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Remington: The Science and Practice of Pharmacy

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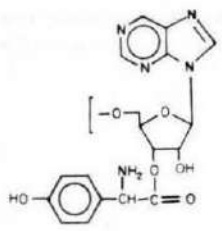
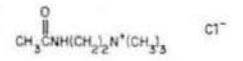


terminus of tyrosinyl-*t*-RNA

30

after puromycin is taken up, it blocks the subsequent protein synthesis.

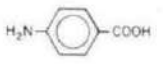
The isosteric replacement of ester groups does not always produce compounds with significant biological activity, as the modification of acetylcholine ester (**3**) with an amide function resulted in the amide analog (**31**)



amide analog of acetylcholine

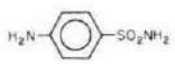
31

that does not show significant agonist or antagonist activity. One of the oldest nonclassic isosteric replacements that provided an important class of antibacterial agents was the replacement of carboxylic acid group of *p*-aminobenzoic acid (PABA, **32**)



p-aminobenzoic acid

32

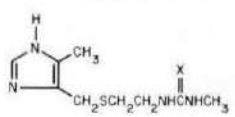


sulfanilamide

33

with a sulfonamide group to give sulfanilamide (**33**).

A final illustration of bioisosteric replacement in drug design is the replacement of the thiourea functional group of metiamide (**34**),



X = S, metiamide

34

X = NCN, cimetidine

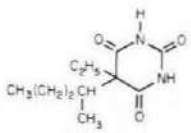
35

a histamine H_2-blocker, with the cyanoguanidine group to produce the drug cimetidine (**35**). This bioisosteric replacement overcame the granulocytopenia toxicity that had been observed with metiamide, thus producing the popular antiulcer drug cimetidine.

Stereochemistry

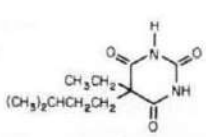
An important consideration in drug–receptor interactions is the stereochemistry of the drug and the proper positioning of functional groups so that they will interact optimally with an enzyme or receptor. Four types of isomeric drugs will be considered: positional isomers, geometrical isomers, optical isomers, and diastereomers.

With *positional*, or *constitutional*, *isomers* the compounds have the same empirical formula but the atoms of the molecule are rearranged in a different order. To illustrate positional isomers, one can consider the relationship of pentobarbital (**36**)



pentobarbital

36

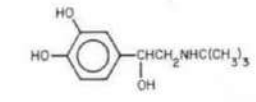


amobarbital

37

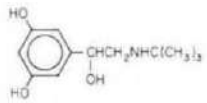
and amobarbital (**37**), both of which belong to the barbiturate family. These positional isomers differ only in the makeup of the 5-carbon side chain attached to the barbiturate ring system. The former compound has a short duration of action while the latter has an intermediate duration of action.

Another example of positional isomers is *N*-(*tert*-butyl)-norepinephrine (**38**)



N-tertiary-butyl norepinephrine

38

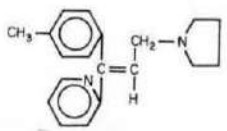


terbutaline

39

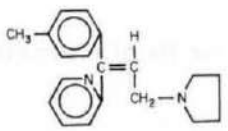
and terbutaline (**39**). The resorcinol portion of 39 has served as a biologically effective replacement of the catechol group in 38. The resorcinol analog (39), in contrast to the catechol (38), is not a substrate for catechol-*O*-methyltransferase (COMT), an important metabolic enzyme; therefore, it has a longer duration of action. Terbutaline is a useful selective β_2-adrenergic stimulant for the treatment of bronchial asthma and related conditions, and it can be administered orally.

Geometrical isomers are another important set of molecules in which a possible difference in biological activity between isomers may exist. The *trans*, or *E*, isomer of triprolidine (**40**)



(*trans* or *E*-isomer)
triprolidine

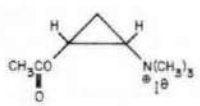
40



(*cis* or *Z*-isomer)
triprolidine

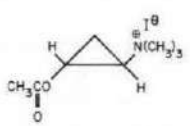
41

is over 1000 times as potent as the *cis*, or *Z*, isomer (**41**) as a H_1-histamine antagonist. Another example of a set of geometrical isomers is the *cis* and *trans*-2-acetoxycyclopropyltrimethyl ammonium iodides (**42** and **43**),



(*cis*-isomer) (*Z*)
cis-2-acetoxycyclopropyltrimethyl ammonium iodide

42

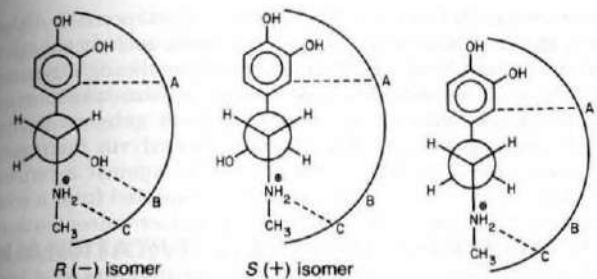


(*trans*-isomer) (*E*)
trans-2-acetoxycyclopropyltrimethyl ammonium iodide

43

respectively. The *trans* isomer is much more potent as a muscarinic agonist than the *cis* isomer and also is a good substrate for the enzyme acetylcholinesterase.

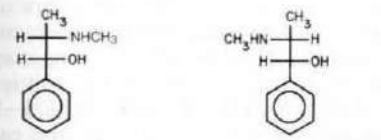
The term *absolute configuration* refers to the arrangement of atoms in space of a chiral compound. In a number of instances there is a distinct difference in biological activity of the *optical isomers* (enantiomers). For example, the *R*(−) isomer of epinephrine (**44**)



is more potent on both α- and β-adrenergic receptors than the $S(+)$ isomer (**45**). The binding of the isomers of epinephrine and epinine (**46**) (the desoxy analog of epinephrine) is illustrated. The three points of binding on the receptor are the catechol binding site (*A*), hydroxy binding site (*B*), and anionic binding site (*C*).

According to the Easson–Stedman theory,[5] the relative order of activity of the isomers on adrenergic receptors are $R > S \sim$ deoxy. Only the *R* isomer can bind to all three sites, whereas both the *S* isomer and the deoxy isomer, which show similar activity, can bind only to two of the sites. Refer to Chapter 13 for a discussion of isomerism.

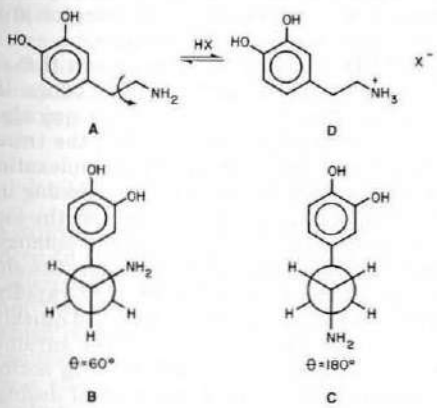
Although enantiomers have the same chemical and physical properties, except for the direction of rotation of polarized light, diastereomers have different physical properties. *Diastereomers* are compounds with two or more chiral centers. While 1*R*,2*S*(−)-ephedrine (**47**)



has direct activity on both α- and β-adrenergic receptors, the 1*R*,2*R* (−)-ψ-ephedrine (**48**) shows α-adrenergic blocking activity. Both diastereomers show indirect adrenergic activity.

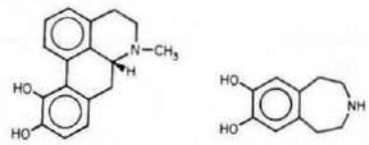
An important strategy often used in drug design is to take a conformationally flexible molecule and to convert it into a conformationally rigid molecule in order to find the optimum conformation for binding to a drug receptor. This approach may be used to introduce selectivity for receptors, eliminate undesired side effects, and learn about the spatial relationships of functional groups for receptors.

Dopamine (**49A**)

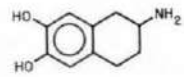


can exist in an infinite number of conformations about the side-chain carbon–carbon bond. Two such conformations are illustrated [$\theta = 60°$ *gauche* and $\theta = 180°$ *trans* conformation (49B and C)].

Apomorphine (**50**)



and 6,7-dihydroxy-2-aminotetralin (ADTN) (**52**)



are two potent dopamine D_1 and D_2 agonists that exist in the *trans* conformation, whereas the selective D_1 agonist SKF 38393 (**51**) does not exist in a similar conformation. Apomorphine, a conformationally rigid molecule, can bind to dopamine receptors.

In other instances, a drug molecule may need conformational flexibility for proper binding to the receptor to produce biological activity in an induced-fit receptor model. Thus, conformational flexibility may in some instances be a prerequisite for drug agonist activity.

Ionization

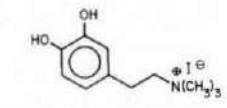
Many of the substances used as drugs are weak acids or weak bases. Therefore, an important question is whether the charged or uncharged form of the drug binds to the receptor. Also of importance is the degree of ionization and the effect ionization may have upon absorption and distribution. In general, the ionization can be demonstrated as

$$\text{[Weak Acids]} \quad \underset{\text{(nonionized drug)}}{\text{AH}} \rightleftharpoons \underset{\text{(ionized drug)}}{\text{A}^- + \text{H}^+}$$

$$\text{[Weak Bases]} \quad \underset{\text{(ionized drug)}}{\text{BH}^+} \rightleftharpoons \underset{\text{(nonionized drug)}}{\text{B} + \text{H}^+}$$

It is very difficult to know which molecular form of the drug is active if the charged and uncharged form of a drug is in equilibrium in physiological solution; for example, with dopamine the pK_a of the amine is $\sim$ 10. Thus, although most of the drug in solution is in the ionized form (49D), the un-ionized form of the drug molecule still may be the active form.

The quaternary salt of dopamine (**53**)



has been prepared and exhibits agonist activity on D_2-receptors, indicating that the ionized form of the drug is an active molecular species. However, it is almost impossible to determine if a primary, secondary, or tertiary amine is active as the un-ionized form of the drug because these amines are always in equilibrium under physiological conditions.

It has been shown that the permanently charged dimethylsulfonium analog (**54**)

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

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

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

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

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

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

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

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

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

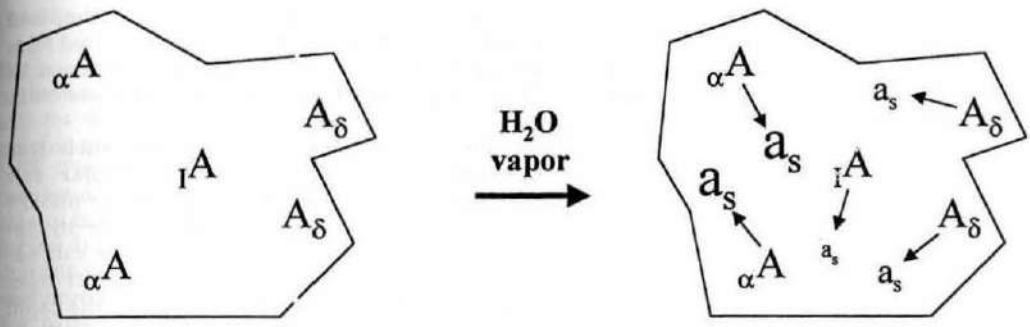


Figure 38-3. Surface of a milled API and dissolution of surface regions due to adsorbed moisture.

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,:

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

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]

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

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

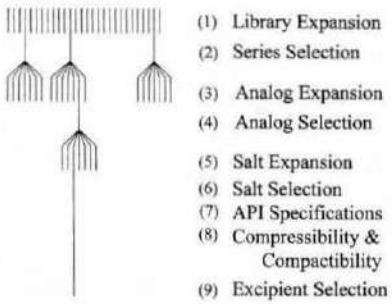


Figure 38-4. Typical API sequential decision-making: selection and expansion cycles.

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, HAn is used to represent a counter-acid that forms an anion An^-. Common counter-acids like HCl and maleic acid are listed in Table 38-2. 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 HAn, An^-. For salt formation, A^0 must be sufficiently basic to remove the proton from HAn (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.

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.

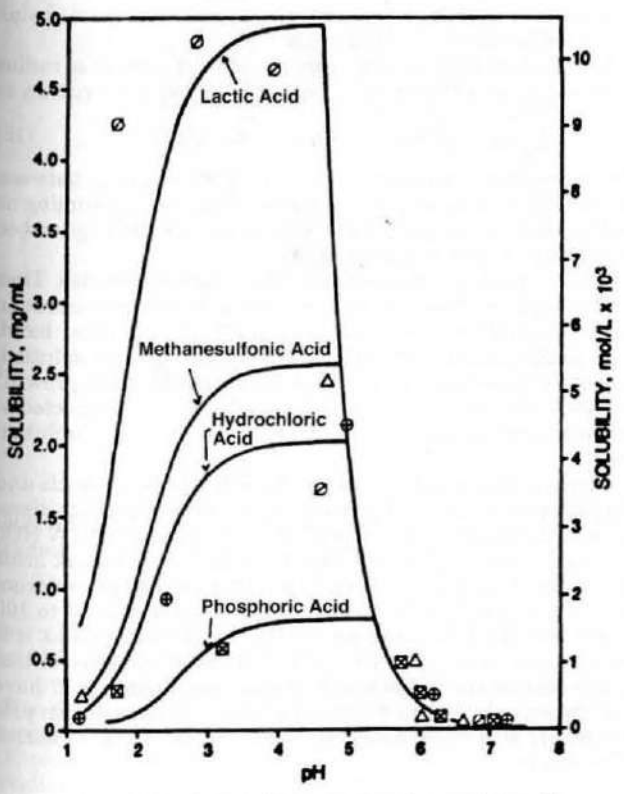


Figure 38-5. pH solubility profile of a weak base.[3]

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.

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:

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

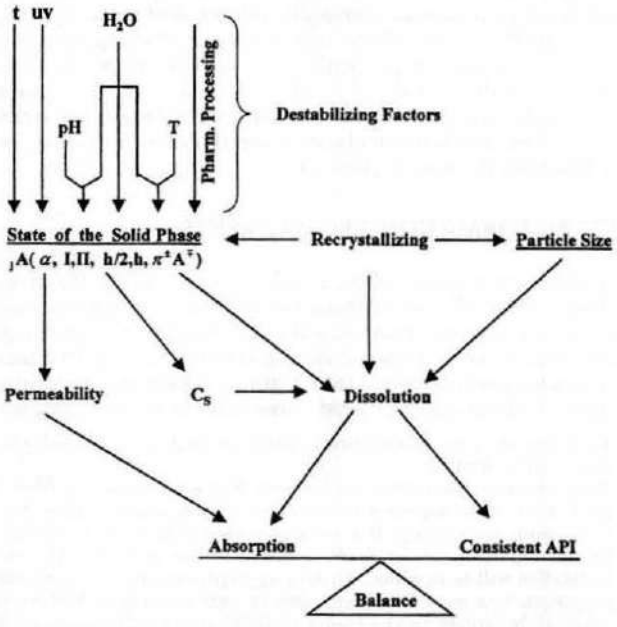


Figure 38-6. API salt selection decision: a balance between absorption and consistency.

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

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,

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

where

A is the amount of drug dissolved.
dA/dt is the rate of dissolution (Q sometimes is used for this rate).
k_d is the intrinsic dissolution constant for the drug.
S_a is the total surface area of the dissolving particle.
C_S is the saturation solubility of the drug at the surface of the particle.
C_{bulk} is the concentration of the drug in the bulk solution.

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

The expression for the maximum dissolution rate is found by setting C_{bulk} equal to 0:[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

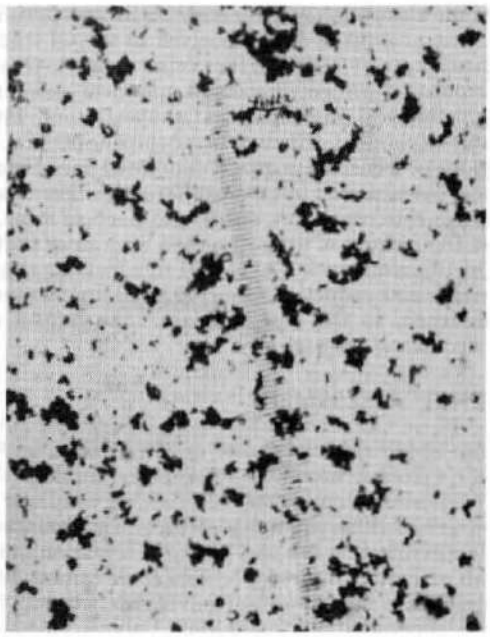
$$dA/dt = (3k_d m/\rho)\,(1/r)\,C_S \qquad (18)$$

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.

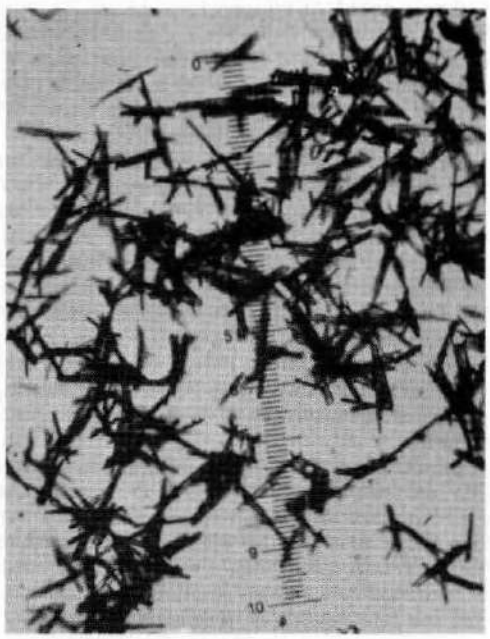
Reactive Media 1: Implications for Salts of Weak Acids and Weak Bases—When a drug reacts with gastric fluids, its dissolution deviates from Equation 17. For dissolution in 0.1 N HCl, acid–base reactivity is most important for salts of weak acids and for free bases. It has been found that the low pH environment 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

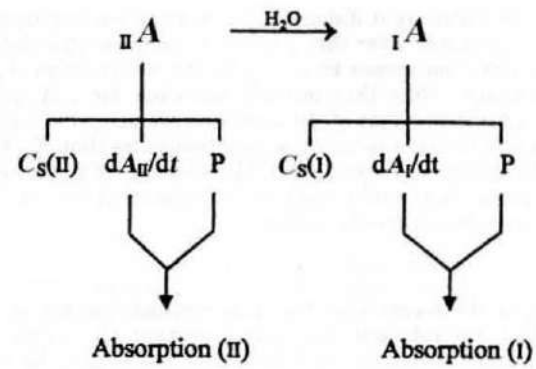


Figure 38-8. Absorption changes due to aqueous-phase transformations.

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, ${}_{0h}A$,

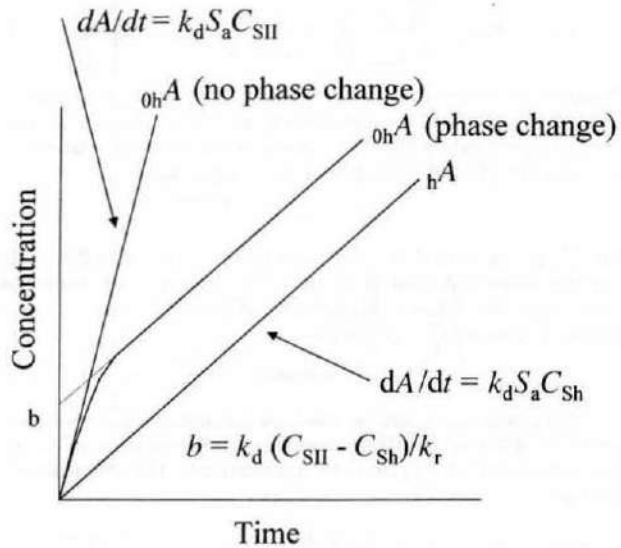


Figure 38-9. Biphasic dissolution of anhydrous to hydrous forms.[11]

becomes hydrated as it dissolves and forms a surface layer of ${}_{h}A$. 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 ${}_{h}A$ (no phase change), the hydrated form. Modifications of Equation 17 to take into account surface recrystallization of ${}_{h}A$ 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.

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

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 $a^0_{\text{bulk}}\uparrow$ indicates the buildup of the drug in the bulk solution.

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

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

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

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.

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

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.

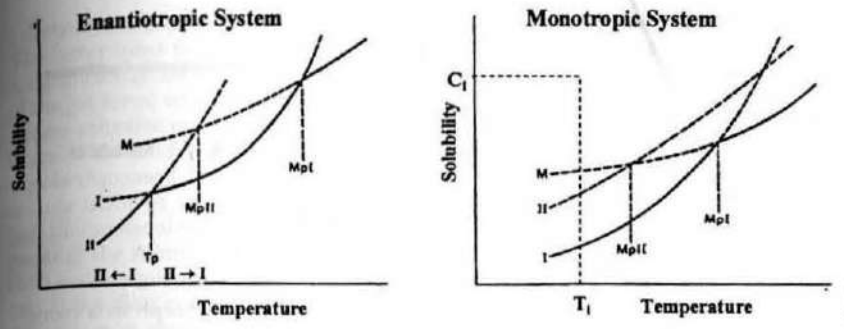


Figure 38-10. Thermal stability of polymorphic systems.[13,14]

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 $C_S(II) > C_S(I)$ if we assume that S_a and k_d are the same for both polymorphs. Thus, Equation 17 provides a working definition for the solubility differences between Polymorph II and Polymorph I, and it provides a method for measuring them from dissolution experiments. More precisely, it provides the solubility at the surface of the API, which is the solubility that is most relevant for dissolution (see the section *Reactive Media 1*, 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.

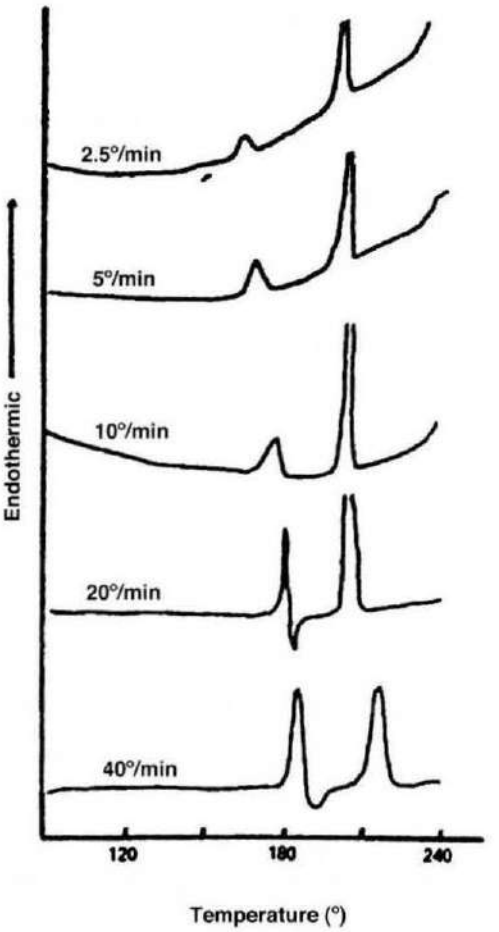


Figure 38-11. Detection of polymorphs by varying the DSC scanning rate.[17]

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

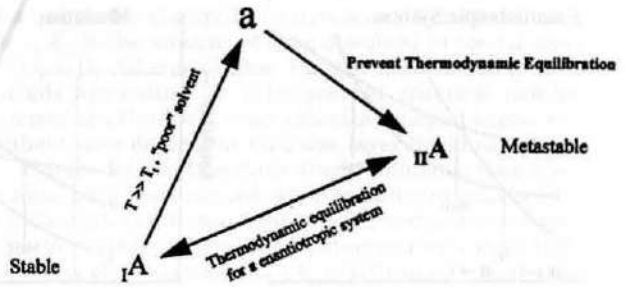
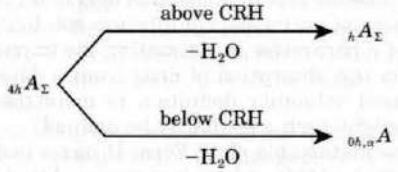


Figure 38-12. Formation of a metastable polymorph in a monotropic system.[14]

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]



(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

$_hA$ 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 $_hA$ 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 $_{0h,\alpha}A_\Sigma$ means that any subsequent water vapor will encounter a more hygroscopic surface than $_{4h}A_\Sigma$ and thus a different hydration kinetic behavior. On the other hand, conversion of $_{4h}A$ to $_hA$ 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.

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

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

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 $_\alpha B_\Sigma$, 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, $_\alpha A_\Sigma$. The consequences of these amorphous surfaces will now be explored.

$$_IA_\Sigma \xrightarrow{+H_2O} {}_{I,>h}A_\Sigma \rightarrow {}_\alpha B_\Sigma \quad (32)$$

$$_hA_\Sigma \xrightarrow{-H_2O} {}_{<h}A_\Sigma \rightarrow {}_\alpha A_\Sigma \quad (33)$$

Transformation of Amorphous Surfaces—Because amorphous layers are more prone to be hygroscopic than crystalline solids, the chemical transformation of $_IA_\Sigma$ to $_\alpha B_\Sigma$ in Equation 32 is significant because the latter can attract more water to the surface. Dissolution of $_\alpha B_\Sigma$ shown in the first downward reaction of Equation 34 will then form a surface coated with b_Σ, 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_Σ, promotes the dissolution of the surface of A, A_Σ, to form a surface coated also with a_Σ , the dissolved form of A on the surface, which then undergoes further decomposition to b_Σ. This is shown in the horizontal and final downward reactions of Equation 34.

$$\begin{array}{l} {}_\alpha B_\Sigma \\ \downarrow +H_2O \\ A_\Sigma \xrightarrow{b_\Sigma} a_\Sigma + b_\Sigma \\ \downarrow \\ b_\Sigma \end{array} \quad (34)$$

In Equation 35, two possible solid-state changes for $_\alpha A_\Sigma$ are shown. First, the reactive amorphous surface can undergo a degradation reaction to form C_Σ. Second, the surface can continue to lose water below the CRH so that the subsurface $_hA$ undergoes a solid phase transformation to a crystalline phase, $_IA$. 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.

$$\begin{array}{l} \xrightarrow{T} C_\Sigma \\ {}_\alpha A_\Sigma \\ \xrightarrow[-H_2O,\ T]{} {}_IA_\Sigma \end{array} \quad (35)$$

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_Σ, which is assumed to be saturated:[1]

$$A_\Sigma \xrightarrow{\text{excess } H_2O} a_\Sigma \quad (36)$$

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:

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

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.

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

Contamination Control

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

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

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

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

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

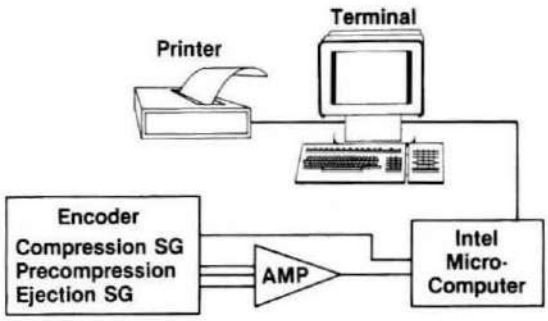


Figure 45-31. Schematic of an instrumentation system using a microcomputer as developed by Schering-Plough.

Tablet Formulations

WET GRANULATION

CT Acetaminophen, 300 mg

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

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

CT Ascorbic Acid USP, 50 mg

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

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

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

Chewable Antacid Tablets

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

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

CT Hexavitamin

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

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

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

CT Theobromine-Phenobarbital

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

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

FLUID-BED GRANULATION

CT Ascorbic Acid USP, 50 mg

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

[a] Includes 10% in excess of claim.

Add the first three ingredients to the granulator. Mix for 5 to 15 min or until well mixed. Dissolve the ethylcellulose in anhydrous ethanol and spray this solution and any additional ethanol into the fluidized mixture. Cease spraying when good granules are produced. Dry to approximately 3% moisture. Remove the granules and place them in a suitable blender. Sequentially add the remaining three ingredients with mixing steps in between each addition. Compress, using a flat, beveled, ¼-inch punch. Twenty tablets should weigh 2.39 g.

Sustained-Release (SR) Procainamide Tablets

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

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

DRY GRANULATION

CT Acetylsalicylic Acid

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

Dry the starch to a moisture content of 10%.Thoroughly mix this with the acetylsalicylic acid. Compress into slugs. Grind the slugs to 14- to 16-mesh size. Recompress into tablets, using a 13/32-inch punch. Ten tablets should weigh 3.575 g.

CT Sodium Phenobarbital

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

Mix all the ingredients thoroughly. Compress into slugs. Grind and screen to 14- to 16-mesh granules. Recompress into tablets, using a 9/32-inch concave punch. Ten tablets should weigh 1.3 g.

CT Vitamin B Complex

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

[a] Includes 10% in excess of label claim.
Mix all the ingredients thoroughly. Compress into slugs. Grind and screen to 14- to 16-mesh granules. Recompress into tablets, using a 1/4-inch concave punch. Ten tablets should weigh 1.25 g.
Sufficient tartaric acid should be used in these tablets to adjust the pH to 4.5.

DIRECT COMPRESSION

APC Tablets

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

[a] *Amstar.*
[b] *Davison Chem.*
Blend ingredients in a twin-shell blender for 15 min and compress on a 13/32-inch standard concave punch (courtesy, *Amstar*).

CT Ascorbic Acid USP, 250 mg

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

[a] Avicel-PH-101.
[b] Cab-O-Sil.
Blend all ingredients in a suitable blender. Compress, using 7/16-inch standard concave punch. Ten tablets should weigh 4.25 g (courtesy, *FMC*).

Breath Freshener Tablets

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

[a] *Davison* Chem.
Mix the flavor oils and menthol until liquid. Adsorb onto the silica gel. Add the remaining ingredients. Blend and compress on 5/16-inch, flat-face bevel-edge punch to a thickness of 3.1 mm (courtesy, *Atlas*).

Chewable Antacid Tablets

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

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

Chewable Multivitamin Tablets

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

Blend all ingredients in a suitable blender. Compress, using a 3/8-inch, flat-face, bevel-edge punch (courtesy, *Atlas*).

CT Ferrous Sulfate

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

Grind to 12- to 14-mesh, lubricate, and compress. Coat immediately to avoid oxidation to the ferric state with 0.410 gr of tolu balsam (dissolved in alcohol) and 0.060 gr of salol and chalk. Use a deep, concave, 13/32-inch punch. Ten tablets should weigh 3.25 g.

CT Methenamine

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

Compress directly, using a 7/16-inch punch. Ten tablets should weigh 3.25 g.

CT Phenobarbital USP, 30 mg

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

[a] Avicel-PH-101.
[b] QUSO F-22.
Screen the phenobarbital to break up lumps and blend with the microcrystalline cellulose. Add spray-dried lactose and blend. Finally, add the stearic acid and colloidal silica; blend to obtain a homogeneous mixture. Compress, using a 9/32-inch, shallow, concave punch. Ten tablets should weigh 1.33 g (courtesy, *FMC*).

Molded Tablets or Tablet Triturates (TT)

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

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

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

FORMULATION

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

It is also permissible in the development of the formula to weigh the quantity of medication needed for the number of tablets represented by the number of perforations in the mold, triturate with a weighed portion (more than ½) of the diluent, moisten the mixture, and press it into the perforations of the mold. An additional quantity of the diluent is moistened immediately and also forced into the perforations in the plate until they are filled completely. All excess diluent is removed, the trial tablets are forced from the mold, then triturated until uniform, moistened again, if necessary, and remolded. When these tablets are dried thoroughly and weighed, the difference between their total weight and the weight of medication taken will indicate the amount of diluent required and accordingly supply the formula for future use for that particular tablet triturate.

For proper mixing procedures of the medication with the diluent see Chapter 37.

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

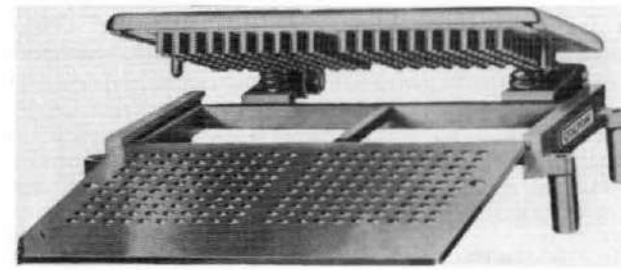


Figure 45-34. Tablet triturate mold (courtesy, Vector/Colton).

PREPARATION

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

HAND-MOLDING TABLET TRITURATES

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

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

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

MACHINE-MOLDING TABLET TRITURATES

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

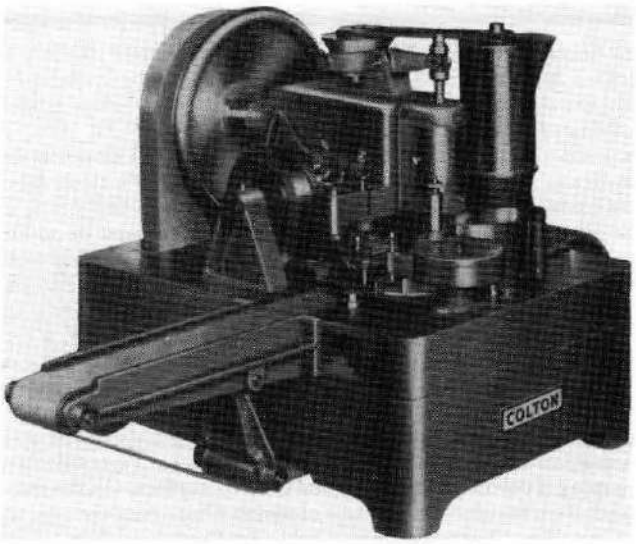


Figure 45-35. Automatic tablet triturate machine (courtesy, Vector-Colton).

COMPRESSED TABLET TRITURATES

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

TABLET CHARACTERISTICS

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

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

Tablet Hardness

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

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

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

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

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

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

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

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

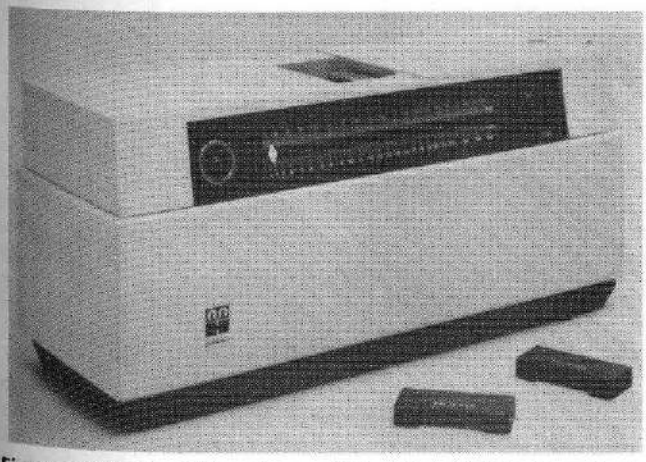


Figure 45-36. The Schleuniger or Heberlein tablet hardness tester shown with calibration blocks (courtesy, Vector).

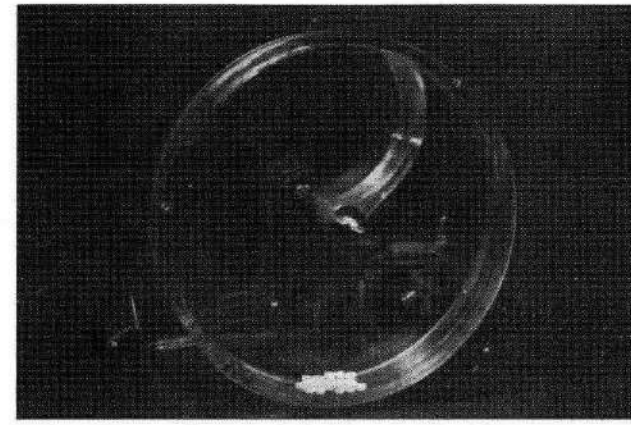


Figure 45-37. The Roche friabilator (courtesy, Hoffmann-LaRoche).

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

The higher the bonding index, the stronger a tablet is likely to be. The higher the strain index, the weaker the tablet. Since the two parameters are opposite in their effect on the tablet, it is possible for a material (such as Avicel) to have a relatively high strain index, but yet have superior compaction properties because of an extraordinary bonding potential. The higher the brittleness index, the more friable the tablet is likely to be. For a more detailed discussion of this subject, the reader is directed to References 22, 37, 38.

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

Tablet Thickness

The thickness of the tablet from production-run to production-run is controlled carefully. Thickness can vary with no change in weight because of difference in the density of the granulation and the pressure applied to the tablets, as well as the speed of tablet compression. Not only is the tablet thickness important in reproducing tablets identical in appearance but also to en-

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

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

sure that every production lot will be usable with selected packaging components. If the tablets are thicker than specified, a given number no longer may be contained in the volume of a given size bottle. Tablet thickness also becomes an important characteristic in counting tablets using filling equipment. Some filling equipment uses the uniform thickness of the tablets as a counting mechanism. A column containing a known number of tablets is measured for height; filling is accomplished by continually dropping columns of tablets of the same height into bottles. If thickness varies throughout the lot, the result will be variation in count. Other pieces of filling equipment can malfunction because of variation in tablet thickness, since tablets above specified thickness may cause wedging of tablets in previously adjusted depths of the counting slots. Tablet thickness is determined with a caliper or thickness gauge that measures the thickness in millimeters. Plus or minus 5% may be allowed, depending on the size of the tablet.

Uniformity of Dosage Forms

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

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

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

Tablet Disintegration

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

Exact specifications are given for the test apparatus, inasmuch as a change in the apparatus can cause a change in the results of the test. The apparatus consists of a basket rack holding six plastic tubes, open at the top and bottom; the bottom of the tubes is covered with 10-mesh screen. See Figure 45-38. The basket rack is immersed in a bath of suitable liquid, held at 37°, preferably in a 1-L beaker. The rack moves up and down in the fluid at a specified rate. The volume of the fluid is such that on the upward stroke the wire mesh remains at least 2.5 cm below the surface of the fluid and descends to not less than 2.5 cm from the bottom on the downward stroke. Tablets are placed in each of the six cylinders along with a plastic disc over the tablet unless otherwise directed in the monograph. The endpoint of the test is indicated when any residue remaining is a soft mass with no palpably soft core. The plastic discs help to force any soft mass that forms through the screen.

For compressed, uncoated tablets the testing fluid is usually water at 37°, but in some cases the monographs direct that Simulated Gastric Fluid TS be used. If one or two tablets fail to disintegrate, the test is to be repeated using 12 tablets. Of the 18 tablets then tested, 16 must have disintegrated within the given period of time. The conditions of the test are varied somewhat for coated tablets, buccal tablets, and sublingual

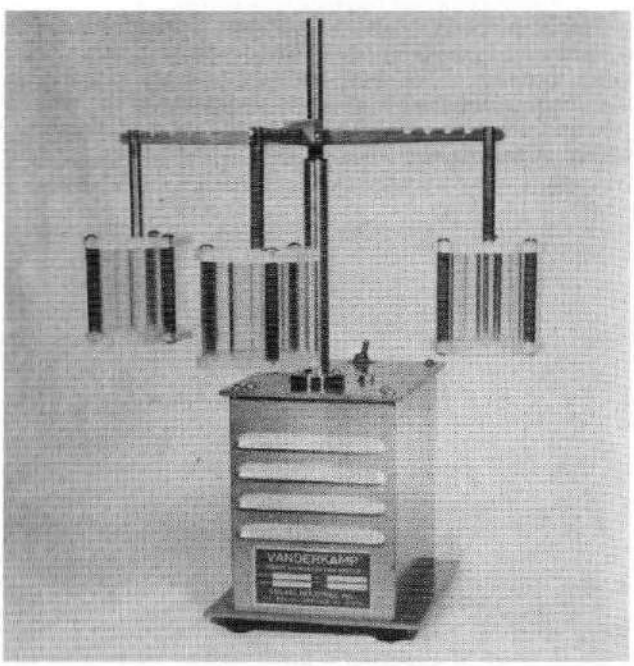


Figure 45-38. Vanderkamp tablet disintegration tester (courtesy, VanKel).

tablets. Disintegration times are included in the individual tablet monograph. For most uncoated tablets the period is 30 min, although the time for some uncoated tablets varies greatly from this. For coated tablets up to 2 hr may be required, while for sublingual tablets, such as CT Isoproterenol Hydrochloride, the disintegration time is 3 min. For the exact conditions of the test, consult the USP.

Dissolution Test

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

Validation

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

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

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

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

CAPSULES

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

The encapsulation of medicinal agents remains a popular method for administering drugs. Capsules are tasteless, easily administered, and easily filled either extemporaneously or in large quantities commercially. In prescription practice the use of hard gelatin capsules permits a choice in prescribing a single drug or a combination of drugs at the exact dosage level considered best for the individual patient. This flexibility is an advantage over tablets. Some patients find it easier to swallow capsules than tablets, therefore preferring to take this form when possible. This preference has prompted pharmaceutical manufacturers to market the product in capsule form, even though the product already has been produced in tablet form. While the industry prepares approximately 75% of its solid dosage forms as compressed tablets, 23% as hard gelatin capsules, and 2% as soft elastic capsules, market surveys have indicated a consumer preference of 44.2% for soft elastic capsules, 39.6% for tablets, and 19.4% for hard gelatin capsules.[51]

HARD GELATIN CAPSULES

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

Companies having equipment for preparing empty hard gelatin capsules include *Lilly, Parke-Davis, Scherer,* and *SmithKline.* The latter's production is mainly for its own use; the others are suppliers to the industry. With this equip-

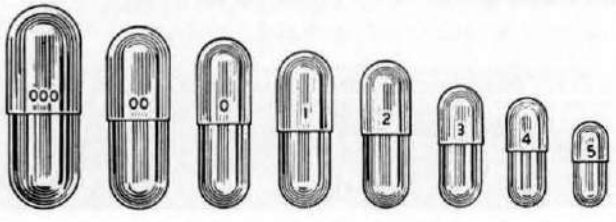


Figure 45-39. Hard gelatin capsules showing relative sizes (courtesy, Parke-Davis).

ment, stainless steel pins, set in plates, are dipped into the gelatin solution, which must be maintained at a uniform temperature and an exact degree of fluidity. If the gelatin solution varies in viscosity, it correspondingly will decrease or increase the thickness of the capsule wall. This is important since a slight variation is sufficient to make either a loose or a tight joint. When the pins have been withdrawn from the gelatin solution, they are rotated while being dried in kilns through which a strong blast of filtered air with controlled humidity is forced. Each capsule is stripped, trimmed to uniform length and joined, the entire process being mechanical. Capsule-making equipment is illustrated in Figures 45-40 and 45-41. These show the stainless steel pins being dipped into the gelatin solutions and then being rotated through the drying kiln.

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

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

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

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

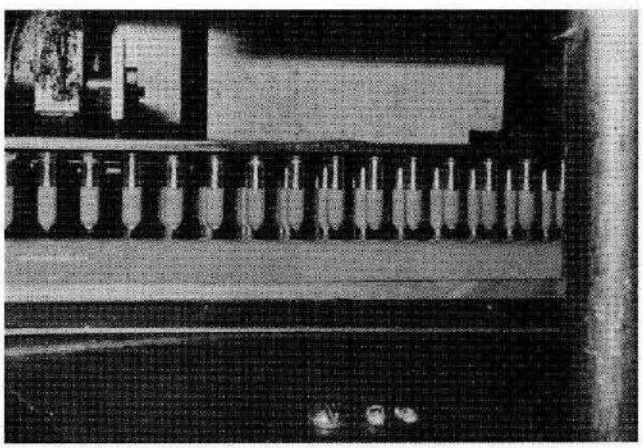


Figure 45-40. Manufacture of hard gelatin capsules by dipping stainless steel pins into gelatin solutions (courtesy, Lilly).

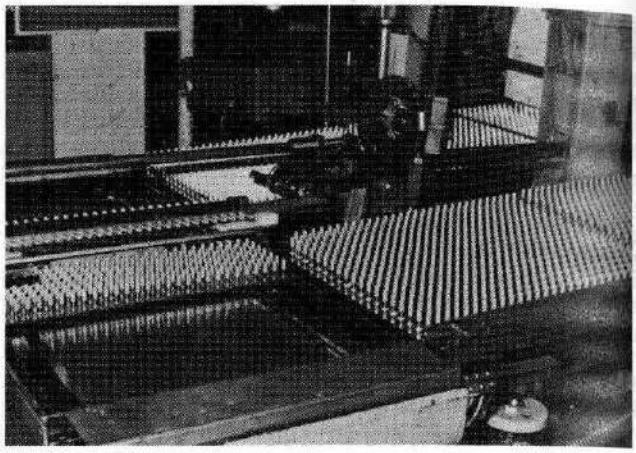


Figure 45-41. Formed capsules being dried by rotating through a drying kiln (courtesy, Lilly).

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

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

Extemporaneous Filling Methods

When filling capsules on prescription, the usual procedure is to mix the ingredients by trituration, reducing them to a fine and uniform powder. The principles and methods for the uniform distribution of an active medicinal agent in a powder mixture are discussed in Chapter 37. Granular powders do not pack readily in capsules, and crystalline materials, especially those that consist of a mass of filament-like crystals such as the quinine salts, are not fitted easily into capsules unless powdered. Eutectic mixtures that tend to liquefy may be dispensed in capsules if a suitable absorbent such as magnesium carbonate is used. Potent drugs given in

small doses usually are mixed with an inert diluent such as lactose before filling into capsules. When incompatible materials are prescribed together, it is sometimes possible to place one in a smaller capsule and then enclose it with the second drug in a larger capsule.

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

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

Machine Filling Methods

Large-scale filling equipment for capsules operates on the same principle as the manual machines described above, namely the filling of the base of the capsule. Compared with tablets, powders for filling into hard gelatin capsules require a minimum of formulation efforts. The powders usually contain diluents such as lactose, mannitol, calcium carbonate, or magnesium carbonate. Since the flow of material is of great importance in the rapid and accurate filling of the capsule bodies, lubricants such as the stearates also are used frequently.

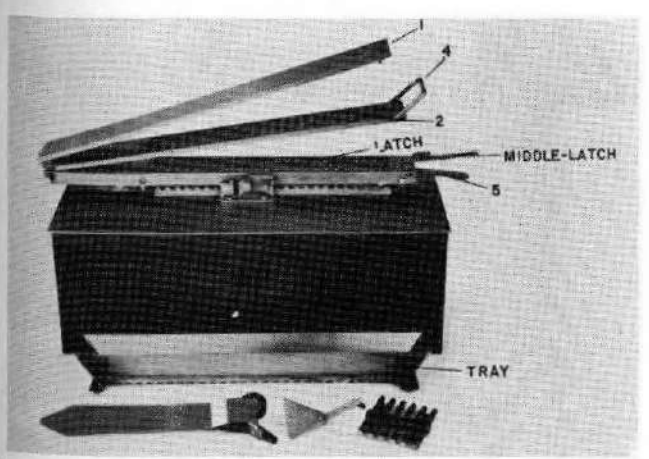


Figure 45-42. Hand-operated capsule machine (courtesy, ChemiPharm).

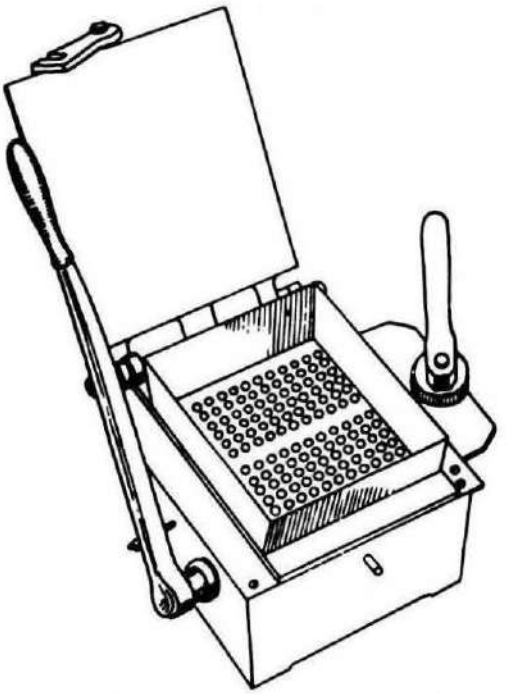


Figure 45-43. Hand-operated capsule machine, Model 300 (courtesy, ChemiPharm).

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

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

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

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

As the capsules fall into the holding ring, the cap half has a seat on the counter bore in each hole for the top ring. The body

Table 45-5. Capsule Fill Chart
Capsule Fill Weights (mg) Based on Size and Density

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

half is pulled by vacuum down into the bottom ring. When all rows in the ring assembly are full, the top ring, filled with caps only, is removed and set aside for later assembly. The body halves now are located in the bottom ring, ready for filling.

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

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

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

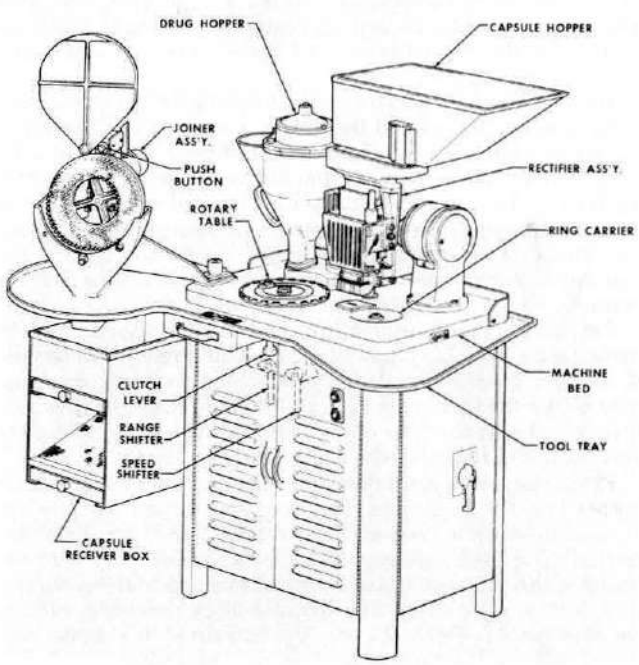


Figure 45-44. Schematic of Type 8 capsule-filling machine (courtesy, Parke-Davis).

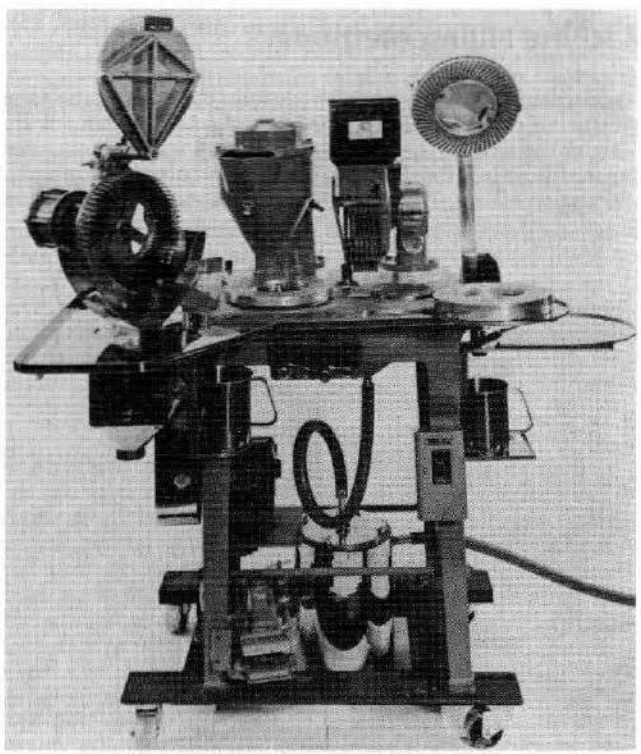


Figure 45-45. Type 8 capsule-filling machine (courtesy, Lilly).

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

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

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

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

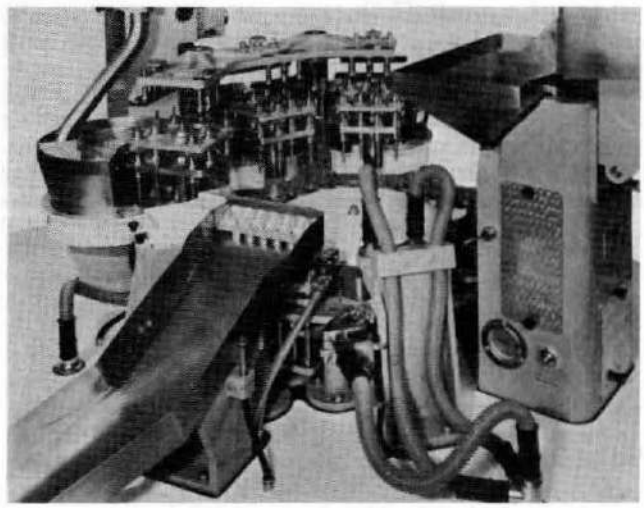


Figure 45-47. Zanasi automatic filling machine, Model AZ-60. The set of filling heads shown at the left collects the powder from the hopper, compresses it into a soft slug, and inserts it into the bottom half of the capsule (courtesy, United Machinery).

Uniformity of Dosage Units

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

Disintegration tests usually are not required for capsules unless they have been treated to resist solution in gastric fluid (enteric-coated). In this case they must meet the requirements for disintegration of enteric-coated tablets. For certain capsule dosage forms a dissolution requirement is part of the monograph. Procedures used are similar to those employed in the case of compressed tablets. See Chapter 35.

SOFT ELASTIC CAPSULES

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

Formerly, empty soft gelatin capsules were available to the pharmacist for the extemporaneous compounding of solutions

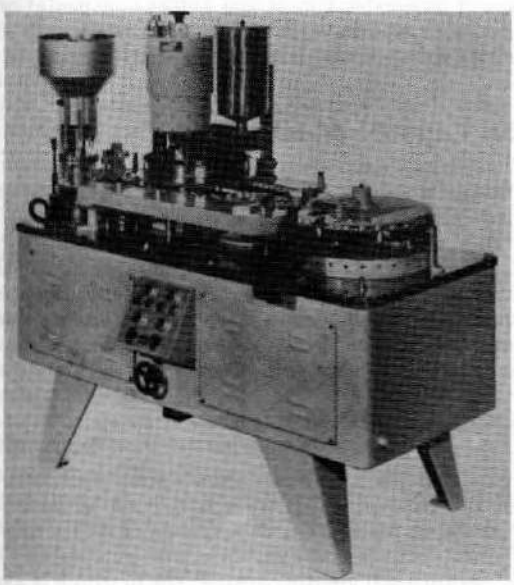


Figure 45-46. MG-2, automatic capsule-filling machine (courtesy, Supermatic).

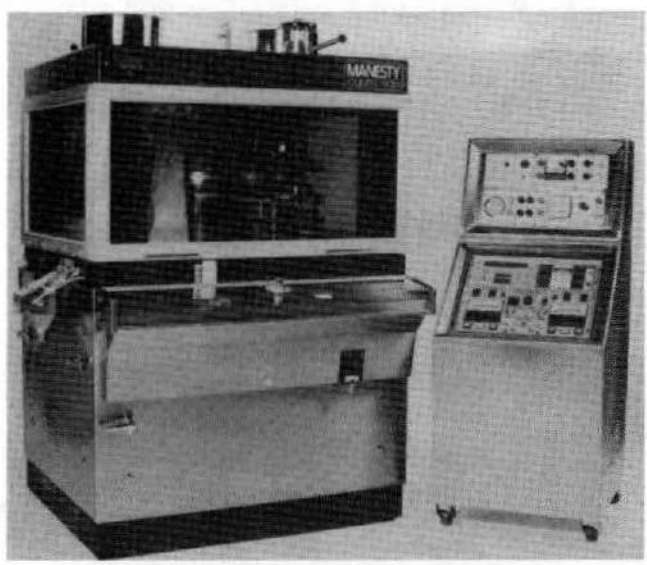


Figure 45-48. Hoefliger & Karg automatic capsule-filling machine, Model GFK 1200 (courtesy, Amaco).

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

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

Plate Process

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

Rotary-Die Process

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

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

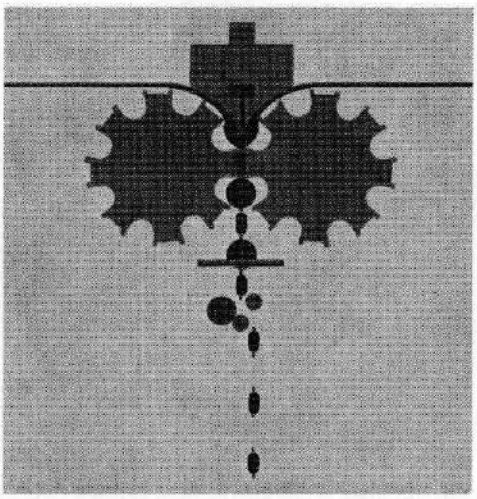


Figure 45-49. Rotary-die elastic capsule filler.

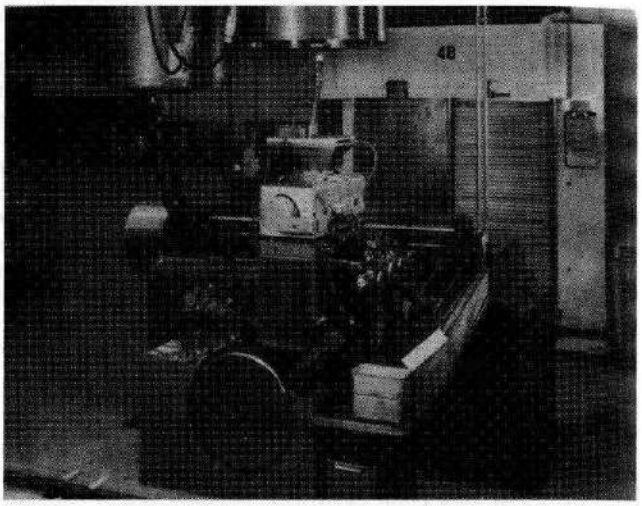


Figure 45-50. Scherer soft elastic capsule machine (courtesy, Scherer).

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

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

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

Norton Capsule Machine

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

Accogel Capsule Machine

Another means of soft gelatin encapsulation uses the Accogel machine and process which were developed at *Lederle*. The Accogel, or Stern machine, uses a system of rotary dies but is unique in that it is the only machine that successfully can fill dry powder into a soft gelatin capsule. The machine is available to the entire pharmaceutical industry by a lease arrangement and is used in many countries of the world. It is extremely

versatile, not only producing capsules with dry powder but also encapsulating liquids and combinations of liquids and powders. By means of an attachment, slugs or compressed tablets may be enclosed in a gelatin film. The capsules can be made in a variety of colors, shapes, and sizes.

Microencapsulation

As a technology, microencapsulation is placed in the section on capsules only because of the relationship in terminology to mechanical encapsulation described above. The topic also could have been included in a discussion of coating procedures. Essentially, microencapsulation is a process or technique by which thin coatings can be applied reproducibly to small particles of solids, droplets of liquids, or dispersions, thus forming microcapsules. It can be differentiated readily from other coating methods in the size of the particles involved; these range from several tenths of a micrometer to 5000 μm in size.

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

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

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

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

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

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

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

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

Other Oral Solid Dosage Forms

PILLS

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

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

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

TROCHES

These forms of oral medication, also known as *lozenges* or *pastilles,* are discoid-shaped solids containing the medicinal agent in a suitably flavored base. The base may be a hard sugar

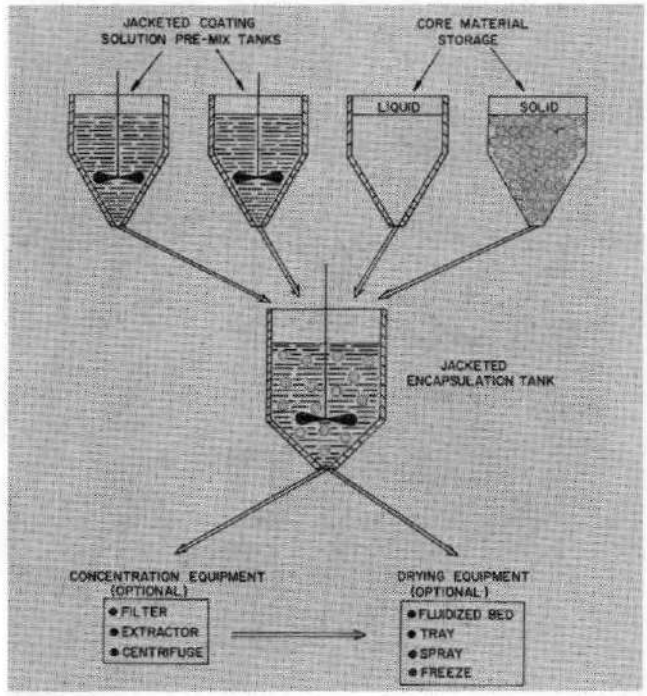


Figure 45-51. Production installation for the microencapsulation process (courtesy, NCR).

deposition. Chemically, it is $Al_2O_3 \cdot 4SiO_2 \cdot H_2O$ plus other minerals as impurities. It consists of colloidal crystalline plates, of less than microscopic dimensions in thickness, and of colloidal dimensions in breadth. This fact accounts for the extreme swelling that occurs when it is placed in water, since the water penetrates between an infinite number of plates. A good specimen swells 12 to 14 times its volume.

Solubility—Insoluble in water or acids, but it has the property of adsorbing large quantities of water, swelling to approximately 12 times its original volume, and forming highly viscous thixotropic suspensions or *gels.* This property makes it highly useful in pharmacy. Its gel-forming property is augmented by the addition of small amounts of alkaline substances, such as magnesium oxide. It does not swell in organic solvents.

Incompatibilities—*Acids* and *acid salts* decrease its water-absorbing power and thus cause a breakdown of the magma. Suspensions are most stable at a pH above 7.

Uses—A *protective colloid* for the *stabilization of suspensions.* It also has been used as an emulsifier for oil and as a base for plasters, ointments, and similar preparations.

Bentonite Magma—*Preparation:* Sprinkle bentonite (50 g), in portions, on hot purified water (800 g), allowing each portion to become thoroughly wetted without stirring. Allow it to stand with occasional stirring for 24 hr. Stir until a uniform magma is obtained, add purified water to make 1000 g, and mix. The magma may be prepared also by mechanical means such as by use of a blender, as follows: Place purified water (about 500 g) in the blender, and while the machine is running, add bentonite (50 g). Add purified water to make up to about 1000 g or up to the operating capacity of the blender. Blend the mixture for 5 to 10 min, add purified water to make 1000 g, and mix. *Uses:* A *suspending agent* for insoluble medicaments.

CARBOMER

Carboxypolymethylene

A synthetic high-molecular-weight cross-linked polymer of acrylic acid; contains 56 to 68% of carboxylic acid (-COOH) groups. The viscosity of a neutralized preparation (2.5 g/500 mL water) is 30,000 to 40,000 centipoises.

Description—White, fluffy powder with a slight, characteristic odor; hygroscopic; pH (1 in 100 dispersion) about 3; specific gravity about 1.41.

Solubility—neutralized with alkali hydroxides or amines); dissolves in water, alcohol, or glycerin.

Uses—A *thickening, suspending, dispersing* and *emulsifying agent* for pharmaceuticals, cosmetics, waxes, paints, and other industrial products.

CARRAGEENAN

Carrageenan [9000-07-1].

Preparation—The hydrocolloid extracted with water or aqueous alkali from certain red seaweeds of the class *Rhodophyceae,* and separated from the solution by precipitation with alcohol (methanol, ethanol, or isopropanol) or by drum-roll drying or freezing.

Constituents—It is a variable mixture of potassium, sodium, calcium, magnesium, and ammonium sulfate esters of galactose and 3,6-anhydrogalactose copolymers, the hexoses being alternately linked α-1,3 and β-1,4 in the polymer. The three main types of copolymers present are *kappa*-carrageenan, *iota*-carrageenan, and *lambda*-carrageenan, which differ in the composition and manner of linkage of monomeric units and the degree of sulfation (the ester sulfate content for carrageenans varies from 18 to 40%). *Kappa*-carrageenan and *iota*-carrageenan are the gelling fractions; *lambda*-carrageenan is the non-gelling fraction. The gelling fractions may be separated from the non-gelling fraction by addition of potassium chloride to an aqueous solution of carrageenan. Carrageenan separated by drum-roll drying may contain mono- and di-glycerides or up to 5% of polysorbate 80, used as roll-stripping agents.

Description—Yellow-brown to white, coarse to fine powder; odorless; tasteless, producing a mucilaginous sensation on the tongue.

Solubility—All carrageenans hydrate rapidly in cold water, but only *lambda*-carrageenan and sodium carrageenans dissolve completely. Gelling carrageenans require heating to about 80° for complete solution when potassium and calcium ions are present.

Uses—In the pharmaceutical and food industries as an emulsifying, suspending, and gelling agent.

CARBOXYMETHYLCELLULOSE SODIUM

Carbose D; Carboxymethocel S; CMC; Cellulose Gum

Cellulose, carboxymethyl ether, sodium salt [9004-32-4]; contains 6.5 to 9.5% of sodium (Na), calculated on the dried basis. It is available in several viscosity types: low, medium, high, and extra high.

Description—White to cream-colored powder or granules; the powder is hygroscopic; pH (1 in 100 aqueous solution) about 7.5.

Solubility—Easily dispersed in water to form colloidal solutions; insoluble in alcohol, ether, or most other organic solvents.

Uses—*Pharmaceutic aid* (suspending agent, tablet excipient, or viscosity-increasing agent). In tablet form it is used as a hydrophilic colloid laxative.

POWDERED CELLULOSE

Cellulose [9004-34-6] $(C_6H_{10}O_5)_n$; purified, mechanically disintegrated cellulose prepared by processing alpha cellulose obtained as a pulp from fibrous plant materials.

Description—White, odorless substance, consisting of fibrous particles, which may be compressed into self-binding tablets that disintegrate rapidly in water; exists in various grades, exhibiting degrees of fineness ranging from a free-flowing dense powder to a coarse, fluffy, nonflowing material; pH (supernatant liquid of a 10 g/90 mL aqueous suspension after 1 hr) 5 to 7.5.

Solubility—Insoluble in water, dilute acids, or nearly all organic solvents; slightly soluble in NaOH solution (1 in 20).

Uses—*Pharmaceutic aid* (tablet diluent, adsorbent, or suspending agent).

CETYL ALCOHOL—page 1035.

CHOLESTEROL

Cholest-5-en-3-ol, (3β)-, Cholesterin

Cholest-5-en-3β-ol [57-88-5] $C_{27}H_{46}O$ (386.66).

For the structural formula, see page 418.

A steroid alcohol widely distributed in the animal organism. In addition to cholesterol and its esters, several closely related steroid alcohols occur in the yolk of eggs, the brain, milk, fish oils, wool fat (10 to 20%), etc. These closely resemble it in properties. One of the methods of commercial production involves extraction of it from the unsaponifiable matter in the spinal cord of cattle, using petroleum benzin. Wool fat also is used as a source.

Description—White or faintly yellow, almost odorless pearly leaflets or granules; usually acquires a yellow to pale tan color on prolonged exposure to light or to elevated temperatures; melts 147 to 150°.

Solubility—Insoluble in water; 1 g slowly dissolves in 100 mL alcohol or about 50 mL dehydrated alcohol; soluble in acetone, hot alcohol, chloroform, dioxane, ether, ethyl acetate, solvent hexane, or vegetable oils.

Uses—To enhance incorporation and emulsification of medicinal products in oils or fats. It is a pharmaceutical necessity for *Hydrophilic Petrolatum,* in which it enhances water-absorbing capacity. See Chapter 21.

DOCUSATE SODIUM—page 1233.

GELATIN

White Gelatin

A product obtained by the partial hydrolysis of collagen derived from the skin, white connective tissues, and bones of animals. Gelatin derived from an acid-treated precursor is known as Type A and exhibits an isoelectric point between pH 7 and 9, while gelatin derived from an alkali-treated precursor is known as Type B and exhibits an isoelectric point between pH 4.7 and 5.2.

Gelatin for use in the manufacture of capsules in which to dispense medicines or for the coating of tablets may be colored with a certified color, may contain not more than 0.15% of sulfur dioxide, may contain a suitable concentration of sodium lauryl sulfate and suitable antimicrobial agents, and may have any suitable gel strength that is designated by Bloom Gelometer number.

Regarding the special gelatin for use in the preparation of emulsions, see *Emulsions* (page 737).

Description—Sheets, flakes, shreds, or a coarse-to-fine powder; faintly yellow or amber in color, the color varying in depth according to the particle size; slight, characteristic bouillon-like odor; stable in air when dry, but is subject to microbial decomposition when moist or in solution.

Solubility—Insoluble in cold water, but swells and softens when immersed in it, gradually absorbing from 5 to 10 times its own weight of water; soluble in hot water, acetic acid, or hot mixtures of glycerin or water; insoluble in alcohol, chloroform, ether, or fixed and volatile oils.

Uses—In pharmacy, to coat pills and form capsules, and as a vehicle for suppositories. It also is recommended as an emulsifying agent. See under *Emulsions* in Chapters 20 and 39, also *Suppositories* (page 851), and *Absorbable Gelatin Sponge* (page 1261). It also has been used as an adjuvant protein food in malnutrition.

GLYCERYL MONOSTEARATE—page 1036.

HYDROXYETHYL CELLULOSE

Cellulose, 2-hydroxyethyl ether; Cellosize; Natrosol

Cellulose hydroxyethyl ether 9004-62-0.

Preparation—Cellulose is treated with NaOH and then reacted with ethylene oxide.

Description—White, odorless, tasteless, free-flowing powder; softens at about 137°; refractive index (2% solution) about 1.336; pH about 7; solutions are nonionic.

Solubility—Dissolves readily in cold or hot water to give clear, smooth, viscous solutions; partially soluble in acetic acid; insoluble in most organic solvents.

Uses—Resembles carboxymethylcellulose sodium in that it is a cellulose ether, but differs in being nonionic, and hence, its solutions are unaffected by cations. It is used pharmaceutically as a thickener, protective colloid, binder, stabilizer, and suspending agent in emulsions, jellies and ointments, lotions, ophthalmic solutions, suppositories, and tablets.

HYDROXYPROPYL CELLULOSE

Cellulose, 2-hydroxypropyl ether; Klucel

Cellulose hydroxypropyl ether [9004-64-2].

Preparation—After treating with NaOH, cellulose is reacted with propylene oxide at elevated temperature and pressure.

Description—Off-white, odorless, tasteless powder; softens at 130°; burns out completely about 475° in N_2 or O_2; refractive index (2% solution) about 1.337; pH (aqueous solution) 5 to 8.5; solutions are nonionic.

Solubility—Soluble in water below 40° (insoluble above 45°); soluble in many polar organic solvents.

Uses—A broad combination of properties useful in a variety of industries. It is used pharmaceutically as a binder, granulation agent, and film-coater in the manufacture of tablets; an alcohol-soluble thickener and suspending agent for elixirs and lotions; and a stabilizer for emulsions.

HYDROXYPROPYL METHYLCELLULOSE

Cellulose, 2-hydroxypropyl methyl ether

Cellulose hydroxypropyl methyl ether [9004-65-3], available in grades containing 16.5 to 30.0% of methoxy and 4.0 to 32.0% of hydroxypropoxy groups, and thus in viscosity and thermal gelation temperatures of solutions of specified concentration.

Preparation—The appropriate grade of methylcellulose (see below) is treated with NaOH and reacted with propylene oxide at elevated temperature and pressure for a reaction time sufficient to produce the desired degree of attachment of methyl and hydroxypropyl groups by ether linkages to the anhydroglucose rings of cellulose.

Description—White to slightly off-white, fibrous or granular, free-flowing powder.

Solubility—Swells in water and produces a clear to opalescent, viscous, colloidal mixture; undergoes reversible transformation from sol to gel on heating and cooling, respectively. Insoluble in anhydrous alcohol, ether, or chloroform.

Uses—A protective colloid that is useful as a dispersing and thickening agent, and in ophthalmic solutions to provide the demulcent action and viscous properties essential for contact-lens use and in *artificial-tear* formulations. See *Hydroxypropyl Methylcellulose Ophthalmic Solution* (page 1204).

LANOLIN, ANHYDROUS—page 1035.

METHYLCELLULOSE

Cellulose, methyl ether; Methocel

Cellulose methyl ether [9004-67-5]; a methyl ether of cellulose containing 27.5 to 31.5% of methoxy groups.

Preparation—By the reaction of methyl chloride or of dimethyl sulfate on cellulose dissolved in sodium hydroxide. The cellulose methyl ether so formed is coagulated by adding methanol or other suitable agent and centrifuged. Since cellulose has 3 hydroxyl groups/glucose residue, several methylcelluloses can be made that vary in, among other properties, solubility and viscosity. Types useful for pharmaceutical application contain from 1 to 2 methoxy radicals/glucose residue.

Description—White, fibrous powder or granules; aqueous suspensions neutral to litmus; stable to alkalies and dilute acids.

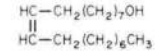
Solubility—Insoluble in ether, alcohol, or chloroform; soluble in glacial acetic acid or in a mixture of equal parts of alcohol and chloroform; swells in water, producing a clear to opalescent, viscous colloidal solution; insoluble in hot water and saturated salt solutions; salts of minerals, acids, and particularly polybasic acids, phenols, and tannins coagulate its solutions, but this can be prevented by the addition of alcohol or of glycol diacetate.

Uses—A synthetic substitute for natural gums that has both pharmaceutic and therapeutic applications. Pharmaceutically, it is used as a *dispersing, thickening, emulsifying, sizing,* and *coating agent*. It is an ingredient of many nose drops, eye preparations, burn medications, cosmetics, tooth pastes, liquid dentifrices, hair fixatives, creams, and lotions. It functions as a protective colloid for many types of dispersed substances and is an effective stabilizer for oil-in-water emulsions.

Therapeutically, it is used as a *bulk laxative* in the treatment of *chronic constipation*. Taken with 1 or 2 glassfuls of water, it forms a colloidal solution in the upper alimentary tract; this solution loses water in the colon, forming a gel that increases the bulk and softness of the stool. The gel is bland, demulcent, and nonirritating to the GI tract. Once a normal stool develops, the dose should be reduced to a level adequate for maintenance of good function. Although it takes up water from the GI tract quite readily, methylcellulose tablets have caused fecal impaction and intestinal obstruction when taken with a limited amount of water. It also is used as a topical ophthalmic protectant, in the form of 0.5 to 1% solution serving as artificial tears or a contact-lens solution applied to the conjunctiva, 0.05 to 0.1 mL at a time, 3 or 4 times a day as needed.

OLEYL ALCOHOL

9-Octadecen-1-ol, *(Z)*-, Aldol 85



(Z)-9-Octadecen-1-ol [143-28-2] $C_{18}H_{36}O$ (268.48); a mixture of unsaturated and saturated high-molecular-weight fatty alcohols consisting chiefly of oleyl alcohol.

Preparation—One method reacts ethyl oleate with absolute ethanol and metallic sodium (*Org Syn Coll III:* 673, 1955).

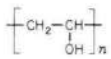
Description—Clear, colorless to light yellow, oily liquid; faint characteristic odor and bland taste; iodine value between 85 and 90; hydroxyl value between 205 and 215.

Solubility—Soluble in alcohol, ether, isopropyl alcohol, or light mineral oil; insoluble in water.

Uses—A *pharmaceutic aid* (emulsifying agent or emollient).

POLYVINYL ALCOHOL

Ethenol, homopolymer



Vinyl alcohol polymer [9002-89-5] $(C_2H_4O)_n$.

Preparation—Polyvinyl acetate is approximately 88% hydrolyzed in a methanol-methyl acetate solution using either mineral acid or alkali as a catalyst.

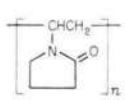
Description—White to cream-colored powder or granules; odorless.

Solubility—Freely soluble in water; solution effected more rapidly at somewhat elevated temperatures.

Uses—A *suspending agent* and *emulsifier,* either with or without the aid of a surfactant. It commonly is employed as a lubricant and protectant in various ophthalmic preparations, such as decongestants, artificial tears, and contact-lens products (see page 832).

POVIDONE

2-Pyrrolidinone, 1-ethenyl-, homopolymer; Polyvinylpyrrolidone; PVP



1-Vinyl-2-pyrrolidinone polymer [9003-39-8] $(C_6H_9NO)_n$; a synthetic polymer consisting of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights. It is produced commercially as a series of products having mean molecular weights ranging from about 10,000 to about 700,000. The viscosity of solutions containing 10% or less is essentially the same as that of water; solutions more concentrated than 10% become more

viscous, depending upon the concentration and the molecular weight of the polymer used. It contains 12 to 13% nitrogen.

Preparation—1,4-Butanediol is dehydrogenated thermally with the aid of copper to γ-butyrolactone, which then is reacted with ammonia to form 2-pyrrolidinone. Addition of the latter to acetylene yields vinylpyrrolidinone (monomer), which is polymerized thermally in the presence of hydrogen peroxide and ammonia.

Description—White to creamy white, odorless powder, hygroscopic; pH (1 in 20 solution) 3 to 7.

Solubility—Soluble in water, alcohol, or chloroform; insoluble in ether.

Uses—A *dispersing* and *suspending agent* in pharmaceutical preparations.

PROPYLENE GLYCOL MONOSTEARATE

Octadecanoic acid, monoester with 1,2-propanediol

1,2-Propanediol monostearate [1323-39-3]; a mixture of the propylene glycol mono- and diesters of stearic and palmitic acids. It contains not less than 90% monoesters of saturated fatty acids, chiefly propylene glycol monostearate ($C_{21}H_{42}O_3$) and propylene glycol monopalmitate ($C_{19}H_{38}O_3$).

Preparation—By reacting propylene glycol with stearoyl chloride in a suitable dehydrochlorinating environment.

Description—White, wax-like solid or white, wax-like beads or flakes; slight, agreeable, fatty odor and taste; congeals not lower than 45°; acid value not more than 2; saponification value 155 to 165; hydroxyl value 150 to 170; iodine value not more than 3.

Solubility—Dissolves in organic solvents such as alcohol, mineral or fixed oils, benzene, ether, or acetone; insoluble in water but may be dispersed in hot water with the aid of a small amount of soap or other suitable surface-active agent.

Uses—A *surfactant*. It is particularly useful as a dispersing agent for perfume oils or oil-soluble vitamins in water, and in cosmetic preparations.

SILICON DIOXIDE, COLLOIDAL—page 1046.

SODIUM LAURYL SULFATE

Sulfuric acid monododecyl ester sodium salt; Irium; Duponol C; Gardinol WA

Sodium monododecyl sulfate [151-21-3]; a mixture of sodium alkyl sulfates consisting chiefly of sodium lauryl sulfate. The combined content of sodium chloride and sodium sulfate is not more than 8%.

Preparation—The fatty acids of coconut oil, consisting chiefly of lauric acid, are catalytically hydrogenated to form the corresponding alcohols. The latter are then esterified with sulfuric acid (sulfated) and the resulting mixture of alkyl bisulfates (alkylsulfuric acids) is converted into a mixture of sodium salts by reacting with alkali under controlled conditions of pH.

Description—Small, white or light yellow crystals having a slight, characteristic odor.

Solubility—1 g in 10 mL water, forming an opalescent solution.

Incompatibilities—Reacts with *cationic surface-active agents* with loss of activity, even in concentrations too low to cause precipitation. Unlike soaps, it is compatible with dilute acids and calcium and magnesium ions.

Uses—An emulsifying, detergent, and wetting agent in ointments, tooth powders, and other pharmaceutical preparations, and in the metal, paper, and pigment industries.

SORBITAN ESTERS

Spans

Sorbitan esters (*monolaurate* [1338-39-2]; *monooleate* [1338-43-8]; *monopalmitate* [26266-57-9]; *monostearate* [1338-41-6]; *trioleate* [26266-58-0]; *tristearate* [26658-19-5]).

Preparation—Sorbitol is dehydrated to form a hexitan that is then esterified with the desired fatty acid. See *Polysorbates,* page 1037, which are polyethylene glycol ethers of sorbitan fatty acid esters.

Description—*Monolaurate:* Amber, oily liquid; may become hazy or form a precipitate; viscosity about 4250 cps; HLB no. 8.6; acid no. 7.0 max; saponification no. 158 to 170; hydroxyl no. 330 to 358. *Monooleate:* Amber liquid; viscosity about 1000 cps; HLB no. 4.3; acid no. 8.0 max; saponification no. 145 to 160; hydroxyl no. 193 to 210. *Monopalmitate:* Tan, granular waxy solid; HLB no. 6.7; acid no. 4 to 7.5; saponification no. 140 to 150; hydroxyl no. 275 to 305. *Monostearate:* Cream to tan beads; HLB no. 4.7; acid no. 5 to 10; saponification no. 147 to 157; hydroxyl no. 235 to 260. *Trioleate:* Amber, oily liquid; viscosity about 200 cps; HLB no. 1.8; acid no. 15 max; saponification no. 170 to 190; hydroxyl no. 55 to 70. *Tristearate:* Tan, waxy beads; HLB no. 2.1; acid no. 12 to 15; saponification no. 176 to 188; hydroxyl no. 66 to 80.

Solubility—*Monolaurate:* Soluble in methanol or alcohol; dispersible in distilled water and hard water (200 ppm); insoluble in hard water (20,000 ppm). *Monooleate:* Soluble in most mineral or vegetable oils; slightly soluble in ether; dispersible in water; insoluble in acetone. *Monopalmitate:* Dispersible (50) in distilled water or hard water (200 ppm); soluble in ethyl acetate; insoluble in cold distilled water or hard water (20,000 ppm). *Monostearate:* Soluble (above melting point) in vegetable oils or mineral oil; insoluble in water, alcohol, or propylene glycol. *Trioleate:* Soluble in mineral oil, vegetable oils, alcohol, or methanol; insoluble in water. *Tristearate:* Soluble in isopropyl alcohol; insoluble in water.

Uses—Nonionic *surfactants* used as *emulsifying agents* in the preparation of water-in-oil emulsions.

STEARIC ACID—page 1036.

STEARYL ALCOHOL

1-Octadecanol [112-92-5] $C_{18}H_{38}O$ (270.50); contains not less than 90% of stearyl alcohol, the remainder consisting chiefly of cetyl alcohol [$C_{16}H_{34}O$ = 242.44].

Preparation—Through the reducing action of lithium aluminum hydride on ethyl stearate.

Description—White, unctuous flakes or granules having a faint, characteristic odor and a bland taste; melts 55 to 60°.

Solubility—Insoluble in water; soluble in alcohol, chloroform, ether, or vegetable oils.

Uses—A surface-active agent used to *stabilize emulsions* and increase their ability to retain large quantities of water. See *Hydrophilic Ointment* (page 1036); *Hydrophilic Petrolatum* (page 1035).

TRAGACANTH

Gum Tragacanth; Hog Gum; Goat's Thorn

The dried gummy exudation from *Astragalus gummifer* Labillardière or other Asiatic species of *Astragalus* (Fam *Leguminosae*).

Constituents—60 to 70% bassorin and 30 to 40% soluble gum *(tragacanthin)*. The bassorin swells in the presence of water to form a gel, and tragacanthin forms a colloidal solution. Bassorin, consisting of complex methoxylated acids, resembles pectin. Tragacanthin yields glucuronic acid and arabinose when hydrolyzed.

Description—Flattened, lamellated, frequently curved fragments or straight or spirally twisted linear pieces 0.5 to 2.5 mm in thickness; white to weak-yellow in color; translucent; horny in texture; odorless; insipid, mucilaginous taste. When powdered, it is white to yellowish white.

Introduced into water, tragacanth absorbs a certain proportion of that liquid, swells very much, forms a soft adhesive paste, but does not dissolve. If agitated with an excess of water, this paste forms a uniform mixture; but in the course of 1 or 2 days the greater part separates and is deposited, leaving a portion dissolved in the supernatant fluid. The finest mucilage is obtained from the whole gum or *flake* form. Several days should be allowed for obtaining a uniform mucilage of the maximum gel strength. A common adulterant is *Karaya Gum,* and the USP has introduced tests to detect its presence.

Solubility—Insoluble in alcohol.

Uses—A *suspending agent* in lotions, mixtures, and extemporaneous preparations and prescriptions. It is used with emulsifying agents largely to increase consistency and retard creaming. It is sometimes used as a *demulcent* in sore throat, and the jelly-like product formed when the gum is allowed to swell in water serves as a basis for pharmaceutical jellies, eg, *Ephedrine Sulfate Jelly*. It also is used in various confectionery products. In the form of a glycerite, it has been used as a pill excipient.

Tragacanth Mucilage—*Preparation:* Mix glycerin (18 g) with purified water (75 mL) in a tared vessel, heat the mixture to boiling, discontinue the application of heat, add tragacanth (6 g) and benzoic acid (0.2 g), and macerate the mixture during 24 hr, stirring occasionally. Then add enough purified water to make the mixture weigh 100 g, stir actively until of uniform consistency, and strain forcibly through muslin. *Uses:* A suspending agent for insoluble substances in internal mixtures. It is also a *protective* agent.

XANTHAN GUM

Keltrol

A high-molecular-weight polysaccharide gum produced by a pure-culture fermentation of a carbohydrate with *Xanthomonas campestris,* then purified by recovery with isopropyl alcohol, dried and milled; contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid and is prepared as a sodium, potassium, or calcium salt; yields 4.2 to 5% carbon dioxide.

Preparation—See above and US Patents 3,433,708 and 3,557,016.

Description—White or cream-colored, tasteless powder with a slight organic odor; powder and solutions stable at 25° or less; does not exhibit polymorphism; aqueous solutions are neutral to litmus.

Solubility—1 g in about 3 mL alcohol; soluble in hot or cold water.

Uses—A hydrophilic colloid to thicken, suspend, emulsify, and stabilize water-based systems.

OTHER EMULSIFYING AND SUSPENDING AGENTS

Chondrus [Irish Moss; Carrageenan]—The dried sun-bleached plant of *Chondrus crispus* (Linné) Stackhouse (Fam *Gigartinaceae*). *Uses:* Principally, as an emulsifying agent for liquid petrolatum and for cod liver oil. It is also a protective. See also page 1030.

Malt—The partially germinated grain of one or more varieties of *Hordeum vulgare* Linné (Fam *Gramineae*) and contains amylolytic enzymes. Yellowish or amber-colored grains, with a characteristic odor and a sweet taste. The evaporated aqueous extract constitutes malt extract.

Malt Extract—The product obtained by extracting malt, the partially and artificially germinated grain of one or more varieties of *Hordeum vulgare* Linné (Fam *Gramineae*). *Uses:* An infrequently used emulsifying agent.

OINTMENT BASES

Ointments are semisolid preparations for external application to the body. They should be of such composition that they soften, but not necessarily melt, when applied to the skin. Therapeutically, ointments function as protectives and emollients for the skin, but are used primarily as vehicles or bases for the topical application of medicinal substances. Ointments also may be applied to the eye or eyelids.

Ideally, an ointment base should be compatible with the skin, stable, permanent, smooth and pliable, nonirritating, nonsensitizing, inert, and readily able to release its incorporated medication. Since there is no single ointment base that possesses all these characteristics, continued research in this field has resulted in the development of numerous new bases. Indeed, ointment bases have become so numerous as to require classification. Although ointment bases may be grouped in several ways, it is generally agreed that they can be classified best according to composition. Hence, the following four classes are recognized here: oleaginous, emulsifiable, emulsion bases, and water-soluble.

For completeness, substances are included that, although not used alone as ointment bases, contribute some pharmaceutical property to one or more of the various bases.

Oleaginous Ointment Bases and Components

The oleaginous ointment bases include fixed oils of vegetable origin, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. The vegetable oils are used chiefly in ointments to lower the melting point or to soften bases. These oils can be used as a base in themselves when a high percentage of powder is incorporated.

The vegetable oils and the animal fats have two marked disadvantages as ointment bases: their water-absorbing capacity is low and they have a tendency to become rancid. Insofar as vegetable oils are concerned, the second disadvantage can be overcome by hydrogenation, a process that converts many fixed oils into white, semisolid fats or hard, almost brittle, waxes.

The hydrocarbon bases comprise a group of substances with a wide range of melting points so that any desired consistency and melting point may be prepared with representatives of this group. They are stable, bland, and chemically inert and will mix with virtually any chemical substance. Oleaginous bases are excellent emollients.

WHITE OINTMENT

Ointment USP XI; Simple Ointment

White Wax	50 g
White Petrolatum	950 g
To make	1000 g

Melt the white wax in a suitable dish on a water bath, add the white petrolatum, warm until liquefied, then discontinue the heating and stir the mixture until it begins to congeal. It is permissible to vary the proportion of wax to obtain a suitable consistency of the ointment under different climatic conditions.

Uses—An emollient and vehicle for other ointments.

YELLOW OINTMENT

Yellow Wax	50 g
Petrolatum	950 g
To make	1000 g

Melt the yellow wax in a suitable dish on a steam bath, add the petrolatum, warm until liquefied, then discontinue the heating and stir the mixture until it begins to congeal. It is permissible to vary the proportion of wax to obtain a suitable consistency of the ointment under different climatic conditions.

Uses—An emollient and vehicle for other ointments. Both white and yellow ointment are known as *simple ointment.* White ointment should be used to prepare white ointments and yellow ointments should be used to prepare colored ointments when simple ointment is prescribed.

CETYL ESTERS WAX

Synthetic Spermaceti

A mixture consisting primarily of esters of saturated fatty alcohols (C_{14} to C_{18}) and saturated fatty acids (C_{14} to C_{18}). It has a saponification value of 109 to 120 and an acid value of not more than 5.

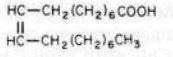
Description—White to off-white, somewhat translucent flakes; crystalline structure and pearly luster when caked; faint odor and a bland, mild taste; free from rancidity; specific gravity 0.820 to 0.840 at 50°; iodine value not more than 1; melts 43 to 47°.

Solubility—Insoluble in water; practically insoluble in cold alcohol; soluble in boiling alcohol, ether, chloroform, or fixed and volatile oils; slightly soluble in cold solvent hexane.

Uses—A replacement for spermaceti used to give consistency and texture to ointments, eg, *Cold Cream* and *Rose Water Ointment.*

OLEIC ACID

***(Z)*-9-Octadecenoic acid; Oleinic Acid; Elaic Acid**



Oleic acid [112-80-1] obtained from tallow and other fats and consists chiefly of *(Z)*-9-octadecenoic acid (282.47). Oleic acid used in preparations for internal administration is derived from edible sources.

It usually contains variable amounts of the other fatty acids present in tallow, such as linolenic and stearic acids.

Preparation—Obtained as a by-product in the manufacture of the solid stearic and palmitic acids used in the manufacture of candles, stearates, and other products. The crude oleic acid is known as *red oil,* the stearic and palmitic acids being separated by cooling.

Description—Colorless to pale yellow, oily liquid; lard-like odor and taste; specific gravity 0.889 to 0.895; congeals at a temperature not above 10°; pure acid solidifies at 4°; at atmospheric pressure it decomposes when heated at 80 to 100°; on exposure to air it gradually absorbs oxygen, darkens, and develops a rancid odor.

Solubility—Practically insoluble in water; miscible with alcohol, chloroform, ether, benzene, or fixed and volatile oils.

Incompatibilities—Reacts with *alkalies* to form soaps. *Heavy metals* and *calcium salts* form insoluble oleates. *Iodine solutions* are decolorized by formation of the iodine addition compound of the acid. It is oxidized to various derivatives by *nitric acid, potassium permanganate,* and other agents.

Uses—Classified as an emulsion adjunct, which reacts with alkalis to form soaps that function as emulsifying agents; it is used for this purpose in such preparations as *Benzyl Benzoate Lotion* and *Green Soap.* It also is used to prepare oleate salts of bases.

PARAFFIN

Paraffin Wax; Hard Paraffin

A purified mixture of solid hydrocarbons obtained from petroleum.

Description—Colorless or white, more or less translucent mass with a crystalline structure; slightly greasy to the touch; odorless and tasteless; congeals 47 to 65°.

Solubility—Freely soluble in chloroform, ether, volatile oils, or most warm fixed oils; slightly soluble in dehydrated alcohol; insoluble in water or alcohol.

Uses—Mainly, to increase the consistency of some ointments.

PETROLATUM

Yellow Soft Paraffin; Amber Petrolatum; Yellow Petrolatum; Petroleum Jelly; Paraffin Jelly

A purified mixture of semisolid hydrocarbons obtained from petroleum. It may contain a suitable stabilizer.

Preparation—The *residuums,* as they are termed technically, which are obtained by the distillation of petroleum, are purified by melting, usually treating with sulfuric acid and then percolating through recently burned bone black or adsorptive clays; this removes the odor and modifies the color. Selective solvents are also sometimes employed to extract impurities.

It has been found that the extent of purification required to produce *Petrolatum* and *Light Mineral Oil* of official quality removes antioxidants that are naturally present, and the purified product subsequently has a tendency to oxidize and develop an offensive odor. This is prevented by the addition of a minute quantity of α-tocopherol or other suitable antioxidant, as is now permissible.

Description—Unctuous mass of yellowish to light amber color; not more than a slight fluorescence after being melted; transparent in thin layers; free or nearly free from odor and taste; specific gravity 0.815 to 0.880 at 60; melts between 38 and 60°.

Solubility—Insoluble in water; almost insoluble in cold or hot alcohol or in cold dehydrated alcohol; freely soluble in benzene, carbon disulfide, chloroform, or turpentine oil; soluble in ether, solvent hexane, or in most fixed and volatile oils, the degree of solubility in these solvents varying with the composition of the petrolatum.

Uses—A base for ointments. It is highly occlusive and therefore a good emollient, but it may not release some drugs readily.

WHITE PETROLATUM

White Petroleum Jelly; White Soft Paraffin

A purified mixture of semisolid hydrocarbons obtained from petroleum, and wholly or nearly decolorized. It may contain a suitable stabilizer.

Preparation—In the same manner as petrolatum, the purification treatment being continued until the product is practically free from yellow color.

Description—White or faintly yellowish, unctuous mass; transparent in thin layers, even after cooling to 0°; specific gravity 0.815 to 0.880 at 60; melts 38 to 60°.

Solubility—Similar to that described under *Petrolatum.*

Uses—Similar to yellow petrolatum but often is preferred because of its freedom from color. It is employed as a protective, as a base for ointments and cerates, and to form the basis for burn dressings. See *Petrolatum Gauze* (page 1201).

Absorbent Ointment Bases

The term absorbent is used here to denote the water-absorbing or emulsifying properties of these bases and not to describe their action on the skin. These bases, sometimes called *emulsifiable ointment bases,* are generally anhydrous substances that have the property of absorbing (emulsifying) considerable quantities of water and still retaining their ointment-like consistency. Preparations of this type do not contain water as a component of their basic formula, but if water is incorporated, when and as desired, a W/O emulsion results. The following official products fall into this category.

LANOLIN ANHYDROUS

Anhydrous Lanolin; Wool Fat USP XVI; Refined Wool Fat

Lanolin that contains not more than 0.25% of water.

Constituents—Contains the sterols *cholesterol* [$C_{27}H_{45}OH$] and *oxycholesterol,* as well as triterpene and aliphatic alcohols. About 7% of the alcohols are found in the free state, the remainder occurring as esters of the following fatty acids: *carnaubic, cerotic, lanoceric, lanopalmitic, myristic,* and *palmitic.* Some of these are found free. The emulsifying and emollient actions of lanolin are due to the alcohols that are found in the unsaponifiable fraction when lanolin is treated with alkali. Constituting approximately one-half of this fraction and known as *lanolin alcohols,* the latter is composed of *cholesterol* (30%), *lanosterol* (25%), *cholestanol (dihydrocholesterol)* (3%), *agnosterol (2%),* and various other alcohols (40%).

Preparation—By purifying the fatty matter *(suint)* obtained from the wool of the sheep. This natural wool fat contains about 30% of free fatty acids and fatty acid esters of *cholesterol* and other higher alcohols. The cholesterol compounds are the important constituents, and to secure these in a purified form, many processes have been devised. In one of these the crude wool fat is treated with weak alkali and the saponified fats and emulsions are centrifuged to secure the aqueous soap solution, from which, on standing, a layer of partially purified wool fat separates. This product is further purified by treating it with calcium chloride and then dehydrated by fusion with unslaked lime. It is finally extracted with acetone, and the solvent subsequently separated by distillation. This differs from lanolin in that the former contains practically no water.

Description—Yellow, tenacious, unctuous mass; slight, characteristic odor; melts between 36 and 42°.

Solubility—Insoluble in water but mixes without separation with about twice its weight of water; sparingly soluble in cold alcohol; more soluble in hot alcohol; freely soluble in ether or chloroform.

Uses—An ingredient of ointments, especially when an aqueous liquid is to be incorporated. It gives a distinctive quality to the ointment, increasing absorption of active ingredients and maintaining a uniform consistency for the ointment under most climatic conditions. However, it has been omitted from many ointments on the recommendation of dermatologists who have found that many patients are allergic to this animal wax.

HYDROPHILIC PETROLATUM

Cholesterol	30 g
Stearyl Alcohol	30 g
White Wax	80 g
White Petrolatum	860 g
To make	1000 g

Melt the stearyl alcohol, white wax, and white petrolatum together on a steam bath, then add the cholesterol and stir until it completely dissolves. Remove from the bath, and stir until the mixture congeals.

Uses—A *protective* and *water-absorbable ointment base.* It will absorb a large amount of water from aqueous solutions of medicating substances, forming a W/O type of emulsion. See *Ointments* (page 845).

Emulsion Ointment Bases and Components

Emulsion ointment bases are actually semisolid emulsions. These preparations can be divided into two groups on the basis of emulsion type: emulsion ointment base water-in-oil (W/O) type and emulsion ointment base oil-in-water (O/W) type. Bases of both types will permit the incorporation of some additional amounts of water without reducing the consistency of the base below that of a soft cream. However, only O/W emulsion ointment bases can be removed readily from the skin and clothing with water. W/O emulsions are better emollients and protectants than are O/W emulsions. W/O emulsions can be diluted with oils.

CETYL ALCOHOL

Cetostearyl Alcohol; Palmityl Alcohol; Aldol 52

$CH_3(CH_2)_{14}CH_2OH$

1-Hexadecanol [124-29-8] $C_{16}H_{34}O$ (242.44); a mixture of not less than 90% of cetyl alcohol, the remainder chiefly stearyl alcohol.

Preparation—By catalytic hydrogenation of palmitic acid or saponification of spermaceti, which contains cetyl palmitate.

Description—Unctuous, white flakes, granules, cubes, or castings; faint characteristic odor and a bland, mild taste; melts 45 to 50°; not less than 90% distills between 316 and 336°.

Solubility—Insoluble in water; soluble in alcohol, chloroform, ether, or vegetable oils.

Uses—Similar to *Stearyl Alcohol* (page 1033). It also imparts a smooth texture to the skin and is used widely in cosmetic creams and lotions.

COLD CREAM

Petrolatum Rose Water Ointment USP XVI

Cetyl Esters Wax	125 g
White Wax	120 g
Mineral Oil	560 g
Sodium Borate	5 g
Purified Water	190 mL
To make about	1000 g

Reduce the cetyl esters wax and the white wax to small pieces, melt them on a steam bath with the mineral oil, and continue heating until the temperature of the mixture reaches 70°. Dissolve the sodium borate in the purified water, warmed to 70°, and gradually add the warm solution to the melted mixture, stirring rapidly and continuously until it has congealed.

If the ointment has been chilled, warm it slightly before attempting to incorporate other ingredients (see USP for allowable variations).

Uses—Useful as an emollient, cleansing cream, and ointment base. It resembles *Rose Water Ointment,* differing only in that mineral oil is used in place of almond oil and omitting the fragrance. This change produces an ointment base that is not subject to rancidity as is one containing a vegetable oil. This is a W/O emulsion.

GLYCERYL MONOSTEARATE

Octadecanoic acid, monoester with 1,2,3-propanetriol

Monostearin [31566-31-1]; a mixture chiefly of variable proportions of glyceryl monostearate [$C_3H_5(OH)_2C_{18}H_{35}O_2$ = 358.56] and glyceryl monopalmitate [$C_3H_5(OH)_2C_{16}H_{31}O_2$ = 330.51].

Preparation—Among other ways, by reacting glycerin with commercial stearoyl chloride.

Description—White, wax-like solid or occurs in the form of white, wax-like beads, or flakes; slight, agreeable, fatty odor and taste; does not melt below 55°; affected by light.

Solubility—Insoluble in water, but may be dispersed in hot water with the aid of a small amount of soap or other suitable surface-active agent; dissolves in hot organic solvents such as alcohol, mineral or fixed oils, benzene, ether, or acetone.

Uses—A thickening and emulsifying agent for ointments. See *Ointments* (page 845).

HYDROPHILIC OINTMENT

Methylparaben	0.25 g
Propylparaben	0.15 g
Sodium Lauryl Sulfate	10 g
Propylene Glycol	120 g
Stearyl Alcohol	250 g
White Petrolatum	250 g
Purified Water	370 g
To make about	1000 g

Melt the stearyl alcohol and the white petrolatum on a steam bath, and warm to about 75°. Add the other ingredients, previously dissolved in the water and warmed to 75°, and stir the mixture until it congeals.

Uses—A *water-removable ointment base* for the so-called *washable ointments.* This is an O/W emulsion.

LANOLIN

Hydrous Wool Fat

The purified, fat-like substance from the wool of sheep, *Ovis aries* Linné (Fam *Bovidae*); contains 25 to 30% water.

Description—Yellowish white, ointment-like mass, with a slight, characteristic odor; when heated on a steam bath it separates into an upper oily and a lower water layer; when the water is evaporated a residue of *Lanolin* remains that is transparent when melted.

Solubility—Insoluble in water; soluble in chloroform or ether with separation of its water of hydration.

Uses—Largely as a vehicle for ointments, for which it is admirably adapted on account of its compatibility with skin lipids. It emulsifies aqueous liquids. Lanolin is a W/O emulsion.

ROSE WATER OINTMENT

Cold Cream; Galen's Cerate

Cetyl Esters Wax	125 g
White Wax	120 g
Almond Oil	560 g
Sodium Borate	5 g
Stronger Rose Water	25 mL
Purified Water	165 mL
Rose Oil	0.2 mL
To make about	1000 g

Reduce the cetyl esters wax and the white wax to small pieces, melt them on a steam bath, add the almond oil, and continue heating until the temperature of the mixture reaches 70°. Dissolve the sodium borate in the purified water and stronger rose water, warmed to 70°, and gradually add the warm solution to the melted mixture, stirring rapidly and continuously until it has cooled to about 45°. Incorporate the rose oil.

It must be free from rancidity. If the ointment has been chilled, warm it slightly before attempting to incorporate other ingredients (see USP for allowable variations).

History—Originated by Galen, the famous Roman physician-pharmacist of the 1st century AD; was known for many centuries by the name of *Unguentum* or *Ceratum Refrigerans.* It has changed but little in proportions or method of preparation throughout many centuries.

Uses—An *emollient* and *ointment base.* It is a W/O emulsion.

STEARIC ACID

Octadecanoic acid; Cetylacetic Acid; Stearophanic Acid

Stearic acid [57-11-4]; a mixture of stearic acid [$C_{18}H_{36}O_2$ = 284.48] and palmitic acid [$C_{16}H_{32}O_2$ = 256.43], which together constitute not less than 90.0% of the total content. The content of each is not less than 40.0% of the total.

Purified Stearic Acid USP is a mixture of the same acids that together constitute not less than 96.0% of the total content, and the content of $C_{18}H_{36}O_2$ is not less than 90.0% of the total.

Preparation—From edible fats and oils (see exception below) by boiling them with soda lye, separating the glycerin, and decomposing the resulting soap with sulfuric or hydrochloric acid. The stearic acid subsequently is separated from any oleic acid by cold expression. It also is prepared by the hydrogenation and subsequent saponification of *olein.* It may be purified by recrystallization from alcohol.

Description—Hard, white or faintly yellowish, somewhat glossy and crystalline solid, or a white or yellowish white powder; an odor and taste suggestive of tallow; melts about 55.5° and should not congeal at a temperature below 54°; the purified acid melts at 69 to 70° and congeals between 66 and 69°; slowly volatilizes between 90 and 100°.

Solubility—Practically insoluble in water; 1 g in about 20 mL alcohol, 2 mL chloroform, 3 mL ether, 25 mL acetone, or 6 mL carbon tetrachloride; freely soluble in carbon disulfide; also soluble in amyl acetate, benzene, or toluene.

Incompatibilities—Insoluble stearates are formed with many *metals.* Ointment bases made with stearic acid may show evidence of drying out or lumpiness due to such a reaction when *zinc* or *calcium* salts are compounded therein.

Uses—In the preparation of sodium stearate, which is the solidifying agent for the official glycerin suppositories; in enteric tablet coating; ointments; and for many other commercial products, such as toilet creams, vanishing creams, solidified alcohol, etc. (When labeled solely for external use, it is exempt from the requirement that it be prepared from edible fats and oils.)

Water-Soluble Ointment Bases and Components

Included in this section are bases prepared from the higher ethylene glycol polymers (PEGs). These polymers are marketed under the trademark of Carbowax. The polymers have a wide range in molecular weight. Those with molecular weights ranging from 200 to 700 are liquids; those above 1000 are wax-like solids. The polymers are water-soluble, nonvolatile, and unctuous agents. They do not hydrolyze or deteriorate and will not support mold growth. These properties account for their wide use in washable ointments. Mixtures of PEGs are used to give bases of various consistency, such as very soft to hard bases for suppositories.

GLYCOL ETHERS AND DERIVATIVES

This special class of ethers is of considerable importance in pharmaceutical technology. Both mono- and polyfunctional compounds are represented in the group. The simplest member is ethylene oxide, [CH_2CH_2O], the internal or cyclic ether of the simplest glycol, ethylene glycol [$HOCH_2CH_2OH$]. External mono- and diethers of ethylene glycol $ROCH_2CH_2OH$ and $ROCH_2CH_2OR'$ are well known largely because of research done by Union Carbide.

PREPARATION—In the presence of NaOH at temperatures of the order of 120 to 135° and under a total pressure of about 4 atmospheres, ethylene oxide reacts with ethylene glycol to form compounds having the general formula $HOCH_2(CH_2OCH_2)_nCH_2OH$, commonly referred to as condensation polymers and termed polyethylene (or polyoxyethylene) glycols. Other glycols besides ethylene glycol function in a similar capacity, and the commercial generic term adopted for the entire group is polyalkylene (or polyoxyalkylene) glycols.

NOMENCLATURE—It is to be noted that these condensation polymers are bifunctional; ie, they contain both ether and alcohol linkages. The compound in which $n = 1$ is the commercially important diethylene glycol [$HOCH_2CH_2OCH_2CH_2OH$], and its internal ether is the familiar dioxane [$CH_2CH_2OCH_2CH_2O$]. The mono- and diethers derived from diethylene glycol have the formulas $ROCH_2CH_2OCH_2CH_2OH$ and $ROCH_2CH_2OCH_2CH_2OR'$. The former commonly are termed *Carbitols* and the latter *Cellosolves,* registered trademarks belonging to Union Carbide.

Polyethylene glycols are differentiated in commercial nomenclature by adding a number to the name, which represents the average molecular weight. Thus, polyethylene glycol 400 has an average molecular weight of about 400 (measured values for commercial samples range between 380 and 420), corresponding to a value of n for this particular polymer of approximately 8. Polymers have been produced in which the value of n runs into the hundreds. Up to n = approximately 15, the compounds are liquids at room temperature, and viscosity and boiling point increase with increasing molecular weight. Higher polymers are waxy solids and are termed commercially *Carbowaxes* (another Union Carbide trademark).

It should be observed that the presence of the two terminal hydroxyl groups in the polyalkylene glycols makes possible the formation of both ether and ester derivatives, several of which are marketed products.

USES—Because of their vapor pressure, solubility, solvent power, hygroscopicity, viscosity, and lubricating characteristics, the polyalkylene glycols or their derivatives function in many applications as effective replacements for glycerin and water-insoluble oils. They find considerable use as plasticizers, lubricants, conditioners, and finishing agents for processing textiles and rubber. They also are important as emulsifying agents and as dispersants for such diverse substances as dyes, oils, resins, insecticides, and various types of pharmaceuticals. In addition, they are employed frequently as ingredients in ointment bases and in a variety of cosmetic preparations.

POLYETHYLENE GLYCOLS

Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, Carbowaxes; Atpeg

$$H{-}[OCH_2CH_2{-}]_nOH$$

Polyethylene glycols [25322-68-3].

Preparation—Ethylene glycol is reacted with ethylene oxide in the presence of NaOH at temperatures in the range of 120 to 135° under pressure of about 4 atm.

Description—*Polyethylene glycols 200, 300, 400,* and *600* are clear, viscous liquids at room temperature. *Polyethylene glycols 900, 1000, 1450, 3350, 4500,* and *8000* are white, waxy solids. The glycols do not hydrolyze or deteriorate under typical conditions. As their molecular weight increases, their water solubility, vapor pressure, hygroscopicity, and solubility in organic solvents decrease; at the same time, freezing or melting range, specific gravity, flash point, and viscosity increase. If these compounds ignite, small fires should be extinguished with carbon dioxide or dry-chemical extinguishers and large fires with *alcohol*-type foam extinguishers.

Solubility—All members of this class dissolve in water to form clear solutions and are soluble in many organic solvents.

Uses—These possess a wide range of solubilities and compatibilities, which make them useful in pharmaceutical and cosmetic preparations. Their blandness renders them highly acceptable for hair dressings, hand lotions, sun-tan creams, leg lotions, shaving creams, and skin creams (eg, a peroxide ointment that is stable may be prepared using these compounds, while oil-type bases inactivate the peroxide). Their use in washable ointments is discussed under *Ointments* (page 845). They also are used in making suppositories, hormone creams, etc. See *Polyethylene Glycol Ointment* (below) and *Glycol Ethers* (above). The liquid polyethylene glycol 400 and the solid polyethylene glycol 3350, used in the proportion specified (or a permissible variation thereof) in the official Polyethylene Glycol Ointment, provide a water-soluble ointment base used in the formulation of many dermatological preparations. The solid, waxy, water-soluble glycols often are used to increase the viscosity of liquid polyethylene glycols and to stiffen ointment and suppository bases. In addition, they are used to compensate for the melting point-lowering effect of other agents, ie, chloral hydrate, etc, on such bases.

Polyethylene Glycol Ointment USP—*Preparation:* Heat polyethylene glycol 3350 (400 g) and polyethylene glycol 400 (600 g) on a water bath to 65°. Allow to cool, and stir until congealed. If a firmer preparation is desired, replace up to 100 g of polyethylene glycol 400 with an equal amount of polyethylene glycol 3350. If 6 to 25% of an aqueous solution is to be incorporated in this ointment, replace 50 g of polyethylene glycol 3350 by 50 g of stearyl alcohol. *Uses:* A water-soluble ointment base.

POLYOXYL 40 STEARATE

Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, octadecanoate; Myrj

$RCOO(C_2H_4O)_nH$ (*R*COO is the stearate moiety; n is approximately 40).

Polyethylene glycol monostearate [9004-99-3]; a mixture of monostearate and distearate esters of mixed polyoxyethylene diols and corresponding free glycols, the average polymer length being equivalent to about 40 oxyethylene units. *Polyoxyethylene 50 Stearate* is a similar mixture in which the average polymer length is equivalent to about 50 oxyethylene units.

Preparation—One method consists of heating the corresponding polyethylene glycol with an equimolar portion of stearic acid.

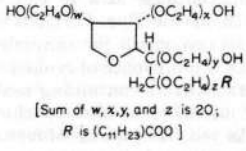
Description—White to light-tan waxy solid; odorless or has a faint fat-like odor; congeals between 37 and 47°.

Solubility—Soluble in water, alcohol, ether, or acetone; insoluble in mineral or vegetable oils.

Uses—Contains ester and alcohol functions that impart both lyophilic and hydrophilic characteristics to make it useful as a surfactant and emulsifier. It is an ingredient of some water-soluble ointment and cream bases.

POLYSORBATES

Sorbitan esters, poly(oxy-1,2-ethanediyl) derivs; Tweens



[Sum of w, x, y, and z is 20; *R* is $(C_{11}H_{23})COO$]

Sorbitan esters, polyoxyethylene derivatives; fatty acid esters of sorbitol and its anhydrides copolymerized with a varying number of moles of ethylene oxide. The NF recognizes *Polysorbate 20 (structure given above),* a laurate ester; *Polysorbate 40,* a palmitate ester; *Polysorbate 60,* a mixture of stearate and palmitate esters; and *Polysorbate 80,* an oleate ester.

Preparation—These important nonionic surfactants (page 286) are prepared starting with sorbitol by (1) elimination of water-forming sorbitan (a cyclic sorbitol anhydride); (2) partial esterification of the sorbitan with a fatty acid such as oleic or stearic acid, yielding a hexitan ester known commercially as a *Span;* and (3) chemical addition of ethylene oxide, yielding a *Tween* (the polyoxyethylene derivative).

Description—*Polysorbate 80:* Lemon- to amber-colored, oily liquid; faint, characteristic odor; warm, somewhat bitter taste; specific gravity 1.07 to 1.09; pH (1:20 aqueous solution) 6 to 8.

Solubility—*Polysorbate 80:* Very soluble in water, producing an odorless and nearly colorless solution; soluble in alcohol, cottonseed

oil,corn oil, ethyl acetate, methanol, or toluene; insoluble in mineral oil.

Uses—Because of their hydrophilic and lyophilic characteristics, these nonionic surfactants are very useful as emulsifying agents, forming O/W emulsions in pharmaceuticals, cosmetics, and other types of products. Polysorbate 80 is an ingredient in *Coal Tar Ointment* and *Solution*. See *Glycol Ethers* (page 1037).

PHARMACEUTICAL SOLVENTS

The remarkable growth of the solvent industry is attested by the more than 300 solvents now being produced on an industrial scale. Chemically, these include a great variety of organic compounds, ranging from hydrocarbons through alcohols, esters, ethers, and acids to nitroparaffins. Their main applications are in industry and the synthesis of organic chemicals. Comparatively few, however, are used as solvents in pharmacy, because of their toxicity, volatility, instability, and/or flammability. Those commonly used as pharmaceutical solvents are described in this section.

ACETONE

2-Propanone; Dimethyl Ketone

CH_3COCH_3

Acetone [67-64-1] C_3H_6O (58.08).

Caution—It is very flammable. Do not use where it may be ignited.

Preparation—Formerly obtained exclusively from the destructive distillation of wood. The distillate, consisting principally of methanol, acetic acid, and acetone was neutralized with lime, and the acetone was separated from the methyl alcohol by fractional distillation. Additional quantities were obtained by pyrolysis of the calcium acetate formed in the neutralization of the distillate.

It now is obtained largely as a by-product of the butyl alcohol industry. This alcohol is formed in the fermentation of carbohydrates such as corn starch, molasses, etc, by the action of the bacterium *Clostridium acetobutylicum* (Weizmann fermentation), and it is always one of the products formed in the process. It also is obtained by the catalytic oxidation of isopropyl alcohol, which is prepared from propylene resulting from the *cracking* of crude petroleum.

Description—Transparent, colorless, mobile, volatile, flammable liquid with a characteristic odor; specific gravity not more than 0.789; distills between 55.5 and 57; congeals about −95°; aqueous solution neutral to litmus.

Solubility—Miscible with water, alcohol, ether, chloroform, or most volatile oils.

Uses—An *antiseptic* in concentrations above 80%. In combination with alcohol it is used as an antiseptic *cleansing* solution. It is employed as a menstruum in the preparation of oleoresins in place of ether. It is used as a *solvent* for dissolving fatty bodies, resins, pyroxylin, mercurials, etc, and also in the manufacture of many organic compounds such as chloroform, chlorobutanol, and ascorbic acid.

ALCOHOL

Ethanol; Spiritus Vini Rectificatus; S. V. R.; Spirit of Wine; Methylcarbinol

Ethyl alcohol [64-17-5]; contains 92.3 to 93.8%, by weight (94.9 to 96.0%, by volume), at 15.56° (60°F) of C_2H_5OH (46.07).

Preparation—Has been made for centuries by fermentation of certain carbohydrates in the presence of *zymase,* an enzyme present in yeast cells. Usable carbohydrate-containing materials include molasses, sugar cane, fruit juices, corn, barley, wheat, potato, wood, and waste sulfite liquors. As yeast is capable of fermenting only D-glucose, D-fructose, D-mannose, and D-galactose, it is essential that more complex carbohydrates, such as starch, be converted to one or more of these simple sugars before they can be fermented. This is accomplished variously, commonly by enzyme- or acid-catalyzed hydrolysis.

The net reaction that occurs when a hexose, glucose for example, is fermented to alcohol may be represented as

$$C_6H_{12}O_6 \rightarrow 2\ C_2H_5OH + 2\ CO_2$$

but the mechanism of the process is very complex. The fermented liquid, containing about 15% alcohol, is distilled to obtain a distillate containing 94.9% C_2H_5OH, by volume. To produce *absolute alcohol,* the 95% product is dehydrated by various processes.

It may be produced also by hydration of ethylene, abundant supplies of which are available from natural and coke oven gases, from waste gases of the petroleum industry, and other sources. In another synthesis acetylene is hydrated catalytically to acetaldehyde, which then is hydrogenated catalytically to ethyl alcohol.

Description—Transparent, colorless, mobile, volatile liquid; slight but characteristic odor; burning taste; boils at 78° but volatilizes even at a low temperature, and is flammable; when pure, it is neutral toward all indicators; specific gravity at 15.56 (the US Government standard temperature for Alcohol) not above 0.816, indicating not less than 92.3% of C_2H_5OH by weight, or 94.9% by volume.

Solubility—Miscible with water, acetone, chloroform, ether, or many other organic solvents.

Incompatibilities—This and preparations containing a high percentage of alcohol will precipitate many inorganic salts from an aqueous solution. *Acacia* generally is precipitated from a hydroalcoholic medium when the alcohol content is greater than about 35%.

Strong *oxidizing agents* such as *chlorine, nitric acid, permanganate,* or *chromate* in acid solution react, in some cases violently, with it to produce oxidation products.

Alkalies cause a darkening in color because of the small amount of aldehyde usually present in it.

Uses—In pharmacy principally for its solvent powers (page 218). It also is used as the starting point in the manufacture of many important compounds, like ether, chloroform, etc. It also is used as a fuel, chiefly in the denatured form.

It is a CNS depressant. Consequently, it occasionally has been administered intravenously for preoperative and postoperative sedation in patients in whom other measures are ineffective or contraindicated. The dose employed is 1 to 1.5 mL/kg. Its intravenous use is a specialized procedure and should be employed only by one experienced in the technique of such use.

It is used widely and abused by lay persons as a sedative. It has, however, no medically approved use for this purpose. Moreover, alcohol potentiates the CNS effects of numerous sedative and depressant drugs. Hence, it should not be used by patients taking certain prescription drugs or OTC medications (see page 1746).

Externally, it has a number of medical uses. It is a solvent for the toxicodendrol causing *ivy poisoning* and should be used to wash the skin thoroughly soon after contact. In a concentration of 25% it is employed for bathing the skin for the purpose of *cooling* and *reducing fevers*. In high concentrations it is a *rubefacient* and an ingredient of many liniments. In a concentration of 50% it is used to prevent sweating in *astringent* and *anhidrotic* lotions. It also is employed to cleanse and harden the skin and is helpful in preventing bedsores in bedridden patients. In a concentration of 60 to 90% it is germicidal. At optimum concentration (70% by weight) it is a good *antiseptic* for the skin *(local anti-infective)* and also for instruments. It also is used as a *solvent* to cleanse the skin splashed with phenol. High concentrations of it often are injected into nerves and ganglia for the *relief of pain,* accomplishing this by causing nerve degeneration.

DENATURED ALCOHOL

An act of Congress, June 7, 1906, authorizes the withdrawal of alcohol from bond without the payment of internal revenue tax, for the purpose of denaturation and use in the arts and industries. This is ethyl alcohol to which has been added such denaturing materials as to render the alcohol unfit for use as an intoxicating beverage. It is divided into two classes, namely, *completely denatured alcohol* and *specially denatured alcohol,* prepared in accordance with approved formulas prescribed in Federal Industrial Alcohol Regulations 3.

Information regarding the use of alcohol and permit requirements may be obtained from the Regional Director, Bureau of Alcohol, Tobacco and Firearms, in any of the following offices: Cincinnati, OH; Philadelphia, PA; Chicago, IL; New York, NY; Atlanta, GA; Dallas, TX; and San Francisco, CA. Federal regulation provides that completely and specially denatured alcohols may be purchased by properly qualified persons from duly established denaturing plants or bonded dealers. No permit is required for the purchase and use of completely denatured alcohol unless the purchaser intends to recover the alcohol.

Completely Denatured Alcohol—This term applies to ethyl alcohol to which has been added materials (methyl isobutyl ketone, pyronate, gasoline, acetaldol, kerosene, etc) of such nature that the products may be sold and used within certain limitations without permit and bond.

Specially Denatured Alcohol—This alcohol is intended for use in a greater number of specified arts and industries than completely

denatured alcohol, and the character of the denaturant or denaturants used is such that specially denatured alcohol may be sold, possessed, and used only by those persons or firms that hold basic permits and are covered by bond.

Formulas for products using specially denatured alcohol must be approved, prior to use, by the Regional Director, Bureau of Alcohol, Tobacco and Firearms in any of the regional offices listed above.

Uses—Approximately 50 specially denatured alcohol formulas containing combinations of more than 90 different denaturants are available to fill the needs of qualified users. Large amounts of specially denatured alcohols are used as raw materials in the production of acetaldehyde, synthetic rubber, vinegar, and ethyl chloride as well as in the manufacture of proprietary solvents and cleaning solutions. Ether and chloroform can be made from suitably denatured alcohols, and formulas for the manufacture of Iodine Tincture, Green Soap Tincture, and Rubbing Alcohol are set forth in the regulations.

Specially denatured alcohols also are used as solvents for surface coatings, plastics, inks, toilet preparations, and external pharmaceuticals. Large quantities are used in the processing of such food and drug products as pectin, vitamins, hormones, antibiotics, alkaloids, and blood products. Other uses include supplemental motor fuel, rocket and jet fuel, antifreeze solutions, refrigerants, and cutting oils. Few products are manufactured today that do not require the use of alcohol at some stage of production. Specially denatured alcohol may not be used in the manufacture of foods or internal medicines when any of the alcohol remains in the finished product.

DILUTED ALCOHOL

Diluted Ethanol

A mixture of alcohol and water containing 41.0 to 42.0%, by weight (48.4 to 49.5%, by volume), at 15.56°, of C_2H_5OH (46.07).

Preparation—

Alcohol	500 mL
Purified Water	500 mL

Measure the alcohol and the purified water separately at the same temperature, and mix. If the water and the alcohol and the resulting mixture are measured at 25°, the volume of the mixture will be about 970 mL.

When equal volumes of alcohol and water are mixed together, a rise in temperature and a contraction of about 3% in volume take place. In small operations the contraction generally is disregarded; in larger operations it is very important. If 50 gal of official alcohol are mixed with 50 gal of water, the product will not be 100 gal of diluted alcohol, but only 96 1/4 gal, a contraction of 3 3/4 gal. US *Proof Spirit* differs from this and is stronger; it contains 50%, by volume, of absolute alcohol at 15.56° (60°F). This corresponds to 42.5% by weight and has a specific gravity of 0.9341 at the same temperature. If spirits have a specific gravity lower than that of *proof spirit* (0.9341), they are said to be *above proof;* if greater, *below proof.*

It also may be prepared from the following:

Alcohol	408 g
Purified Water	500 g

Rules for Dilution—The following rules are applied when making an alcohol of any required lower percentage from an alcohol of any given higher percentage:

I. By Volume—Designate the volume percentage of the stronger alcohol by *V* and that of the weaker alcohol by *v*.

Rule—Mix *v* volumes of the stronger alcohol with purified water to make *V* volumes of product. Allow the mixture to stand until full contraction has taken place and until it has cooled, then make up the deficiency in the *V* volumes by adding more purified water.

Example—An alcohol of 30% by volume is to be made from an alcohol of 94.9% by volume.—Take 30 volumes of the 94.9% alcohol, and add enough purified water to produce 94.9 volumes at room temperature.

II. By Weight—Designate the weight-percentage of the stronger alcohol by *W* and that of the weaker alcohol by *w*.

Rule—Mix *w* parts by weight of the stronger alcohol with purified water to make *W* parts by weight of product.

Example—An alcohol of 50% by weight is to be made from an alcohol of 92.3% by weight.—Take 50 parts by weight of the 92.3% alcohol, and add enough purified water to produce 92.3 parts by weight.

Description—As for *Alcohol,* except its specific gravity is 0.935 to 0.937 at 15.56°, indicating that the strength of C_2H_5OH corresponds to that given in the official definition.

Uses—A menstruum in making tinctures, fluidextracts, extracts, etc. Its properties already have been described fully in connection with the various preparations. Its value consists not only in its *antiseptic* properties, but also in its possessing the solvent powers of both water and alcohol. See *Alcohol*.

NONBEVERAGE ALCOHOL

This is tax-paid alcohol or distilled spirits used in the manufacture, by approved formula, of such medicines, medicinal preparations, food products, flavors, or flavoring extracts as are unfit for beverage purposes. Internal Revenue Service Regulations provide that qualified holders of Special Tax Stamps who use tax paid alcohol or distilled spirits in the types of products listed above, may file a claim for *alcohol tax drawback* or refund of a considerable part of the tax paid.

CHLOROFORM—page 1042.

GLYCERIN

1,2,3-Propanetriol; Glycerol

Glycerol [56-81-5] $C_3H_8O_3$ (92.09).

Chemically, it is the simplest trihydric alcohol. It is worthy of special note because the two terminal alcohol groups are primary, whereas the middle one is secondary. Thus this becomes the first polyhydric alcohol that can yield both an aldose (glyceraldehyde) and a ketose (dihydroxyacetone).

Preparation—

1. By saponification of fats and oils in the manufacture of soap.
2. By hydrolysis of fats and oils through pressure and superheated steam.
3. By fermentation of beet sugar molasses in the presence of large amounts of sodium sulfite. Under these conditions a reaction takes place expressed as

$$\underset{\text{Glucose}}{C_6H_{12}O_6} \rightarrow \underset{\text{Glycerin}}{C_3H_5(OH)_3} + \underset{\text{Acetaldehyde}}{CH_3CHO} + CO_2$$

4. Glycerin is now prepared in large quantities from propylene, a petroleum product. This hydrocarbon is chlorinated at about 400° to form allyl chloride, which is converted to allyl alcohol. Treatment of the unsaturated alcohol with hypochlorous acid (HOCl) yields the chlorohydrin derivative. Extraction of HCl with soda lime yields 2,3-epoxypropanol, which undergoes hydration to glycerin.

Description—Clear, colorless, syrupy liquid with a sweet taste and not more than a slight, characteristic odor, which is neither harsh nor disagreeable; when exposed to moist air it absorbs water and also such gases as H_2S and SO_2; solutions are neutral; specific gravity not below 1.249 (not less than 95% $C_3H_5(OH)_3$); boils at about 290° under 1 atm, with decomposition, but can be distilled intact in a vacuum.

Solubility—Miscible with water, alcohol, or methanol; 1 g in about 12 mL ethyl acetate or about 15 mL acetone; insoluble in chloroform, ether, or fixed and volatile oils.

Incompatibilities—An explosion may occur if it is triturated with strong *oxidizing agents* such as *chromium trioxide, potassium chlorate,* or *potassium permanganate*. In dilute solutions the reactions proceed at a slower rate, forming several oxidation products. Iron is an occasional contaminant of it and may be the cause of a darkening in color in mixtures containing *phenols, salicylates, tannin,* etc.

With *boric acid* or *sodium borate,* it forms a complex, generally spoken of as glyceroboric acid, which is a much stronger acid than boric acid.

Uses—One of the most valuable products known to pharmacy by virtue of its *solvent* property. It is useful as a *humectant* in keeping substances moist, owing to its hygroscopicity. Its agreeable taste and high viscosity adapt it for many purposes. Some modern ice collars and ice bags contain it and water hermetically sealed within vulcanized rubber bags. The latter are sterilized by dipping in a germicidal solution and are stored in the refrigerator until needed. It also has some therapeutic uses. In pure anhydrous form, it is used in the eye to reduce corneal edema and to facilitate ophthalmoscopic examination. It is used orally as an evacuant and, in 50 to 75% solution, as a systemic osmotic agent.

ISOPROPYL ALCOHOL—page 1510.

METHYL ALCOHOL

Methanol; Wood Alcohol

CH_3OH

Methanol [67-56-1] CH_4O (32.04).

Caution—It is poisonous.

Preparation—By the catalytic reduction of carbon monoxide or carbon dioxide with hydrogen. A zinc oxide–chromium oxide catalyst is used commonly.

Description—Clear, colorless liquid; characteristic odor; flammable; specific gravity not more than 0.790; distills within a range of 1 between 63.5 and 65.7°.

Solubility—Miscible with water, alcohol, ether, benzene, or most other organic solvents.

Uses— *pharmaceutic aid* (solvent). It is toxic. Ingestion may result in blindness; vapors also may cause toxic reactions.

METHYL ISOBUTYL KETONE

2-Pentanone, 4-methyl-,

$(CH_3)_2CHCH_2COCH_3$ [108-10-1]; contains not less than 99% of $C_6H_{12}O$ (100.16).

Description—Transparent, colorless, mobile, volatile liquid; faint, ketonic and camphoraceous odor, distills between 114 and 117°.

Solubility—Slightly soluble in water; miscible with alcohol, ether, or benzene.

Uses—A *denaturant* for rubbing alcohol and also a *solvent* for gums, resins, nitrocellulose, etc. It may be irritating to the eyes and mucous membranes, and, in high concentrations, narcotic.

MONOETHANOLAMINE

Ethanol, 2-amino-, Ethanolamine; Ethylolamine

$HOCH_2CH_2NH_2$ [141-43-5] C_2H_7NO (61.08).

Preparation—This alkanolamine is prepared conveniently by treating ethylene oxide with ammonia.

Description—Clear, colorless, moderately viscous liquid; distinctly ammoniacal odor; affected by light; specific gravity 1.013 to 1.016; distills between 167 and 173°.

Solubility—Miscible in all proportions with water, acetone, alcohol, glycerin, or chloroform; immiscible with ether, solvent hexane, or fixed oils; dissolves many essential oils.

Uses—A *solvent* for fats, oils, and many other substances, it is a pharmaceutical necessity for *Thimerosal Solution* (see RPS-17 page 1173). It combines with fatty acids to form soaps that find application in various types of emulsions such as lotions, creams, etc.

PROPYLENE GLYCOL

$CH_3CH(OH)CH_2OH$

1,2-Propanediol [57-55-6 $C_3H_8O_2$] (76.10).

Preparation—Propylene is converted successively to its chlorohydrin (with HOCl), epoxide (with Na_2CO_3), and glycol (with water in presence of protons).

Description—Clear, colorless, viscous, and practically odorless liquid; slightly acrid taste; specific gravity 1.035 to 1.037; completely distills between 184 and 189°; absorbs moisture from moist air.

Solubility—Miscible with water, alcohol, acetone, or chloroform; soluble in ether; dissolves many volatile oils; immiscible with fixed oils.

Uses—A *solvent, preservative,* and *humectant*. See *Hydrophilic Ointment* (page 1036).

TROLAMINE

Ethanol, 2,2′,2″-nitrilotris-, Triethanolamine

2,2′,2″-Nitrilotriethanol [102-71-6] $N(C_2H_4OH)_3$ (149.19); a mixture of alkanolamines consisting largely of triethanolamine, containing some diethanolamine [$NH(C_2H_4OH)_2$ = 105.14] and monoethanolamine [$NH_2C_2H_4OH$ = 61.08].

Preparation—Along with some mono- and diethanolamine, by the action of ammonia on ethylene oxide.

Description—Colorless to pale yellow, viscous, hygroscopic liquid; slight odor of ammonia; aqueous solution is very alkaline; melts about 21°; specific gravity 1.120 to 1.128; a strong base and readily combines even with weak acids to form salts.

Solubility—Miscible with water or alcohol; soluble in chloroform; slightly soluble in ether or benzene.

Uses—In combination with a fatty acid, eg, oleic acid (see *Benzyl Benzoate Lotion,* 748), as an *emulsifier*. See *Monoethanolamine*.

WATER—page 1027.

OTHER PHARMACEUTICAL SOLVENTS

Alcohol, Dehydrated, BP, PhI [Dehydrated Ethanol; Absolute Alcohol]—Transparent, colorless, mobile, volatile liquid; characteristic odor; burning taste; specific gravity not more than 0.798 at 15.56°; hygroscopic, flammable and boils about 78°. Miscible with water, ether, or chloroform. *Uses:* A pharmaceutical solvent; also used by injection for relief of pain (see *Alcohol,* pages 1038 and 1507).

MISCELLANEOUS PHARMACEUTICAL NECESSITIES

The agents listed in this section comprise a heterogeneous group of substances with both pharmaceutical and industrial applications. Pharmaceutically, some of these agents are used as diluents, enteric coatings, excipients, and filtering agents and as ingredients in products considered in other chapters. Industrially, some of these agents are used in various chemical processes, in the synthesis of other chemicals, and in the manufacture of fertilizers, explosives, etc.

ACETIC ACID

Acetic acid; a solution containing 36 to 37%, by weight, of $C_2H_4O_2$ (60.05).

Preparation—By diluting with distilled water an acid of higher concentration, such as the 80% product, or more commonly glacial acetic acid, using 350 mL of the latter for the preparation of each 1000 mL of acetic acid.

Description—Clear, colorless liquid, having a strong characteristic odor and a sharply acid taste; specific gravity about 1.045; congeals about −14°; acid to litmus.

Solubility—Miscible with water, alcohol, or glycerin.

Uses—In pharmacy as a *solvent* and *menstruum* and for making diluted acetic acid. It also is used as a starting point in the manufacture of many other organic compounds, eg, acetates, acetanilid, sulfonamides, etc. It is official primarily as a *pharmaceutic necessity* for the preparation of *Aluminum Subacetate Solution*.

DILUTED ACETIC ACID

Dilute Acetic Acid

A solution containing, in each 100 mL, 5.7 to 6.3 g of $C_2H_4O_2$.

Preparation—

Acetic Acid	158 mL
Purified Water, a sufficient quantity to make	1000 mL

Mix the ingredients.

Note—This acid also may be prepared by diluting 58 mL of glacial acetic acid with sufficient purified water to make 1000 mL.

Description—Essentially the same properties, solubility, purity, and identification reactions as *Acetic Acid,* but its specific gravity is about 1.008, and it congeals about −2°.

Uses—*Bactericidal* to many types of microorganisms and occasionally is used in 1% solution for surgical dressings of the skin. A 1% solution is *spermatocidal*. It also is used in vaginal douches for the management of *Trichomonas, Candida,* and *Haemophilus* infections.

GLACIAL ACETIC ACID

Concentrated Acetic Acid; Crystallizable Acetic Acid; Ethanolic Acid; Vinegar Acid

CH_3COOH

Glacial acetic acid [64-19-7] $C_2H_4O_2$ (60.05).

Preparation—This acid is termed *glacial* because of its solid, glassy appearance when congealed. In one process it is produced by distillation of weaker acids to which has been added a water-entraining substance such as ethylene dichloride. In this method, referred to as *azeotropic distillation,* the ethylene dichloride distills out with the water before the acid distills over, thereby effecting concentration of the latter.

In another process the aqueous acid is mixed with triethanolamine and heated. The acid combines with the triethanolamine to form a triethanolamine acetate. The water is driven off first; then, at a higher temperature, the triethanolamine compound decomposes to yield this acid.

A greater part of the acid now available is made synthetically from acetylene. When acetylene is passed into this acid containing a metallic catalyst such as mercuric oxide, ethylidene diacetate is produced, which yields, upon heating, acetic anhydride and acetaldehyde. Hydration of the former and air oxidation of the latter yield this acid.

Description—Clear, colorless liquid; pungent, characteristic odor; when well diluted with water, it has an acid taste; boils about 118°;

congeals at a temperature not lower than 15.6°, corresponding to a minimum of 99.4% of CH_3COOH; specific gravity about 1.05.

Solubility—Miscible with water, alcohol, acetone, ether, or glycerin; insoluble in carbon tetrachloride or chloroform.

Uses—A *caustic* and *vesicant* when applied externally and is often sold under various disguises as a *corn solvent*. It is an excellent solvent for fixed and volatile oils and many other organic compounds. It is used primarily as an *acidifying agent*.

ALUMINUM

Aluminum Al (26.98); the free metal in the form of finely divided powder. It may contain oleic acid or stearic acid as a lubricant. It contains not less than 95% Al and not more than 5% *Acid-insoluble substances,* including any added fatty acid.

Description—Very fine, free-flowing, silvery powder free from gritty or discolored particles.

Solubility—Insoluble in water or alcohol; soluble in hydrochloric and sulfuric acids or in solutions of fixed alkali hydroxides.

Uses—A *protective*. An ingredient in *Aluminum Paste*.

ALUMINUM MONOSTEARATE

Aluminum, dihydroxy(octadecanoato-*O*-)-,

Dihydroxy(stearato)aluminum [7047-84-9]; a compound of aluminum with a mixture of solid organic acids obtained from fats, and consists chiefly of variable proportions of aluminum monostearate and aluminum monopalmitate. It contains the equivalent of 14.5 to 16.5% of Al_2O_3 (101.96).

Preparation—By interaction of a hydroalcoholic solution of potassium stearate with an aqueous solution of potassium alum, the precipitate being purified to remove free stearic acid and some aluminum distearate simultaneously produced.

Description—Fine, white to yellowish white, bulky powder; faint, characteristic odor.

Solubility—Insoluble in water, alcohol, or ether.

Uses—A *pharmaceutical necessity* used in the preparation of *Sterile Procaine Penicillin G with Aluminum Stearate Suspension*.

STRONG AMMONIA SOLUTION

Stronger Ammonia Water; Stronger Ammonium Hydroxide Solution; Spirit of Hartshorn

Ammonia [1336-21-6]; a solution of NH_3 (17.03), containing 27.0 to 31.0% (w/w) of NH_3. Upon exposure to air it loses ammonia rapidly.

Caution—Use care in handling it because of the caustic nature of the Solution and the irritating properties of its vapor. Cool the container well before opening, and cover the closure with a cloth or similar material while opening. Do not taste it, and avoid inhalation of its vapor.

Preparation—Ammonia is obtained commercially chiefly by synthesis from its constituent elements, nitrogen and hydrogen, combined under high pressure and at high temperature in the presence of a catalyst.

Description—Colorless, transparent liquid; exceedingly pungent, characteristic odor; even when well diluted it is strongly alkaline to litmus; specific gravity about 0.90.

Solubility—Miscible with alcohol.

Uses—Only for chemical and pharmaceutical purposes. It is used primarily in making ammonia water by dilution and as a chemical reagent. It is too strong for internal administration. It is an ingredient in *Aromatic Ammonia Spirit*.

BISMUTH SUBNITRATE

Basic Bismuth Nitrate; Bismuth Oxynitrate; Spanish White; Bismuth Paint; Bismuthyl Nitrate

Bismuth hydroxide nitrate oxide [1304-85-4] $Bi_5O(OH)_9(NO_3)_4$ (1461.99); a basic salt that, dried at 105° for 2 hr, yields upon ignition not less than 79% of Bi_2O_3 (465.96).

Preparation—A solution of bismuth nitrate is added to boiling water to produce the subnitrate by hydrolysis.

Description—White, slightly hygroscopic powder; suspension in distilled water is faintly acid to litmus (pH about 5).

Solubility—Practically insoluble in water or organic solvents; dissolves readily in an excess of hydrochloric or nitric acid.

Incompatibilities—Slowly hydrolyzed in *water* with liberation of nitric acid; thus, it possesses the incompatibilities of the acid. *Reducing agents* darken it with the production of metallic bismuth.

Uses—A *pharmaceutical necessity* in the preparation of milk of bismuth. It also is used as an *astringent, adsorbent,* and *protective;* however, its value as a protective is questionable. This agent, like other insoluble bismuth salts, is used topically in lotions and ointments.

BORIC ACID

Boric Acid (H_3BO_3); Boracic Acid; Orthoboric Acid

Boric acid [10043-35-3] H_3BO_3 (61.83).

Preparation—Lagoons of the volcanic districts of Tuscany formerly furnished the greater part of this acid and borax of commerce. Borax is now found native in California and some of the other western states; calcium and magnesium borates are found there also. It is produced from native borax or from the other borates by reacting with hydrochloric or sulfuric acid.

Description—Colorless scales of a somewhat pearly luster, or crystals, but more commonly a white powder slightly unctuous to the touch; odorless and stable in the air; volatilizes with steam.

Solubility—1 g in 18 mL water, 18 mL alcohol, 4 mL glycerin, 4 mL boiling water, or 6 mL boiling alcohol.

Uses—A buffer, and it is this use that is recognized officially. It is a very weak *germicide (local anti-infective)*. Its nonirritating properties make its solutions suitable for application to such delicate structures as the cornea of the eye. Aqueous solutions are employed as an eye wash, mouth wash, and for irrigation of the bladder. A 2.2% solution is isotonic with lacrimal fluid. Solutions, even if they are made isotonic, will hemolyze red blood cells. It also is employed as a dusting powder, when diluted with some inert material. It can be absorbed through irritated skin, eg, infants with diaper rash.

Although it is not absorbed significantly from intact skin, it is absorbed from damaged skin and fatal poisoning, particularly in infants, has occurred with topical application to burns, denuded areas, granulation tissue, and serous cavities. *Serious poisoning can result from oral ingestion* of as little as 5 g. Symptoms of poisoning are nausea, vomiting, abdominal pain, diarrhea, headache, and visual disturbance. Toxic alopecia has been reported from the chronic ingestion of a mouth wash containing it. The kidney may be injured, and death may result. Its use as a preservative in beverages and foods is prohibited by national and state legislation. *There is always present the danger of confusing it with dextrose when compounding milk formulas for infants. Fatal accidents have occurred*. For this reason boric acid in bulk is colored, so that it cannot be confused with dextrose.

It is used to prevent discoloration of physostigmine solutions.

CALCIUM HYDROXIDE

Slaked Lime; Calcium Hydrate

Calcium hydroxide [1305-62-0] $Ca(OH)_2$ (74.09).

Preparation—By reacting freshly prepared calcium oxide with water.

Description—White powder; alkaline, slightly bitter taste; absorbs carbon dioxide from the air, forming calcium carbonate; solutions exhibit a strong alkaline reaction.

Solubility—1 g in 630 mL water or 1300 mL boiling water; soluble in glycerin or syrup; insoluble in alcohol; the solubility in water is decreased by the presence of fixed alkali hydroxides.

Uses—In the preparation of *Calcium Hydroxide Solution*.

CALCIUM HYDROXIDE TOPICAL SOLUTION

Calcium Hydroxide Solution; Lime Water

A solution containing, in each 100 mL, not less than 140 mg of $Ca(OH)_2$ (74.09).

Note—The solubility of calcium hydroxide varies with the temperature at which the solution is stored, being about 170 mg/100 mL at 15° and less at a higher temperature. The official concentration is based upon a temperature of 25°.

Preparation—

Calcium Hydroxide	3 g
Purified Water	1000 mL

Add the calcium hydroxide to 1000 mL of cool, purified water, and agitate the mixture vigorously and repeatedly during 1 hr. Allow the excess calcium hydroxide to settle. Dispense only the clear, supernatant liquid.

The undissolved portion of the mixture is not suitable for preparing additional quantities of the solution.

The object of keeping lime water over undissolved calcium hydroxide is to ensure a saturated solution.

Description—Clear, colorless liquid; alkaline taste; strong alkaline reaction; absorbs carbon dioxide from the air, a film of calcium carbonate forming on the surface of the liquid; when heated, it becomes turbid, owing to the separation of calcium hydroxide, which is less soluble in hot than in cold water.

Uses—Too dilute to be effective as a gastric antacid. It is employed *topically* as a *protective* in various types of lotions. In some lotion formulations it is used with olive oil or oleic acid to form calcium oleate,

which functions as an emulsifying agent. The USP classes it as an *astringent*.

CALCIUM PANTOTHENATE, RACEMIC—page 1814.

CALCIUM STEARATE

Octadecanoic acid, calcium salt

Calcium stearate [1592-23-0]; a compound of calcium with a mixture of solid organic acids obtained from fats, and consists chiefly of variable proportions of stearic and palmitic acids [calcium stearate, $C_{36}H_{70}CaO_4$ = 607.03; calcium palmitate, $C_{32}H_{62}CaO_4$ = 550.92]; contains the equivalent of 9 to 10.5% of CaO (calcium oxide).

Preparation—By precipitation from interaction of solutions of calcium chloride and the sodium salts of the mixed fatty acids (stearic and palmitic).

Description—Fine, white to yellowish white, bulky powder; slight, characteristic odor; unctuous and free from grittiness.

Solubility—Insoluble in water, alcohol, or ether.

Uses—A *lubricant* in the manufacture of compressed tablets. It also is used as a conditioning agent in food and pharmaceutical products. Its virtually nontoxic nature and unctuous properties makes it ideal for these purposes.

CALCIUM SULFATE

Sulfuric acid, calcium salt (1:1); Gypsum; Terra Alba

Calcium sulfate (1:1) [7778-18-9] $CaSO_4$ (136.14); *dihydrate* [10101-41-4] (172.17).

Preparation—From natural sources or by precipitation from interaction of solutions of calcium chloride and a soluble sulfate.

Description—Fine, white to slightly yellow-white, odorless powder.

Solubility—Dissolves in diluted HCl; slightly soluble in water.

Uses—A *diluent* in the manufacture of compressed tablets. It is sufficiently inert that few undesirable reactions occur in tablets made with this substance. It also is used for making plaster casts and supports.

CARBON TETRACHLORIDE

Methane, tetrachloro-, Tetrachloromethane

Carbon tetrachloride [56-23-5] CCl_4 (153.82).

Preparation—One method consists of catalytic chlorination of carbon disulfide.

Description—Clear, colorless liquid; characteristic odor resembling that of chloroform; specific gravity 1.588 to 1.590; boils about 77°.

Solubility—Soluble in about 2000 volumes water; miscible with alcohol, acetone, ether, chloroform, or benzene.

Uses—Officially recognized as a *pharmaceutical necessity* (solvent). Formerly it was used as a cheap *anthelmintic* for the treatment of *hookworm* infections, but it causes severe injury to the liver if absorbed.

CARNAUBA WAX

Obtained from the leaves of *Copernicia cerifera* Mart (Fam *Palmae*).

Preparation—Consists chiefly of myricyl cerotate with smaller quantities of myricyl alcohol, ceryl alcohol, and cerotic acid. It is obtained by treating the leaf buds and leaves of *Copernicia cerifera,* the so-called Brazilian Wax Palm, with hot water.

Description—Light-brown to pale-yellow, moderately coarse powder; characteristic bland odor; free from rancidity; specific gravity about 0.99; melts about 84°.

Solubility—Insoluble in water; freely soluble in warm benzene; soluble in warm chloroform or toluene; slightly soluble in boiling alcohol.

Uses—A pharmaceutic aid used as a *polishing agent* in the manufacture of coated tablets.

CELLULOSE ACETATE PHTHALATE

Cellulose, acetate, 1,2-benzenedicarboxylate

Cellulose acetate phthalate [9004-38-0]; a reaction product of the phthalic anhydride and a partial acetate ester of cellulose. When dried at 105° for 2 hr, it contains 19 to 23.5% of acetyl (C_2H_3O) groups and 30 to 36.0% of phthalyl (*o*-carboxybenzoyl, $C_8H_5O_3$) groups.

Preparation—Cellulose is esterified by treatment with acetic and phthalic acid anhydrides.

Description—Free-flowing, white powder; may have a slight odor of acetic acid.

Solubility—Insoluble in water or alcohol; soluble in acetone or dioxane.

Uses—An *enteric tablet-coating material*. Coatings of this substance disintegrate because of the hydrolytic effect of the intestinal esterases, even when the intestinal contents are acid. *In vitro* studies indicate that cellulose acetate phthalate will withstand the action of artificial gastric juices for long periods of time but will disintegrate readily in artificial intestinal juices.

MICROCRYSTALLINE CELLULOSE

Cellulose [9004-34-6]; purified, partially depolymerized cellulose prepared by treating alpha cellulose, obtained as a pulp from fibrous plant material, with mineral acids.

Preparation—Cellulose is subjected to the hydrolytic action of 2.5 *N* HCl at the boiling temperature of about 105 for 15 min, whereby amorphous cellulosic material is removed and aggregates of crystalline cellulose are formed. These are collected by filtration, washed with water and aqueous ammonia, and disintegrated into small fragments, often termed cellulose crystallites, by vigorous mechanical means such as a blender. US Pat 3,141,875.

Description—Fine, white, odorless, crystalline powder; consists of free-flowing, nonfibrous particles.

Solubility—Insoluble in water, dilute acids, or most organic solvents; slightly soluble in NaOH solution (1 in 20).

Uses—A tablet diluent and disintegrant. It can be compressed into self-binding tablets that disintegrate rapidly when placed in water.

Microcrystalline Cellulose and Sodium Carboxymethylcellulose—A colloid-forming, attrited mixture of microcrystalline cellulose and sodium carboxymethylcellulose. *Description and Solubility:* Tasteless, odorless, white to off-white, coarse to fine powder; pH (dispersion) 6 to 8; swells in water, producing, when dispersed, a white, opaque dispersion or gel. Insoluble in organic solvents or dilute acids. *Uses:* Pharmaceutic aid (suspending agent). *Grades Available* (amounts of sodium carboxymethylcellulose producing viscosities in the concentrations designated): 8.5%, 120 cps in 2.1% solution; 11%, 120 cps in 1.2% solution; 11%, 65 cps in 1.2% solution.

POWDERED CELLULOSE—page 1031.

CHLOROFORM

Methane, trichloro-,

Trichloromethane [67-66-3] $CHCl_3$ (119.38); contains 99 to 99.5% $CHCl_3$, the remainder consisting of alcohol.

Caution—Care should be taken not to vaporize it in the presence of a flame, because of the production of harmful gases (hydrogen chloride and phosgene).

Preparation—Made by the reduction of carbon tetrachloride with water and iron and by the controlled chlorination of methane.

The pure compound readily decomposes on keeping, particularly if exposed to moisture and sunlight, resulting in formation of phosgene (carbonyl chloride $COCl_2$) and other products. The presence of a small amount of alcohol greatly retards or prevents this decomposition; hence, the requirement that it contain 0.5 to 1% of alcohol. The alcohol combines with any phosgene, forming ethyl carbonate, which is nontoxic.

Description—Clear, colorless, mobile liquid; characteristic, ethereal odor; burning, sweet taste; not flammable, but its heated vapors burn with a green flame; affected by light and moisture; specific gravity 1.474 to 1.478, indicating 99 to 99.5% of $CHCl_3$; boils about 61°; not affected by acids but is decomposed by alkali hydroxide into alkali chloride and sodium formate.

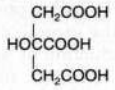
Solubility—Soluble in 210 volumes of water; miscible with alcohol, ether, benzene, solvent hexane, acetone, or fixed and volatile oils.

Uses—An obsolete *inhalation anesthetic*. Although it possesses advantages of nonflammability and great potency, it rarely is used because of the serious toxic effects it produces on the heart and liver. Internally, it has been used, in small doses, as a *carminative*. Externally, it is an *irritant* and when used in liniments it may produce blisters.

It is categorized as a pharmaceutic aid. It is used as a *preservative* during the aqueous percolation of vegetable drugs to prevent bacterial decomposition in the process of manufacture. In most instances it is evaporated before the product is finished. It is an excellent solvent for alkaloids and many other organic chemicals and is used in the manufacture of these products and in chemical analyses.

CITRIC ACID

1,2,3-Propanetricarboxylic acid, 2-hydroxy-,



Citric acid [77-92-9] $C_6H_8O_7$ (192.12); *monohydrate* [5949-29-1] (210.14).

Preparation—Found in many plants. It formerly was obtained solely from the juice of limes and lemons and from pineapple wastes. Since about 1925 the acid has been produced largely by fermentation of sucrose solution, including molasses, by fungi belonging to the *Aspergillus niger* group, theoretically according to the following reaction

$$\underset{\text{Sucrose}}{C_{12}H_{22}O_{11}} + \underset{\text{Oxygen}}{3O_2} \rightarrow \underset{\text{Citric Acid}}{2H_3C_6H_5O_7} + \underset{\text{Water}}{3H_2O}$$

but in practice there are deviations from this stoichiometric relationship.

Description—Colorless, translucent crystals, or a white, granular to fine crystalline powder; odorless; strongly acid taste; the hydrous form effloresces in moderately dry air but is slightly deliquescent in moist air; loses its water of crystallization at about 50°; dilute aqueous solutions are subject to molding (fermentation), oxalic acid being one of the fermentation products.

Solubility—1 g in 0.5 mL water, 2 mL alcohol, or about 30 mL ether; freely soluble in methanol.

Uses—In the preparation of *Anticoagulant Citrate Dextrose Solution, Anticoagulant Citrate Phosphate Dextrose Solution, Citric Acid Syrup,* and *effervescent salts*. It also has been used to dissolve urinary bladder calculi and as a mild astringent.

COCOA BUTTER

Cacao Butter; Theobroma Oil; Oil of Theobroma

The fat obtained from the roasted seed of *Theobroma cacao* Linné (Fam *Sterculiaceae*).

Preparation—By grinding the kernels of the *chocolate bean* and expressing the oil in powerful, horizontal hydraulic presses. The yield is about 40%. It also has been prepared by dissolving the oil from the unroasted beans by the use of a volatile solvent.

Constituents—Chemically, it is a mixture of stearin, palmitin, olein, laurin, linolein, and traces of other glycerides.

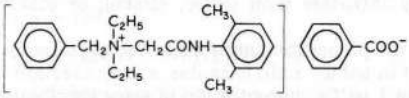
Description—Yellowish, white solid; faint, agreeable odor; bland (if obtained by extraction) or chocolate-like (if obtained by pressing) taste; usually brittle below 25°; specific gravity 0.858 to 0.864 at 100°/25°; refractive index 1.454 to 1.458 at 40°.

Solubility—Slightly soluble in alcohol; soluble in boiling dehydrated alcohol; freely soluble in ether or chloroform.

Uses—Valuable in pharmacy for making suppositories by virtue of its low fusing point and its property of becoming solid at a temperature just below the melting point. See *Suppositories* (page 851). In addition to this use, it is an excellent emollient application to the skin when inflamed; it also is used in various skin creams, especially the so-called *skin foods.* It also is used in massage.

DENATONIUM BENZOATE

Benzenemethanaminium *N*-2-(2,6-dimethylphenyl)amino-2-oxoethyl-*N,N*-diethyl-, benzoate;



Benzyldiethyl (2,6-xylylcarbamoyl)methylammonium benzoate [3734-33-6] $C_{28}H_{34}N_2O_3$ (446.59).

Preparation—2-(Diethylamino)-2′,6′-xylidide is quaternized by reaction with benzyl chloride. The quaternary chloride then is treated with methanolic potassium hydroxide to form the quaternary base that, after filtering off the KCl, is reacted with benzoic acid. The starting xylidide may be prepared by condensing 2,6-xylidine with chloroacetyl chloride and condensing the resulting chloroacetoxylidide with diethylamine. US Pat 3,080,327.

Description—White, odorless, crystalline powder; an intensely bitter taste; melts about 168°.

Solubility—1 g in 20 mL water, 2.4 mL alcohol, 2.9 mL chloroform, or 5000 mL ether.

Uses—A *denaturant* for ethyl alcohol.

DEXTRIN

British Gum; Starch Gum; Leiocom

Dextrin [9004-53-9] $(C_6H_{10}O_5)_n$.

Preparation—By the incomplete hydrolysis of starch with dilute acid or by heating dry starch.

Description—White or yellow, amorphous powder (*white:* practically odorless; *yellow:* characteristic odor); dextrorotatory; $[\alpha]_D^{20}$ generally above 200°; does not reduce Fehling's solution; gives a reddish color with iodine.

Solubility—Soluble in 3 parts of boiling water, forming a gummy solution; less soluble in cold water.

Uses—An *excipient* and *emulsifier*.

DEXTROSE

Anhydrous Dextrose; Dextrose Monohydrate; Glucose; D(+)-Glucose; α-D(+)-Glucopyranose; Medicinal Glucose; Purified Glucose; Grape Sugar; Bread Sugar; Cerelose; Starch Sugar; Corn Sugar

D-Glucose monohydrate [5996-10-1] $C_6H_{12}O_6 \cdot H_2O$ (198.17); *anhydrous* [50-99-7] (180.16). A sugar usually obtained by the hydrolysis of starch. For the structure, see page 411.

Preparation—See *Liquid Glucose* (page 1044).

Description—Colorless crystals or a white, crystalline or granular powder; odorless; sweet taste; specific rotation (anhydrous) +52.5 to +53; anhydrous dextrose melts at 146°; dextrose slowly reduces alkaline cupric tartrate TS in the cold and rapidly on heating, producing a red precipitate of cuprous oxide (difference from *sucrose*).

Solubility—1 g in 1 mL of water or 100 mL of alcohol; more soluble in boiling water or boiling alcohol.

Uses—See *Dextrose Injection* (page 1248). It also is used, instead of lactose as a supplement to milk for infant feeding.

DICHLORODIFLUOROMETHANE

Methane, dichlorodifluoro-, CCl_2F_2

Dichlorodifluoromethane [75-71-8] CCl_2F_2 (120.91).

Preparation—Carbon tetrachloride is reacted with antimony trifluoride in the presence of antimony pentafluoride.

Description—Clear, colorless gas; faint, ethereal odor; vapor pressure at 25° about 4883 torr.

Uses—A *propellant* (No 12, see page 968).

DICHLOROTETRAFLUOROETHANE

Ethane, 1,2-dichloro-1,1,2,2-tetrafluoro-, $CClF_2CClF_2$

1,2-Dichlorotetrafluoroethane [76-14-2] $C_2Cl_2F_4$ (170.92).

Preparation—By reacting 1,1,2-trichloro-1,2,2-trifluoroethane with antimony trifluorodichloride $[SbF_3Cl_2]$, whereupon one of the 1-chlorine atoms is replaced by fluorine. The starting trichlorofluoroethane may be prepared from hexachloroethane by treatment with SbF_3Cl_2 (Henne AL: *Org Reactions II:* 65, 1944).

Description—Clear, colorless gas; faint, ethereal odor; vapor pressure at 25° about 1620 torr; usually contains 6 to 10% of its isomer, $CFCl_2$-CF_3.

Uses—A *propellant* (No 114 and 114a, see page 968).

EDETIC ACID

Glycine, *N,N′*-1,2-ethanediylbis[*N*-(carboxymethyl)], $(HOOCCH_2)_2NCH_2CH_2N(CH_2COOH)_2$

(Ethylenedinitrilo)tetraacetic acid [60-00-4] $C_{10}H_{16}N_2O_8$ (292.24).

Preparation—Ethylenediamine is condensed with sodium monochloroacetate with the aid of sodium carbonate. An aqueous solution of the reactants is heated to about 90° for 10 hr, then cooled and acidified with HCl whereupon the acid precipitates. US Pat 2,130,505.

Description—White, crystalline powder; melts with decomposition above 220°.

Solubility—Very slightly soluble in water; soluble in solutions of alkali hydroxides.

Uses—A *pharmaceutic aid* (metal complexing agent). The acid, rather than any salt, is the form most potent in removing calcium from solution. It may be added to shed blood to prevent clotting. It also is used in pharmaceutical analysis and the removal or inactivation of unwanted ions in solution. Salts of the acid are known as edetates. See *Edetate Calcium Disodium* (page 1267) and *Edetate Disodium* (page 1268).

ETHYLCELLULOSE

Cellulose ethyl ether [9004-57-3]; an ethyl ether of cellulose containing 44 to 51% of ethoxy groups. The *medium-type* viscosity grade contains less than 46.5% ethoxy groups; the *standard-type* viscosity grade contains 46.5% or more ethoxy groups.

Preparation—By the same general procedure described on page 1032 for *Methylcellulose* except that ethyl chloride or ethyl sulfate is employed as the alkylating agent. The 45 to 50% of ethoxy groups in the official ethylcellulose corresponds to from 2.25 to 2.61 ethoxy groups/$C_6H_{10}O_5$ unit, thus representing from 75 to 87% of the maximum theoretical ethoxylation, which is 3 ethoxy groups/$C_6H_{10}O_5$ unit.

Description—Free-flowing, white to light tan powder; forms films that have a refractive index of about 1.47; aqueous suspensions are neutral to litmus.

Solubility—The medium type is freely soluble in tetrahydrofuran, methyl acetate, chloroform, or mixtures of aromatic hydrocarbons with alcohol; the standard type is freely soluble in alcohol, methanol, toluene, chloroform, or ethyl acetate; both types are insoluble in water, glycerin, or propylene glycol.

Uses—A *pharmaceutic aid* as a tablet binder and for film-coating tablets and drug particles.

GELATIN—page 1031.

LIQUID GLUCOSE

GLUCOSE; STARCH SYRUP; CORN SYRUP

A product obtained by the incomplete hydrolysis of starch. It consists chiefly of dextrose [D-(+)-glucose, $C_6H_{12}O_6$ = 180.16] dextrins, maltose, and water.

Preparation—Commercially by the action of very weak H_2SO_4 or HCl on starch.

One of the processes for its manufacture is as follows: The starch, usually from corn, is mixed with 5 times its weight of water containing less than 1% of HCl, the mixture is heated to about 45° and then transferred to a suitable reaction vessel, into which steam is passed under pressure until the temperature reaches 120°. The temperature is maintained at this point for about 1 hr or until tests show complete disappearance of starch. The mass is then heated to volatilize most of the hydrochloric acid, sodium carbonate or calcium carbonate is added to neutralize the remaining traces of acid, the liquid is filtered, then decolorized in charcoal or bone-black filters, as is done in sugar refining, and finally concentrated in vacuum to the desired consistency.

When made by the above process, it contains about 30 to 40% of dextrose mixed with about an equal proportion of dextrin, together with small amounts of other carbohydrates, notably maltose. By varying the conditions of hydrolysis, the relative proportions of the sugars also vary.

If the crystallizable dextrose is desired, the conversion temperature is higher, and the time of conversion longer. The term *glucose,* as customarily used in the chemical or pharmaceutical literature, usually refers to dextrose, the crystallizable product.

The name *grape sugar* sometimes is applied to the solid commercial form of dextrose because the principal sugar of the grape is dextrose, although the fruit has never been used as a source of the commercial supply.

Description—Colorless or yellowish, thick, syrupy liquid; odorless, or nearly so; sweet taste; differs from sucrose in that it readily reduces hot alkaline cupric tartrate TS, producing a red precipitate of cuprous oxide.

Solubility—Miscible with water; sparingly soluble in alcohol.

Uses—As an ingredient of *Cocoa Syrup* (page 1027), as a tablet binder and coating agent, and as a diluent in pilular extracts; it has replaced glycerin in many pharmaceutical preparations. It is sometimes given *per rectum* as a *food* in cases when feeding by stomach is impossible. It should not be used in the place of dextrose for intravenous injection.

HYDROCHLORIC ACID

Chlorhydric Acid; Muriatic Acid; Spirit of Salt

Hydrochloric acid [7647-01-0] HCl (36.46); contains 36.5 to 38.0%, by weight, of HCl.

Preparation—By the interaction of NaCl and H_2SO_4 or by combining chlorine with hydrogen. It is obtained as a by-product in the manufacture of sodium carbonate from NaCl by the Leblanc process in which common salt is decomposed with H_2SO_4. HCl is also a by-product in the electrolytic production of NaOH from NaCl.

Description—Colorless, fuming liquid; pungent odor; fumes and odor disappear when it is diluted with 2 volumes of water; strongly acid to litmus even when highly diluted; specific gravity about 1.18.

Solubility—Miscible with water or alcohol.

Uses—Officially classified as a pharmaceutic aid that is used as an acidifying agent. It is used in preparing *Diluted Hydrochloric Acid.*

HYPOPHOSPHOROUS ACID

Phosphinic acid

Hypophosphorous acid [6303-21-5] HPH_2O_2 (66.00); contains 30 to 32% by weight, of H_3PO_2.

Preparation—By reacting barium or calcium hypophosphite with sulfuric acid or by treating sodium hypophosphite with an ion-exchange resin.

Description—Colorless or slightly yellow, odorless liquid; solution is acid to litmus even when highly diluted; specific gravity about 1.13.

Solubility—Miscible with water or alcohol.

Incompatibilities—Oxidized on exposure to air and by nearly all *oxidizing agents. Mercury, silver,* and *bismuth salts* are reduced partially to the metallic state as evidenced by a darkening in color. *Ferric compounds* are changed to ferrous.

Uses—An *antioxidant* in pharmaceutical preparations.

ISOPROPYL MYRISTATE

Tetradecanoic acid, 1-methylethyl ester

$CH_3(CH_2)_{12}COOCH(CH_3)_2$

Isopropyl myristate [110-27-0] $C_{17}H_{34}O_2$ (270.45).

Preparation—By reacting myristoyl chloride with 2-propanol with the aid of a suitable dehydrochlorinating agent.

Description—Liquid of low viscosity; practically colorless and odorless; congeals about 5° and decomposes at 208°; withstands oxidation and does not become rancid readily.

Solubility—Soluble in alcohol, acetone, chloroform, ethyl acetate, toluene, mineral oil, castor oil, or cottonseed oil; practically insoluble in water, glycerin, or propylene glycol; dissolves many waxes, cholesterol, or lanolin.

Uses—*Pharmaceutic aid* used in cosmetics and topical medicinal preparations as an emollient, as a lubricant, and to enhance absorption through the skin.

KAOLIN—page 1238.

LACTIC ACID

Propanoic acid, 2-hydroxy-, 2-Hydroxypropionic Acid; Propanoloic Acid; Milk Acid

$CH_3CH(OH)COOH$

Lactic acid [50-21-5] $C_3H_6O_3$ (90.08); a mixture of lactic acid and lactic acid lactate ($C_6H_{10}O_5$) equivalent to a total of 85 to 90%, by weight, of $C_3H_6O_3$.

Discovered by Scheele in 1780, it is the acid formed in the souring of milk, hence the name *lactic,* from the Latin name for milk. It results from the decomposition of the lactose (milk sugar) in milk.

Preparation—A solution of glucose or of starch previously hydrolyzed with diluted sulfuric acid is inoculated, after the addition of suitable nitrogen compounds and mineral salts, with *Bacillus lactis.* Calcium carbonate is added to neutralize the lactic acid as soon as it is formed, otherwise the fermentation stops when the amount of acid exceeds 0.5%. When fermentation is complete, as indicated by failure of the liquid to give a test for glucose, the solution is filtered, concentrated, and allowed to stand. The calcium lactate that crystallizes is decomposed with dilute sulfuric acid and filtered with charcoal. The lactic acid in the filtrate is extracted with ethyl or isopropyl ether, the ether is distilled off, and the aqueous solution of the acid is concentrated under reduced pressure.

Description—Colorless or yellowish, nearly odorless, syrupy liquid; acid to litmus; absorbs water on exposure to moist air; when a dilute solution is concentrated to above 50%, lactic acid lactate begins to form; in the official acid the latter amounts to about 12 to 15%; specific gravity about 1.20; decomposes when distilled under normal pressure but may be distilled without decomposition under reduced pressure.

Solubility—Miscible with water, alcohol, or ether; insoluble in chloroform.

Uses—In the preparation of *Sodium Lactate Injection* (page 1265). It also is used in babies' milk formulas, as an acidulant in food preparations, and in 1 to 2% concentration in some spermatocidal jellies. A 10% solution is used as a bactericidal agent on the skin of neonates. It is corrosive to tissues on prolonged contact. A 16.7% solution in flexible collodion is used to remove warts and small cutaneous tumors.

LACTOSE

D-Glucose, 4-*O*-β-D-galactopyranosyl-, Milk Sugar

Lactose [63-42-3] $C_{12}H_{22}O_{11}$ (342.30); *monohydrate* [10039-26-6] (360.31); a sugar obtained from milk.

For the structural formula, see page 411.

Preparation—From skim milk, to which is added diluted HCl to precipitate the casein. After removal of the casein by filtration, the reaction of the whey is adjusted to a pH of about 6.2 by addition of lime, and the remaining albuminous matter is coagulated by heating; this is filtered out and the liquid set aside to crystallize. Animal charcoal is used to decolorize the solution in a manner similar to that used in purifying sucrose.

Another form of lactose, known as β-lactose, also is available on the market. It differs in that the D-glucose moiety is β instead of α. It is reported that this variety is sweeter and more soluble than ordinary lactose and for that reason is preferable in pharmaceutical manufacturing where lactose is used. Chemically, β-lactose does not appear to differ from ordinary α-lactose. It is manufactured in the same way as α-lactose up to the point of crystallization, then the solution is heated to a temperature above 93.5°, the temperature at which the α form is

converted to the β variety. The β form occurs only as an anhydrous sugar, whereas the α variety may be obtained either in the anhydrous form or as a monohydrate.

Description—White or creamy white, hard, crystalline masses or powder; odorless; faintly sweet taste; stable in air, but readily absorbs odors; pH (1 in 10 solution) 4 to 6.5; specific rotation +54.8 to +55.5.

Solubility—1 g in 5 mL water or 2.6 mL boiling water; very slightly soluble in alcohol; insoluble in chloroform or ether.

Uses—A *diluent* largely used in medicine and pharmacy. It is generally an ingredient of the medium used in penicillin production. It is used extensively as an addition to milk for infant feeding.

MAGNESIUM CHLORIDE

Magnesium chloride hexahydrate [7791-18-6] $MgCl_2 \cdot 6H_2O$ (203.30); *anhydrous* [7786-30-3] (95.21).

Preparation—By treating magnesite or other suitable magnesium minerals with HCl.

Description—Colorless, odorless, deliquescent flakes or crystals, which lose water when heated to 100° and lose HCl when heated to 110°; pH (1 in 20 solution in carbon dioxide-free water) 4.5 to 7.

Solubility—Very soluble in water; freely soluble in alcohol.

Uses—*Electrolyte replenisher; pharmaceutical necessity* for hemodialysis and peritoneal dialysis fluids.

MAGNESIUM STEARATE

Octadecanoic acid, magnesium salt

Magnesium stearate [557-04-0]. A compound of magnesium with a mixture of solid organic acids obtained from fats, which consists chiefly of variable proportions of magnesium stearate and magnesium palmitate. It contains the equivalent of 6.8 to 8.0% MgO (40.30).

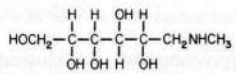
Description—Fine, white, bulky powder; faint, characteristic odor; unctuous, adheres readily to the skin and free from grittiness.

Solubility—Insoluble in water, alcohol, or ether.

Uses—A *pharmaceutical necessity (lubricant)* in the manufacture of compressed tablets.

MEGLUMINE

D-Glucitol, 1-deoxy-1-(methylamino)-,



1-Deoxy-1-(methylamino)-D-glucitol [6284-40-8] $C_7H_{17}NO_5$ (195.21).

Preparation—By treating glucose with hydrogen and methylamine under pressure and in the presence of Raney nickel.

Description—White to faintly yellowish white, odorless crystals or powder; melts about 130°.

Solubility—Freely soluble in water; sparingly soluble in alcohol.

Uses—In forming salts of certain pharmaceuticals, surface-active agents and dyes. See *Diatrizoate Meglumine Injections* (page 1195), *Iodipamide Meglumine Injection* (page 1187) and *Iothalamate Meglumine Injection* (page 1197).

LIGHT MINERAL OIL

Light Liquid Petrolatum NF XII; Light Liquid Paraffin; Light White Mineral Oil

A mixture of liquid hydrocarbons obtained from petroleum. It may contain a suitable stabilizer.

Description—Colorless, transparent, oily liquid, free, or nearly free, from fluorescence; odorless and tasteless when cold, and develops not more than a faint odor of petroleum when heated; specific gravity 0.818 to 0.880; kinematic viscosity not more than 33.5 centistokes at 40°.

Solubility—Insoluble in water or alcohol; miscible with most fixed oils, but not with castor oil; soluble in volatile oils.

Uses—Officially recognized as a *vehicle*. Once it was used widely as a vehicle for nose and throat medications; such uses are now considered dangerous because of the possibility of lipoid pneumonia. It sometimes is used to cleanse dry and inflamed skin areas and to facilitate removal of dermatological preparations from the skin. It should never be used for internal administration because of *leakage*. See *Mineral Oil* (page 1233).

NITRIC ACID

Nitric acid [7697-37-2] HNO_3 (63.01); contains about 70%, by weight, of HNO_3.

Preparation—May be prepared by treatment of sodium nitrate (Chile saltpeter) with sulfuric acid, but usually produced by catalytic oxidation of ammonia.

Description—Highly corrosive fuming liquid; characteristic, highly irritating odor; stains animal tissues yellow; boils about 120°; specific gravity about 1.41.

Solubility—Miscible with water.

Uses—*Pharmaceutic aid* (acidifying agent).

NITROGEN

Nitrogen [7727-37-9] N_2 (28.01); contains not less than 99%, by volume, of N_2.

Preparation—By the fractional distillation of liquefied air.

Uses—A diluent for medicinal gases. Pharmaceutically, is employed to replace air in the containers of substances that would be affected adversely by air oxidation. Examples include its use with fixed oils, certain vitamin preparations, and a variety of injectable products. It also is used as a propellant.

PHENOL

Carbolic Acid

C_6H_5OH

Phenol [108-95-2] C_6H_6O (94.11).

Preparation—For many years made only by distilling crude carbolic acid from coal tar and separating and purifying the distillate by repeated crystallizations; it now is prepared synthetically.

One process uses chlorobenzene as the starting point in the manufacture. The chlorobenzene is produced in a vapor phase reaction, with benzene, HCl, and oxygen over a copper catalyst, followed by hydrolysis with steam to yield HCl and phenol (which is recovered).

Description—Colorless to light pink, interlaced, or separate, needle-shaped crystals, or a white or light pink, crystalline mass; characteristic odor; when undiluted, it whitens and cauterizes the skin and mucous membranes; when gently heated, phenol melts, forming a highly refractive liquid; liquefied by the addition of 10% of water; vapor is flammable; gradually darkens on exposure to light and air; specific gravity 1.07; boils at 182°; congeals not lower than 39°.

Solubility—1 g in 15 mL water; very soluble in alcohol, glycerin, chloroform, ether, or fixed and volatile oils; sparingly soluble in mineral oil.

Incompatibilities—Produces a liquid or soft mass when triturated with *camphor, menthol, acetanilid, acetophenetidin, aminopyrine, antipyrine, ethyl aminobenzoate, methenamine, phenyl salicylate, resorcinol, terpin hydrate, thymol,* and several other substances including some *alkaloids*. It also softens *cocoa butter* in suppository mixtures.

It is soluble in about 15 parts of water; stronger solutions may be obtained by using as much glycerin as phenol. Only the crystallized form is soluble in fixed oils and liquid petroleum, the liquefied form is not all soluble because of its content of water. *Albumin* and *gelatin* are precipitated by it. *Collodion* is coagulated by the precipitation of pyroxylin. Traces of *iron* in various chemicals such as *alum, borax,* etc, may produce a green color.

Uses—A *caustic, disinfectant, topical anesthetic,* and pharmaceutical necessity as a *preservative* for injections, etc. At one time widely used as a germicide and still the standard against which other antiseptics are compared, it has few legitimate uses in modern medicine. Nevertheless, it is still used in several proprietary antiseptic mouthwashes, hemorrhoidal preparations, and burn remedies. In full strength, a few drops of the liquefied form may be used to cauterize small wounds, dog bites, snake bites, etc. It commonly is employed as an *antipruritic,* in the form of either phenolated calamine lotion (1%), phenol ointment (2%), or a simple aqueous solution (0.5 to 1%). It has been used for sclerosing hemorrhoids, but more effective and safer drugs are available. A 5% solution in glycerin is used in simple earache. Crude carbolic acid is an effective, economical agent for disinfecting excrement. It is of some therapeutic value as a *fungicide,* but more effective and less toxic agents are available. If accidentally spilled, it should be removed promptly from the skin by swabbing with alcohol.

Liquefied Phenol [Liquefied Carbolic Acid]—Phenol maintained in a liquid condition by the presence of 10.0% of water. It contains not less than 89.0%, by weight, of C_6H_6O. *Note—When it is to be mixed with a fixed oil, mineral oil, or white petrolatum, use the crystalline Phenol, not Liquefied Phenol. Preparation:* Melt phenol (a convenient quantity) by placing the unstoppered container in a steam bath and applying heat gradually. Transfer the liquid to a tared vessel, weigh, add 1 g of purified water for each 9 g of phenol, and mix thoroughly. *Description:* Colorless liquid, which may develop a red tint upon exposure to air and light; characteristic, somewhat aromatic odor; when undiluted it cauterizes and whitens the skin and mucous membranes; specific gravity about 1.065; when it is subjected to distillation, the boiling temperature does not rise above 182°, which is the boiling temperature of phenol; partially solidifies at about 15°. *Solubility:* Miscible with alcohol, ether,