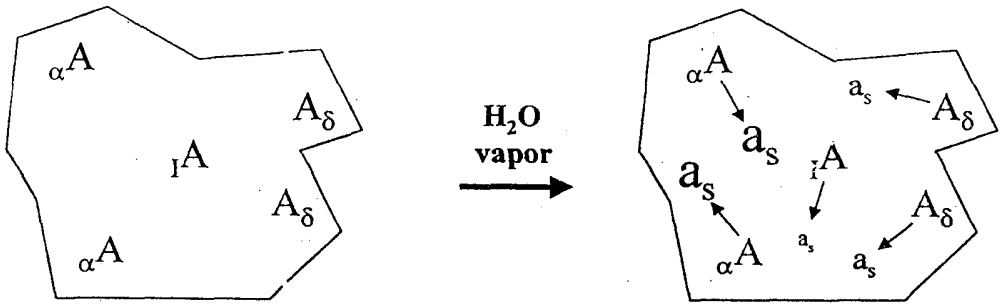

Figure 38-3. Surface of a milled API and dissolution of surface regions due to adsorbed moisture.

creases 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.[1] Equation 4 shows a chain of reactions from A to a degradant B,:

$$A \xrightarrow{[H_2O]_{vapor}} a \xrightarrow[\text{catalytic impurity}]{[H_2O]_{vapor}} b \xrightarrow{[H_2O]_{vapor}} B \qquad (4)$$

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 Acids/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:

$$A_{\Sigma}^{-} \xrightarrow{[H_2O]_{vapor}} A_{\Sigma}^{0} \qquad (5)$$

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

$$A_{\Sigma}^{+} \xrightarrow{[H_2O]_{vapor}} A_{\Sigma}^{0} \qquad (6)$$

where $A^+ = HA^+$. 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*).

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*, page 704). When this form is put in contact with water, the following solvent-mediated transformation can be promoted:

$${}_{II}A \xrightarrow{H_2O} {}_{I}A \qquad (7)$$

Water, in the vapor phase, has also been shown to be capable of mediating transformations between amorphous and crystalline forms in both directions.[2]

$${}_{\alpha}A \underset{\leftarrow}{\xrightarrow{[H_2O]_{vapor}}} {}_{I}A \qquad (8)$$

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

$${}_{II}A \xrightarrow{H_2O} {}_{h}A \qquad (9)$$

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

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

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 are 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

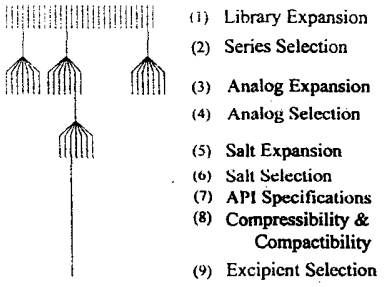

Figure 38-4. Typical API sequential decision-making: selection and expansion cycles.

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 $_jA^i$, is the first critical solid-state decision for preformulation in the developmental arena.

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 38-4, 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, H*An* is used to represent a counter-acid that forms an anion An^-. Common counter-acids like HCl and maleic acid are listed in Table 38-2. 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 38-2 along with organic counter-bases.

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 H*An*, An^-. For salt formation, A^0 must be sufficiently basic to remove the proton from H*An* (see *Salt-Forming Reactivity Potential*, page 705).

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:

$$A^0H^+An^- \longrightarrow A^0H^+ + An^- \quad \text{and} \quad A^0H^+ \underset{\text{high } pK_a}{\overset{\text{low } pK_a}{\rightleftharpoons}} A^0 + H^+ \qquad (11)$$

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*, page 717). 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.

Table 38-2. Molecular Forms Marketed Worldwide Between 1983–1996

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

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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.[3–5] 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 38-5 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 38-2 gives potential counter-ions and their pK_a values from a listing of all drugs approved worldwide from 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*, page 702). 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 doxylamine (pK_a 4.4) is possible[6] 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 38-2 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:

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

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

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.

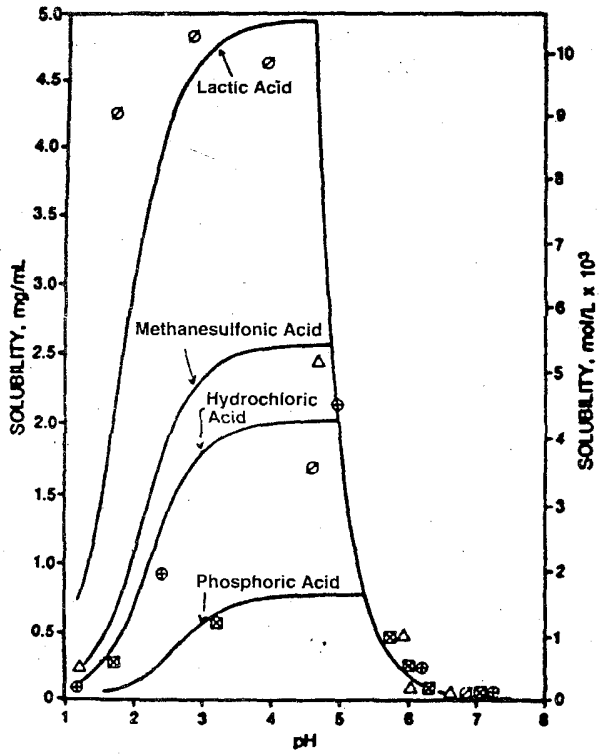

Figure 38-5. pH solubility profile of a weak base.[3]

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.[6] Table 38-2 shows counter-acids organized into different 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, $\Delta pK_a = pK_{a\,A^0} - pK_{a\,\text{counter-acid},\,HAn} > 0$, 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*, page 712.

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.

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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*, page 710.

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*, page 712). Figure 38-6 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 38-4). 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:

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

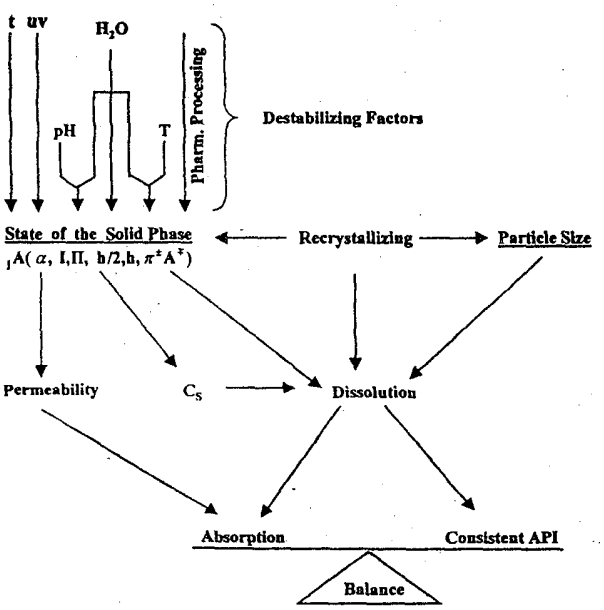


Figure 38-6. API salt selection decision: a balance between absorption and consistency.

Either dissolution of solid drug, A_{solid}, after the dosage form disintegrates in the GI tract, or the permeation of the dissolved drug, $a_{GI\ tract}$, 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.

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*, page 714. Dissolution-limited absorption will now be considered.

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

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

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 $C_{bulk} = 0$ (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:[7]

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

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

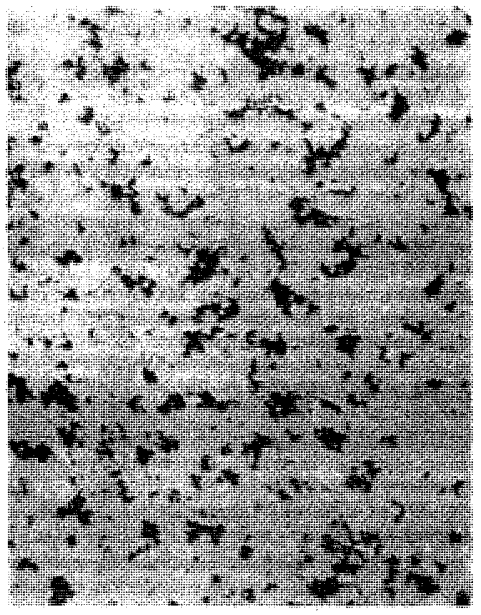
$$dA/dt = (3k_d m/\rho)(1/r) C_S \qquad (18)$$

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[8] (Fig 38-7). 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.[9] On the other hand, it is the free base, and not its HCl salt, that dissolves faster in this same environment.[10] 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

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



FORM I
INITIAL SUSPENSION

FORM I
SUSPENSION AFTER 6 HOURS

Figure 38-7. Photomicrographs showing change in crystal size for a suspension of Form I of an experimental drug.

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

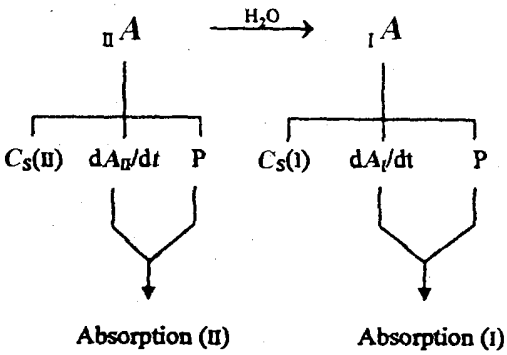


Figure 38-8. Absorption changes due to aqueous-phase transformations.

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.[11] In Figure 38-8, 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 38-9 shows the biphasic dissolution characteristics for Equation 9. In this situation, an anhydrous substance, $_{0h}A$,

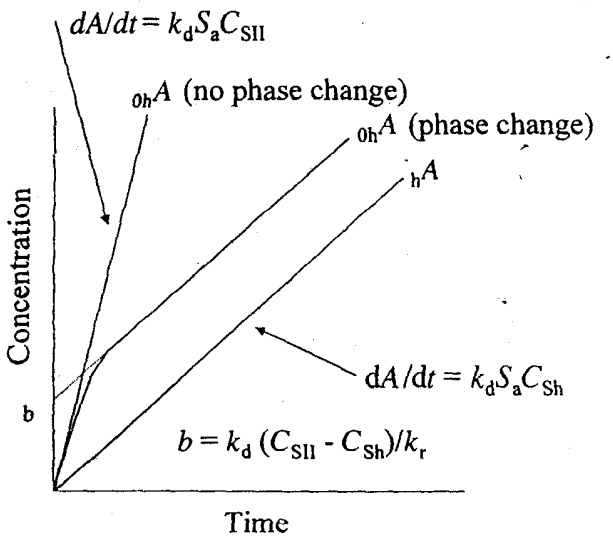


Figure 38-9. Biphasic dissolution of anhydrous to hydrous forms.[11]

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 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,

$$dA/dt = k_d S_a\{C_{S_{II}}e^{-k_r t} + C_{S_h}[1 - e^{k_r t}]\} \tag{20}$$

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.[12]

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.

$$A^0_\Sigma \xrightarrow{milling} A^0_{\Sigma\uparrow} \xrightarrow{faster} a^0_S \tag{21}$$

This enhancement, however, is assumed to be under sink conditions and is driven by $C_S = a^0_S$ 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 $a^0_{bulk}\uparrow$ indicates the buildup of the drug in the bulk solution.

$$A^0 \xrightarrow{slow} a^0_{bulk}\uparrow \tag{22}$$

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

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

Reduction of dissolution, on the other hand, can occur for an anhydrous API when the hydrated form recrystallizes on the surface as in Figure 38-9. 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.

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

Acceptance Criteria Guidance—A simple model to assess the impact of particle size on dissolution and absorption of a nonionized drug considers the intestine as a single compartment.[12] If the number of particles of uniform size at time t is

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

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

$$S_a = 4\pi r^2(t)N(t) \tag{26}$$

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

$$F \propto \frac{k_a X_d \hat{t}_r}{X_0} \tag{27}$$

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 38-3 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*, page 702; 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 38-10 shows a solubility versus temperature diagram for an enantiotropic polymorphic system.[13,14] For the enantiotropic 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.[14] 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,

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

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.[15] The more

Table 38-3. Reduced Absorption with Increasing Particle Size for a Poorly Soluble Drug

	PERCENT OF DOSE ABSORBED			
DOSE	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

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

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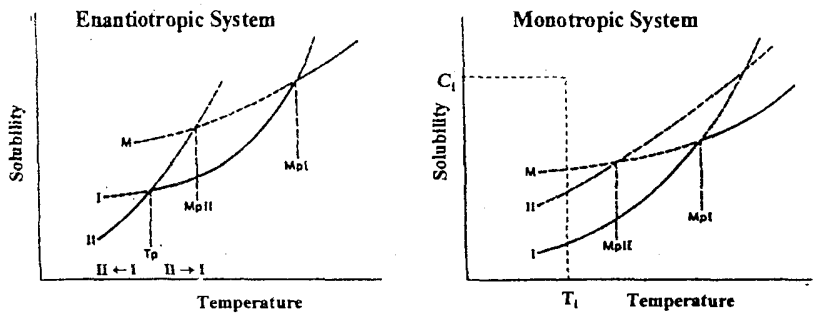

Figure 38-10. Thermal stability of polymorphic systems.[13,14]

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 38-10). However, if a transition point is not found below the melting point of Form I, it does not mean that the system is monotropic.[14] 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 38-10). 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.[16] 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 $C_S(\mathrm{II}) > C_S(\mathrm{I})$ 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*, page 706).

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.[14] 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 38-10 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 can measure 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 38-11, crystallization of the more stable polymorph shows up as exothermic depressions as the scanning-rate increases.[17] Hot-stage microscopy can be used to confirm these thermal changes.

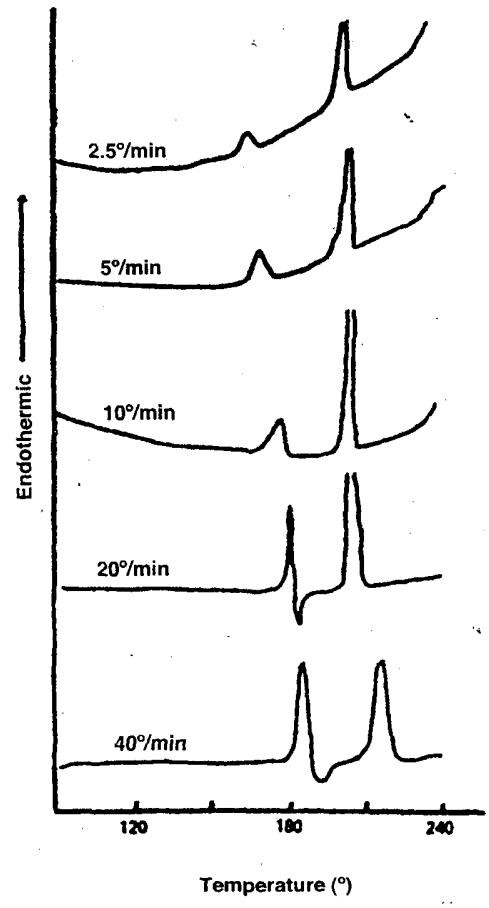

Figure 38-11. Detection of polymorphs by varying the DSC scanning rate.[17]

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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.[18] The more stable polymorph can often be observed as exotherms due to crystallization after heat–cool cycles.[19] 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°.[17]

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.[20]

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 38-12.

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

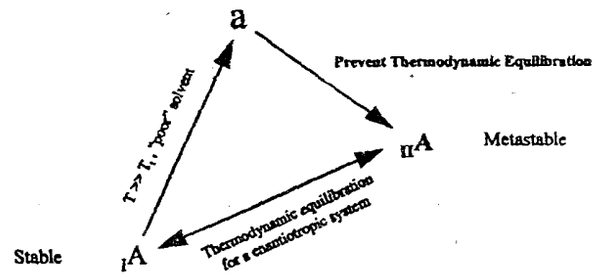

Figure 38-12. Formation of a metastable polymorph in a monotropic system.[14]

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).[21] 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 *Hydrate Formation*, page 711), 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.[22]

$$
{}_{4h}A_{\Sigma} \xrightarrow[-H_2O]{\text{above CRH}} {}_{h}A_{\Sigma} \qquad {}_{4h}A_{\Sigma} \xrightarrow[-H_2O]{\text{below CRH}} {}_{0h,\alpha}A \tag{29}
$$

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.[23] Similarly, elevation of both temperature and RH were required to convert the ${}_{0h}A$ form of paroxetine HCl to the ${}_{0.5h}A$ form.[24] 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.[25] Difficult hydrate situations have been dealt with by carefully defining the RH ranges of different species and setting specifications consistent with typical manufacturing environments.[26]

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.[24] 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.[22] In the sections *H-Bonding Networks* (page 717), and *Hydrate Formation* (page 717), 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 ${}_{0h,\alpha}A_{\geq}$ means that any subsequent water vapor will encounter a more hygroscopic surface than ${}_{4h}A_{\geq}$ 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.[27] 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.

$${}_{0h}A_{\geq} \xrightarrow[-H_2O]{\text{below CRH}} {}_{>0h}A_{\geq} \quad \text{(partial oxidation protection)} \qquad (30)$$

$$A \xrightarrow{\text{below CRH}} A \quad \text{(increased chemical reactivity)} \qquad (31)$$

Formation of an Amorphous (α) 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 ${}_{\alpha}B_{\geq}$, which is amorphous. This type of surface hydrolysis at RHs below the CRH was shown to occur for meclofenoxate HCl decomposition[28] and for propantheline bromide hydrolysis.[29] 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, ${}_{\alpha}A_{\geq}$. The consequences of these amorphous surfaces will now be explored.

$${}_{I}A_{\geq} \xrightarrow{-H_2O} {}_{I,>h}A_{\geq} \rightarrow {}_{\alpha}B_{\geq} \qquad (32)$$

$${}_{h}A_{\geq} \xrightarrow{-H_2O} {}_{<h}A_{\geq} \rightarrow {}_{\alpha}A_{\geq} \qquad (33)$$

Transformation of Amorphous Surfaces—Because amorphous layers are more prone to be hygroscopic than crystalline solids, the chemical transformation of ${}_{I}A_{\geq}$ to ${}_{\alpha}B_{\geq}$ in Equation 32 is significant because the latter can attract more water to the surface. Dissolution of ${}_{\alpha}B_{\geq}$ shown in the first downward reaction of Equation 34 will then form a surface coated with $b_{\geq}$, as shown in Figure 38-3. The reaction of meclofenoxate HCl below the CRH to form amorphous dimethylaminoethanol HCl (see Eq 32) is a good example of this.[28] Next, the water adsorbed to the surface due to the dissolved form of B on the surface, $b_{\geq}$, promotes the dissolution of the surface of A, $A_{\geq}$, to form a surface coated also with $a_{\geq}$, the dissolved form of A on the surface, which then undergoes further decomposition to $b_{\geq}$. This is shown in the horizontal and final downward reactions of Equation 34.

$$\begin{array}{c} {}_{\alpha}B_{\geq} \\ \downarrow +H_2O \\ A_{\geq} \xrightarrow{h} a_{\geq} + b_{\geq} \\ \downarrow \\ b_{\geq} \end{array} \qquad (34)$$

In Equation 35, two possible solid-state changes for ${}_{\alpha}A_{\geq}$ are shown. First, the reactive amorphous surface can undergo a degradation reaction to form $C_{\geq}$. 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.[31] The partially dehydrated form of this compound was more unstable than the fully hydrated or the completely dehydrated crystalline forms.

$${}_{\alpha}A_{\geq} \begin{array}{l} \xrightarrow{T} C_{\geq} \\ \xrightarrow[-H_2O,\ T]{} {}_{I}A_{\geq} \end{array} \qquad (35)$$

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, $a_{\geq}$, which is assumed to be saturated:[1]

$$A_{\geq} \xrightarrow{\text{excess } H_2O} a_{\geq} \qquad (36)$$

Degradation under these conditions is assumed to occur solely in the dissolved layer. This situation has been extensively discussed.[1] 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[32] and tromethamine.[33,34]

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.[35] 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.[36] Stronger bases like pelrinone (pK_a 4.71) can form stable and nonhygroscopic HCl salts.[30]

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,[37]

$$ {}_{III}A \xrightarrow{\text{grinding}} {}_{II}A \xrightarrow{\text{more grinding}} {}_{I}A \qquad (37) $$

grinding causes a successive change to the ${}_{II}A$ polymorph (Form B) and finally to the ${}_{I}A$ polymorph (Form A).[38] Correspondingly, dissolution from the fastest to the slowest is in the order

$$ {}_{\text{ground II}}A > {}_{\text{ground I}}A > {}_{II}A > {}_{I}A \qquad (38) $$

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

$$ {}_{3h}A \xrightarrow{\text{grinding}} {}_{\alpha,0h}A \qquad (39) $$

Water in this situation plays an essential role in crystal formation. Its removal causes a collapse of the crystal lattice.[39] Other pharmaceutical processing operations and their impact on crystals have been reviewed.[40]

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.[41] 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.

Multitiered 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.[41] 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,[42] 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 38-13, prioritized problems are shown, absorption being the highest priority.

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.[43] By using functional groupings (see Table 38-2), salt forms would be considered that could address specific problems.[6]

Compressibility and Compactibility

Because tablets remain the preferred oral dosage form due to high-speed manufacturing, information obtained during preformulation studies on the ability of powdered drugs to be compressed and compacted can be a valuable aid to market-image formulators. Compressibility and compactibility relate directly to tableting performance. *Compressibility* can be defined as the ability of a powder to decrease in volume under pressure; *compactibility* can be defined as the ability of a powder to be compressed into a tablet of a certain strength or hardness. Even though powdered drugs usually are formulated with excipients to modify compression and compaction properties, the properties of the powdered drug alone may be the primary determinant of its ability to be manufactured into a tablet. Significant differences in compression and compaction behavior often can be observed in different lots of the same drug. For example, changes in crystallization or milling procedures may produce differences in behavior.

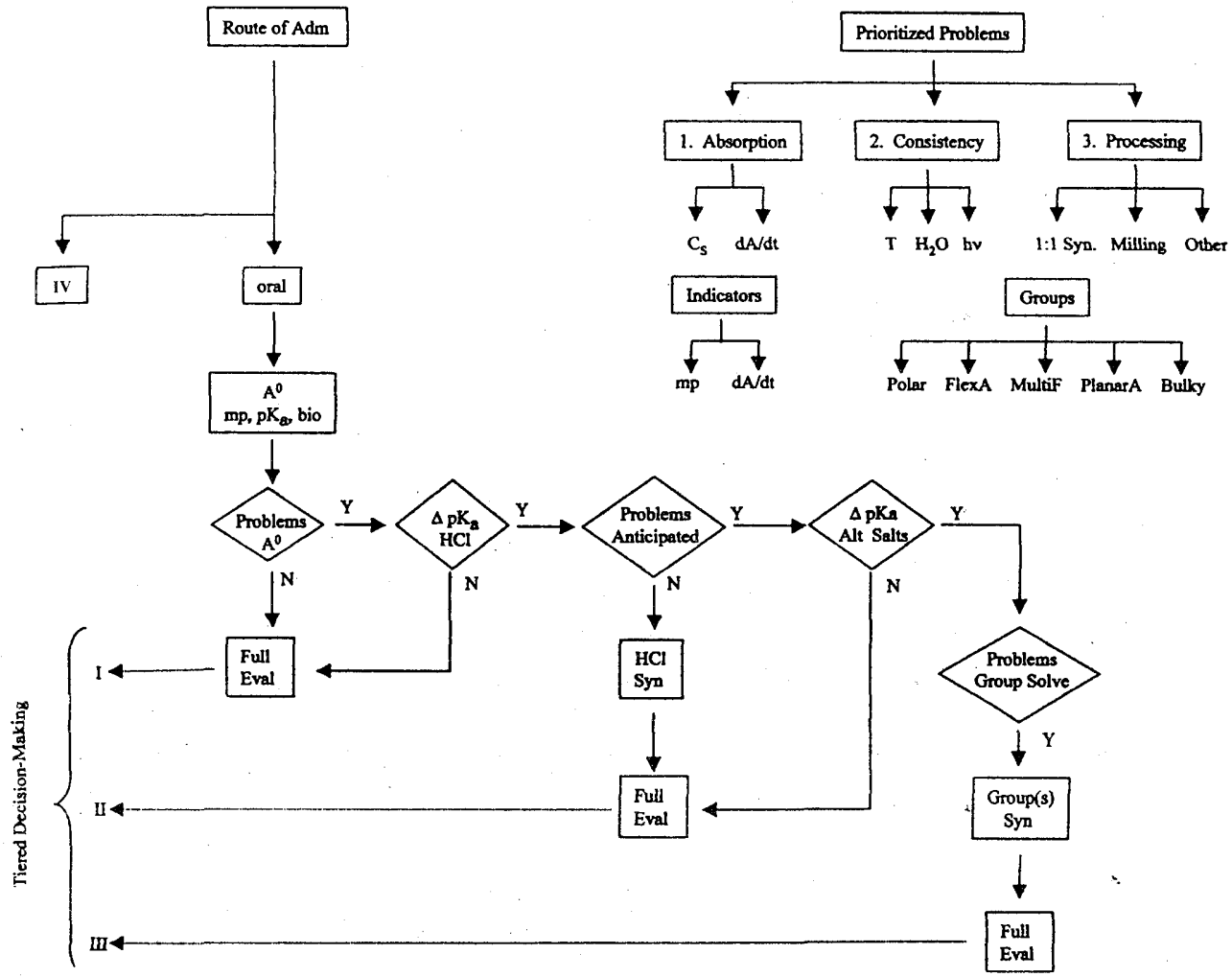

Figure 38-13. Absorption-dominated decision-tree.

Compression and compaction most often are evaluated by measuring the tensile strength and hardness of compacts. Tensile strength commonly is measured by radial compression of round tablets, where the analysis of strength accounts for the dimensions of the tablets. Transverse compression of square compacts between platens narrower than the compact is reported to provide more reproducible results on a wider variety of powders.

Hardness can be defined as the resistance of a solid to local permanent deformation. Static impression or dynamic methods usually measure deformation hardness tests. The static method involves the formation of a permanent indentation on a solid surface by a gradual and regularly increasing stress load. Hardness is determined by the load and size of the indentation and is expressed as force per unit area. In dynamic tests, the solid surface is exposed to an abrupt impact such as a swinging pendulum or an indenter allowed to fall under gravity onto the surface. Hardness then is determined from the rebound height of the pendulum or the volume of the resulting indentation.

Hiestand has used adaptations of a compression test and a hardness test to obtain measurements that are used to formulate three dimensionless parameters or indices.[44] The indices are used to characterize the relative tableting performance of individual components or mixtures. The *Strain Index* is the ratio of dynamic indentation hardness to reduced Young's modulus. The *Bonding Index* is the ratio of tensile strength to indentation hardness. The *Brittle Fracture Index* is obtained by comparing the tensile strengths of square compacts with and without a hole at their center. The indices themselves do not measure intrinsic properties of a chemical compound, but rather the traits that influence the tableting performances of a specific lot of chemical. It is necessary to know the magnitude of all three indices to predict the variety of tableting properties that may be incurred. Such information can act as a guide in selecting excipients to overcome problem properties of a drug ingredient.

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

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together after wet granulation, 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.[45] 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.[46] Blending studies have shown the potential benefits of using sodium lauryl sulfate to offset these types of effects.[47]

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 focused recently 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 38-14[48,49] summarizes some of the potential solid states that can exist for the un-ionized 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 38-14 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 38-15 shows a decision-tree approach, suggested by the International Committee on Harmonization, for determining whether a particle-size acceptance criterion is needed.[50] Previous sections in this chapter have discussed nearly every aspect of this tree. Although dissolution-limited absorption is a major concern, Figure 38-15 also includes dosage form issues such as content uniformity.

BIOPHARMACEUTICAL CLASSIFICATION OF API—Although it is possible to alter the solid state, $_jA$, such that dissolution and absorption can be enhanced, solubility and passive permeability are, in general, intrinsic properties of the NCE. Thus, even though the amorphous state, $_aA$, 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 38-4 shows the four major classes based on solubility and passive permeability.

ENGINEERING THE SOLID STATE

Speed is essential for any preformulation innovation if it is to be effective in influencing discovery decision-making. In Figure 38-4, the early discovery stages, Steps 1 to 4 were introduced. The potential focal points of high-throughput physical screening, predictions of physical properties, and artificial intelligence are shown in an expanded version of these early steps in Figure 38-16.

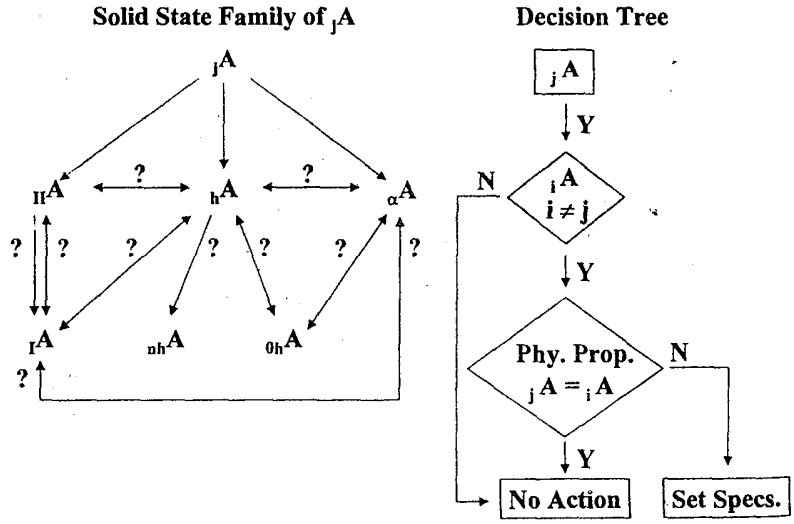

Figure 38-14. Solid-state forms and specification setting.[48,49]

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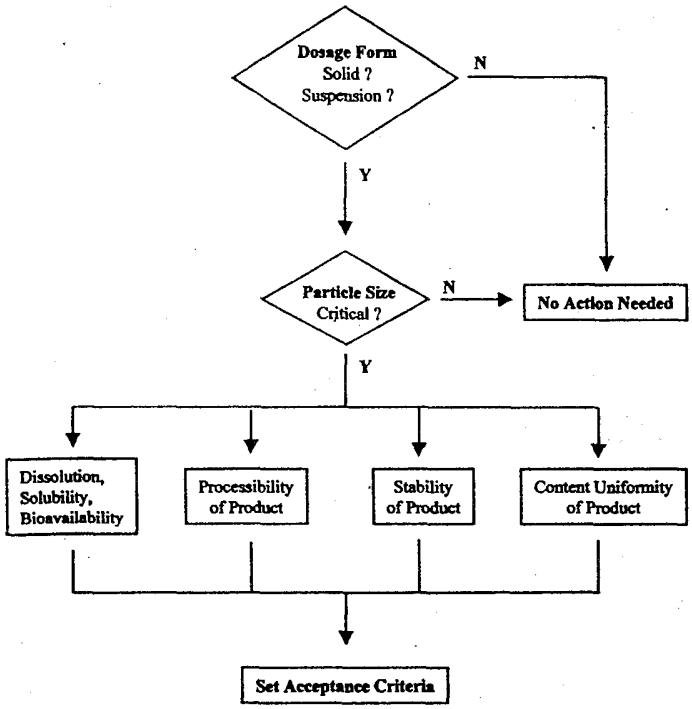

Figure 38-15. Decision-tree for drug substance particle-size distribution.[50]

Library Expansion

The development of mass-screening technologies has spawned a number of technologies that complement a company's in-house library. Besides the massive influx of compounds that can be obtained from combinatorial synthesis, computer-based analyses can be used to assess the diversity of the in-house chemical library and identify areas of weakness. Negotiations with other companies then might take place to fill in deficiencies. In addition, a number of commercial libraries, including natural products, are also available for mass screening. Figure 38-17 shows these aspects of library expansion.

Modern mechanism-based screens, based on recombinant proteins, have vastly increased the number and specificity of *in vitro* screens. However, because the goal of mass screening is to find compounds that have high *in vitro* activity, this exclusive focus tends to produce compounds with poor physical properties. Such compounds, either because of their conformational restriction or their H-bonding with receptors, have much greater activity and selectivity than previous generations of NCEs that were obtained from tissue screens and *in vivo* tests. These attributes have caused modern chemical libraries to expand with compounds that have high melting points and low aqueous solubility. Chemists affectionately call such compounds *brick dust.*

Although brick dust compounds may provide a point of departure for an *in vitro* activity search, most of them are unacceptable for development because of their poor physical properties, especially poor aqueous solubility. It would be undesirable for chemical library expansion to be dominated exclusively by such compounds because of their poor development potential. Selection of a good API, an active chemical with acceptable pharmaceutical properties, could be delayed. For this reason, there is an urgent need to integrate pharmaceutical properties into the chemical library expansion and the mass-screening paradigm.

However, a greater mechanistic understanding is needed of those factors that promote desirable physical properties and good absorption. In lieu of this understanding, computed parameters based on marketed drugs have been used to direct immediate library expansion based on the assumption that these drugs have physical and chemical properties that are desirable.[51] The potential future role pharmaceutics can play in influencing the rational direction of library expansions based on a more fundamental, more molecular-based understanding of physical properties will now be discussed.

Table 38-4. *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.

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

AQUEOUS INSOLUBILITY: MOLECULAR MECHANISMS

Although aqueous solubility is a major factor that affects drug absorption, better methods of understanding the molecular mechanisms and predicting this parameter are needed. Aqueous insolubility occurs when the attraction between molecules is greater than the ability of water to solvate the molecule and

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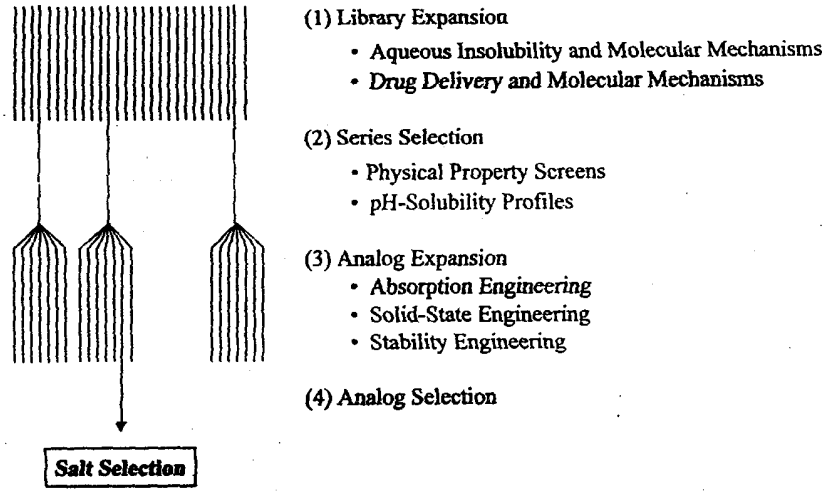

Figure 38-16. Proactive pharmaceutical API decision-making: potential opportunities for high-throughput physical innovations.

dislodge it from its solid phase. Generally speaking, most pharmaceutical solids are manufactured in the form of crystals as opposed to amorphous solids because crystals are more stable. Crystals are arrays of molecules that pack in a regular pattern and thus have long-range order, ie, packing patterns that extend in space over large numbers of molecules. Single-crystal X-ray diffraction can be used to visualize the conformation of molecules in the crystal, the interactions between molecules, and exactly how repeating units of molecules are arranged in three-dimensional space. When the forces that form crystals are sufficiently strong, either because the forces are sufficiently strong in themselves or because there are a large number of forces on a given molecule, insolubility results. These forces are termed *intermolecular forces* (between molecules) as opposed to *intramolecular forces* (within a molecule).

In the past, most of the predictive methods for solubility have been either thermodynamically or statistically based. Insight into the molecular basis of insolubility is now possible. By using single crystal X-ray diffraction, correlations between molecular packing motifs and solubility can be carried out. The major intermolecular factors that have been identified to date are

1. Hydrophobicity
2. Conformational restriction
3. H-bonding networks
4. Hydrate formation
5. Zwitterion formation

Hydrophobicity needs no explanation; this brief focus will concentrate on the cohesive aspects of the latter factors.

Conformational Restriction—Using biotechnology, very specific biological targets can be synthesized from genes. For example, pure dopamine receptor subtypes, D_1–D_5, have been used as mechanistic targets for schizophrenia; cycloxygenase$_1$ and cycloxygenase$_2$ similarly are now available for anti-inflammatory screening. Developing a drug specifically for cycloxygenase$_2$ inhibition promises to minimize the side effects of nonsteroidal anti-inflammatory inhibitors like aspirin.

Such molecular specificity is now possible because screening-feedback enables chemists to rigidify drug molecules such that interactions with the target protein are restricted to only a few conformations. However, this rigidity has a physical impact. Rigidified molecules appear to pack better because they can be arranged in fewer ways than flexible molecules. Consequently, such molecules have increased dispersion force interactions (very short ranged). This increased intermolecular interaction leads to a conformationally based insolubility that has been observed especially in molecules that are planar or linear.

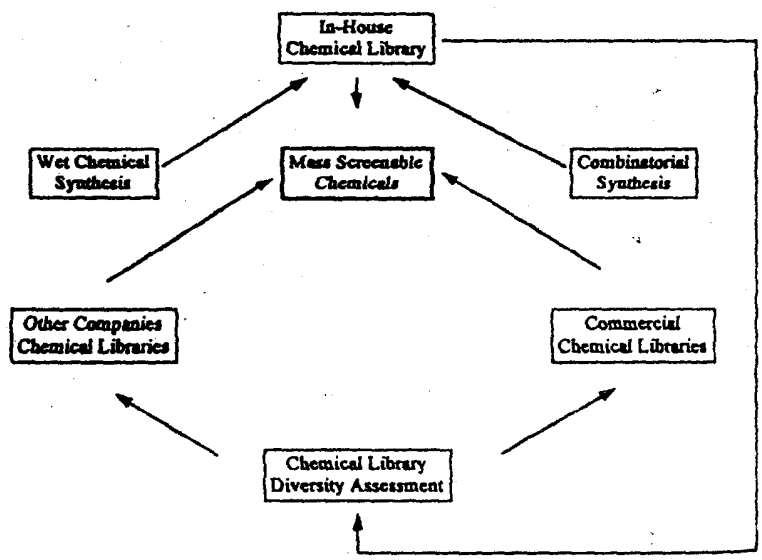

Figure 38-17. Expansion of mass-screenable chemicals.

H-Bonding Networks—Polar groups generally impart water solubility to a flexible molecule. Functional groups that have an H-bond donor and an acceptor group can help the molecule to form a hydration shell around itself and increase solubility. However, in more rigid molecules, these same groups can bind one molecule to another in the crystalline state through intermolecular H-bonding. Single-crystal X-ray diffraction studies of crystals provide a detailed picture of how H-bonds form between such molecules. Insolubility due to H-bonding in conformationally restricted molecules appears to increase as the number of H-bonds per molecule and between molecules increases. Predicting exactly how such molecules arrange in a crystal is difficult because there are two mutually opposing tendencies in crystal formation: (1) packing molecules as closely as possible, and (2) maximizing the number of H-bonding interactions. Crystals often achieve a balance between these opposing tendencies in unexpected ways.

Conformational restriction also seems to increase the efficiency of H-bonding in crystals by increasing molecular rigidity. This may be because rigid molecules can form more uniform, consistent H-bonds that are needed for long-ranged crystal order. Intramolecular H-bonding often adds to this rigidity.

The forces directing initial crystal formation would be expected to be dominated by H-bonds due to their electrostatic nature. These are the longest-ranged intermolecular forces in a nonelectrolyte. Packing and dispersion interactions would then be expected to dominate the final crystal form. For some molecules, the H-bonding of water can be very important in crystal formation. When the number of H-bonding acceptor groups is large compared to the number of donor groups, hydrates are more probable. Water, due to its high H-bonding capacity, often strongly binds molecules together in crystals by making up for molecular deficiencies. This can increase aqueous insolubility. It is generally observed that hemihydrates and monohydrates are more insoluble than the anhydrous forms.

Hydrate Formation—Hydrate formation in organic crystals increases the number of molecular options for satisfying the dual crystal maximization constraints of H-bonding and dense packing. Water, because of its small size and di-donor and di-acceptor capacity for H-bonding, often acts as an interstitial H-bonding cement and spacer.[52] Crystal surveys have found that water is a very weak donor, but the water oxygen is the strongest acceptor. On the other hand, water almost always donates two H-bonds but usually accepts one, not two, H-bonds. Because of its unique characteristics and flexibility, predicting how water will interact with an H-bonding NCE is not possible. The earlier presumption of linear and single acceptor H-bonds has been shown to be wrong. Nevertheless, although the exact structure of water interactions with NCEs cannot be predicted, generalizations can be drawn regarding the type of structure that is most likely to be hydrated. Water with its di-donor/mono-acceptor role tends to reduce proton deficiencies of the parent molecule. Molecules that have donor/acceptor ratios of less that 0.5 are most likely to be hydrate candidates.

Zwitterion Formation—Zwitterions are molecules that at a given pH have both a positive and negative charge. If they are conformationally restricted, they tend to be very insoluble. Evidently the localization of opposite charges at different regions in the same rigid molecule provide scaffolding that enables very efficient salt-bridge dimers to form. Sometimes a zwitterion not only forms dimers, but also has ample H-bonding groups to form H-bonding networks in addition to the dimers. Occasionally, zwitterion insolubility is caused by metabolism, for example by aromatic hydroxylation and subsequent sulfation of a strong basic drug. Such metabolites have the potential to precipitate in the kidneys as urine becomes concentrated in the renal tubules.

DRUG DELIVERY: MOLECULAR MECHANISMS

Membrane-Active Sites—The rich interaction of drugs with membrane receptors is modulated partially by their complex lipid matrix. For drugs that partition into membranes, lateral diffusion provides a rapid surface-dispersion mechanism for transporting drug to any integral membrane receptor. Functional groups on a molecule that help position it within the membrane help explain why some drugs act superficially or more deeply on integral membrane proteins.

Finally, intrinsic membrane curvature, with its concomitant asymmetric distribution of phospholipids, provides a rich potential for specific and allosteric interactions. Drugs, depending on their amphipathic nature, may insert themselves preferentially into the phosphatidylcholine–rich outer leaflet or the phosphatidylserine inner negative leaflet. Protein crystallographic studies have confirmed the relationship between membrane localization and duration of action of a number of drugs.

Membrane Permeability—Computational approaches have been used to develop molecular models for passive membrane permeability. Exploration of a number of models, including homogeneous solubility-diffusion, defect, and free volume, have shown an inability to completely explain the permeability of simple molecules like water and ethanol. Recent progress has been made in this area by dividing the membrane into zones in which the mechanisms of diffusion differ. The preferential impact of different zones on diffusion and the dynamic simulation of spontaneously occurring membrane conformational alterations can then be used to simulate and average diffusion trajectories to estimate permeation rates.

Series Selection

PHYSICAL PROPERTY SCREENS

Until computational methods for predicting physical properties reach an advanced state of reliability, high-throughput screens for physical properties will play a major role in understanding how molecules can be designed for better absorption. New instrumentation makes this task more feasible than it was in the past. Rapid advances in analytical detection sensitivity, especially in powder X-ray diffraction and chromatography–mass spectrometry, have helped reduce material consumption and analytical development time. Robots, and specialized automated dispensers and spectrophotometers that have been developed for mass screens can be used creatively for developmental purposes. In short, the more rapidly and reliably physical properties can be assessed, the more impact these measurements will have on the flow of new leads for development. However, the greatest advantage of automation is not physical evaluations on a grand scale, but rather the ability to customize determinations to solve particular problems rapidly.

pH-SOLUBILITY PROFILES

High-throughput determinations of A^0 and A^i solubilities and pK_a values provide the basis for pH-solubility profiles. Series selection can then focus on the feasibility of modifying the pK_a for a given series as part of an optimization strategy to enhance absorption. Ideally, a pK_a that allows for ionization to enhance solubility while still providing some un-ionized form for absorption is ideal. Consider Equation 40.

$$A^i \text{ (ionizing reservoir)} \xleftrightarrow{\text{rapid equilibration}} A^0 \downarrow \xrightarrow{k_a} \text{GI membrane} \rightarrow \text{systemic circulation (sink)} \quad (40)$$

If 99% of the drug in the GI tract is in the ionized form A^i, and 1% in the un-ionized form A^0 (eg, 99%), A^i provides a reservoir of dissolved drug while the systemic circulation provides a sink for A^0. These conditions should allow for good absorption as long as k_m is not rate limiting. Modifying the pH solubility profile to approach this situation is one way to optimize absorption. The impact of this type of optimization cannot be overestimated, because pK_a values and intrinsic solubilities are molecular parameters that neither salt selection nor formulation can alter. Further techniques to enhance absorption will be discussed in the next section.

Analog Expansion

ABSORPTION ENGINEERING

Absorption-enhancement engineering of analogs can be addressed after the rate-limiting mechanism for poor absorption has been identified. Like the pK_a, absorption-enhanced properties must be designed into the NCE before it is passed on to development. For this reason, it is important for preformulation to integrate physical property design into the molecule as early as possible.

Crystal Engineering—If aqueous solubility and dissolution are the problem, crystal engineering might be possible. In this case, it is important to identify the mechanism of insolubility as discussed above. Each mechanism will require a different approach. Hydrophobic problems are usually the simplest and can often be handled using formulation approaches. The more difficult problems require a molecular understanding of the intermolecular forces in the crystal. For H-bonding problems, it may be possible to adjust the mix of H-bond donor and acceptor groups to reduce the number and strength of H-bonds. It has been found that simple changes can alter H-bonding networks and solubility in a dramatic way. The substitution, for example, of a *t*-butyl group for a phenyl group for one insoluble compound increased the intrinsic solubility 4-fold, and the solubility at pH 5 increased it 10,000-fold, despite the fact that the resulting compound had the exact ionization potential of the original compound. These enhancements were due to changes in H-bonding network structure that released a water-solubilizing group for ionization. Other modifications would be directed at minimizing conformational restriction to reduce crystal-packing efficiency, such as by introducing an acyl chain in a compact heterocyclic system. Practical applications of these design suggestions can be difficult because they often reduce activity. However, as preformulation scientists work more closely with synthetic chemists, crystal-packing disruption strategies that are compatible with ease of synthesis and *in vitro* activity will become commonplace. In addition, as computer predictions of crystal-packing structure and H-bonding networks from molecular structure become more practical (see *Engineering The Solid State*, page 714), these types of design considerations will be made as a matter of course as activity is being optimized.

Permeability Enhancement—This is another intrinsic parameter of an API that, in general, is not enhanced in oral formulations. Recently, increased knowledge has helped to design drugs that will passively penetrate membrane barriers more easily. There has been a great emphasis in the past on the partitioning of a solute out of the aqueous phase into a lipophilic membrane and not enough emphasis on the need for a drug molecule to desolvate from the aqueous phase. Molecules have been designed successfully to enhance permeability by reducing the desolvating step. One way this has been accomplished is by reducing a molecule's solvation through the promotion of intramolecular H-bonding in the molecule. In addition, the ability of a membrane-bound drug to flip-flop from the outer leaflet of the bilayer membrane to the inner leaflet appears to be important for efficient membrane permeability. Ultimately, such insight may be possible from molecular modeling studies of membranes.

Intrinsic Dissolution Engineering—Correlating molecular orientation with morphology in crystals has provided insight into molecular mechanisms of dissolution. In one study, it was shown that the relatively strong binding of a solvent at one subset of surface sites and repulsion at others provided a *relay* type of dissolution that favored erosion from particular faces of the crystal. Such a mechanism also perpetuates the natural corrugation of the surface at the molecular level and helps define the factors that may limit dissolution in the bulk phase. In this regard, some progress has been made in predicting the intrinsic dissolution rate of an API from considerations of the surface pH of the API. Modifications of the classic Noyes–Whitney relationship have to be made for weak acids, bases, and their salts. The impact of dissolution in a reactive media was discussed under *Preformulation Challenges*, page 700. Predictions using such considerations are possible for NCEs when the pH of the medium, the solubility of the un-ionized form of the drug in water, and the pK_a of the NCE are known.[53]

SOLID-STATE ENGINEERING

The computational ability to link molecular structure with crystal packing has advanced to the point that polymorphic predictions are becoming more reliable for small molecules. This has a number of implications.

1. Exploring the polymorphic possibilities of a given molecular structure should allow evaluations to be made regarding which structures have more elaborate polymorphic possibilities. In some instances, it may be desirable to avoid such structures; in others, these structures may provide the means for improving physical properties, assuming adequate conditions can be found to ensure physical and chemical stability.
2. As our molecular understanding of the dissolution process increases (see *Intrinsic Dissolution Engineering*, above), it will eventually be possible to predict molecular structures that can enhance dissolution for a particular analog series and to predict the solvents that will be necessary to obtain the most advantageous crystal habit. Hydrate predictions are also within the realm of possibility as the molecular study of existing hydrates yields rules that can be used by expert systems and molecular-modeling programs. Finally, an increased understanding of the molecular conditions necessary for the homogeneous and heterogeneous nucleation process of crystallization will aid in the practical synthesis of industrial APIs.

STABILITY ENGINEERING

The ability to predict the products of chemical reactions means that evaluations of potential NCEs that are being considered at the analog-expansion stage can be considered on the basis of their presumptive chemical stability and degradation pathways before they are even synthesized. Although poor predictions have the potential to inhibit the synthesis of potentially valuable compounds, with future advances in computer-generated molecular diversity such considerations may become less important as predictions become more accurate. The preformulation implications for such predictions are also evident. Anticipation of potential degradants and their characterization can be used to identify proactively unknown chromatography peaks and predict pharmaceutical excipient incompatibilities.

Analog Selection

Physical properties that are oriented toward *in vivo* conditions are most useful at this stage. Solubility and dissolution determinations in media and pHs that mimic physiological pHs can be used as an early indicator of how well an *in vitro/in vivo* correlation can be drawn. At this stage, a number of other

studies from different divisions will be carried out. *In vitro* and *in vivo* metabolism studies, bioavailability studies in different animals, as well as possible selective toxicological studies can be used to determine the best analog. Degradant predictions of the different analogs at this stage may also help to differentiate and minimize problems that can occur later in development. In addition, high-throughput methods to determine the best salt form for a particular analog would mean that therapeutic testing could be carried out on the salt form that will be eventually used in development.

Conclusion: Application of Knowledge

"The actual product of the pharmaceutical industry is knowledge; pills and prescriptions ointments are no more than packaging for knowledge."[54] 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.[55] 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 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.

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.[56] 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.[57] 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."[54]

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 development 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 41

Parenteral Preparations

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The distinctive characteristics of parenteral (Gk, *para enteron*, beside the intestine) dosage forms of drugs are discussed in this chapter. These dosage forms differ from all other drug dosage forms because of the unique requirements imposed because they are injected directly into body tissue through the primary protective system of the human body, the skin, and mucous membranes. Therefore, they must be exceptionally pure and free from physical, chemical, and biological contaminants. These requirements place a heavy responsibility on the pharmaceutical industry to practice good manufacturing practices (GMPs) in the manufacture of parenteral dosage forms and upon pharmacists to practice good aseptic practices (GAPs) in dispensing them for administration to patients.

Many of the newer drugs, particularly those derived from the new developments in biotechnology, can only be given parenterally because they are inactivated in the gastrointestinal tract when given by mouth. Further, the potency and specificity of many of these drugs require strict control of their administration to the patient. A parenteral route of administration meets both of these critical requirements.

This chapter begins with a brief review of the historical events contributing to the development of this distinctive dosage form. Consideration is then given to some of the distinguishing characteristics of these dosage forms and how they are administered to patients. Most of the remainder of the chapter discusses the various factors required for the preparation of a pure, safe, and effective parenteral product.

HISTORY[1]

One of the most significant events in the beginnings of parenteral therapy was the first recorded injection of drugs into the veins of living animals, in about 1657, by the architect Sir Christopher Wren. From such a very crude beginning, the technique for intravenous injection and knowledge of the implications developed slowly during the next century and a half. In 1855 Dr Alexander Wood of Edinburgh described what was probably the first subcutaneous injection of drugs for therapeutic purposes using a true hypodermic syringe.

The latter half of the 19th century brought increasing concern for safety in the administration of parenteral solutions, largely because of the work of Robert Koch and Louis Pasteur. While Charles Chamberland was developing both hot-air and steam sterilization techniques and the first bacteria-retaining filter (made of unglazed porcelain), Stanislaus Limousin was developing a suitable container, the all-glass ampul. In the middle 1920s Dr Florence Seibert provided proof that the disturbing chills and fever that often followed the intravenous injection of drugs was caused by potent products of microbial growth, pyrogens, which could be eliminated from water by distillation and from glassware by heating at elevated temperatures.

Of the technical developments that have contributed to the high quality standards currently achievable in the preparation of parenteral dosage forms, the two that probably have contributed most are the development of high-efficiency particulate air (HEPA)-filtered laminar airflow and membrane microfiltration for solutions. The former made it possible to achieve ultraclean environmental conditions for processing, and the latter to achieve removal from solutions by filtration of both viable and nonviable particles of microbial size and smaller. However, many other developments in recent years have produced an impressive advance in the technology associated with the safe and reliable preparation of parenteral dosage forms. The following list identifies a few of the events that have contributed to that development.

1926—Parenterals were accepted for inclusion in the fifth edition of the *National Formulary*.
1933—The practical application of freeze-drying to clinical materials was accomplished by a team of scientists at the University of Pennsylvania.
1938—The Food, Drug and Cosmetic Act was passed by Congress, establishing the Food and Drug Administration (FDA).
1944—The sterilant ethylene oxide was discovered.
1946—The Parenteral Drug Association was organized.
1961—The concept of laminar airflow was developed by WJ Whitfield.
1962—The FDA was authorized by Congress to establish current good manufacturing practice (cGMP or GMP) regulations.
1965—Total parenteral nutrition (TPN) was developed by SJ Dudrick.
1972—The Limulus Amebocyte Lysate test for pyrogens in parenteral products was developed by JF Cooper.
1974—The concept of validation of processes used in the manufacture of parenteral products was introduced by the FDA.
1977—The principles for clean-in-place (CIP) and steam-in-place (SIP) were introduced.
Early 1980s—Home health care emerged as an alternative for patients whose health status permitted release from a hospital to care in the home environment.
1982—Insulin, derived through the new discipline of biotechnology, ushered in the drug class of polypeptides with their inherent stability challenges for parenteral dosage-form development.
1987—Parametric release was accepted by the FDA for selected products terminally sterilized by a validated heat process.
The FDA published *Guideline on Sterile Products Produced by Aseptic Processing*, one of several nonregulatory publications to help industry know what the FDA considers to be acceptable.
Late 1980s—The development of computer capabilities has led to the automation of many process operations and to a revolution in documentation and recordkeeping.
1991—The FDA proposed requiring manufacturers to use a terminal sterilization process when preparing a sterile drug product unless such a process adversely affects the drug product.
Mid-1990s—The development of isolator technology to separate the product from the operator(s) to increase the sterility-assurance level of the processed product.
1995—The USP published an informational chapter, ⟨1206⟩ on the preparation of sterile products by pharmacists.

*Deceased

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Late 1990s—Acceleration of international cooperation in establishing standards for the pharmaceutical industry.

ADMINISTRATION

Injections may be classified in six general categories:

1. Solutions ready for injection.
2. Dry, soluble products ready to be combined with a solvent just prior to use.
3. Suspensions ready for injection.
4. Dry, insoluble products ready to be combined with a vehicle just prior to use.
5. Emulsions.
6. Liquid concentrates ready for dilution prior to administration.

These injections may be administered by such routes as intravenous, subcutaneous, intradermal, intramuscular, intra-articular, and intrathecal. The nature of the product will determine the particular route of administration that may be employed. Conversely, the desired route of administration will place requirements on the formulation. For example, suspensions would not be administered directly into the bloodstream because of the danger of insoluble particles blocking capillaries. Solutions to be administered subcutaneously require strict attention to tonicity adjustment, otherwise irritation of the plentiful supply of nerve endings in this anatomical area would give rise to pronounced pain. Injections intended for intraocular, intraspinal, intracisternal, and intrathecal administration require the highest purity standards because of the sensitivity of tissues encountered to irritant and toxic substances.

When compared with other dosage forms, injections possess select advantages. If immediate physiological action is needed from a drug, it usually can be provided by the intravenous injection of an aqueous solution. Modification of the formulation or another route of injection can be used to slow the onset and prolong the action of the drug. The therapeutic response of a drug is controlled more readily by parenteral administration, since the irregularities of intestinal absorption are circumvented. Also, since the drug normally is administered by a professionally trained person, it confidently may be expected that the dose was actually and accurately administered. Drugs can be administered parenterally when they cannot be given orally because of the unconscious or uncooperative state of the patient or because of inactivation or lack of absorption in the intestinal tract. Among the disadvantages of this dosage form are the requirement of asepsis at administration, the risk of tissue toxicity from local irritation, the real or psychological pain factor, and the difficulty in correcting an error, should one be made. In the latter situation, unless a direct pharmacological antagonist is immediately available, correction of an error may be impossible. One other disadvantage is that daily or frequent administration poses difficulties, patients must either visit a professionally trained person or learn to inject themselves. However, the advent of home health care as an alternative to extended institutional care has mandated the development of programs for training lay persons to administer these dosage forms.

PARENTERAL COMBINATIONS

During the administration of large-volume injections (LVIs), such as 1000 mL of 0.9% sodium chloride solution, it is common practice for a physician to order the addition of a small-volume therapeutic injection (SVI), such as an antibiotic, to avoid the discomfort for the patient of a separate injection. While the pharmacist is the most qualified health professional to be responsible for preparing such combinations, as is clearly stated in the hospital accreditation manual of the Joint Commission on Accreditation of Healthcare Organizations,[2] interactions among the combined products can be troublesome even for the pharmacist. In fact, incompatibilities can occur and cause inactivation of one or more ingredients or other undesired reactions. Patient deaths have been reported from the precipitate formed by two incompatible ingredients. In some instances incompatibilities are visible as precipitation or color change, but in other instances there may be no visible effect.

The many potential combinations present a complex situation even for the pharmacist. To aid in making decisions concerning potential problems, a valuable compilation of relevant data has been assembled by Trissel[3] and is updated regularly. Further, the advent of computerized data storage and retrieval systems has provided a means to organize and gain rapid access to such information. Further information on this subject may be found in Chapter 42.

As studies have been undertaken and more information has been gained, it has been shown that knowledge of variable factors such as pH and the ionic character of the active constituents aids substantially in understanding and predicting potential incompatibilities. Kinetic studies of reaction rates may be used to describe or predict the extent of degradation. Ultimately, a thorough study should be undertaken of each therapeutic agent in combination with other drugs and IV fluids, not only of generic but also of commercial preparations, from the physical, chemical, and therapeutic aspects.

Ideally, no parenteral combination should be administered unless it has been studied thoroughly to determine its effect on the therapeutic value and the safety of the combination. However, such an ideal situation may not exist. Nevertheless, it is the responsibility of the pharmacist to be as familiar as possible with the physical, chemical, and therapeutic aspects of parenteral combinations and to exercise the best possible judgment as to whether or not the specific combination extemporaneously prescribed is suitable for use in a patient.

GENERAL CONSIDERATIONS

An inherent requirement for parenteral preparations is that they be of the very best quality and provide the maximum safety for the patient. Further, the constant adherance to high moral and professional ethics on the part of the responsible persons are the ingredients most vital to achieving the desired quality in the products prepared.

Types of Processes

The preparation of parenteral products may be categorized as small-scale dispensing, usually one unit at a time, or large-scale manufacturing, in which hundreds of thousands of units may constitute one lot of product. The former category illustrates the type of processing that is done in institutions such as hospital pharmacies. The latter category is typical of the processing done in the pharmaceutical industry, where the vast majority of parenteral products marketed today are made. Wherever they are made, parenteral products must be subjected to the same basic practices of good aseptic processing essential for the preparation of a safe and effective sterile product of very high quality, but the methods used must be modified appropriately for the scale of operation.

The small-scale preparation and dispensing of parenteral products usually uses sterile components in their preparation. Therefore, the overall process focuses on maintaining rather than achieving sterility in the process steps. Further, the final product normally has a shelf life measured in hours, as in a hospital setting. However, the extensive movement of patients out of the hospital to home care has modified dispensing of parenteral products, wherein multiple units are made for a given patient and a shelf life of 30 days or more is required.

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Such products are sometimes made in hospital pharmacies but increasingly in centers set up to provide this service. A discussion of such processing can be found in USP 24, ⟨1206⟩.

This chapter emphasizes the preparation of parenteral products from nonsterile components in the highly technologically advanced plants of the pharmaceutical industry, using cGMP principles. In the pursuit of cGMP, consideration should be given to

1. Ensuring that the personnel responsible for assigned duties are capable and qualified to perform them.
2. Ensuring that ingredients used in compounding the product have the required identity, quality, and purity.
3. Validating critical processes to be sure that the equipment used and the processes followed will ensure that the finished product will have the qualities expected.
4. Maintaining a production environment suitable for performing the critical processes required, addressing such matters as orderliness, cleanliness, asepsis, and avoidance of cross contamination.
5. Confirming through adequate quality-control procedures that the finished products have the required potency, purity, and quality.
6. Establishing through appropriate stability evaluation that the drug products will retain their intended potency, purity, and quality until the established expiration date.
7. Ensuring that processes always are carried out in accord with established, written procedures.
8. Providing adequate conditions and procedures for the prevention of mixups.
9. Establishing adequate procedures, with supporting documentation, for investigating and correcting failures or problems in production or quality control.
10. Providing adequate separation of quality-control responsibilities from those of production to ensure independent decision making.

The pursuit of cGMP is an ongoing effort that must flex with new technological developments and new understanding of existing principles. Because of the extreme importance of quality in health care of the public, the US Congress has given the responsibility of regulatory scrutiny over the manufacture and distribution of drug products to the FDA. Therefore, the operations of the pharmaceutical industry are subject to the oversight of the FDA and, with respect to manufacturing practices, to the application of the cGMPs.[4] These regulations are discussed more fully in Chapter 51.

In concert with the pursuit of cGMPs, the pharmaceutical industry has shown initiative and innovation in the extensive technological development and improvement in quality, safety, and effectiveness of parenteral dosage forms in recent years, eg, developments in sterilizing filtration, aseptic processing technology, and the control of particulate matter. These factors have been additive in providing the public with outstanding parenteral dosage forms of drugs at this time in history.

GENERAL MANUFACTURING PROCESS

The preparation of a parenteral product may be considered to encompass four general areas

1. Procurement and accumulation in a warehouse area until released to manufacturing.
2. Processing the dosage form in appropriately designed and operated facilities.

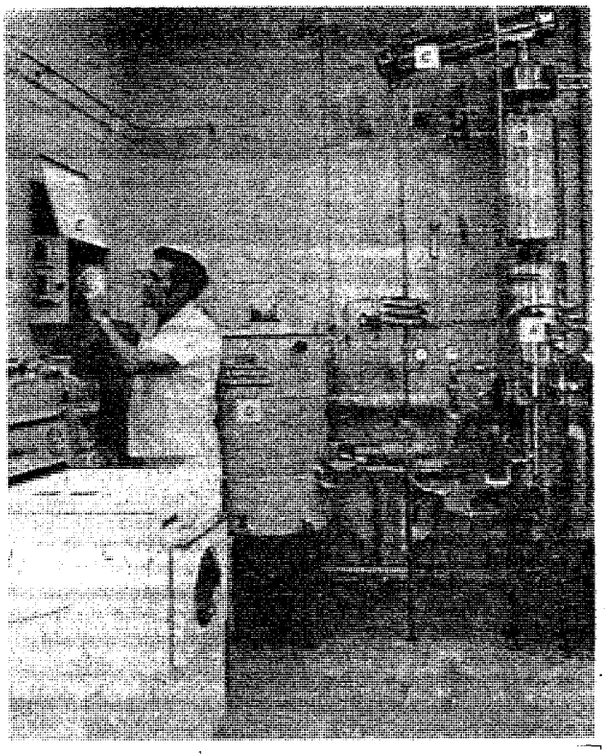

Figure 41-1. High-purity stilled and sealed water-storage system. *A*, evaporator; *B*, high-purity baffle unit; *C*, condenser; *D*, storage tank with ultraviolet lamp; *E*, control panel (courtesy, Ciba-Geigy).

3. Packaging and labeling in a quarantine area to ensure integrity and completion of the product.
4. Controlling the quality of the product throughout the process.

Procurement encompasses selecting and testing according to specifications of the raw-material ingredients and the containers and closures for the primary and secondary packages.

Processing includes cleaning containers and equipment to validated specifications, compounding the solution (or other dosage form), filtering the solution, sanitizing or sterilizing the containers and equipment, filling measured quantities of product into the sterile containers, and, finally, sealing them.

Packaging normally consists of the labeling and cartoning filled and sealed primary containers. The control of quality begins with the incoming supplies, being sure that specifications are met. Each step of the process involves checks and tests to be sure that the developing product is meeting the required specifications at the respective step. Finally, the quality control department must review the batch history and perform the release testing required to clear the product for shipment to users.

The following pages of this chapter present material organized in the approximate manner just discussed.

COMPONENTS

Establishing specifications to ensure the quality of each of the components of an injection is essential. These specifications will be coordinated with the requirements of the specific formulation and will not necessarily be identical for a particular component used in several different formulations. For example, particle-size control may be necessary for powders used in formulating a suspension but be relatively unimportant for preparing a solution.

The most stringent chemical-purity requirements normally will be encountered with aqueous solutions, particularly if the product is to be sterilized at an elevated temperature where reaction rates will be accelerated greatly. Modification of aque-

ous vehicles to include a glycol, for example, usually will reduce reaction rates. Dry preparations pose relatively few reaction problems but may require definitive physical specifications for ingredients that must have certain solution or dispersion characteristics when a vehicle is added.

Containers and closures are in prolonged, intimate contact with the product and may release substances into, or remove ingredients from, the product. Assessment and selection of containers and closures are necessary parts of product formulation, to ensure that the product retains its purity, potency, and quality during the intimate contact with the container throughout its shelf life. Administration devices that come in contact with the product should be assessed and selected with the same care as are containers and closures, even though the contact period is usually brief.

VEHICLES

Since most liquid injections are quite dilute, the component present in the highest proportion is the vehicle. A vehicle normally has no therapeutic activity and is nontoxic. However, it is of great importance in the formulation, since it presents to body tissues the form of the active constituent for absorption. Absorption normally occurs most rapidly and completely when a drug is presented as an aqueous solution. Modification of the vehicle with water-miscible liquids or substitution with water-immiscible liquids normally decreases the rate of absorption. Absorption from a suspension may be affected by such factors as the viscosity of the vehicle, its capacity for wetting the solid particles, the solubility equilibrium produced by the vehicle, and the distribution coefficient between the vehicle and aqueous body systems.

The vehicle of greatest importance for parenteral products is water. Water of suitable quality for compounding and rinsing product contact surfaces may be prepared either by distillation or by reverse osmosis, to meet USP specifications for Water for Injection (WFI). Only by these two methods is it possible to separate adequately various liquid, gas, and solid contaminating substances from water. These two methods for preparation of WFI are discussed in this chapter. It should be noted that there is no unit operation more important and none more costly to install and operate than the one for the preparation of WFI.

Preparation of Water for Injection (WFI)

The source water can be expected to be contaminated with natural suspended mineral and organic substances, dissolved mineral salts, colloidal silicates, and industrial or agricultural chemicals. The degree of contamination will vary with the source and will be markedly different, whether obtained from a well or from surface sources, such as a stream or lake. Hence, the source water usually must be pretreated by one or a combination of the following treatments: chemical softening, filtration, deionization, carbon adsorption, or reverse osmosis purification. Space does not permit discussion of these processes here; the interested reader is referred elsewhere for this information.[5,6]

In general, a conventional still consists of a boiler (evaporator) containing feed water (distilland); a source of heat to vaporize the water in the evaporator; a headspace above the level of distilland, with condensing surfaces for refluxing the vapor, thereby returning nonvolatile impurities to the distilland; a means for eliminating volatile impurities before the hot water vapor is condensed; and a condenser for removing the heat of vaporization, thereby converting the water vapor to a liquid distillate.

The specific construction features of a still and the process specifications will have a marked effect on the quality of distillate obtained from a still. Several factors must be considered in selecting a still to produce WFI.

1. The quality of the feed water will affect the quality of the distillate. Controlling the quality of the feed water is essential for meeting the required specifications for the distillate.
2. The size of the evaporator will affect the efficiency. It should be large enough to provide a low vapor velocity, thus reducing the entrainment of the distilland either as a film on vapor bubbles or as separate droplets.
3. The baffles (condensing surfaces) determine the effectiveness of refluxing. They should be designed for efficient removal of the entrainment at optimal vapor velocity, collecting and returning the heavier droplets contaminated with the distilland.
4. Redissolving volatile impurities in the distillate reduces its purity. Therefore, they should be separated efficiently from the hot water vapor and eliminated by aspirating them to the drain or venting them to the atmosphere.
5. Contamination of the vapor and distillate from the metal parts of the still can occur. Present standards for high-purity stills are that all parts contacted by the vapor or distillate should be constructed of metal coated with pure tin, 304 or 316 stainless-steel, or chemically resistant glass.

The design features of a still also influence its efficiency of operation, relative freedom from maintenance problems, or extent of automatic operation. Stills may be constructed of varying size, rated according to the volume of distillate that can be produced per hour of operation under optimum conditions. Only stills designed to produce high-purity water may be considered for use in the production of WFI. Conventional commercial stills designed for the production of high-purity water are available from several suppliers (see Fig 41-1) *(AMSCO, Barnstead, Corning, Vaponics)*.

COMPRESSION DISTILLATION—The vapor-compression still, primarily designed for the production of large volumes of high-purity distillate with low consumption of energy and water, is illustrated diagrammatically in Figure 41-2. To start, the feed water is heated from an external source in the evaporator to boiling. The vapor produced in the tubes is separated from the entrained distilland in the separator and conveyed to a compressor that compresses the vapor and raises its temperature to approximately 107°. It then flows to the steam chest where it condenses on the outer surfaces of the tubes containing the distilland; the vapor is thus condensed and drawn off as a distillate, while giving up its heat to bring the distilland in the tubes to the boiling point.

Vapor-compression stills are available in capacities from 50 to 2800 gal/hr *(Aqua-Chem, Barnstead, Meco)*.

MULTIPLE-EFFECT STILLS—The multiple-effect still also is designed to conserve energy and water usage. In principle, it is simply a series of single-effect stills running at

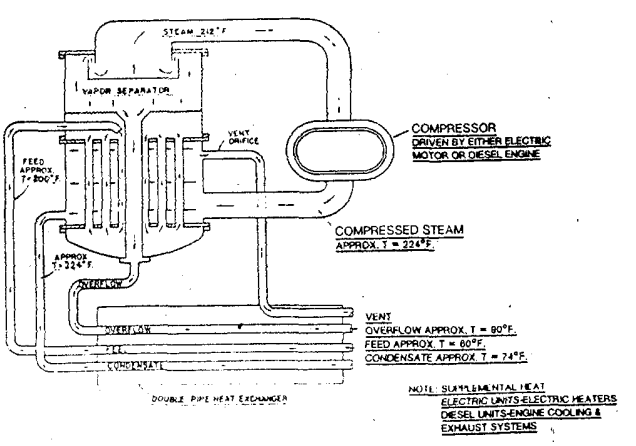

Figure 41-2. Vapor-compression still.

differing pressures. A series of up to seven effects may be used, with the first effect operated at the highest pressure and the last effect at atmospheric pressure. See a schematic drawing of a multiple-effect still in Figure 41-3. Steam from an external source is used in the first effect to generate steam under pressure from feed water; it is used as the power source to drive the second effect. The steam used to drive the second effect condenses as it gives up its heat of vaporization and forms a distillate. This process continues until the last effect, when the steam is at atmospheric pressure and must be condensed in a heat exchanger.

The capacity of a multiple-effect still can be increased by adding effects. The quantity of the distillate also will be affected by the inlet steam pressure; thus, a 600-gal/hr unit designed to operate at 115 psig steam pressure could be run at approximately 55 psig and would deliver about 400 gal/hr. These stills have no moving parts and operate quietly. They are available in capacities from about 50 to 7000 gal/hr *(AMSCO, Barnstead, Finn-Aqua, Kuhlman, Vaponics)*.

REVERSE OSMOSIS (RO)—As the name suggests, the natural process of selective permeation of molecules through a semipermeable membrane separating two aqueous solutions of different concentrations is reversed. Pressure, usually between 200 and 400 psig, is applied to overcome osmotic pressure and force pure water to permeate through the membrane. Membranes, usually composed of cellulose esters or polyamides, are selected to provide an efficient rejection of contaminant molecules in raw water. The molecules most difficult to remove are small inorganic ones such as sodium chloride. Passage through two membranes in series is sometimes used to increase the efficiency of removal of these small molecules and to decrease the risk of structural failure of a membrane to remove other contaminants, such as bacteria and pyrogens. For additional information, see *Reverse Osmosis* in Chapter 36 and *Water* in Chapters 39 and 55.

Reverse osmosis systems are available in a range of production sizes *(AMSCO, Aqua-Chem, Finn-Aqua, Meco, Millipore,* etc).

Whichever system is used for the preparation of WFI, validation is required to be sure that the system, consistently and reliably, will produce the chemical, physical, and microbiological quality of water required. Such validation should start with the determined characteristics of the source water and include the pretreatment, production, storage, and distribution systems. All of these systems together, including their proper operation and maintenance, determine the ultimate quality of the WFI. Because of space limitations here, more details concerning the design, operation, and validation of these highly important systems may be found in other literature sources.[5,6]

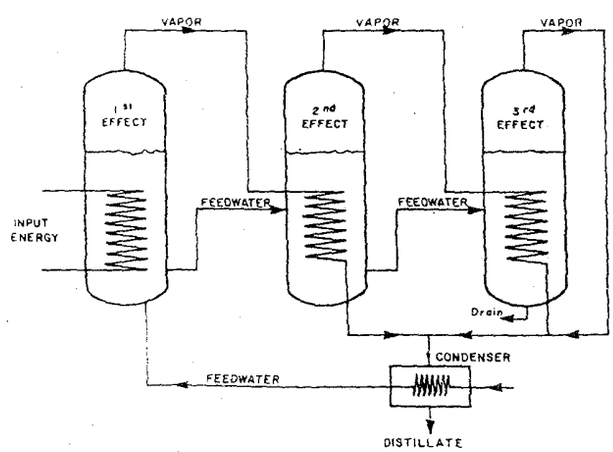

Figure 41-3. Multiple-effect still (courtesy, Dekker). (From Avis KE, Lieberman HA, Lachman L. *Pharmaceutical Dosage Forms: Paren-* ... York: Dekker, 1993.)

STORAGE AND DISTRIBUTION—The rate of production of WFI usually is not sufficient to meet processing demands; therefore, it is collected in a holding tank for subsequent use. In large operations the holding tanks may have a capacity of several thousand gallons and be a part of a continuously operating system. In such instances the USP requires that the WFI be held at a temperature too high for microbial growth. Normally, this temperature is a constant 80°.

The USP also permits the WFI to be stored at room temperature but for a maximum of 24 hr. Under such conditions the WFI usually is collected as a batch for a particular use with any unused water being discarded within 24 hr. Such a system requires frequent sanitization to minimize the risk of viable microorganisms being present. The stainless-steel storage tanks in such systems usually are connected to a welded stainless-steel distribution loop supplying the various use sites with a continuously circulating water supply. The tank is provided with a hydrophobic membrane vent filter capable of excluding bacteria and nonviable particulate matter. Such a vent filter is necessary to permit changes in pressure during filling and emptying. The construction material for the tank and connecting lines usually is electropolished 316L stainless steel with welded pipe. The tanks also may be lined with glass or a coating of pure tin. Such systems are very carefully designed and constructed and often constitute the most costly installation within the plant.

When the water cannot be used at 80°, heat exchangers must be installed to reduce the temperature at the point of use. Bacterial retentive filters should not be installed in such systems because of the risk of bacterial buildup on the filters and the consequent release of pyrogenic substances.

PURITY—While certain purity requirements have been alluded to above, the USP monographs provide the official standards of purity for WFI and Sterile Water for Injection (SWFI).

The chemical and physical standards for WFI recently have undergone significant changes, culminating in the simplified specifications in supplement 8 of USP 23. The only physical/chemical tests remaining are the new *total organic carbon* (TOC), with a limit of 500 ppb, and *conductivity*, with a limit of 1.3 μS/cm at 25 or 1.1 μS/cm at 20. The former is an instrumental method capable of detecting all organic carbon present, and the latter is a three-tiered instrumental test measuring the conductivity contributed by ionized particles (in microSiemens or micromhos) relative to pH. Since conductivity is integrally related to pH, the pH requirement of 5 to 7 in previous revisions has been eliminated. The TOC and conductivity specifications are now considered to be adequate minimal predictors of the chemical/physical purity of WFI. However, the *wet chemistry* tests still are used when WFI is packaged for commercial distribution and for SWFI.

Biological requirements continue to be, for WFI, not more than 10 colony-forming units (CFUs)/mL and 0.25 USP endotoxin units/mL. The SWFI requirements differ in that since it is a final product, it must pass the USP Sterility Test.

WFI and SWFI may not contain added substances. Bacteriostatic Water for Injection (BWFI) may contain one or more suitable antimicrobial agents in containers of 30 mL or less. This restriction is designed to prevent the administration of a large quantity of a bacteriostatic agent that probably would be toxic in the accumulated amount of a large volume of solution, even though the concentration was low.

The USP also provides monographs giving the specifications for Sterile Water for Inhalation and Sterile Water for Irrigation. The USP should be consulted for the minor differences between these specifications and those for SWFI.

Types of Vehicles

AQUEOUS VEHICLES—Certain aqueous vehicles are recognized officially because of their valid use in parenterals. Often they are used as isotonic vehicles to which a drug may be added at the time of administration. The additional osmotic effect of the drug may not be enough to produce any discomfort when administered. These vehicles include Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection.

WATER-MISCIBLE VEHICLES—A number of solvents that are miscible with water have been used as a portion of the vehicle in the formulation of parenterals. These solvents are used primarily to affect the solubility of certain drugs and to reduce hydrolysis. The most important solvents in this group are ethyl alcohol, liquid polyethylene glycol and propylene glycol. Ethyl alcohol is used particularly in the preparation of solutions of cardiac glycosides and the glycols in solutions of barbiturates, certain alkaloids and certain antibiotics. Such preparations usually are given intramuscularly. These solvents, as well as nonaqueous vehicles, have been reviewed by Spiegel and Noseworthy.[6]

NONAQUEOUS VEHICLES—The most important group of nonaqueous vehicles are the fixed oils. The USP provides specifications for such vehicles, indicating that the fixed oils must be of vegetable origin so that they will be metabolized, will be liquid at room temperature, and will not become rancid readily. The USP also specifies limits for the degree of unsaturation and free fatty acid content. The oils most commonly used are corn oil, cottonseed oil, peanut oil, and sesame oil. Fixed oils are used particularly as vehicles for certain hormone preparations. The label must state the name of the vehicle so that the user may beware in case of known sensitivity or other reactions to it.

SOLUTES

Care must be taken in selecting bulk active chemicals and excipients to ensure that their quality is suitable for parenteral administration. A low microbial level will enhance the effectiveness of either the aseptic or terminal sterilization process used for the drug product. Likewise, nonpyrogenic ingredients enhance the nonpyrogenicity of the finished injectable product. Chemical impurities should be virtually nonexistent in bulk substances for parenterals, because impurities are not likely to be removed by the processing of the product. Depending on the chemical involved, even trace residues may be harmful to the patient or cause stability problems in the product. Therefore, the compounder should use the best grade of chemicals obtainable and use its analytical profile to determine that each lot of chemical used in the formulation meets the required specifications.

Reputable chemical manufacturers accept the stringent quality requirements for parenteral products and, accordingly, apply good manufacturing practices to their chemical manufacturing. Examples of critical bulk manufacturing precautions include using dedicated equipment or properly validated cleaning to prevent cross-contamination and transfer of impurities, using WFI for rinsing equipment and for bulk manufacturing steps not followed by further purification, using closed systems wherever possible, and adhering to specified endotoxin and bioburden testing limits for the substance.

ADDED SUBSTANCES—The USP includes in this category all substances added to a preparation to improve or safeguard its quality. An added substance may

Effect solubility, as does sodium benzoate in Caffeine and Sodium Benzoate Injection.

Provide patient comfort, as do substances added to make a solution isotonic or near physiological pH.

Enhance the chemical stability of a solution, as do antioxidants, inert gases, chelating agents, and buffers.

Protect a preparation against the growth of microorganisms. The term *preservative* sometimes is applied only to those substances that prevent the growth of microorganisms in a preparation. However, such limited use is inappropriate, being better used for all substances that act to retard or prevent the chemical; physical, or biological degradation of a preparation.

While added substances may prevent a certain reaction from taking place, they may induce others. Not only may visible incompatibilities occur, but hydrolysis, complexation, oxidation, and other invisible reactions may decompose or otherwise inactivate the therapeutic agent or other added substances. Therefore, added substances must be selected with due consideration and investigation of their effect on the total formulation and the container-closure system.

ANTIMICROBIAL AGENTS—The USP states that antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to preparations contained in multiple-dose containers. They must be present in adequate concentration at the time of use to prevent the multiplication of microorganisms inadvertently introduced into the preparation while withdrawing a portion of the contents with a hypodermic needle and syringe. The USP provides a test for Antimicrobial Preservative Effectiveness to determine that an antimicrobial substance or combination adequately inhibits the growth of microorganisms in a parenteral product. Because antimicrobials may have inherent toxicity for the patient, the USP prescribes concentration limits for those that are used commonly in parenteral products, eg

Phenylmercuric nitrate and thimerosal 0.01%.
Benzethonium chloride and benzalkonium chloride 0.01%.
Phenol or cresol 0.5%.
Chlorobutanol 0.5%.

The above limit rarely is used for phenylmercuric nitrate, most frequently employed in a concentration of 0.002%. Methyl *p*-hydroxybenzoate 0.18% and propyl *p*-hydroxybenzoate 0.02% in combination, and benzyl alcohol 2% also are used frequently. In oleaginous preparations, no antibacterial agent commonly employed appears to be effective. However, it has been reported that hexylresorcinol 0.5% and phenylmercuric benzoate 0.1% are moderately bactericidal. A few therapeutic compounds have been shown to have antibacterial activity, thus obviating the need for added agents.

Antimicrobial agents must be studied with respect to compatibility with all other components of the formula. In addition, their activity must be evaluated in the total formula. It is not uncommon to find that a particular agent will be effective in one formulation but ineffective in another. This may be due to the effect of various components of the formula on the biological activity or availability of the compound; for example, the binding and inactivation of esters of *p*-hydroxybenzoic acid by macromolecules such as Polysorbate 80 or the reduction of phenylmercuric nitrate by sulfide residues in rubber closures. A physical reaction encountered is that bacteriostatic agents sometimes are removed from solution by rubber closures.

Single-dose containers and pharmacy bulk packs that do not contain antimicrobial agents are expected to be used promptly after opening or to be discarded. Large-volume, single-dose containers may not contain an added antimicrobial preservative. Therefore, special care must be exercised in storing such products after the containers have been opened to prepare an admixture, particularly those that can support the growth of microorganisms, such as total parenteral nutrition (TPN) solutions and emulsions. It should be noted that while refrigeration slows the growth of most microorganisms, it does not prevent their growth.

Buffers are used primarily to stabilize a solution against the chemical degradation that might occur if the pH changes appreciably. Buffer systems employed should normally have as low a buffering capacity as feasible so as not to disturb significantly the body's buffering systems when injected. In addition, the buffer range and effect on the activity of the product must

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be evaluated carefully. The acid salts most frequently employed as buffers are citrates, acetates, and phosphates.

Antioxidants are required frequently to preserve products because of the ease with which many drugs are oxidized. Sodium bisulfite 0.1% is used most frequently. The use of sulfites has been reviewed by Schroeter.[7] Acetone sodium bisulfite, sodium formaldehyde sulfoxylate, and thiourea also are used sometimes. The sodium salt of ethylenediaminetetraacetic acid has been found to enhance the activity of antioxidants in some cases, apparently by chelating metallic ions that would otherwise catalyze the oxidation reaction.

Displacing the air (oxygen) in and above the solution by purging with an inert gas, such as nitrogen, also can be used as a means to control oxidation of a sensitive drug. Process control is required for assurance that every container is deaerated adequately and uniformly.

Tonicity agents are used in many parenteral and ophthalmic products to adjust the tonicity. However, not all preparations need to be isotonic. The agents most commonly used are electrolytes and mono- or disaccharides. This subject is considered much more extensively in Chapter 18.

A recent publication surveys excipients being used today in parenteral formulations in the United States.[8]

PYROGENS (ENDOTOXINS)

Pyrogens are products of metabolism of microorganisms. The most potent pyrogenic substances (endotoxins) are constituents of the cell wall of gram-negative bacteria. Gram-positive bacteria and fungi also produce pyrogens but of lower potency and of different chemical nature. Endotoxins are high-molecular-weight (about 20,000 daltons) lipopolysaccharides. Studies have shown that the lipid portion of the molecule is responsible for the biological activity. Since endotoxins are the most potent pyrogens and gram-negative bacteria are ubiquitous in the environment, this discussion focuses on endotoxins and the risk of their presence as contaminants in sterile products.

Pyrogens, when present in parenteral drug products and injected into patients, can cause fever, chills, pain in the back and legs, and malaise. While pyrogenic reactions are rarely fatal, they can cause serious discomfort and, in the seriously ill patient, shock-like symptoms that can be fatal. The intensity of the pyrogenic response and its degree of hazard will be affected by the medical condition of the patient, the potency of the pyrogen, the amount of the pyrogen, and the route of administration (intrathecal is most hazardous followed by intravenous, intramuscular, and subcutaneous). When bacterial (exogenous) pyrogens are introduced into the body, leukocytic phagocytosis is believed to occur, and endogenous pyrogen is produced. The endogenous pyrogen then produces the familiar physiological effects. Space does not permit further elaboration of these matters here; the reader is referred to the work by Pearson[9] if more information is needed.

CONTROL OF PYROGENS—Pyrogens are contaminants if present in parenteral drug products and should not be there. In general, it is impractical, if not impossible, to remove pyrogens once present without adversely affecting the drug product. Therefore, the emphasis should be on preventing the introduction or development of pyrogens in all aspects of the compounding and processing of the product.

Pyrogens may enter a preparation through any means that will introduce living or dead microorganisms. However, current technology generally permits the control of such contamination, and the presence of pyrogens in a finished product indicates processing under inadequately controlled conditions. It also should be noted that time for microbial growth to occur increases the risk for elevated levels of pyrogens. Therefore, compounding and manufacturing processes should be carried out as expeditiously as possible, preferably planning completion of the process, including sterilization, within one working day. [illegible]

Pyrogens can be destroyed by heating at high temperatures. A typical procedure for depyrogenation of glassware and equipment is maintaining a dry heat temperature of 250° for 45 min. It has been reported that 650° for 1 min or 180° for 4 hr likewise will destroy pyrogens. The usual autoclaving cycle will not do so. Heating with strong alkali or oxidizing solutions will destroy pyrogens. It has been claimed that thorough washing with detergent will render glassware pyrogen-free if subsequently rinsed thoroughly with pyrogen-free water. Rubber stoppers cannot withstand pyrogen-destructive temperatures, so reliance must be placed on an effective sequence of washing, thorough rinsing with WFI, prompt sterilization, and protective storage to ensure adequate pyrogen control. Similarly, plastic containers and devices must be protected from pyrogenic contamination during manufacture and storage, since known ways of destroying pyrogens affect the plastic adversely. It has been reported that anion-exchange resins and positively charged membrane filters will remove pyrogens from water. Also, although reverse osmosis membranes will eliminate them, the most reliable method for their elimination from water is distillation.

A method that has been used for the removal of pyrogens from solutions is adsorption on adsorptive agents. However, since the adsorption phenomenon also may cause selective removal of chemical substances from the solution, this method has limited application. Other in-process methods for their destruction or elimination include selective extraction procedures and careful heating with dilute alkali, dilute acid, or mild oxidizing agents. In each instance, the method must be studied thoroughly to be sure it will not have an adverse effect on the constituents of the product. Although ultrafiltration now makes possible pyrogen separation on a molecular-weight basis and the process of tangential flow is making large-scale processing more practical, use of this technology is limited, except in biotechnological processing.

SOURCES OF PYROGENS—Through understanding the means by which pyrogens may contaminate parenteral products, their control becomes more achievable. Therefore, it is important to know that water is probably the greatest potential source of pyrogenic contamination, since water is essential for the growth of microorganisms. When microorganisms metabolize, pyrogens will be produced. Therefore, raw water can be expected to be pyrogenic and only when it is appropriately treated to render it free from pyrogens, such as WFI, should it be used for compounding the product or rinsing product contact surfaces such as tubing, mixing vessels, and rubber closures. Even when such rinsed equipment and supplies are left wet and improperly exposed to the environment, there is a high risk that they will become pyrogenic. Although proper distillation will provide pyrogen-free water, storage conditions must be such that microorganisms are not introduced and subsequent growth is prevented.

Other potential sources of contamination are containers and equipment. Pyrogenic materials adhere strongly to glass and other surfaces. Residues of solutions in used equipment often become bacterial cultures, with subsequent pyrogenic contamination. Since drying does not destroy pyrogens, they may remain in equipment for long periods. Adequate washing will reduce contamination and subsequent dry-heat treatment can render contaminated equipment suitable for use. However, all such processes must be validated to ensure their effectiveness.

Solutes may be a source of pyrogens. For example, the manufacturing of bulk chemicals may involve the use of pyrogenic water for process steps such as crystallization, precipitation, or washing. Bulk drug substances derived from fermentation will almost certainly be heavily pyrogenic. Therefore, all lots of solutes used to prepare parenteral products should be tested to ensure that they will not contribute unacceptable quantities of endotoxin to the finished product.

The manufacturing process must be carried out with great care and as rapidly as possible, to minimize the risk of microbial contamination. Preferably, no more product should be prepared than can be processed completely within one working

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CONTAINERS AND CLOSURES

Containers are an integral part of the formulation of an injection. No container is totally insoluble or does not in some way affect the liquid it contains, particularly if the liquid is aqueous. Therefore, the selection of a container for a particular injection must be based on consideration of the composition of the container, as well as of the solution, and the treatment to which it will be subjected.

Table 41-1 provides a generalized comparison of the three compatibility properties—leaching, permeation, and adsorption—of container materials most likely to be involved in the formulation of aqueous parenterals. Further, the integrity of the container/closure system depends upon several characteristics, including container opening finish, closure modulus, durometer and compression set, and aluminum seal application force. These considerations have been reviewed by Morton.[10]

CONTAINER TYPES

Plastic

Thermoplastic polymers have been established as packaging materials for sterile preparations such as large-volume parenterals, ophthalmic solutions, and, increasingly, small-volume parenterals. For such use to be acceptable a thorough understanding of the characteristics, potential problems, and advantages for use must be developed. A historical review of these factors relative to pharmaceuticals has been prepared by Autian.[11] A discussion of polymers for IV solutions has been published by Lambert.[12] Autian stated that three principal problem areas exist in using these materials:

1. Permeation of vapors and other molecules in either direction through the wall of the plastic container.
2. Leaching of constituents from the plastic into the product.
3. Sorption (absorption and/or adsorption) of drug molecules or ions on the plastic material.

Permeation, the most extensive problem, may be troublesome by permitting volatile constituents, water, or specific drug molecules to migrate through the wall of the container to the outside and thereby be lost. This problem has been resolved, for example, by the use of an overwrap in the packaging of IV solutions in PVC bags to prevent the loss of water during storage. Reverse permeation also may occur in which oxygen or other molecules may penetrate to the inside of the container and cause oxidative or other degradation of susceptible constituents. Leaching may be a problem when certain constituents in the plastic formulation, such as plasticizers or antioxidants, migrate into the product. Thus, plastic polymer formulations should have as few additives as possible, an objective characteristically achievable for most plastics being used for parenteral packaging. *Sorption* is a problem on a selective basis, that is, sorption of a few drug molecules occurs on specific polymers. For example, sorption of insulin, vitamin A acetate, and warfarin sodium has been shown to occur on PVC bags and tubing when these drugs were present as additives in IV admixtures. A brief summary of some of these compatibility relationships is given in Table 41-1.

One of the principle advantages of using plastic packaging materials is that they are not breakable as is glass; also, there is a substantial weight reduction. The flexibility of the low-density polyethylene polymer, for ophthalmic preparations, makes it possible to squeeze the side wall of the container and discharge one or more drops without introducing contamination into the remainder of the product. The flexible bags of polyvinyl chloride or select polyolefins, currently in use for large-volume intravenous fluids, have the added advantage that no air interchange is required; the flexible wall simply collapses as the solution flows out of the bag.

Most plastic materials have the disadvantage that they are not as clear as glass and, therefore, inspection of the contents is impeded. In addition, many of these materials will soften or melt under the conditions of thermal sterilization. However, careful selection of the plastic used and control of the autoclave cycle has made thermal sterilization of some products possible, large-volume parenterals in particular. Ethylene oxide or radiation sterilization may be em-

Table 41-1. Comparative Compatibility Properties of Container Materials

	LEACHING		PERMEATION		ADSORPTION (SELECTIVE)
	EXTENT[a]	POTENTIAL LEACHABLES	EXTENT[a]	POTENTIAL AGENTS	EXTENT[a]
Glass					
Borosilicate	1	Alkaline earth and heavy metal oxides	0	N/A	2
Soda-lime	5	Alkaline earth and heavy metal oxides	0	N/A	2
Plastic polymers					
Polyethylene					
Low density	2	Plasticizers, antioxidants	5	Gases, water vapor, other molecules	2
High density	1	Antioxidants	3	Gases, water vapor, other molecules	2
PVC	4	HCl, especially plasticizers, antioxidants, other stabilizers	5	Gases, especially water vapor and other molecules	2
Polyolefins	2	Antioxidants	2	Gases, water vapor, other molecules	2
Polypropylene	2	Antioxidants, lubricants	4	Gases, water vapor	1
Rubber polymers					
Natural and related synthetic	5	Heavy metal salts, lubricants, reducing agents	3	Gases, water vapor	3
Butyl	3	Heavy metal salts, lubricants, reducing agents	1	Gases, water vapor	2
Silicone	2	Minimal	5	Gases, water vapor	1

[a] Approximate scale of 1 to 5, with 1 as the lowest.

ployed for the empty container with subsequent aseptic filling. However, careful evaluation of the residues from ethylene oxide or its degradation products and their potential toxic effect must be undertaken. Investigation is required concerning potential interactions and other problems that may be encountered when a parenteral product is packaged in plastic. For further details see Chapter 54.

Glass

Glass is employed as the container material of choice for most SVIs. It is composed principally of silicon dioxide, with varying amounts of other oxides such as sodium, potassium, calcium, magnesium, aluminum, boron, and iron. The basic structural network of glass is formed by the silicon oxide tetrahedron. Boric oxide will enter into this structure, but most of the other oxides do not. The latter are only loosely bound, are present in the network interstices, and are relatively free to migrate. These migratory oxides may be leached into a solution in contact with the glass, particularly during the increased reactivity of thermal sterilization. The oxides thus dissolved may hydrolyze to raise the pH of the solution and catalyze or enter into reactions. Additionally, some glass compounds will be attacked by solutions and, in time, dislodge glass flakes into the solution. Such occurrences can be minimized by the proper selection of the glass composition.[13]

TYPES—The USP has aided in this selection by providing a classification of glass:

Type I, a borosilicate glass.
Type II, a soda-lime treated glass.
Type III, a soda-lime glass.
NP, a soda-lime glass not suitable for containers for parenterals.

Type I glass is composed principally of silicon dioxide and boric oxide, with low levels of the non-network-forming oxides. It is a chemically resistant glass (low leachability) also having a low thermal coefficient of expansion.

Types II and III glass compounds are composed of relatively high proportions of sodium oxide and calcium oxide. This makes the glass chemically less resistant. Both types melt at a lower temperature, are easier to mold into various shapes, and have a higher thermal coefficient of expansion than Type I. While there is no one standard formulation for glass among manufacturers of these USP type categories, Type II glass usually has a lower concentration of the migratory oxides than Type III. In addition, Type II has been treated under controlled temperature and humidity conditions with sulfur dioxide or other dealkalizers to neutralize the interior surface of the container. While it remains intact, this surface will increase substantially the chemical resistance of the glass. However, repeated exposures to sterilization and alkaline detergents will break down this dealkalized surface and expose the underlying soda-lime compound.

The glass types are determined from the results of two USP tests: the Powdered Glass Test and the Water Attack Test. The latter is used only for Type II glass and is performed on the whole container, because of the dealkalized surface; the former is performed on powdered glass, which exposes internal surfaces of the glass compound. The results are based upon the amount of alkali titrated by 0.02 *N* sulfuric acid after an autoclaving cycle with the glass sample in contact with a high-purity distilled water. Thus, the *Powdered Glass Test* challenges the leaching potential of the interior structure of the glass while the *Water Attack Test* challenges only the intact surface of the container.

Selecting the appropriate glass composition is a critical facet of determining the overall specifications for each parenteral formulation.

In general, Type I glass will be suitable for all products, although sulfur dioxide treatment sometimes is used for a further increase in resistance. Because cost must be considered, one of the other, less-expensive types may be acceptable. Type II glass may be suitable, for example, for a solution that is buffered, has a pH below 7, or is not reactive with the glass. Type III glass usually will be suitable principally for anhydrous liquids or dry substances. However, some manufacturer-to-manufacturer variation in glass composition should be anticipated within each glass type. Therefore, for highly chemically sensitive parenteral formulations it may be necessary to specify both USP Type and a specific manufacturer.

PHYSICAL CHARACTERISTICS—Some of the physical shapes of glass ampuls and vials are illustrated in Figure 41-4. Commercially available containers vary in size from 0.5 to 1000 mL. Sizes up to 100 mL may be obtained as ampuls and vials, and larger sizes as bottles. The latter are used mostly for intravenous and irrigating solutions. Smaller sizes also are available as cartridges. Ampuls and cartridges are drawn from glass tubing. The smaller vials may be made by molding or from tubing. Larger vials and bottles are made only by molding. Containers made by drawing tubing are generally optically clearer and have a thinner wall than molded containers (Fig 41-4). Molded containers are uniform in external dimensions, stronger, and heavier.

Easy-opening ampuls that permit the user to break off the tip at the neck constriction without the use of a file are weakened at the neck by scoring or applying a ceramic paint with a different coefficient of thermal expansion. An example of a modification of container design to meet a particular need is the double-chambered vial, under the name Univial *(Univial)*, designed to contain a freeze-dried product in the lower, and solvent in the upper, chamber. Other examples are wide-mouth ampuls with flat or rounded bottoms to facilitate filling with dry materials or suspensions, and various modifications of the cartridge for use with disposable dosage units.

Glass containers must be strong enough to withstand the physical shocks of handling and shipping and the pressure differentials that develop, particularly during the autoclave sterilization cycle. They must be able to withstand the thermal shock resulting from large temperature changes during processing, for example, when the hot bottle and contents are exposed to room air at the end of the sterilization cycle. Therefore, a glass with a low coefficient of thermal expansion is necessary. The container also must be transparent to permit inspection of the contents.

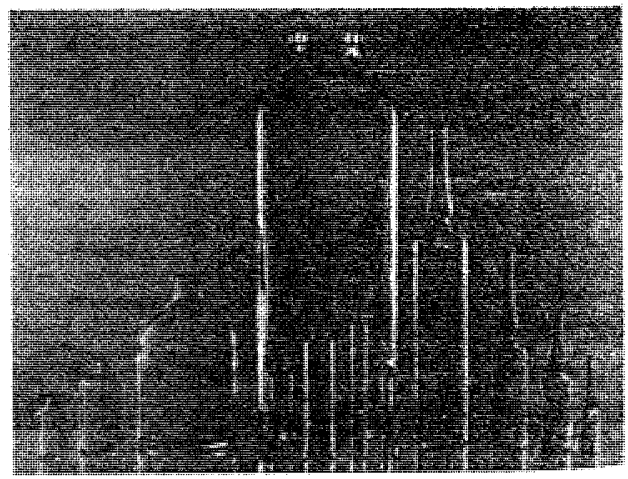

Figure 41-4. Various types of ampuls and multiple-dose vials for parenterals (courtesy, Kimble).

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Preparations that are light-sensitive must be protected by placing them in amber glass containers or by enclosing flint glass containers in opaque cartons labeled to remain on the container during the period of use. It should be noted that the amber color of the glass is imparted by the incorporation of potentially leachable heavy metals, mostly iron and manganese, which may act as catalysts for oxidative degradation reactions. Silicone coatings sometimes are applied to containers to produce a hydrophobic surface, for example, as a means of reducing the friction of a rubber-tip of a syringe plunger.

The size of single-dose containers is limited to 1000 mL by the USP and multiple-dose containers to 30 mL, unless stated otherwise in a particular monograph. Multiple-dose vials are limited in size to reduce the number of punctures for withdrawing doses and the accompanying risk of contamination of the contents. As the name implies, single-dose containers are opened or penetrated with aseptic care, and the contents used at one time. These may range in size from 1000-mL bottles to 1-mL or less ampuls, vials, or syringes. The integrity of the container is destroyed when opened, so that the container cannot be closed and reused.

A multiple-dose container is designed so that more than one dose can be withdrawn at different times, the container maintaining a seal between uses. It should be evident that with full aseptic precautions, including sterile syringe and needle for withdrawing the dose and disinfection of the exposed surface of the closure, there is still a substantial risk of introducing contaminating microorganisms and viruses into the contents of the vial. Because of this risk, the USP requires that all multiple-dose vials must contain an antimicrobial agent or be inherently antimicrobial, as determined by the USP *Antimicrobial Preservatives-Effectiveness* tests. There are no comparable antiviral effectiveness tests, nor are antiviral agents available for such use. In spite of the advantageous flexibility of dosage provided by multiple-dose vials, single-dose, disposable container units provide the clear advantage of greater sterility assurance and patient safety.

RUBBER CLOSURES

To permit introduction of a needle from a hypodermic syringe into a multiple-dose vial and provide for resealing as soon as the needle is withdrawn, each vial is sealed with a rubber closure held in place by an aluminum cap. Figure 41-5 illustrates how this is done. This principle also is followed for single-dose containers of the cartridge type, except that there is only a single introduction of the needle to make possible the withdrawal or expulsion of the contents.

Rubber closures are composed of multiple ingredients that are plasticized and mixed together at an elevated temperature on milling machines. Subsequently, the plasticized mixture is placed in molds and vulcanized (cured) under high temperature and pressure. During vulcanization the polymer strands are cross-linked by the vulcanizing agent, assisted by the accelerator and activator, so that motion is restricted and the molded closure acquires the elastic, resilient character required for its use. Ingredients not involved in the cross-linking reactions remain dispersed within the compound and, along with the degree of curing, affect the properties of the finished closure. Examples of rubber-closure ingredients are given in Table 41-2.

Table 41-2. Examples of Ingredients Found in Rubber Closures

INGREDIENT	EXAMPLES
Elastomer	Natural rubber (latex)
	Butyl rubber
	Neoprene
Vulcanizing (curing) agent	Sulfur
	Peroxides
Accelerator	Zinc dibutyldithiocarbamate
Activator	Zinc oxide
	Stearic acid
Antioxidant	Dilauryl thiodipropionate
Plasticizer/lubricant	Paraffinic oil
	Silicone oil
Fillers	Carbon black
	Clay
	Barium sulfate
Pigments	Inorganic oxides
	Carbon black

The physical properties to be considered in the selection of a particular formulation include elasticity, hardness, tendency to fragment, and permeability to vapor transfer. The elasticity is critical in establishing a seal with the lip and neck of a vial or other opening and in resealing after withdrawal of a hypodermic needle from a vial closure. The hardness should provide firmness but not excessive resistance to the insertion of a needle through the closure, while minimal fragmentation of pieces of rubber should occur as the hollow shaft of the needle is pushed through the closure. While vapor transfer occurs to some degree with all rubber formulations, appropriate selection of ingredients makes it possible to control the degree of permeability. Physicochemical and toxicological tests for evaluating rubber closures are described in section ⟨381⟩ in the USP.

The ingredients dispersed throughout the rubber compound may be subject to leaching into the product contacting the closure. These ingredients, examples of which are given in Table 41-2, pose potential compatibility interactions with product ingredients if leached into the product solution, and these effects must be evaluated.[14,15] Further, some ingredients must be evaluated for potential toxicity. To reduce the problem of leachables, coatings have been applied to the product contact surfaces of closures, with various polymers, the most successful being Teflon. Recently, polymeric coatings have been developed that are claimed to have more integral binding with the rubber matrix, but details of their function are trade secrets.

The physical shape of some typical closures may be seen in Figure 41-5. Most of them have a lip and a protruding flange that extends into the neck of the vial or bottle. Many disk closures are being used now, particularly in the high-speed packaging of antibiotics. Slotted closures are used on freeze-dried products to permit the escape of water vapor, since they are inserted only partway into the neck of the vial until completion of the drying phase of the cycle. The plunger type is used to seal one end of a cartridge. At the time of use, the plunger expels the product by a needle inserted through the closure at the distal end of the cartridge. Intravenous solution closures often have permanent holes for adapters of administration sets; irrigating solution closures usually are designed for piercing.

Figure 41-5. Extended view of sealing components for a multiple-dose vial (courtesy, West).

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PRODUCTION FACILITIES

The production facility and its associated equipment must be designed, constructed, and operated properly for the manufacture of a sterile product to be achieved at the quality level required for safety and effectiveness. Further, the processes used must meet cGMP standards, both ethical and legal. In fact, the nearer these standards approach perfection, the better and safer should be the products.

FUNCTIONAL AREAS

To achieve the goal of a manufactured sterile product of exceptionally high quality, five functional production areas will be involved: warehousing or procurement, compounding, materials support, aseptic filling, and packaging and quarantine (see Fig 41-1). The extra requirements for the aseptic area are designed to provide an environment where, for example, a sterile fluid may be exposed to the environment for a brief period during subdivision from a bulk container to individual-dose containers without becoming contaminated. Contaminants such as dust, lint, and microorganisms normally are found floating in the air, lying on counters and other surfaces, on clothing and body surfaces of personnel, in the exhaled breath of personnel, and deposited on the floor. The design and control of an aseptic area is directed toward reducing the presence of these contaminants so that they are no longer a hazard to aseptic filling.

Although the aseptic area must be adjacent to support areas so that an efficient flow of components may be achieved, barriers must be provided to minimize ingress of contaminants to the critical aseptic area. Such barriers may consist of a variety of forms, including sealed walls, manual or automatic doors, airlock pass-throughs, ports of various types, or plastic curtains. Figure 41-6 shows an example of a floor plan for a clinical supply production facility (selected as an example of a small-scale, noncomplex facility), in which the two fill rooms and the staging area constitute the walled critical aseptic area, access to which is only by means of pass-through airlocks. Adjacent support areas (rooms) consist of glass preparation, equipment wash, capping, manufacturing (compounding), and various storage areas. Figure 41-7 shows an adjacent arrangement with the utilization of a through-the-wall port for passage of a filtrate into the critical aseptic filling room.

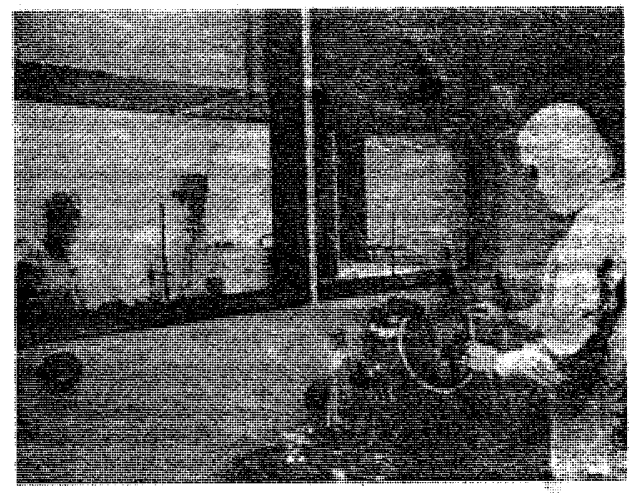

Figure 41-7. Product filtration from the aseptic staging room through a port into the aseptic filling room (courtesy, The University of Tennessee College of Pharmacy).

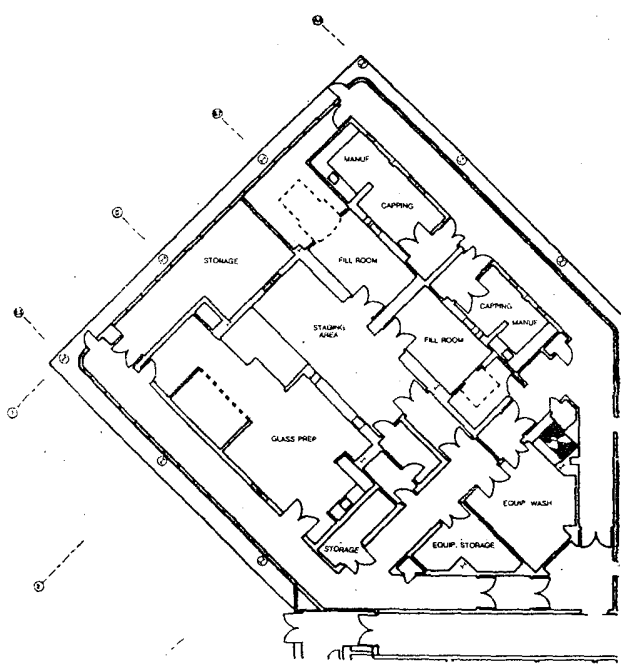

Figure 41-6. Floor plan of aseptic filling rooms and staging room with adjacent support areas (courtesy, Glaxo).

FLOW PLAN—In general, the components for a parenteral product flow (see Fig 41-1) either from the warehouse, after release, to the compounding area, as for ingredients of the formula, or to the materials support area, as for containers and equipment. After proper processing in these areas, the components flow into the security of the aseptic area for filling of the product in appropriate containers. From there the product passes into the quarantine and packaging area where it is held until all necessary tests have been performed. If the product is to be sterilized in its final container, its passage normally is interrupted after leaving the aseptic area for subjection to the sterilization process. After the results from all tests are known, the batch records have been reviewed, and the product has been found to comply with its release specifications, it passes to the finishing area for final release for shipment. There sometimes are variations from this flow plan to meet the specific needs of an individual product or to conform to existing facilities. Automated operations normally have much larger capacity and convey the components from one area to another with little or no handling by operators.

Clean Room Classified Areas

Because of the extremely high standards of cleanliness and purity that must be met by parenteral products, it has become standard practice to prescribe specifications for the environments in which these products are manufactured; ie, clean rooms. Clean room specifications are summarized in Federal Standard 209E[16], based on the maximum allowed number of airborne particles/ft^3, of 0.5 μm or larger size. The classifications used in pharmaceutical practice normally range from

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Class 100,000 for materials support areas to Class 100 for aseptic areas. To achieve Class 100 conditions, HEPA filters are required for the incoming air, with the effluent air sweeping the downstream environment at a uniform velocity, normally 90 ft/min ± 20%, along parallel lines (laminar air flow). HEPA filters are defined as 99.97% or more efficient in removing from the air 0.3-μm particles generated by vaporized dioctylphthalate (DOP). More recently other agents, eg, the hydrocarbon Emory 3004, are being used because of concern about the toxicity of DOP.

AIR CLEANING—Since air is one of the greatest potential sources of contaminants in clean rooms, special attention must be given to air being drawn into clean rooms by the heating, ventilating, and air conditioning (HVAC) system. This may be done by a series of treatments that will vary somewhat from one installation to another.

In one such series air from the outside first is passed through a prefilter, usually of glass wool, cloth, or shredded plastic, to remove large particles. Then it may be treated by passage through an electrostatic precipitator (suppliers: *Am Air, Electro-Air*). Such a unit induces an electrical charge on particles in the air and removes them by attraction to oppositely charged plates. The air then passes through the most efficient cleaning device, a HEPA filter with an efficiency of at least 99.97% in removing particles of 0.3 μm and larger, based on the DOP (dioctylphthalate) test (suppliers: *Am Air, Cambridge, Flanders*).

For personnel comfort, air conditioning and humidity control should be incorporated into the system. The latter is also important for certain products such as those that must be lyophilized and for the processing of plastic medical devices. The clean, aseptic air is introduced into the Class 100 area and maintained under positive pressure, which prevents outside air from rushing into the aseptic area through cracks, temporarily open doors, or other openings.

LAMINAR-FLOW ENCLOSURES—The required environmental control of aseptic areas has been made possible by the use of laminar airflow, originating through a HEPA filter occupying one entire side of the confined space. Therefore, it bathes the total space with very clean air, sweeping away contaminants. The orientation for the direction of airflow can be horizontal (Fig 41-8) or vertical (see Fig 41-9), and may involve a limited area such as a workbench or an entire room. Figure 41-9 shows a vial-filling line protected with vertical laminar airflow from ceiling-hung HEPA filters, a Class 100 area. Plastic curtains are installed to maintain the laminarity of airflow to below the filling line and to circumscribe the critical filling portion of the line. The area outside the curtains can be maintained at a slightly lower level of cleanliness than that inside, perhaps Class 1000 or 10,000.

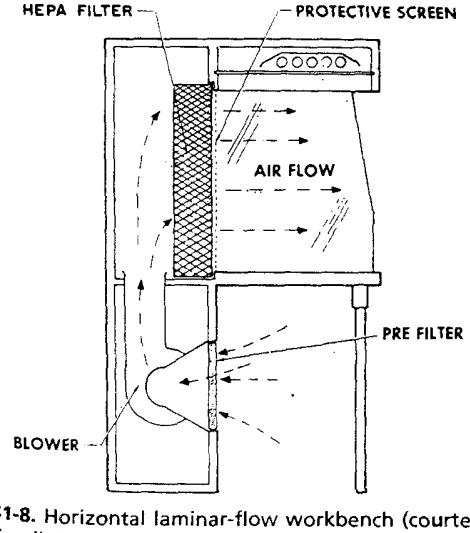

Figure 41-8. Horizontal laminar-flow workbench (courtesy, adaptation, Sandia).

Figure 41-9. Vial filling line under vertical laminar airflow with critical area enclosed within plastic curtains (courtesy, Merck).

Today, it is accepted that critical areas of processing, wherein the product or product contact surfaces may be exposed to the environment, even for a brief period of time, should meet Class 100 clean room standards.

It must be borne in mind that any contamination introduced upstream by equipment, arms of the operator, or leaks in the filter will be blown downstream. In the instance of horizontal flow this may be to the critical working site, the face of the operator, or across the room. Should the contaminant be, for example, penicillin powder, a biohazard material, or viable microorganisms, the danger to the operator is apparent.

Further, great care must be exercised to prevent cross-contamination from one operation to another, especially with horizontal laminar air flow. For most large-scale operations, as shown in Figure 41-9, a vertical system is much more desirable, with the air flowing through perforations in the countertop or through return louvers at floor level, where it can be directed for decontamination. Laminar-flow environments provide well-controlled work areas only if proper precautions are observed. Any reverse air currents or movements exceeding the velocity of the HEPA-filtered airflow may introduce contamination, as may coughing, reaching, or other manipulations of operators. Therefore, laminar-flow work areas should be protected by being located within controlled environments. Personnel should be attired for aseptic processing, as described below. All movements and processes should be planned carefully to avoid the introduction of contamination upstream of the critical work area. Checks of the air stream should be performed initially and at regular intervals to be sure no leaks have developed through or around the HEPA filters. Workbenches and other types of laminar-flow enclosures are available from several commercial sources (suppliers: *Air Control, Atmos-Tech, Baker, Clean Air, Clestra, Envirco, Flanders, Laminaire, Liberty*).

MATERIALS SUPPORT AREA—The area is constructed to withstand moisture, steam, and detergents and is usually a Class 100,000 clean room. The ceiling, walls, and floor should be constructed of impervious materials so that moisture will run off and not be held. One of the finishes with a vinyl or expoxy sealing coat provides a continuous surface free from all holes or crevices. All such surfaces can be washed at regular intervals to keep them thoroughly clean. These areas should be exhausted adequately so that the heat and humidity will be removed for the comfort of personnel. Precautions must be taken to prevent the accumulation of dirt and the growth of

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microorganisms because of the high humidity and heat. In this area preparation for the filling operation, such as cleaning and assembling equipment, is undertaken. Adequate sink and counter space must be provided. This area must be cleanable, and the microbial load must be monitored and controlled. Precautions also must be taken to prevent deposition of particles or other contaminants on clean containers and equipment until they have been properly boxed or wrapped preparatory to sterilization and depyrogenation.

COMPOUNDING AREA—In this area the formula is compounded. Although it is not essential that this area be aseptic, control of microorganisms and particulates should be more stringent than in the materials support area. For example, means may need to be provided to control dust generated from weighing and compounding operations. Cabinets and counters should, preferably, be constructed of stainless steel. They should fit snugly to walls and other furniture so that there are no catch areas where dirt can accumulate. The ceiling, walls, and floor should be similar to those for the materials support area.

ASEPTIC AREA—The aseptic area requires construction features designed for maximum microbial and particulate control. The ceiling, walls, and floor must be sealed so that they may be washed and sanitized with a disinfectant, as needed. All counters should be constructed of stainless steel and hung from the wall so that there are no legs to accumulate dirt where they rest on the floor. All light fixtures, utility service lines, and ventilation fixtures should be recessed in the walls or ceiling to eliminate ledges, joints, and other locations for the accumulation of dust and dirt. As much as possible, tanks containing the compounded product should remain outside the aseptic filling area, and the product fed into the area through hose lines. Figure 41-7 shows such an arrangement. Proper sanitization is required if the tanks must be moved in. Large mechanical equipment that is located in the aseptic area should be housed as completely as possible within a stainless steel cabinet to seal the operating parts and their dirt-producing tendencies from the aseptic environment. Further, all such equipment parts should be located below the filling line. Mechanical parts that will contact the parenteral product should be demountable so that they can be cleaned and sterilized.

Personnel entering the aseptic area should enter only through an airlock. They should be attired in sterile coveralls with sterile hats, masks, goggles, and foot covers. Movement within the room should be minimal and in-and-out movement rigidly be restricted during a filling procedure. The requirements for room preparation and the personnel may be relaxed somewhat if the product is to be sterilized terminally in a sealed container. Some are convinced, however, that it is better to have one standard procedure meeting the most rigid requirements.

ISOLATION (BARRIER) TECHNOLOGY—This technology is a relatively new approach to the control of aseptic processing. It is designed to isolate aseptic operations from personnel and the surrounding environment. Considerable experience has been gained in its use for sterility testing, with very positive results, including reports of essentially no false-positive test results.[17] In European circles favorable results also have been reported from use in hospital IV admixture programs. Because of such results, experimental efforts in adapting automated, large-scale, aseptic filling operations to isolators has gained momentum.[18]

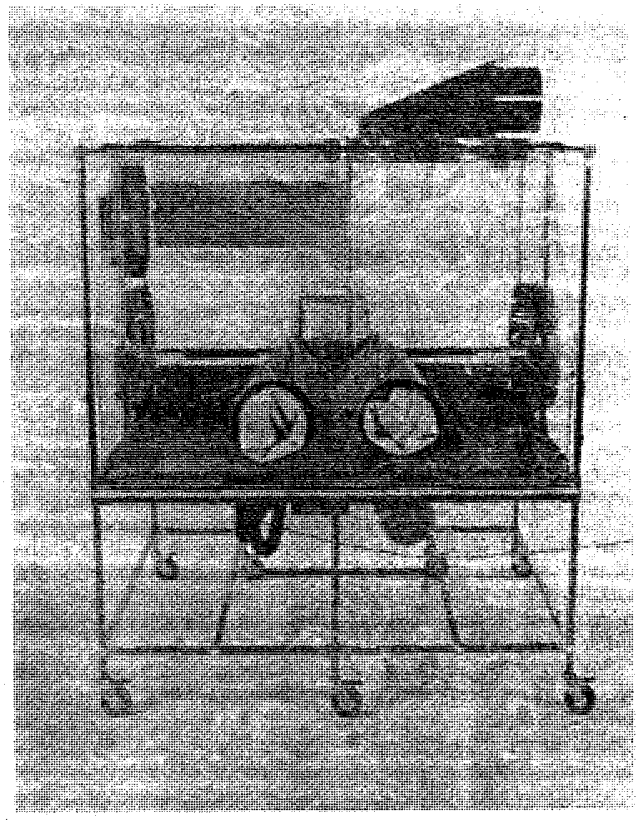

Figure 41-10. One configuration of an isolator (courtesy, Amsco).

Figure 41-10 illustrates a configuration of an isolator with transparent plastic sides and a halfsuit for operator access to the enclosure. Figure 41-11 illustrates the adaptation of a large-scale filling line to isolator technology. The operations are performed within windowed, sealed walls with operators working through glove ports. The sealed enclosures are presterilized, usually with peracetic acid, hydrogen peroxide vapor, or steam. Sterile supplies are introduced from sterilizable movable modules through uniquely engineered transfer ports or directly from attached sterilizers, including autoclaves and hot-air sterilizing tunnels. Results have been very promising, giving expectation of significantly enhanced control of the aseptic processing environment.[18]

MAINTENANCE OF [illegible]

Maintaining the clean and sanitized conditions of clean rooms, particularly the aseptic areas, requires diligence and dedication of expertly trained custodians. Assuming the design of the facilities to be cleanable and sanitizable, a carefully planned schedule of cleaning should be developed, ranging from daily to monthly, depending on the location and its relation to the most critical Class 100 areas. Tools used should be nonlinting, designed for clean room use, held captive to the area and, preferably, sterilizable.

Liquid disinfectants (sanitizing agents) should be selected carefully because of data showing their reliable activity against inherent environmental microorganisms. They should be recognized as supplements to good housekeeping, never as substitutes. They should be rotated with sufficient frequency to avoid the development of resistant strains of microorganisms. Space does not permit a detailed discussion of these agents, but an excellent discussion can be found in the report of a PDA task force.[19]

It should be noted that ultraviolet (UV) light rays of 237.5 nm wavelength, as radiated by germicidal lamps, are an effective surface disinfectant. But, it must also be noted that they are only effective if they contact the target microorganisms at a sufficient intensity for a sufficient time. The limitations of their use must be recognized, including no effect in shadow

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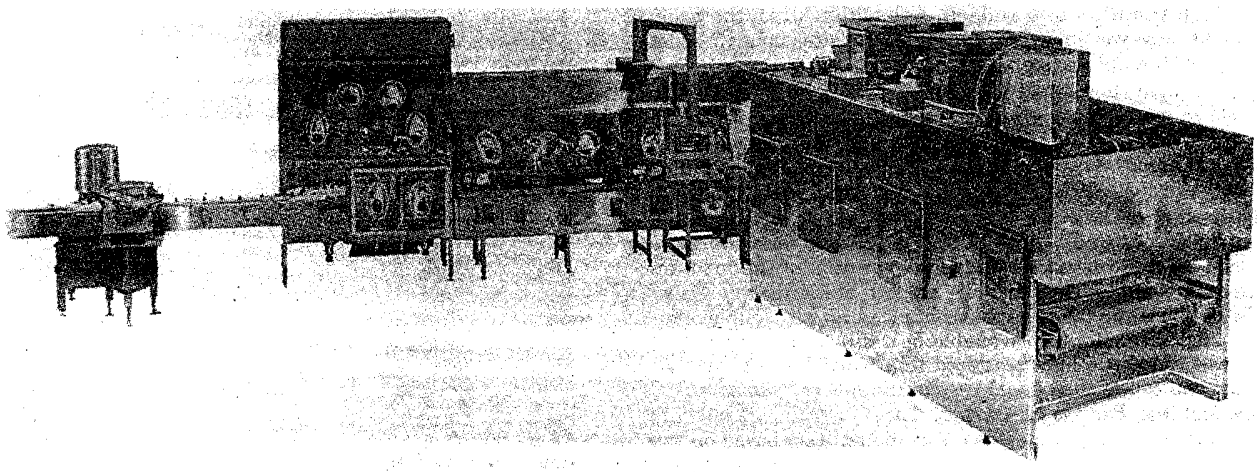

Figure 41-11. Large-scale production line showing, from right to left, container-sterilizing tunnel feeding into isolator enclosing filling and sealing, with access glove ports, and exiting to capper (courtesy, TL Systems).

areas, reduction of intensity by the square of the distance from the source, reduction by particulates in the ray path, and the toxic effect on epithelium of human eyes. It generally is stated that an irradiation intensity of 20 $\mu w/cm^2$ is required for effective antibacterial activity.

PERSONNEL

Personnel selected to work on the preparation of a parenteral product must be neat, orderly, and reliable. They should be in good health and free from dermatological conditions that might increase the microbial load. If they show symptoms of a head cold, allergies, or similar illness, they should not be permitted in the aseptic area until their recovery is complete. However, a healthy person with the best personal hygiene still will shed large numbers of viable and nonviable particles from body surfaces. This natural phenomenon creates continuing problems when personnel are present in clean rooms; effective training and proper gowning can reduce, but not eliminate, the problem of particle shedding from personnel.

Aseptic-area operators should be given thorough, formal training in the principles of aseptic processing and the techniques to be employed. Subsequently, the acquired knowledge and skills should be evaluated, to be sure training has been effective, before they are allowed to participate in the preparation of sterile products. Retraining should be performed on a regular schedule to enhance the maintenance of the required level of expertise. An effort should be made to imbue operators with an awareness of the vital role they play in determining the reliability and safety of the final product. This is especially true of supervisors, since they should be individuals who not only understand the unique requirements of aseptic procedures but who are able to obtain the full participation of other employees in fulfilling these exacting requirements.

The uniform worn is designed to confine the contaminants discharged from the body of the operator, thereby preventing their entry into the production environment. For use in the aseptic area, uniforms should be sterile. Fresh, sterile uniforms should be used after every break period or whenever the individual returns to the aseptic area. In some plants this is not required if the product is to be sterilized in its final container. The uniform usually consists of coveralls for both men and women, hoods to cover the hair completely, face masks, and Dacron or plastic boots (Fig 41-12). Sterile rubber or latex-free gloves are also required for aseptic operations, preceded by thorough scrubbing of the hands with a disinfectant soap. In addition, goggles may be required to complete the coverage of all skin areas.

Dacron or Tyvek uniforms are usually worn, are effective barriers to discharged body particles (viable and nonviable), are essentially lint-free, and are reasonably comfortable. Air showers are sometimes directed on personnel entering the processing area to blow loose lint from the uniforms.

Gowning rooms should be designed to enhance pregowning and gowning procedures by trained operators so that it is possible to ensure the continued sterility of the exterior surfaces of the sterile gowning components. Degowning should be performed in a separate exit room.

ENVIRONMENTAL CONTROL EVALUATION

As evidenced by the above discussion, manufacturers of sterile products use extensive means to control the environment so that these critical products can be prepared free from contamination. Nevertheless, tests should be performed to determine the level of control actually achieved. Normally, the tests consist of counting viable and nonviable particles suspended in the air or settled on surfaces in the workspace. A baseline count, determined by averaging multiple counts when the facility is operating under controlled conditions, is used to establish the optimal test results expected. During the subsequent monitoring program, the test results are followed carefully for high individual counts, a rising trend, or other abnormalities. If they exceed selected alert or action levels, a plan of action must be put into operation to determine if or what corrective measures are required.

The tests used generally measure either the particles in a volume of sampled air or the particles that are settling or are present on surfaces. A volume of air measured by an electronic particle counter will detect all particles instantly but not differentiate between viable and nonviable ones. However, because of the need to control the level of microorganisms in the environment in which sterile products are processed, it also is necessary to detect viable particles. These usually are fewer in number than nonviable ones and are only detectable as colony-forming units (CFUs) after a suitable incubation period at, for example, 30 to 35° for up to 48 hr. Thus, test results will not be known for 48 hr after the samples are taken.

Locations for sampling should be planned to reveal potential contamination levels that may be critical in the control of the environment. For example, the most critical process step is usually the filling of dispensing containers, a site obviously requiring monitoring. Other examples include the gowning

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room, high-traffic sites in and out of the filling area, the penetration of conveyor lines through walls, and sites near the inlet and exit of the air system.

The sample should be large enough to obtain a meaningful particle count. At sites where the count is expected to be low, the size of the sample may need to be increased; for example, in Class 100 areas, Whyte and Niven,[20] suggest that the sample should be at least 30 ft^3 and, probably, much more. They also suggest that settling plates should be exposed in Class 100 areas for an entire fill (up to 7 to 8 hr) rather than the more common 1 hr. However, excessive dehydration of the medium must be avoided, particularly in the path of laminar-flow air.

To measure the total particle content in an air sample, electronic particle counters are available, operating on the principle of the measurement of light scattered from particles as they pass through the cell of the optical system (Suppliers: *Climet, HIAC Royco, Met One, Particle Measuring*). These instruments not only count particles but also provide a size distribution based on the magnitude of the light scattered from the particle.

Several air-sampling devices are used to obtain a count of microorganisms in a measured volume of air. A slit-to-agar (STA) sampler (suppliers: *Mattson-Garvin, New Brunswick, Vai*) draws by vacuum a measured volume of air through an engineered slit, causing the air to impact on the surface of a slowly rotating nutrient agar plate. Microorganisms adhere to the surface of the agar and grow into visible colonies that are counted as CFUs, since it is not known whether the colonies arise from a single microorganism or a cluster. A centrifugal sampler (supplier: *Biotest*) pulls air into the sampler by means of a rotating propeller and slings the air by centrifugal action against a peripheral nutrient agar strip. The advantages of this unit are that it can be disinfected easily and is portable, so that it can be hand-carried wherever needed. These two methods are used quite widely.

A widely used method for microbiological sampling consists of the exposure of nutrient agar culture plates to the settling of microorganisms from the air. This method is very simple and inexpensive to perform but will detect only those organisms that have settled on the plate; therefore, it does not measure the number of microorganisms in a measured volume of air. Nevertheless, if the conditions of exposure are repeated consistently, a comparison of CFUs at one sampling site from one time to another can be meaningful.[21]

The number of microorganisms on surfaces can be determined with nutrient agar plates having a convex surface (*Rodac Plates*). With these it is possible to roll the raised agar surface over flat or irregular surfaces to be tested. Organisms will be picked up on the agar and will grow during subsequent incubation. This method also can be used to assess the number of microorganisms present on the surface of the uniforms of operators, either as an evaluation of gowning technique immediately after gowning or as a measure of the accumulation of microorganisms during processing. Whenever used, care must be taken to remove any agar residue left on the surface tested.

Further discussion of proposed viable particle test methods and the counts to be accepted will be found in Section ⟨1116⟩ "Microbial Evaluation and Classification of Clean Rooms and Other Controlled Environments" in USP 24.[22]

Results from the above tests, although not available until 2 days after sampling, are valuable to keep cleaning, production, and quality-control personnel apprised of the level of contamination in a given area and, by comparison with baseline counts, will indicate when more-extensive cleaning and sanitizing is needed. The results also may serve to detect environmental control defects such as failure in air-cleaning equipment or the presence of personnel who may be disseminating large numbers of bacteria without apparent physical ill effects.

Figure 4 .-12. Appropriate uniform for operators entering an aseptic filling room (courtesy, Abbott).

MEDIA FILL (PROCESS SIMULATION TESTING)—An evaluation that is not strictly an environmental test, but which includes an evaluation of the environment along with the process, the operators, and the equipment, is the *media fill* or *process simulation test*. Sterile trypticase soy broth is filled into sterile containers under conditions simulating as closely as possible those characteristics of a filling process for a product. The entire lot, normally at least 3000 units, is then incubated at a suitable temperature, usually 20 to 25°, for at least 14 days and examined for the appearance of growth of microorganisms.[23] If growth occurs, contamination has entered the container(s) during the processing. To pass the test not more than 0.1% of the units may show growth. This evaluation also has been used as a measure of the proficiency of an individual or team of operators. This test is a very stringent evaluation of the efficiency of an aseptic filling process and, by many, is considered to be the most evaluative test available.

[illegible]

The processes required for preparing sterile products constitute a series of events initiated with the procurement of approved raw materials (drugs, excipients, vehicles, etc) and primary packaging components (containers, closures, etc) and ending with the sterile product sealed in its dispensing package (see Fig 41-1). Each step in the process must be controlled very carefully so that the product will have its required quality. To ensure the latter, each process should be validated to be sure that it is accomplishing what it is intended to do. For example, an autoclave sterilization process must be validated by producing data showing that it effectively kills resistant forms of microorganisms; or, a cleaning process for rubber closures should provide evidence that it is cleaning closures to the required level of cleanliness. The validation of processes re-

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quires extensive and intensive effort to be successful and is an integral part of cGMP requirements.

In the following sections the production procedures used in preparing sterile drug products are discussed.

CLEANING CONTAINERS AND EQUIPMENT

Containers and equipment coming in contact with parenteral preparations must be cleaned meticulously. It should be obvious that even new, unused containers and equipment will be contaminated with such debris as dust, fibers, chemical films, and other materials arising from such sources as the atmosphere, cartons, the manufacturing process, and human hands. Residues from previous use must be removed from used equipment before it will be suitable for reuse. Equipment should be reserved exclusively for use only with parenteral preparations and, where conditions dictate, only for one product in order to reduce the risk of contamination.

A variety of machines are available for cleaning new containers for parenteral products. These vary in complexity from a small, hand loaded, rotary rinser (Fig 41-13) to large automatic washers capable of processing several thousand containers an hour (Figs 41-14 and 41-15). The selection of the particular type will be determined largely by the physical type of containers, the type of contamination, and the number to be processed in a given period of time.

CHARACTERISTICS OF MACHINERY—Regardless of the type of cleaning machine selected, certain fundamental characteristics usually are required.

1. The liquid or air treatment must be introduced in such a manner that it will strike the bottom of the inside of the inverted container, spread in all directions, and smoothly flow down the walls and out the opening with a sweeping action. The pressure of the jet stream should be such that there is minimal splashing and turbulence inside. Splashing may prevent cleaning all areas, and turbulence may redeposit loosened debris. Therefore, direct introduction of the jet stream within the container with control of its flow is required.
2. The container must receive a concurrent outside rinse.
3. The cycle of treatment should provide a planned sequence alternating very hot and cool treatments. The final treatment should be an effective rinse with WFI.
4. All metal parts coming in contact with the containers and with the treatments should be constructed of stainless steel or some other noncorroding and noncontaminating material.

TREATMENT CYCLE—The cycle of treatments to be employed will vary with the condition of the containers to be cleaned. In general, loose debris can be removed by vigorous rinsing with water. Detergents rarely are used for new containers because of the risk of leaving detergent residues. However, a thermal-shock sequence in the cycle usually is employed to aid, by expansion and contraction, loosening of debris that may be adhering to the container wall. Sometimes only an air rinse is used for new containers, if only loose debris is present. In all instances the final rinse, whether air or WFI, must be ultraclean so that no particulate residues are left by the rinsing agent.

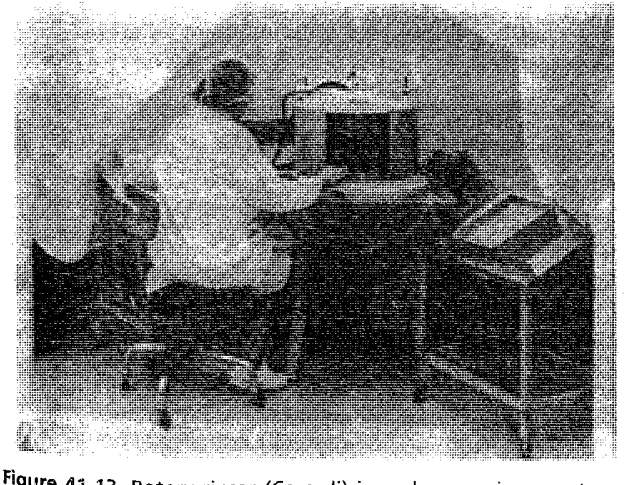

Figure 41-13. Rotary rinser (Cozzoli) in a clean environment provided by vertical laminar airflow within a curtained enclosure (courtesy, Ciba-Geigy).

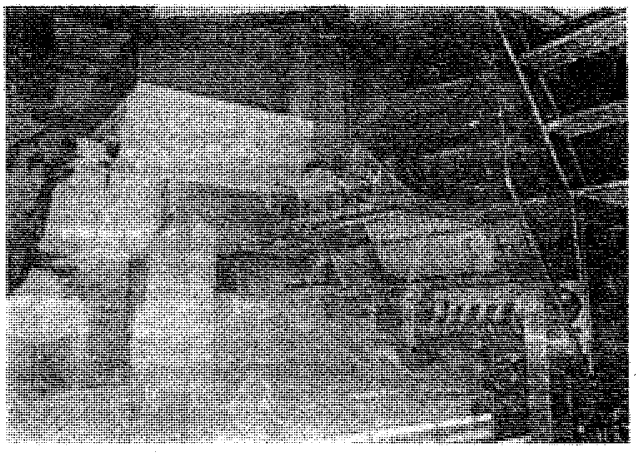

Figure 41-14. Loading end of large conveyor vial washer that subjects inverted vials to a series of cleaning steps before delivery from the far end of the washer. Note the vials in plastic blister packs at right of operator (courtesy, Merck).

Only new containers are used for parenterals. Improvements have been made in maintaining their cleanliness during shipment from the manufacturer through tight, low-shedding packaging, including plastic blister packs, as can be seen stacked on the right of Figure 41-14.

MACHINERY FOR CONTAINERS—The machinery available for cleaning containers embodies the above principles but varies in the mechanics by which it is accomplished. In one manual loading type, the jet tubes are arranged on arms like the spokes of a wheel, which rotate around a center post through which the treatments are introduced. An operator places the unclean containers on the jet tubes as they pass the loading point and removes the clean containers as they complete one rotation. Such a small-scale machine is pictured in Figure 41-14. A washer capable of cleaning hundreds of containers an hour, shown in Figure 41-14, uses a row of jet tubes across a conveyor belt. The belt moves the inverted containers past the programmed series of treatments and discharges the clean containers into a sterilizing oven (not shown), which ultimately discharges them through a wall into a clean room for filling.

Another type of machine is the rack-loading washer. Stainless-steel racks are designed to fit over the open ends of ampuls or vials as configured in trays of shipping cartons or blister packs. Inverting the trays permits the containers to slide into the racks so that they can be handled by the quantity in the tray, as shown in Figure 41-15. The clean containers may be transferred directly to the conveyor of a sterilizing tunnel (as shown), or they may be placed in stainless steel boxes for subsequent dry-heat sterilization and storage. A continuous automated line operation, capable of cleaning hundreds of containers an hour, is shown in Figure 41-16. The vials are fed into the rotary rinser in the foreground, transferred automatically to the covered sterilizing tunnel in the center, conveyed through the wall in the background, and discharged into the filling clean room.

HANDLING AFTER CLEANING—The wet, clean containers must be handled in such a way that contamination will

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not be reintroduced. A wet surface will collect contaminants much more readily than will a dry surface. For this reason wet, rinsed containers must be protected, eg, by a laminar flow of clean air until covered, within a stainless steel box, or within a sterilizing tunnel. Although not clearly visible in each instance, the wet, clean containers in Figures 41-13 to 41-16 were so protected. In addition, microorganisms are more likely to grow in the presence of moisture. Therefore, wet, clean containers should be dry-heat sterilized as soon as possible after washing. Doubling the heating period generally is adequate also to destroy pyrogens; for example, increasing the dwell time at 250° from 1 to 2 hr, but the actual time-temperature conditions required must be validated.

Increases in process rates have necessitated the development of continuous, automated line processing with a minimum of individual handling, still maintaining adequate control of the cleaning and handling of the containers. In Figure 41-16, the clean, wet containers are protected by filtered, laminar-flow air from the rinser through the tunnel and until they are delivered to the filling line.

CLOSURES—The rough, elastic, and convoluted surface of rubber closures renders them difficult to clean. In addition, any residue of lubricant from molding or surface *bloom* of inorganic constituents must be removed. The normal procedure calls for gentle agitation in a hot solution of a mild water softener or detergent. The closures are removed from the solution and rinsed several times, or continuously for a prolonged period, with filtered WFI. The rinsing is to be done in a manner that will flush away loosened debris. The wet closures are carefully protected from pickup of environmental contamination, sterilized, usually by autoclaving, and stored in closed containers until ready for use. This cleaning and sterilizing process also must be validated with respect to rendering the closures free from pyrogens. Actually, it is the cleaning and final, thorough rinsing with WFI that must remove pyrogens, since autoclaving does not destroy pyrogens. If the closures were immersed during autoclaving, the solution is drained off before storage to reduce hydration of the rubber compound. If the closures must be dry for use, they may be subjected to vacuum drying at a temperature in the vicinity of 100°.

The equipment used for washing large numbers of closures is usually an agitator or horizontal basket-type automatic washing machine. Because of the risk of particulate generation from the abrading action of these machines, some procedures simply call for heating the closures in kettles in detergent solution, followed by prolonged flush rinsing. The final rinse always should be with low-particulate WFI.

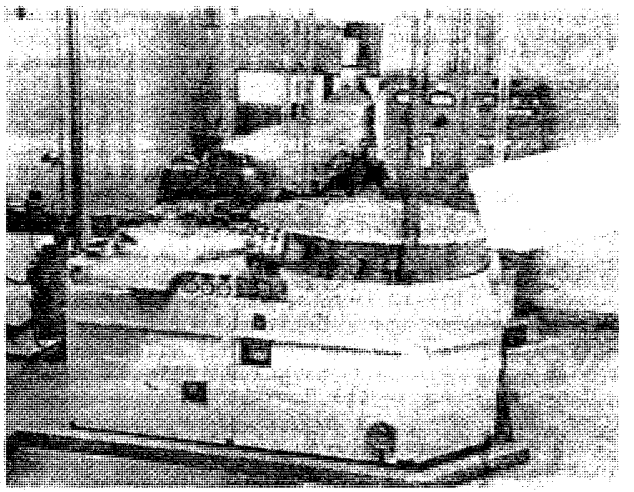

Figure 41-16. Continuous automatic line operation for vials from a rotary rinser through a sterilizing tunnel with vertical laminar-airflow protection of clean vials (courtesy, Abbott).

EQUIPMENT—The details of certain prescribed techniques for cleaning and preparing equipment, as well as of containers and closures, have been presented elsewhere.[24] Here, a few points will be emphasized.

All equipment should be disassembled as much as possible to provide access to internal structures. Surfaces should be scrubbed thoroughly with a stiff brush, using an effective detergent and paying particular attention to joints, crevices, screw threads, and other structures where debris is apt to collect. Exposure to a stream of clean steam will aid in dislodging residues from the walls of stationary tanks, spigots, pipes, and similar structures. Thorough rinsing with distilled water should follow the cleaning steps.

Because of the inherent variation in manual cleaning, the difficult accessibility of large stationary tanks (as shown in Fig 41-17), and the need to validate the process, computer-controlled systems (usually automated) have been developed and are known as CIP.[25] Such an approach involves designing the system, normally of stainless steel, with smooth, rounded internal surfaces and without crevices. That is, for example, with welded rather than threaded connections. The cleaning is

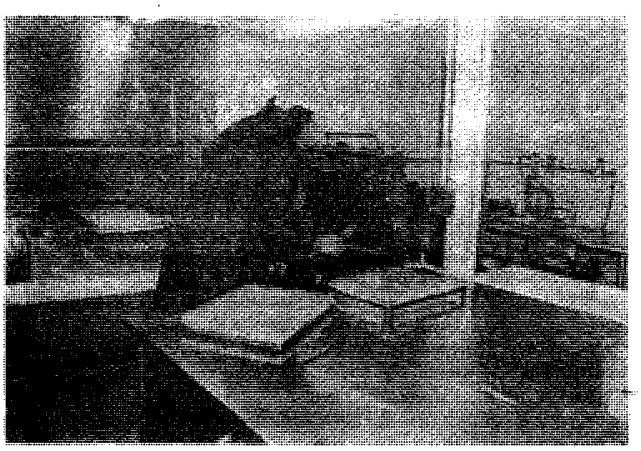

Figure 41-15. Cleaning vials with rack-loading washer, permitting handling vials by a full rack. After multiple-washing treatments, the racks are placed directly on the conveyor belt of the hot-air sterilizing tunnel (courtesy, Merck).

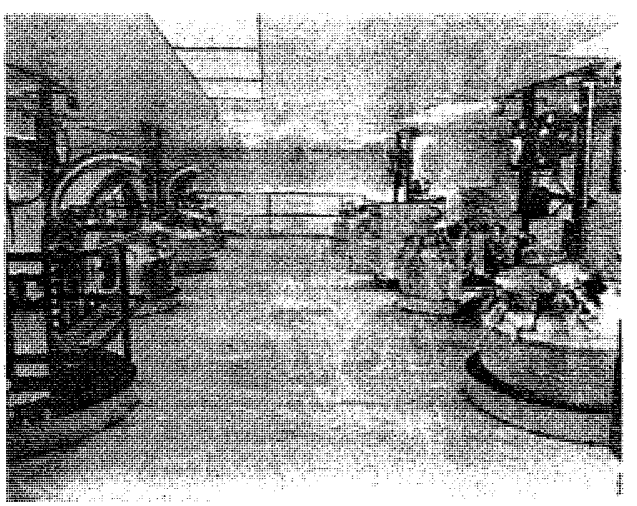

Figure 41-17. Large stainless steel tanks for product preparation showing mezzanine access level (courtesy, Abbott).

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accomplished with the scrubbing action of high-pressure spray balls or nozzles delivering hot detergent solution from tanks captive to the system, followed by thorough rinsing with WFI. The system often is extended to allow sterilizing in place (SIP) to accomplish sanitizing or sterilizing as well.

Rubber tubing, rubber gaskets, and other rubber parts may be washed in a manner such as described for rubber closures. Thorough rinsing of tubing must be done by passing WFI through it. However, because of the relatively porous nature of rubber compounds and the difficulty in removing all traces of chemicals from previous use, it is considered by some inadvisable to reuse rubber or polymeric tubing. Rubber tubing must be left wet when preparing for sterilization by autoclaving.

PRODUCT PREPARATION

The basic principles employed in the compounding of the product are essentially the same as those used historically by pharmacists. However, large-scale production requires appropriate adjustments in the processes and their control.

A master formula would have been developed and be on file. Each batch formula sheet should be prepared from the master and confirmed for accuracy. All measurements of quantities should be made as accurately as possible and checked by a second qualified person. Frequently, today, the formula documents are generated by a computer and the measurements of quantities of ingredients computer controlled. Although most liquid preparations are dispensed by volume, they are prepared by weight, since weighings can be performed more accurately than volume measurements, and no consideration needs to be given to the temperature.

Care must be taken that equipment is not wet enough to dilute the product significantly or, in the case of anhydrous products, to cause a physical incompatibility. The order of mixing of ingredients may affect the product significantly, particularly those of large volume, where attaining homogeneity requires considerable mixing time. For example, the adjustment of pH by the addition of an acid, even though diluted, may cause excessive local reduction in the pH of the product so that adverse effects are produced before the acid can be dispersed throughout the entire volume of product.

Parenteral dispersions, including colloids, emulsions, and suspensions, provide particular problems. Parenteral emulsions have been reviewed by Singh and Ravin.[27] In addition to the problems of achieving and maintaining proper reduction in particle size under aseptic conditions, the dispersion must be kept in a uniform state of suspension throughout the preparative, transfer, and subdividing operations.

The formulation of a stable product is of paramount importance. Certain aspects of this are mentioned in the discussion of components of the product. Exhaustive coverage of the topic is not possible within the limits of this text, but further coverage is provided in Chapter 38. It should be mentioned here, however, that the thermal sterilization of parenteral products increases the possibility of chemical reactions. Such reactions may progress to completion during the period of elevated temperature in the autoclave or be initiated at this time but continue during subsequent storage. The assurance of attaining product stability requires a high order of pharmaceutical knowledge and responsibility.

FILTRATION

After a product has been compounded, it must be filtered if it is a solution. The primary objective of filtration is to clarify a solution. A high degree of clarification is termed *polishing* a solution. This term is used when particulate matter down to approximately 2 μm in size is removed. A further step, removing particulate matter down to 0.2 μm in size, would eliminate microorganisms and would accomplish *cold* sterilization. A solution with a high degree of clarity conveys the impression of high quality and purity, desirable characteristics for a parenteral solution.

Filters are thought to function by one or, usually, a combination of the following: (1) sieving or screening, (2) entrapment or impaction, and (3) electrostatic attraction. When a filter retains particles by sieving, they are retained on the surface of the filter. Entrapment occurs when a particle smaller than the dimensions of the passageway (pore) becomes lodged in a turn or impacted on the surface of the passageway. Electrostatic attraction causes particles opposite in charge to that of the surface of the filter pore to be held or adsorbed to the surface. It should be noted that increasing, prolonging, or varying the force behind the solution may tend to sweep particles initially held by entrapment or electrostatic charge through the pores and into the filtrate.

Membrane filters are used exclusively for parenteral solutions because of their particle-retention effectiveness, nonshedding property, nonreactivity, and disposable characteristics. However, it should be noted that nonreactivity does not apply in all cases. For example, polypeptide products may show considerable adsorption through some membrane filters, but those composed of polysulfone and polyvinylidine difluoride have been developed to be essentially nonadsorptive for these products. The most common membranes are composed of

Cellulose esters, Nylon, Polysulfone, Polycarbonate, Polyvinylidene difluoride, or Polytetrafluoroethylene (Teflon).

They are available as flat membranes or pleated into cylinders to increase surface area and, thus, flow rate (suppliers: *Cuno, Gelman, Meissner, Millipore, Pall, Sartorius Schleicher*). Each filter in its holder should be tested for integrity before and after use, particularly if it is being used to eliminate microorganisms. This integrity test usually is performed as the *bubble-point test,* a test to detect the largest pore or other opening through the membrane. The basic test is performed by gradually raising air pressure on the upstream side of a water-wet filter. The pressure at which bubbles first appear downstream is the bubble point. This pressure is characteristic for each pore size of a filter and is provided by the filter manufacturer. For example, a 0.2-μm cellulose ester filter will bubble at about 50 psig. If the filter is wetted with other liquids, such as a product, the bubble point will differ and must be determined experimentally. If the bubble point is lower than the rated pressure, the filter is defective, probably because of a puncture or tear, and should not be used. As the surface area of filters becomes large, diffusion of air through the water-filled pores tends to obscure the bubble point. Therefore, a diffusion, or pressure hold, test has been developed as an integrity test for filters with large surface areas. Particulars are obtainable from the filter manufacturer, including the most critical functional test for sterilizing grade filters, the bacterial retention test.

While membrane filters are disposable and thus discarded after use, the holders must be cleaned thoroughly between uses. Today, clean, sterile, pretested, disposable assemblies for small as well as large volumes of solutions are available commercially. Other characteristics of these filters, important for a full understanding of their use, are given in Chapter 40 and in a review article.[28]

FILLING

During the filling of containers with a product, the most stringent requirements must be exercised to prevent contamination, particularly if the product has been sterilized by filtration and will not be sterilized in the final container. Under the latter conditions the process usually is called an *aseptic fill* and is validated with media fills (see page 794). During the filling

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operation, the product must be transferred from a bulk container and subdivided into dose containers. This operation exposes the sterile product to the environment, equipment, and manipulative technique of the operators until it can be sealed in the dose container. Therefore, this operation is carried out with a minimum exposure time, even though maximum protection is provided by filling under a blanket of HEPA-filtered laminar-flow air within the aseptic area.

Normally, the compounded product is in the form of either a liquid or a solid. A liquid is more readily subdivided uniformly and introduced into a container having a narrow mouth than is a solid. Mobile, nonsticking liquids are considerably easier to transfer and subdivide than viscous, sticky liquids, which require heavy-duty machinery for rapid production filling.

Although many devices are available for filling containers with liquids, certain characteristics are fundamental to them all. A means is provided for repetitively forcing a measured volume of the liquid through the orifice of a delivery tube that is introduced into the container. The size of the delivery tube will vary from that of about a 20-gauge hypodermic needle to a tube ½ in or more in diameter. The size required is determined by the physical characteristics of the liquid, the desired delivery speed, and the inside diameter of the neck of the container. The tube must enter the neck and deliver the liquid well into the neck to eliminate spillage, allowing sufficient clearance to permit air to leave the container as the liquid enters. The delivery tube should be as large in diameter as possible to reduce the resistance and decrease the velocity of flow of the liquid. For smaller volumes of liquids, the delivery usually is obtained from the stroke of the plunger of a syringe, forcing the liquid through a two-way valve providing for alternate filling of the syringe and delivery of mobile liquids. For heavy, viscous liquids, a sliding piston valve, the turn of an auger in the neck of a funnel, or the oscillation of a rubber diaphragm may be used. For large volumes the quantity delivered usually is measured in the container by the level of fill in the container, the force required to transfer the liquid being provided by gravity, a pressure pump, or a vacuum pump.

The narrow neck of an ampul limits the clearance possible between the delivery tube and the inside of the neck. Since a drop of liquid normally hangs at the tip of the delivery tube after a delivery, the neck of an ampul will be wet as the delivery tube is withdrawn, unless the drop is retracted. Therefore, filling machines should have a mechanism by which this drop can be drawn back into the lumen of the tube.

Since the liquid will be in intimate contact with the parts of the machine through which it flows, these must be constructed of nonreactive materials such as borosilicate glass or stainless steel. In addition, they should easily be demountable for cleaning and sterilization.

Because of the concern for particulate matter in injectable preparations, a final filter often is inserted in the system between the filler and the delivery tube, as shown in Figure 41-18. Most frequently this is a membrane filter, having a porosity of approximately 1 μm and treated to have a hydrophobic edge. This is necessary to reduce the risk of rupture of the membrane caused by filling pulsations. It should be noted that the insertion of the filter at this point should collect all particulate matter generated during the process. Only that which may be found in inadequately cleaned containers or picked up from exposure to the environment after passage through the final filter potentially remain as contaminants. However, the filter does cushion liquid flow and reduces the efficiency of drop retraction from the end of the delivery tube, sometimes making it difficult to control delivery volume as precisely as would be possible without the filter.

LIQUIDS—The filling of a small number of containers may be accomplished with a hypodermic syringe and needle, the liquid being drawn into the syringe and forced through the needle into the container. A device for providing greater speed of filling is the Cornwall Pipet *(Becton Dickinson)*. This has a two-way valve between the syringe and the needle and a means for setting the stroke of the syringe so that the same volume will be delivered each time. Clean, sterile, disposable assemblies (suppliers: *Burron, Pharmaseal*) operating on the same principle have particular usefulness in hospital pharmacy or experimental operations.

Mechanically operated instruments substitute a motor for the operator's hand in the previous devices described. Thereby, a much faster filling rate can be achieved. By careful engineering, the stroke of the syringe can be repeated precisely, and so, once a particular setting has been calibrated to the delivery, high delivery precision is possible. However, the speed of delivery, the expansion of the rubber tubing connecting the valve with the delivery tube, and the rapidity of action of the valves can affect the precision of delivery. A filling machine employing a piston is shown in Figure 41-18. Stainless steel syringes are required with viscous liquids because glass syringes are not strong enough to withstand the high pressures developed during delivery.

When high-speed filling rates are desired but accuracy and precision must be maintained, multiple filling units often are joined together in an electronically coordinated machine, such as shown in Figure 41-19. When the product is sensitive to metals, a peristaltic-pump filler may be used because the product comes in contact only with silicone rubber tubing. However, there is some sacrifice of filling accuracy.

Most high-speed fillers for large-volume solutions use the bottle as the measuring device, transferring the liquid either by vacuum or positive pressure from the bulk reservoir to the individual unit containers. Therefore, a high accuracy of fill is not achievable.

The USP requires that each container be filled with a sufficient volume in excess of the labeled volume to ensure withdrawal of the labeled volume and provides a table of suggested fill volumes.

SOLIDS—Sterile solids, such as antibiotics, are more difficult to subdivide evenly into containers than are liquids. The rate of flow of solid material is slow and often irregular. Even though a container with a larger-diameter opening is used to facilitate filling, it is difficult to introduce the solid particles, and the risk of spillage is ever-present. The accuracy of the quantity delivered cannot be controlled as well as with liquids. Because of these factors, the tolerances permitted for the content of such containers must be relatively large.

Some sterile solids are subdivided into containers by individual weighing. A scoop usually is provided to aid in approx-

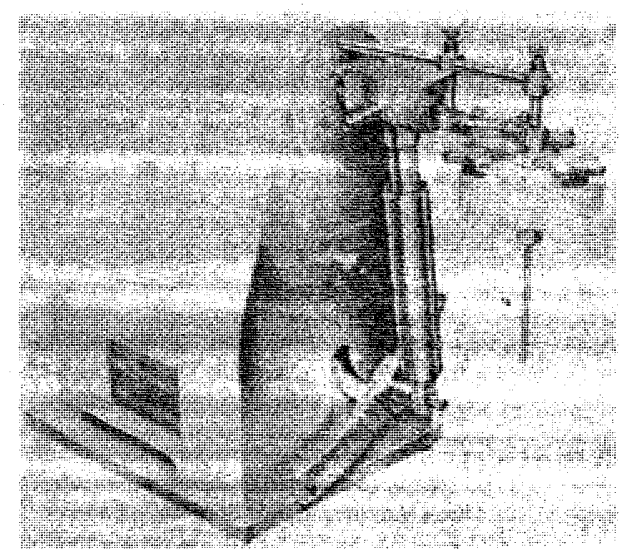

Figure 41-18. Filling machine employing a piston valve, a stainless steel syringe, and a final filter (courtesy, Cozzoli).

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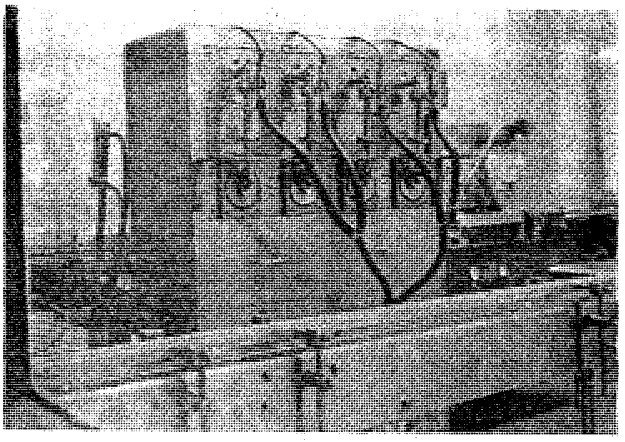

Figure 41-19. Four-pump liquid filler (rear view), with a conveyor line for vials protected by a vertical laminar airflow and plastic curtain; note the automatic stoppering machine on the right within the curtain (courtesy, Abbott)

imating the quantity required, but the quantity filled into the container finally is weighed on a balance. This is a slow process. When the solid is obtainable in a granular form so that it will flow more freely, other methods of filling may be employed. In general, these involve the measurement and delivery of a volume of the granular material that has been calibrated in terms of the weight desired. In the machine shown in Figure 41-20 an adjustable cavity in the rim of a wheel is filled by vacuum and the contents held by vacuum until the cavity is inverted over the container. The solid material then is discharged into the container by a puff of sterile air. Another machine employs an auger in the stem of a funnel at the bottom of a hopper. The granular material is placed in the hopper. By controlling the size of the auger and its rotation, a regulated volume of granular material can be delivered from the funnel stem into the container. Such a machine is shown in Figure 41-21.

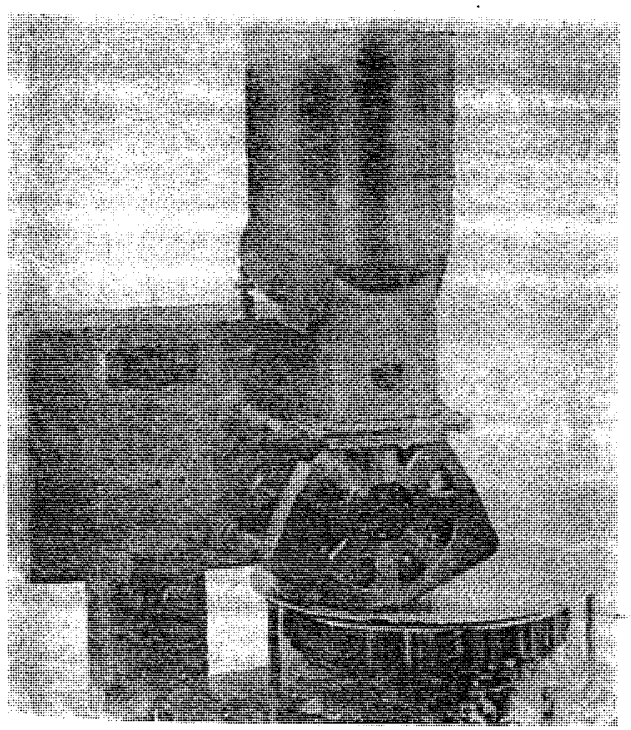

Figure 41-20. Accofil vacuum powder filler (courtesy, Perry).

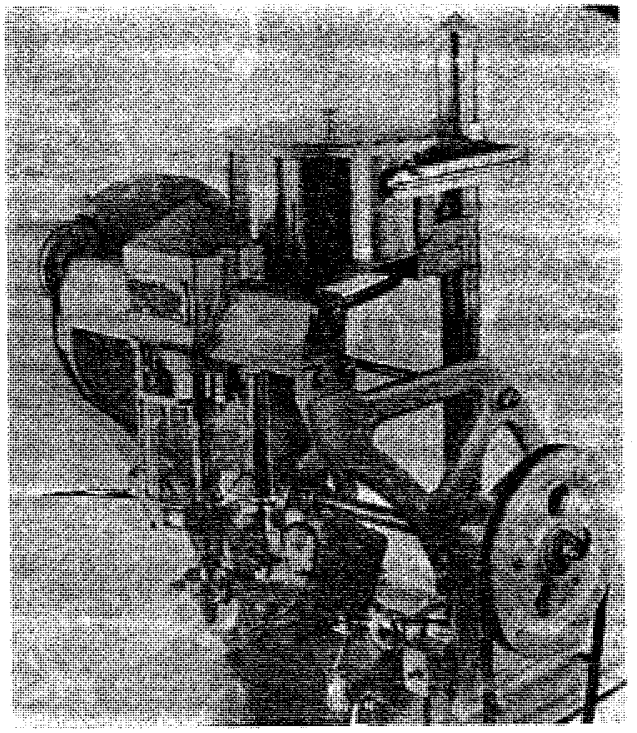

Figure 41-21. Auger-type powder filler (courtesy, Chase-Logeman).

SEALING

AMPULS—Filled containers should be sealed as soon as possible to prevent the contents from being contaminated by the environment. Ampuls are sealed by melting a portion of the glass neck. Two types of seals are employed normally: tip-seals (bead-seals) or pull-seals.

Tip-seals are made by melting enough glass at the tip of the neck of an ampul to form a bead and close the opening. These can be made rapidly in a high-temperature gas-oxygen flame. To produce a uniform bead, the ampul neck must be heated evenly on all sides, such as by burners on opposite sides of stationary ampuls or by rotating the ampul in a single flame. Care must be taken to adjust the flame temperature and the interval of heating properly to completely close the opening with a bead of glass. Excessive heating will result in the expansion of the gases within the ampul against the soft bead seal and cause a bubble to form. If it bursts, the ampul is no longer sealed; if it does not, the wall of the bubble will be thin and fragile. Insufficient heating will leave an open capillary through the center of the bead. An incompletely sealed ampul is called a *leaker*.

Pull-seals are made by heating the neck of the ampul below the tip, leaving enough of the tip for grasping with forceps or other mechanical devices. The ampul is rotated in the flame from a single burner. When the glass has softened, the tip is grasped firmly and pulled quickly away from the body of the ampul, which continues to rotate. The small capillary tube thus formed is twisted closed. Pull-sealing is slower, but the seals are more sure than tip-sealing. Figure 41-22 shows a machine combining the steps of filling and pull-sealing ampuls.

Powder ampuls or other types having a wide opening must be sealed by pull-sealing. Fracture of the neck of ampuls during sealing may occur if wetting of the necks occurred at the time

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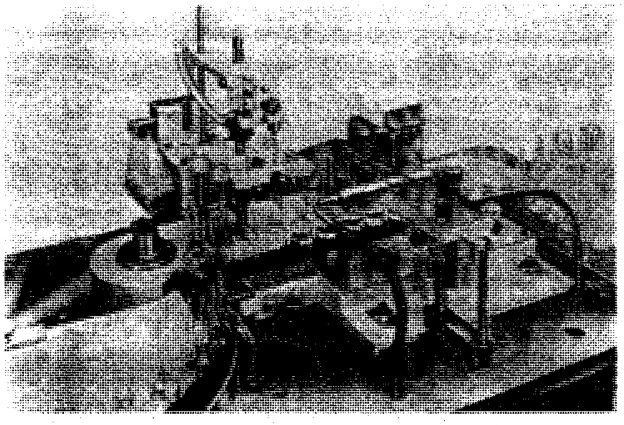

Figure 41-22. Automatic filling and pull-sealing of ampuls (courtesy, Cozzoli).

of filling. Also, wet necks increase the frequency of bubble formation and unsightly carbon deposits if the product is organic.

To prevent decomposition of a product, it is sometimes necessary to displace the air in the space above the product in the ampul with an inert gas. This is done by introducing a stream of the gas, such as nitrogen or carbon dioxide, during or after filling with the product. Immediately thereafter the ampul is sealed before the gas can diffuse to the outside. This process should be validated to ensure adequate displacement of air by the gas in each container.

VIALS AND BOTTLES—These are sealed by closing the opening with a rubber closure (stopper). This must be accomplished as rapidly as possible after filling and with reasoned care to prevent contamination of the contents. The large opening makes the introduction of contamination much easier than with ampuls. Therefore, during the critical exposure time the open containers should be protected from the ingress of contamination, preferably with a blanket of HEPA-filtered laminar airflow, as shown in Figures 41-9 and 41-19.

The closure must fit the mouth of the container snugly enough so that its elasticity will seal rigid to slight irregularities in the lip and neck of the container. However, it must not fit so snugly that it is difficult to introduce into the neck of the container. Closures preferably are inserted mechanically using an automated process, especially with high-speed processing. To reduce friction so that the closure may slide more easily through a chute and into the container opening, the closure surfaces often are halogenated or treated with silicone. When the closure is positioned at the insertion site, it is pushed mechanically into the container opening (Fig 41-23). When small lots are encountered, manual stoppering with forceps may be used, but such a process poses greater risk of introducing contamination than automated processes.

Rubber closures are held in place by means of aluminum caps. The caps cover the closure and are crimped under the lip of the vial or bottle to hold them in place (see Fig 41-5). The closure cannot be removed without destroying the aluminum cap; it is tamperproof. Therefore, an intact aluminum cap is proof that the closure has not been removed intentionally or unintentionally. Such confirmation is necessary to ensure the integrity of the contents as to sterility and other aspects of quality.

The aluminum caps are so designed that the outer layer of double-layered caps, or the center of single-layered caps, can be removed to expose the center of the rubber closure without disturbing the band that holds the closure in the container.

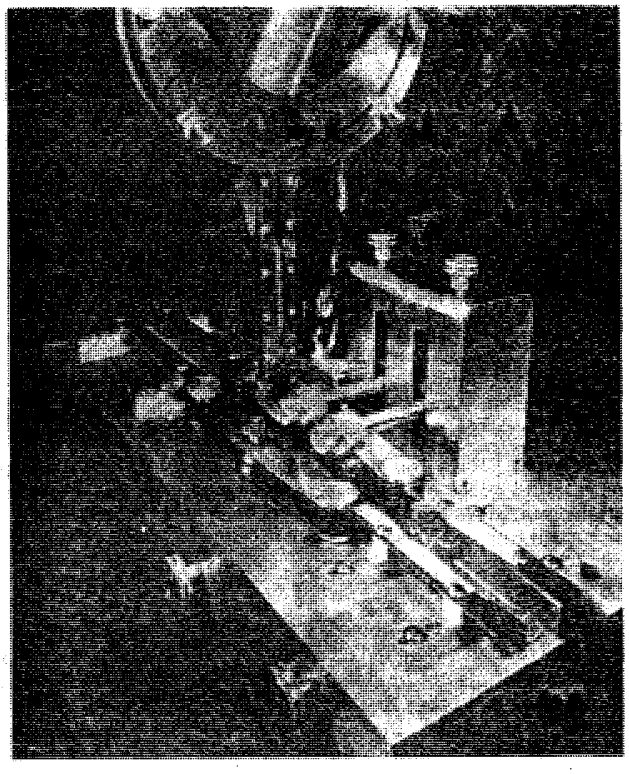

Figure 41-23. Mechanical device for inserting rubber closures in vials (courtesy, Perry).

Rubber closures for use with intravenous administration sets often have a permanent hole through the closure. In such cases, a thin rubber disk overlayed with a solid aluminum disk is placed between an inner and outer aluminum cap, thereby providing a seal of the hole through the closure.

Single-layered aluminum caps may be applied by means of a hand crimper known as the Fermpress (suppliers: *West, Wheaton*). Double- or triple-layered caps require greater force for crimping; therefore, heavy-duty mechanical crimpers (Fig 41-24) are required (suppliers: *Bosch, Cozzoli, Perry, West, Wheaton*).

Figure 41-24. Applying aluminum caps to vials at the end of the process line (courtesy, Abbott).

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STERILIZATION

Whenever possible, the parenteral product should he sterilized after being sealed in its final container (terminal sterilization) and within as short a time as possible after the filling and sealing have been completed. Since this usually involves a thermal process, due consideration must be given to the effect of the elevated temperature upon the stability of the product. Many products, both pharmaceutical and biological, will be affected adversely by the elevated temperatures required for thermal sterilization. Heat-labile products must, therefore, be sterilized by a nonthermal method, usually by filtration through bacteria-retaining filters. Subsequently, all operations must be carried out in an aseptic manner so that contamination will not be introduced into the filtrate. Colloids, oleaginous solutions, suspensions, and emulsions that are thermolabile may require a process in which each component is sterilized separately and the product is formulated and processed under aseptic conditions.

The performance of an aseptic process is challenging, but technical advances in aseptic processing, including improved automation, use of isolator systems, formulations to include antimicrobial effects, and combinations of limited sterilization with aseptic processing, have decreased the risk of contamination. Therefore, the successes realized should encourage continued efforts to improve the assurance of sterility achievable with aseptic processing. The importance of this is that for many drug solutions and essentially all biopharmaceutical products, aseptic processing is the only method that can be considered for preparing a sterile product.

Interaction between environmental conditions, the constituents in the closure, and the product may result in undesirable closure changes such as increased brittleness or stickiness, which may cause loss of container-closure seal integrity. Thus, shelf-life integrity is an important consideration in closure selection and evaluation.

The assessment of aseptic-processing performance is based on the contamination rate resulting from periodic process simulations using media-filling instead of product-filling of containers. A rate no greater than 0.1% has generally been considered as indicative of satisfactory performance in the industry. However, with current advances in aseptic processing capabilities, lower contamination rates may be achievable.[23]

Nonthermal methods of sterilization, such as irradiation, have been proposed for consideration. However, since there is limited understanding of the molecular transformations that may occur in drug molecules and excipients under exposure to the high-energy levels of the process, extensive research will be required to develop the knowledge needed for an adequate evaluation. The use of radiation for the sterilization of materials such as plastic medical devices is well established.

Dry-heat sterilization may be employed for a few dry solids that are not affected adversely by the high temperatures and for the relatively long heating period required. This method is applied most effectively to the sterilization of glassware and metalware. After sterilization, the equipment will be sterile, dry, and, if the sterilization period is long enough, pyrogen-free.

Saturated steam under pressure (autoclaving) is the most commonly used and the most effective method for the sterilization of aqueous liquids or substances that can be reached or penetrated by steam. A survival probability of 10^{-6} is readily achievable with terminal autoclaving of a thermally stable product. However, it needs to be noted that for terminal sterilization, the assurance of sterility is based upon an evaluation of the lethality of the process, ie, of the probable number of viable microorganisms remaining in product units. However, for aseptic processing, where the components used have been sterilized by a validated process and were based upon an evaluation of the probable number of product units that were contaminated during the process. This difference does not alter the outcome, only the basis for evaluating the assurance of sterility.

Figure 41-25 shows liter containers of solution being loaded into an autoclave for sterilization. Since the temperature employed in an autoclave is lower than that for dry-heat sterilization, equipment made of materials such as rubber and polypropylene may be sterilized if the time and temperature are controlled carefully. As mentioned previously, some injections will be affected adversely by the elevated temperature required for autoclaving. For some products, such as Dextrose Injection, a shortened cycle using an autoclave designed to permit a rapid temperature rise and rapid cooling with water spray will make it possible to use this method. It is ineffective in anhydrous conditions, such as within a sealed ampul containing a dry solid or an anhydrous oil. Other products that will not withstand autoclaving temperatures may withstand marginal thermal methods such as tyndallization or pasteurization, eg, 10 to 12 hr at 60°. These methods may be rendered more effective for some injections by the inclusion of a bacteriostatic agent in the product.

Articles to be sterilized must be properly wrapped or placed in suitable containers to permit penetration of sterilants and provide protection from contamination after sterilization. Sheets or bags made of special steam-penetrating paper or polymeric materials are available for this purpose. Further, containers or bags impervious to steam can be equipped with a microbe-excluding vent filter to permit adequate steam penetration and air exit. Multiple wrapping permits sequential removal of outer layers as articles are transferred from zones of lower to higher environmental quality. The openings of equipment subjected to dry-heat sterilization often are covered with silver-aluminum foil or with metal or glass covers. Wrapping materials commonly used for steam sterilization may be combustible or otherwise become degraded under dry-heat sterilization conditions.

The effectiveness of any sterilization technique must be proved (validated) before it is employed in practice. Since the goal of sterilization is to kill microorganisms, the ideal indicator to prove the effectiveness of the process is a resistant form of an appropriate microorganism, normally resistant spores (a biological indicator, or BI). Therefore, during validation of a sterilization process, BIs of known resistance and numbers are used in association with physical-parameter indicators, such as recording thermocouples. Once the lethality of the process is established in association with the physical measurements, the physical measurements can be used for subsequent monitoring of in-use processes without the BIs. Eliminating the use of BIs

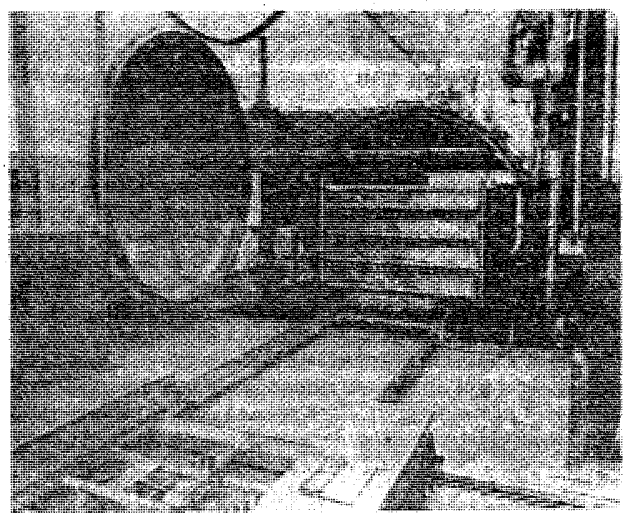

Figure 41-25. Large autoclave being loaded with liter bottles of [illegible]

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in direct association with human-use products is appropriate because of the ever-present risk of an undetected, inadvertent contamination of a product or the environment.

The number of spores and their resistance in BIs used for validation studies must be accurately known or determined. Additionally, the manner in which BIs are used in validation is critical and must be controlled carefully.[30]

In addition to the data printout from thermocouples, sometimes other physical indicators are used, such as color-change and melting indicators, to give visual indication that a package or truckload has been subjected to a sterilization process. Such evidence can become a part of the batch record to confirm that sterilization was accomplished.

Further details concerning methods of sterilization and their application can be found in Chapter 40. In addition, the USP provides suggestions concerning the sterilization of injections and related materials.

FREEZE-DRYING (LYOPHILIZATION)

Freeze-drying is a process of drying in which water is sublimed from the product after it is frozen.[29] The particular advantages of this process are that biologicals and pharmaceuticals that are relatively unstable in aqueous solution can be processed and filled into dosage containers in the liquid state, taking advantage of the relative ease of processing a liquid. They can be dried without elevated temperatures, thereby eliminating adverse thermal effects, and stored in the dry state, in which there are relatively few stability problems.

Further advantages are that these products are often more soluble and/or more rapidly soluble, dispersions are stabilized throughout their shelf life, and products subject to degradation by oxidation have enhanced stability because the process is carried out in a vacuum. However, the increased time and handling required for processing and the cost of the equipment limit the use of this process to those products which have significantly enhanced stability if stored in the dry state.

The fact that ice will sublime at pressures below 3 torr has been a long-established laboratory principle (see Chapter 20). The extensive program for freeze-drying human plasma during World War II provided the impetus for the rapid development of the process.

Freeze-drying essentially consists of

1. Freezing an aqueous product at a temperature below its eutectic temperature.
2. Evacuating the chamber, usually below 0.1 torr (100 μm Hg).
3. Subliming ice onto a cold, condensing surface at a temperature below that of the product, the condensing surface being within the chamber or in a connecting chamber.
4. Introducing heat to the product under controlled conditions, thereby providing energy for sublimation at a rate designed to keep the product temperature below its eutectic temperature.

Figure 41-26 shows a diagram of a small-scale lyophilization system and its functional components. The product may be frozen on the shelf in the chamber by circulating refrigerant (usually Freon, ammonia, or ethylene glycol) from the compressor through pipes within the shelf. After freezing is complete, which may require several hours, the chamber and condenser are evacuated by the vacuum pump, the condenser surface having been chilled previously by circulating refrigerant from the large compressor.

Heat then is introduced from the shelf to the product under graded control by electric resistance coils or by circulating hot water, silicone, or glycol. The process continues until the product is dry (usually 1% or less moisture), leaving a sponge-like matrix of the solids originally present in the product, the input of heat being controlled so as not to degrade the product.

For most pharmaceuticals and biologicals the liquid product is sterilized by filtration before being filled into the dosage container aseptically. The containers must remain open during

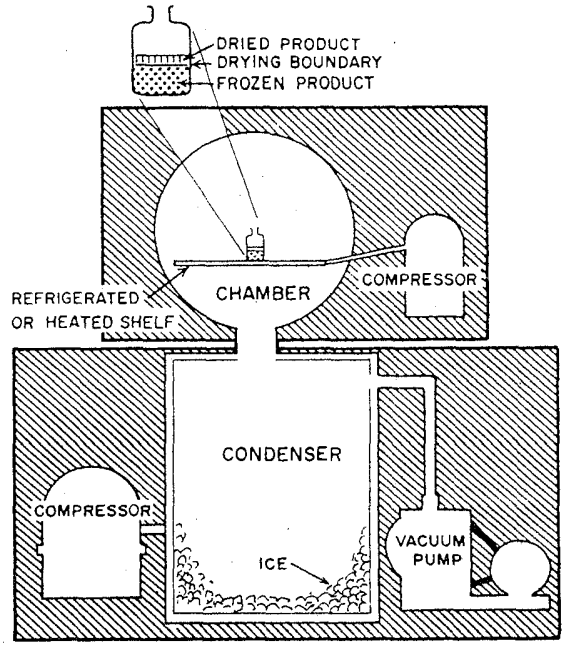

Figure 41-26. Essential components of a freeze-drying system.

the drying process to allow water vapor to escape; therefore, they must be protected from contamination during transfer from the filling area to the freeze-drying chamber, while in the freeze-drying chamber, and at the end of the drying process until sealed.

Chambers of production size may be equipped with hydraulic or pneumatic internal-stoppering devices designed to push slotted rubber closures into the vials to be sealed while the chamber is still evacuated, the closures having been partially inserted immediately after filling, so that the slots were open to the outside. If internal stoppering is not available or containers such as ampuls are used, filtered dry air or nitrogen should be introduced into the chamber at the end of the process to establish atmospheric pressure.

FACTORS AFFECTING THE PROCESS RATE—The greater the depth of the product in the container, the longer will be the drying process. Therefore, a product to be frozen by placing the container on a refrigerated shelf (plug freezing) should be filled to a planned, limited depth. If large volumes of solution must be processed, the surface area relative to the depth may be increased by using such devices as freezing the container in a slanted position to increase the surface area.

The actual driving force for the process is the vapor pressure differential between the vapor at the surface where drying of the product is occurring (the drying boundary) and that at the surface of the ice on the condenser. The latter is determined by the temperature of the condenser as modified by the insulating effect of the accumulated ice. The former is determined by a number of factors, including

1. The rate of heat conduction through the container and the frozen material, both usually relatively poor thermal conductors, to the drying boundary while maintaining all of the product below its eutectic temperature.
2. The impeding effect of the increasing depth of dried, porous product above the drying boundary.
3. The temperature and heat capacity of the shelf itself.

This may be visualized by referring to Figure 41-26.

The passageways between the product surface and the condenser surface must be wide open and direct for effective operation. The condensing surfaces in large freeze-driers may be in the same chamber as the product or located in a separate

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chamber connected by a duct to the drying chamber. Evacuation of the system is necessary to reduce the impeding effect that collisions with air molecules would have on the passage of water molecules. However, the residual pressure in the system must be greater than the vapor pressure of the ice on the condenser or the ice will be vaporized and pulled into the pump, an event detrimental to most pumps.

The amount of solids in the product, their precipitated particle size, and their thermal conductance will affect the rate of drying. The more solids present, the more impediment will be provided to the escape of the water vapor. The smaller the particle size, particularly the crystal size of the ice, the faster the drying generally will be. The poorer the thermal conducting properties of the solids in the product, the slower will be the rate of heat transfer through the frozen material to the drying boundary.

The rate of drying is slow, most often requiring 24 hr or longer for completion. The actual time required, the rate of heat input, and the product temperatures that may be used must be determined for each product and then reproduced carefully with successive processes.

FACTORS AFFECTING FORMULATION—The active constituent of many pharmaceutical products is present in such a small quantity that if freeze-dried alone its presence would be hard to detect visually. Therefore, excipients often are added to increase the amount of solids.

Some consider it ideal for the dried-product plug to occupy essentially the same volume as that of the original solution. To achieve this, the solids content of the original product must be between approximately 5 and 25%. Among the substances found most useful for this purpose, usually as a combination, are sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates such as dextrose, mannitol, and dextran.

Each of these substances contributes appearance characteristics of the plug, such as whether dull and spongy or sparkling and crystalline, firm or friable, expanded or shrunken, and uniform or striated. Therefore, the formulation of a product to be freeze-dried must include consideration not only of the nature and stability characteristics required during the liquid state, both freshly prepared and when reconstituted before use, but also the characteristics desired in the dried plug.

MODIFICATIONS IN THE PROCESS AND EQUIPMENT—In some instances a product may be frozen in a bulk container or in trays rather than in the final container and then handled as a bulk solid. Such a state requires a continuation of aseptic processing conditions as long as the product is exposed to the environment.

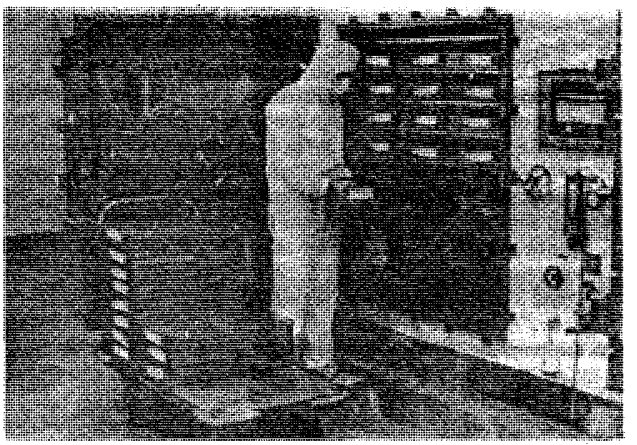

Figure 41-27. Aseptic loading of freeze-drier (courtesy, Upjohn).

When large quantities of material are processed it may be desirable to use ejection pumps in the equipment system. These draw the vapor into the pump and eject it to the outside, thereby eliminating the need for a condensing surface. Such pumps are expensive and usually practical only in large installations.

Available freeze-driers (suppliers: *BOC Edwards, FTS, Hull, Serail, Stokes, Usifroid, Virtic*) range in size from small laboratory units to large industrial models such as the one shown in Figure 41-27. Their selection requires consideration of such factors as

The tray area required
The volume of water to be removed
How the chamber will be sterilized
Whether internal stoppering is required
Whether separate freezers will be used for initial freezing of the product
The degree of automatic operation desired

Other factors involved in the selection and use of equipment are considered in the literature.[29]

Freeze-drying is being used now for research in the preservation of human tissue and is finding increasing application in the food industry. Most biopharmaceuticals require lyophilization to stabilize their protein content effectively. Therefore, many newer developments in the lyophilization process focus on the requirements of this new class of drug products.

The importance of undertaking every possible means to ensure the quality of the finished product cannot be overemphasized. Every component and step of the manufacturing process must be subjected to intense scrutiny to be confident that quality is attained in the finished product. The responsibility for achieving this quality is divided appropriately in concept and practice into Quality Assurance (QA) and Quality Control (QC). QA relates to the studies made and the plans developed for ensuring quality of a product prospectively, with a final confirmation of achievement. QC embodies the carrying out of these plans during production and includes all of the tests and evaluations performed to be sure that quality exists in a specific lot of product.

The principles for achieving quality are basically the same for the manufacture of any pharmaceutical. These are discussed in Chapter 51. During the discussion of the preparation of injections in this chapter, mention was made of numerous quality requirements for components and manufacturing processes. Here, only selected tests characteristically required before a finished parenteral product is released are discussed briefly, including sterility, pyrogen, and particulate tests.

STERILITY TEST

All lots of injections in their final containers must be tested for sterility. The USP prescribes the requirements for this test for official injections. The FDA uses these requirements as a guide for testing unofficial sterile products. The primary official test is performed by means of filtration, but direct transfer is used if membrane filtration is unsuitable. To give greater assurance that viable microorganisms will grow, if present, the USP requires that all lots of culture media be tested for their growth-promotion capabilities. However it must be recognized that the reliability of both test methods has the inherent limitations typical of microbial recovery tests. Therefore, it should be noted that this test is not intended as a thorough, precise test for

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a product subjected to a sterilization method of unknown effectiveness. It is intended primarily as a check test on the probability that a previously validated sterilization procedure has been repeated or to give assurance of its continued effectiveness. A discussion of sterility testing is given in Chapter 40.

In the event of a sterility-test failure, the immediate issue concerns whether the growth observed came from viable microorganisms in the product (true contamination) or from adventitious contamination during the testing (a false positive). The USP does permit a retest, but the position of the FDA is that retest results are only valid if persuasive evidence exists that the cause of the initial sterility-test failure resides in the laboratory. Therefore, a thorough investigation must be launched to support the justification for performing the retest and assessing the validity of the retest results relative to release of the lot of product.

It should be noted that a *lot* with respect to sterility testing is that group of product containers that has been subjected to the same sterilization procedure. For containers of a product that have been sterilized by autoclaving, for example, a lot would constitute those processed in a particular sterilizer cycle. For an aseptic filling operation, a lot would constitute all of those product containers filled during a period when there was no change in the filling assembly or equipment and which is no longer than one working day or shift.

PYROGEN TEST

The USP evaluates the presence of pyrogens in parenteral preparations by a qualitative fever response test in rabbits, the Pyrogen Test (Section ⟨151⟩), and by the Bacterial Endotoxins Test (Section ⟨85⟩). These two USP tests are described in Chapter 31. Rabbits are used as test animals in Section ⟨151⟩ because they show a physiological response to pyrogenic substances similar to that by man. While a minimum pyrogenic dose (MPD), the amount just sufficient to cause a positive USP Pyrogen Test response, sometimes may produce uncertain test results, a content equal to a few times the MPD will leave no uncertainty. Therefore, the test is valid and has continued in use since introduced by Seibert in 1923. It should be understood that not all injections may be subjected to the rabbit test, since the medicinal agent may have a physiological effect on the test animal such that any fever response would be masked.

The *Bacterial Endotoxins Test* (BET) is an *in vitro* test based on the formation of a gel or the development of color in the presence of bacterial endotoxins and the lysate of the amebocytes of the horseshoe crab *(Limulus polyphemus)*. The *Limulus Amebocyte Lysate* (LAL) test, as it also is called, is a biochemical test performed in a test tube and is simpler, more rapid, and of greater sensitivity than the rabbit test.[32] Although it detects only the endotoxic pyrogens of gram-negative bacteria, these are the most prominent environmental microbial contaminants likely to invade sterile products. The test also has been automated.[33]

The LAL test is a semiquantitative test. To provide standardization for the test, the USP has established a reference endotoxin against which lots of the lysate are standardized. Thus, the sensitivity of the lysate is given in terms of endotoxin units (EU). Most USP injections now have been given limits in terms of EUs (eg, Bacteriostatic Sodium Chloride Injection, 1.0 EU/mL), thus indicating an increasing priority for the BET in testing for the presence of endotoxin in parenteral products and in medical devices.

PARTICULATE EVALUATION

Particulate matter in parenteral solutions long has been recognized as unacceptable since the user could be expected to conclude that the presence of visible *dirt* would suggest that the product is of inferior quality. Today, it is recognized that the presence of particles in solution, particularly if injected intravenously, can be harmful. While data defining the extent of risk and the effects produced still are limited, it has been shown that particles of lint, rubber, insoluble chemicals, and other foreign matter can produce emboli in the vital organs of animals and man.[34] Further, it has been shown that the development of infusion phlebitis may be related to the presence of particulate matter in intravenous fluids.[35]

The particle size of particular concern has not been clearly delineated, but it has been suggested that since erythrocytes have a diameter of approximately 4.5 μm, particles of more than 5 μm should be the basis for evaluation. This is a considerably smaller particle than can be seen with the unaided eye; approximately 50 μm is the lower limit unless the Tyndall effect is used whereby particles as small as 10 μm can be seen by the light scattered from them.

The USP specifies that good manufacturing practice requires that each final container of an injection be subjected individually to a visual inspection and that containers in which visible particles can be seen should be discarded. This 100% inspection of a lot of product is designed to prevent the distribution and use of parenterals that contain particulate matter that may be harmful psychologically or organically to the participant. Therefore, all of the product units from a production line currently are being inspected individually by human inspectors under a good light, baffled against reflection into the eye and against a black-and-white background. This inspection is subject to the limitation of the size of particles that can be seen, the variation of visual acuity from inspector to inspector, their emotional state, eye strain, fatigue, and other personal factors that will affect what is seen. However, it does provide a means for eliminating the few units that normally contain visible particles. Automated inspection machines increasingly are being used today.

The assessment of the level of particulate matter below the visible size of about 50 μm has become an increasingly used QC indicator of process cleanliness in the manufacture of injections. The tests used, however, are destructive of container units. Therefore, they are performed on appropriately selected samples of products. Further, all of these methods require very stringent, ultraclean preparation techniques to ensure accuracy in the counting and sizing of particles only in the product, rather than those that may have been introduced inadvertently during the sample preparation or the testing procedure.

The USP has identified two test methods in ⟨788⟩, *Particulate Matter in Injections*. All LVIs for single-dose infusion and those SVIs for which the monograph specifies a limit (primarily those commonly added to infusion solutions) are subject to the specified limits given in Table 41-3. The first test to be used is the light obscuration test, which uses an electronic instrument designed to count and measure the size of particles by means of a shadow cast by the particle as it passes through a high-intensity light beam (suppliers: *Climet, HIAC/Royco*). If the injection formulation is not a clear, colorless solution (eg, an emulsion) or it exceeds the limits specified for the light obscuration test, it is to be subjected to the microscopic count test.

Table 41-3. Subvisible Particulate Matter Limits in USP Injections

Light obscuration particle count test		
	≥10 μm	≥25 μm
SVIs	6000	600/container
LVIs	25	3/mL
Microscopic particle count test		
	≥10 μm	≥25 μm
SVIs	3000	300/container
LVIs	12	2/mL

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The latter method consists of filtering a measured sample of solution through a membrane filter under ultraclean conditions and then counting the particles on the surface of the filter, using a microscope and oblique light at 100× magnification. The time requirements for performing the latter test are very long. These standards are being met readily in the US today by the manufacturers of LVIs and the specified SVIs. Additional information may be found in the literature, particularly in an extensive review article.[36]

Whether or not these standards are realistic toxicologically has not been established; rather, the objective of the compendium is to establish specification limits that would encourage the preparation of clean parenteral solutions, particularly those to be given intravenously.

It also should be realized that administration sets and the techniques used for preparing and administering intravenous infusion fluids may introduce substantial amounts of particulate matter into an otherwise clean solution. Therefore, the pharmaceutical manufacturer, the administration set manufacturer, the pharmacist, the nurse, and the physician must share responsibility for making sure that the patient receives a clean intravenous injection.

LEAKER TEST

Ampuls that have been sealed by fusion must be subjected to a test to determine whether or not a passageway remains to the outside; if so, all or a part of the contents may leak to the outside and spoil the package, or microorganisms or other contaminants may enter. Changes in temperature during storage cause expansion and contraction of the ampul and contents, and will accentuate interchange if a passageway exists, even if microscopic in size.

This test usually is performed by producing a negative pressure within an incompletely sealed ampul while the ampul is submerged entirely in a deeply colored dye solution. Most often, approximately 1% methylene blue solution is employed. After carefully rinsing the dye solution from the outside, color from the dye will be visible within a leaker. Leakers, of course, are discarded.

Vials and bottles are not subjected to such a leaker test because the sealing material (rubber stopper) is not rigid. Therefore, results from such a test would be meaningless. However, assurance of container-closure sealing integrity should be an integral part of product development by developing specifications for the fit of the closure in the neck of the container, the physical characteristics of the closure, the need for lubrication of the closure, and the capping pressure.

SAFETY TEST

The National Institutes of Health requires of most biological products routine safety testing in animals. Under the Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act, most pharmaceutical preparations are now required to be tested for safety. Because it is entirely possible for a parenteral product to pass the routine sterility test, pyrogen test, and chemical analyses, and still cause unfavorable reactions when injected, a safety test in animals is essential, particularly for biological products, to provide additional assurance that the product does not have unexpected toxic properties. Safety tests in animals are discussed in detail in the USP.

A full discussion of the packaging of parenteral preparations is beyond the scope of this text. It is essential, of course, that the packaging should provide ample protection for the product against physical damage from shipping, handling, and storage as well as protecting light-sensitive materials from ultraviolet radiation. An extensive review of this subject has been published.[37]

PACKAGING—The USP includes certain requirements for the packaging and storage of injections, as follows:

1. The volume of injection in single-dose containers is defined as that which is specified for parenteral administration at one time and is limited to a volume of 1 L.
2. Parenterals intended for intraspinal, intracisternal, or peridural administration are packaged only in single-dose containers.
3. Unless an individual monograph specifies otherwise, no multiple-dose container shall contain a volume of injection more than sufficient to permit the withdrawal and administration of 30 mL.
4. Injections packaged for use as irrigation solutions or for hemofiltration or dialysis or for parenteral nutrition are exempt from the foregoing requirements relating to packaging. Containers for injections packaged for use as hemofiltration or irrigation solutions may be designed to empty rapidly and may contain a volume in excess of 1 L.
5. Injections intended for veterinary use are exempt from the packaging and storage requirements concerning the limitation to single-dose containers and to volume of multiple-dose containers.

LABELING—The labeling of an injection must provide the physician or other user with all of the information needed to ensure the safe and proper use of the product. Since all of this information cannot be placed on the immediate container and be legible, it may be provided on accompanying printed matter. General labeling requirements for drugs are discussed in Chapter 90.

A restatement of the labeling definitions and requirements of the USP for Injections is as follows:

The term *labeling* designates all labels and other written, printed, or graphic matter upon an immediate container or upon, or in, any package or wrapper in which it is enclosed, with the exception of the outer shipping container. The term *label* designates that part of the labeling upon the immediate container.

The label states the name of the preparation, the percentage content of drug of a liquid preparation, the amount of active ingredient of a dry preparation, the volume of liquid to be added to prepare an injection or suspension from a dry preparation, the route of administration, a statement of storage conditions and an expiration date. Also, the label must indicate the name of the manufacturer or distributor and carry an identifying lot number. The lot number is capable of providing access to the complete manufacturing history of the specific package, including each single manufacturing step.

The container label is so arranged that a sufficient area of the container remains uncovered for its full length or circumference to permit inspection of the contents.

The label must state the name of the vehicle and the proportions of each constituent, if it is a mixture; the names and proportions of all substances added to increase stability or usefulness; and the expiration date where required by the individual monograph.

Preparations labeled for use as dialysis, hemofiltration, or irrigation solutions must meet the requirements for Injections other than those relating to volume and also must bear on the label statements that they are not intended for intravenous injection.

Injections intended for veterinary use are so labeled.

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