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Essentials of Pharmaceutics

Edited by Linda Felton

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Essentials of Pharmaceutics

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Published by Pharmaceutical Press
1 Lambeth High Street, London SE1 7JN, UK

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Pharmaceutical Press is the publishing division of the Royal Pharmaceutical Society

First edition published 2013

Typeset by Newgen KnowledgeWorks, India

Printed in the United States of America by Edwards Brothers Malloy

ISBN 978 0 85711 105 0

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A catalogue record for this book is available from the British Library.

This book is adapted from contributions published in *Remington: The Science and Practice of Pharmacy* 22nd edition.

Chapter 11

Molecular Structure, Properties, and States of Matter

Thomas Rades, PhD; Keith C. Gordon, PhD and Kirsten Graeser, PhD

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MOLECULAR STRUCTURE AND PROPERTIES

INTRODUCTION

Pharmaceuticals are made up of molecules, the properties of which are determined by their shape and electronic structure (i.e., the nature of their bonds). These, in turn, are determined by the constituent atoms and how those atoms are held together (bonded). A striking example of this is the element carbon. This can exist in a variety of forms – including nanotubes and buckyballs – but the two forms that illustrate the difference in bonding most strongly are graphite and diamond. Both are entirely composed of carbon atoms, but one is a hard crystalline material, colorless in its pure form (diamond), the other a black greasy material used in pencils and as a lubricant.

Atoms are built from neutrons, protons, and electrons; the former are much more massive than the electrons. The properties of these subatomic units are given in Table 11-1. The fundamental ideas for atomic structure and bonding were developed in the early part of the twentieth century.

HISTORICAL PERSPECTIVE

From the early 1800s it had been known that elements had certain properties in relation to their interaction with other elements. This was expounded in Dalton's atomic theory, which stated that

1. Elements are composed of atoms.
2. The atoms for a specific element are unique to that element.
3. Atoms of one element can combine with atoms of other elements to form compounds. Each compound has a specific ratio of the elements of which it is composed, and these have simple integral ratios.
4. Atoms are not created or destroyed in making compounds – they simply associate in differing ways in differing compounds.

By the late nineteenth century, a number of observations had been made that suggested atoms had an internal structure that had some sort of periodicity based on their mass. The weights of the elements had been measured, and it was found that if they were arranged in order, then there were similarities between each eighth element. For example, neon, helium, and krypton were all inert, and lithium, sodium, and potassium reacted in a ratio of 1:1 with chlorine, whereas magnesium and calcium (also eight different) reacted with chlorine in a 1:2 ratio. The English chemist Newland noted that this behavior was similar to the eighth note in a musical octave, and these findings thus became called the law of octaves. Around 1869 Mendeleev and Meyer developed what we now call the periodic table, in which all of the elements known at that time were listed. Mendeleev left gaps for gallium, scandium, and germanium – he even went so far as to predict the properties of these elements. These elements were discovered and purified subsequent to Mendeleev; for example, gallium was discovered in 1875, scandium was purified in 1937, and germanium in 1885. These elements had many of the properties Mendeleev had predicted.

This became known as the periodic law, and although it is not the weights of the elements but rather the atomic number that is periodic, Mendeleev's periodic table led to the idea of some sort of repeating internal structure within the atoms.

The key issues in examining the periodic table are:

1. Each element has an atomic number (Z), which corresponds to the number of protons in the nucleus and is a multiple of the electronic charge.
2. Atomic weight is the average mass for a particular element versus the current standard, which is based on the mass of the carbon-12 isotope. This was given the atomic weight of 12.
3. Isotopes are forms of the same element that differ in the number of neutrons in the nucleus.

At the beginning of the twentieth century, J. J. Thomson proposed a model of the atom based on the data available at the time. In his model (euphemistically called the plum pudding model) the atom was a mass that contained protons and neutrons with the electrons embedded, rather like raisins in a plum pudding. The key issue of this model was that all of the particles occupied the same volume of space. This model was shattered by a series of experiments conducted by Marsden and Geiger in 1909 and interpreted by Rutherford in 1911. The experiment, which became known as the Rutherford backscattering experiment, took high energy particles and fired them at a thin gold foil. The particles in question were alpha particles. These are comprised of two neutrons and two protons, thus carrying a +2 charge. In the plum pudding model, the alpha particles would be unimpeded in penetrating the gold foil since each gold atom was a small mass with no charge because the electrons and protons were in close proximity. However, Marsden and Geiger observed that the high energy alpha particles scattered back towards them. This was a striking result, which Rutherford described as "…quite the most incredible event that has ever happened to me in my life. It was almost as incredible as if you fired a 15-inch shell at a piece of tissue paper and it came back and hit you."[1]

Table 11-1. Masses and Charges for the Neutron, Proton and Electron

Subatomic particle	Mass/kg	Relative mass	Charge/C	Relative charge
Proton	1.673×10^{-27}	1837	1.602×10^{-19}	1
Neutron	1.675×10^{-27}	1839	0	0
Electron	9.109×10^{-31}	1	-1.602×10^{-19}	−1

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Rutherford explained these findings by hypothesizing a new model of the atoms, in which the nucleus contained only protons and neutrons and the electrons were buzzing around this central positively charged core. This model certainly was consistent with the results of the gold foil experiments, but it created some difficulties since an electron orbiting a positive proton would be attracted into the centre. Thus, all atoms would be unstable.

The Bohr model

In 1913 Bohr developed the first model of modern atomic theory. Bohr was trying to develop a model that would explain the nature of emission spectra from atoms such as hydrogen. In the 1880s Rydberg had recognized that the emission spectrum of hydrogen followed a mathematical relationship, such that the wavelength of light (λ) observed was related to integers, n_1 and n_2,… and a constant called the Rydberg constant (R_∞)

$$\frac{1}{\lambda} = R_\infty\left(\frac{1}{n_1^2} - \frac{1}{n_2^2}\right) \tag{1}$$

For example, in a series of emission lines observed at about 400 nm (the Balmer series), the wavelength of each line corresponded to $n_1 = 2$ and $n_2 = 3, 4, 5, 6, 7$, etc.

In Bohr's model (Figure 11-1) he stated that

1. The electrons were restricted to set orbits at fixed distances from the nucleus. These fixed orbits were labeled by a quantum number n.
2. An electron in one of these orbits has an energy associated with being in that orbit (also called the energy level).
3. The jumping from one orbit to another corresponds to the electron moving from one orbit to another. The Balmer series occurs because the electron in a series of high orbits falls to the orbit of $n = 2$.

Bohr's model received further experimental support in a series of experiments conducted by Franck and Hertz on mercury vapor. They found, as they bombarded mercury with electrons of varying energy, that at discrete energies the electrons lost all of their kinetic energy due to absorption of that energy by the mercury atoms.

The Bohr model had a number of shortcomings, not least the unanswered question of why these orbits exist. An elegant explanation of this came in 1925 when de Broglie postulated that a particle such as an electron in an orbit would have a wave associated with it, such that

$$\lambda = \frac{h}{mu} \tag{2}$$

Where: λ is the wavelength; h is the Planck constant (6.63×10^{-34} Js); m is the mass of the particle; and u is the velocity of the particle.

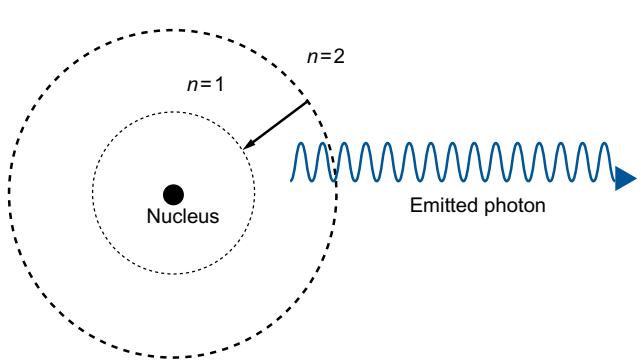

Figure 11-1. The electronic transition from $n = 2$ to $n = 1$ emits a photon matching the energy difference between the orbits.

In the circular orbits proposed by Bohr, standing waves will exist if

$$n\lambda = 2\pi r \tag{3}$$

Where: n is an integer; r is the radius of the orbit.

In the Bohr model, the centripetal force of the electron spinning about the nucleus must be balanced by the electron's angular momentum (Figure 11-2) so that:

$$\frac{Ze^2}{4\pi\varepsilon_0 r^2} = \frac{mu^2}{r} \tag{4}$$

Where: Z is the charge on the nucleus (Table 11-1) or atomic number; e the charge of the electron; r the radius of the orbit; m the mass of the electron; u the electron velocity; and ε_0 the permittivity of free space.

The total energy of the electron in the orbit is a sum of its kinetic energy and potential energy. This is given by:

$$Kinetic\ energy = \frac{1}{2}mu^2 = \frac{Ze^2}{8\pi\varepsilon_0 r} \tag{5}$$

$$Potential\ energy = -\frac{Ze^2}{4\pi\varepsilon_0 r} \tag{6}$$

$$Total\ energy = Potential + Kinetic = -\frac{Ze^2}{8\pi\varepsilon_0 r} \tag{7}$$

With these equations the radius of the orbit (r) may be solved:

$$r = \frac{n^2h^2\varepsilon_0}{Z\pi me^2} = \frac{n^2a_0}{Z} \tag{8}$$

Bohr calculated that $a_0 = 0.0529$ nm (this is called the Bohr radius).

The total energy for each orbit is related to the inverse of the radius and thus the inverse of n^2.

The energy of an orbit is thus: $E_n \infty \frac{1}{n^2}$ and when the election jumps from one orbital to another:

$$\Delta E = E_{n_1} - E_{n_2} \infty \left(\frac{1}{n_2^2} - \frac{1}{n_1^2}\right) \tag{9}$$

The wavelength of the transition is related to the energy difference by:

$$\Delta E = \frac{hc}{\lambda} \tag{10}$$

These equations (9 and 10) show that the inverse of the wavelength is related to the inverse of the square of the energy level number, in this case n_1 and n_2 (equation 1). For example,

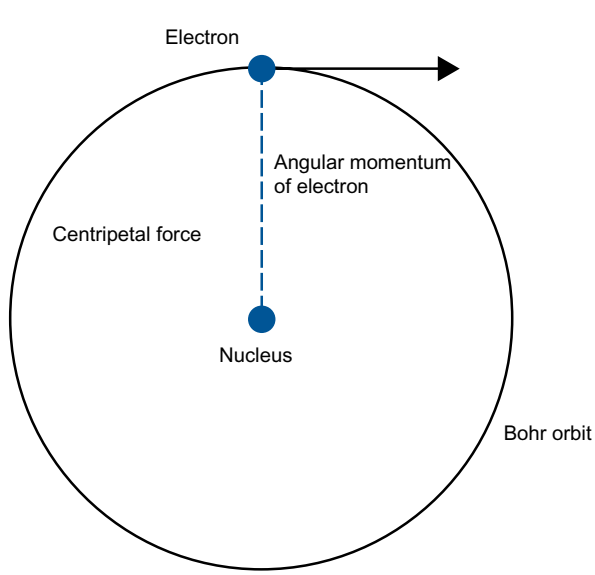

Figure 11-2. Forces acting on the electron in a Bohr model.

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the Balmer emission series observed for the hydrogen atom has lines at 656.3, 486.1 and 434.1 nm; these correspond to emission transitions ($n_2 \rightarrow n_1$) of 3 → 2, 4 → 2 and 5 → 2, respectively.

The Bohr model, despite its shortcomings, was effectively the first modern model of atomic theory. The key issue was that the energy was quantized; this was related to the extent of motion of the electron in space (the orbits) and the fact that electrons could jump from one discrete level to another.

ELECTRONIC CONFIGURATIONS

Now that the existence of internal structure within the atom has been determined, we have to ask the following questions: (1) how are the levels labeled and (2) how do electrons fill the available quantized energy levels. First, these levels are defined by a series of quantum numbers. The principal quantum number n is referred to as the electron shell. Each shell can contain n^2 orbitals, which have orbital angular momentum quantum numbers l, where l can have integer values of 0 to $n-1$; in turn, each value of l has $2l+1$ degenerate orbitals to accommodate electrons. Within each degenerate set of orbitals, a further labeling occurs, based on the magnetic quantum number m_l, which takes integer values from $-l$ to $+l$. For example, for $n = 1$ $l = 0$ there is only one orbital called the s, or 1s, orbital. For $n = 2$ $l = 0$ and 1, there is a 2s orbital ($n = 2$, $l = 0$) and three 2p orbitals ($n = 2$, $l = 1$, with $ml = -1, 0, +1$); in total, the $n = 2$ level has four orbitals (Table 11-2). The orbitals are labeled by letters running s, p, d and f for $l = 0$, 1, 2, and 3, respectively. These labels originate from the nature of the spectroscopic transitions associated with the orbitals which are sharp, principal, diffuse, and fundamental. The principal quantum number levels may also be labeled with letters as *K, L, M* shells for $n = 1$, 2, and 3. There is one final quantum number that relates to the electrons filling these orbitals: it is spin, denoted by ms and taking values of +1/2 or −1/2.

The labeling system tells us how the electrons are to be organized in an atom. The second issue is how these levels are filled. The building up or Aufbau principle provides a method of determining how electrons will fill the available orbitals for the ground state (lowest energy) configuration. The filling of orbitals is depicted in Figure 11-3, and a series of electron configurations for the first 25 elements is presented in Table 11-3.

Two additional issues need to be considered in this picture; first, the *Pauli Exclusion Principle* states that no two electrons may have the same four quantum numbers (n, l, ml, ms) – this limits the occupancy of an orbital to two electrons (+1/2 and −1/2) – and secondly, *Hund's rule* states that if degenerate orbitals are filled, the electrons spread themselves out as much as possible. Thus, if three electrons occupy the 2p orbital set, then the configuration is $2p_x^1 2p_y^1 2p_z^1$ (Figure 11-4).

As atoms interact with each other, the picture becomes somewhat more complex, and indeed, as electrons fill orbitals, they affect the energy of the orbitals and can have a bearing on the configuration. For example, in the case of Cr, in which one might expect a $4s^2 3d^4$ configuration, this is not observed. Because the half-filling of the 3d subshell imbues additional stabilization, the lowest configuration is $4s^1 3d^5$.

Table 11-2. Properties and Labels Used in Describing Orbitals

Orbital	Allowed quantum numbers		Number of orbitals
	l	ml	
s	0	0	1
p	1	−1, 0, +1	3
d	2	−2, −1, 0, +1, +2	5
f	3	−3, −2, −1, 0, +1, +2, +3	7

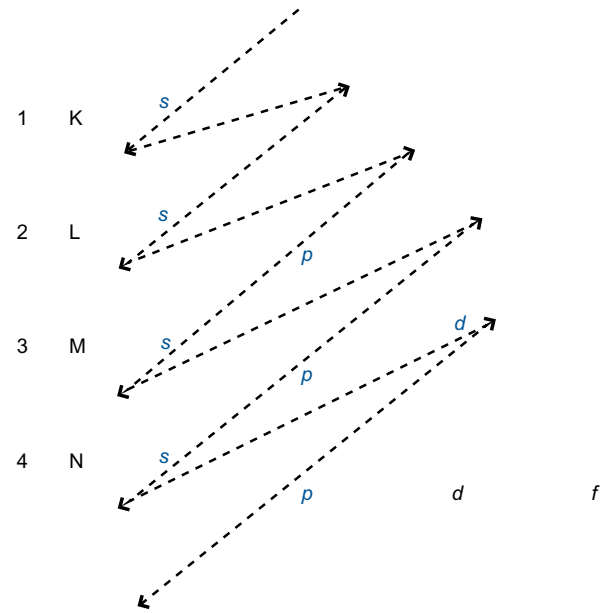

Figure 11-3. Filling diagram of shells and subshells. Levels are filled by following the dashed path.

The historic observation that reactivity has a periodic nature can be attributed to the electronic structure. For example, if halogens (fluorine, chlorine, bromine, and iodine) are reduced they become anions with a filled shell; that is, they have the electronic configuration of the noble gases. Thus, Cl^- and other halogen anions are stable. In a similar fashion, the alkali metals, lithium, sodium, and the like, readily lose an electron to adopt the noble gas closed shell electronic configuration. Thus, Li^+ and Na^+ salts may be readily formed, but Na^{2+} salts are not observed.

Although the labeling of the orbitals and shells may appear a book-keeping exercise, the quantum numbers have important consequences on the chemical and physical properties of the atoms. Furthermore, the quantum numbers affect the shape and energy of the orbitals; for example, s orbitals are spherical, but p and d orbitals have distinct shapes; $p$orbitals appear as dumb-bell shaped (Figure 11-4) and are directed along x, y or z axes, depending on the value of ml. They also possess sign character; that is, the wavefunction that defines the $p$orbital has both a negative and positive part. This is normally depicted by color, as shown in Figure 11-4, using black and white.

FORMATION OF BONDS

The differing electronic configurations of the atoms mean that they can interact with each other to form larger structures, such as molecules or salts. Depending on the nature of the atoms, there are different interactions possible, at which we will take a closer look in the following section.

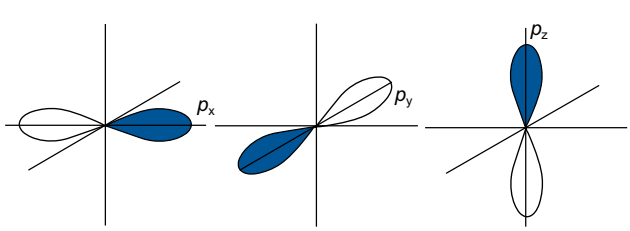

Figure 11-4. Depiction of 2p orbitals.

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Table 11-3. Electronic Configurations for First 25 Elements in Their Ground State

Atomic number (*Z*)	Element	*n*, shell	1	2		3		4	3
			K	*L*		*M*		*N*	*M*
		l, subshell	0	0	1	0	1	0	2
			1*s*	2*s*	2*p*	3*s*	3*p*	4*s*	3*d*
1	H		1						
2	He		2						
3	Li		2	1					
4	Be		2	2					
5	B		2	2	1				
6	C		2	2	2				
7	N		2	2	3				
8	O		2	2	4				
9	F		2	2	5				
10	Ne		2	2	6				
11	Na		2	2	6	1			
12	Mg		2	2	6	2			
13	Al		2	2	6	2	1		
14	Si		2	2	6	2	2		
15	P		2	2	6	2	3		
16	S		2	2	6	2	4		
17	Cl		2	2	6	2	5		
18	Ar		2	2	6	2	6		
19	K		2	2	6	2	6	1	
20	Ca		2	2	6	2	6	2	
21	Sc		2	2	6	2	6	2	1
22	Ti		2	2	6	2	6	2	2
23	V		2	2	6	2	6	2	3
24	Cr		2	2	6	2	6	1	5
25	Mn		2	2	6	2	6	2	5

Ionic bonds coulomb interactions

One way in which atoms can form larger structures is through ionic bonding. This occurs when two elements combine, whereby one adds and the other one loses electrons to become ionic. For example, Na readily loses an electron to become the cation Na^+ (note that the electronic configuration of the Na^+ is a close shell and thus stable), and the chlorine atom can gain an electron to become an anion, Cl^- (this also now has a close shell configuration). These two types of ions attract each other because of their opposite charge, and in this way salts are formed. The bonding that holds these ions together is coulombic in nature, and the structure of the salt is a balance of these coulombic forces. In the case of NaCl, these forces balance to create a crystal of many thousands of atoms, in which the ions are held in a face-centered cubic arrangement (Figure 11-5, also see the section on crystalline solids).

Covalent bonds

Covalent bonds occur when electrons are shared between atoms. If we consider two H atoms interacting as they approach, there is an interplay between the coulomb interactions of the two nuclei and two electrons (which repel) and nuclei and electrons (which attract). At very short distances the coulombic forces of repulsion dominate, and the energy increases. At long distances the atoms cannot sense each other, and there is no interaction; however, at distances of 120 to 200 pm (1 pm = 10^{-12} m), the electrons may be shared between the atoms, and this creates a bond that requires energy to break. The electrons that started in 1*s* atomic orbitals now occupy a new orbital, which is called a molecular orbital (MO), which is a result of the interaction between the atomic orbitals. The new molecular orbital forms from the spatial overlap of the 1*s* orbitals. In general, the strongest overlap occurs where atomic orbitals are similar in energy and occupy the same space as the nuclei approach (Figures 11.6 and 11.7).

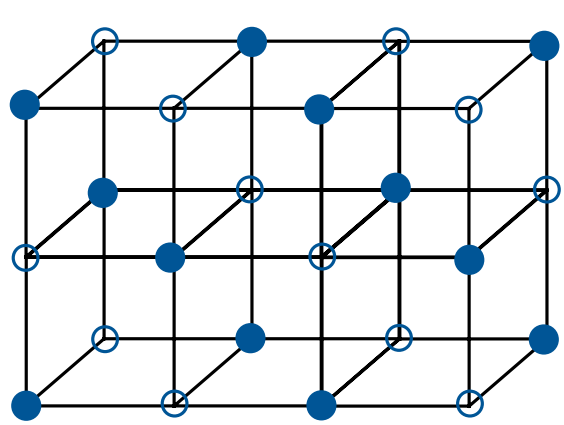

Figure 11-5. Depiction of a section of the NaCl crystal lattice with the Na^+ ions as open circles and Cl^- as closed circles.

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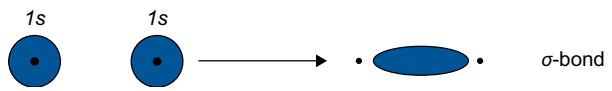

Figure 11-6. Overlap of two 1s orbitals to give a bonding σ-orbital.

Let us take a closer look at these MOs. As the 1s atomic orbitals overlap, two new orbitals are formed. The lower energy orbital is bonding in character and termed a σ MO, but there is also a corresponding antibonding MO, termed σ* (Figure 11-8). In the case of H_2, because there are only two electrons, only the bonding σ MO is populated, and a bond is formed. However, if the atom 1s atomic orbitals are filled, as is the case of He ($1s^2$), He_2 cannot form because the bonding interaction of the σ MO is counteracted by the population of the antibonding σ* MO.

In the case of H_2, only one type of bond can form because each atom has a $1s^1$ electron configuration, but for atoms with many electrons, a number of types of molecular orbitals may be generated. If we consider N atoms, the electron configuration is $1s^2 2s^2 2p^3$, with an electron in each of the *p* orbitals (Hund's rule). A number of molecular orbitals may be formed by the overlap of the atomic orbitals. If we consider the *p*-orbitals, there are two types of bonds that can be formed. For the $2p_z$ orbitals of each atom, these can overlap directly; the resulting molecular orbital holds electron density between the two N atoms – the σ-bond. But the $2p_x$ and $2p_y$ orbitals can also overlap in a face to face fashion. Each of these is a π-bond, in which electron density is not directly between the atoms but above and below the σ-bond (Figure 11-9). In the case of N_2, there are two π-bonds that can be formed (Figure 11-10). A σ-bond typically has a bond energy of 100 kcal mol^{-1}; triple bonds (one σ- and two π-bonds) can have bond energies of 240 kcal mol^{-1}.

H_2 and N_2 are examples of bonding in which both atoms involved are the same, and thus the electrons are shared equally between the nuclei. However, for heteronuclear compounds (in which the atoms differ), the sharing of electrons will not be equal, and the electron density will lie to the more electronegative nucleus. This effect will occur in both σ- and π-bonds, and this results in a polarity in the bonding and dipole moment in the molecule.

The existence of polar bonding has its origin from the electronic configurations of the elements; for example, for halogen gases which are one electron short of a close shell configuration (and the additional stability that is brought by such a configuration), the sharing of electron density in a covalent bond between two differing atoms is not symmetric. The atom with a stronger ability to attract the electron (which can be described

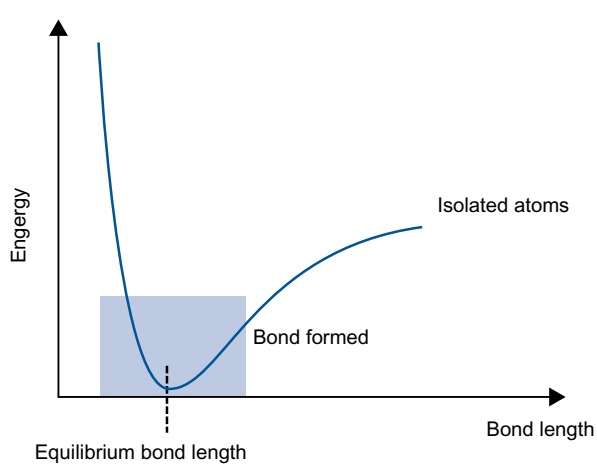

Figure 11-7. Bond length energy diagram, showing the region in which a bond may be said to be formed (gray shading).

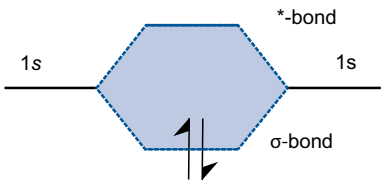

Figure 11-8. Depiction of the changes in energy when two 1s orbitals combine to form a σ and σ* MO.

by the electronegativity of the element) will polarize the bond so that electron density lies closer to a more electronegative atom. This has the important consequence of creating a polar bond which has associated with it a dipole moment (a disparity of charge distribution). Polar bonds and dipole moments are important properties of molecules that have an effect on the bulk properties of the material. The electronegativities for some elements and dipole moments for some simple molecules are shown in Tables 11.4 and 11.5.

More than one bond from a central atom

Because a large number of pharmaceutically important compounds are carbon-based, we will take a closer look at the carbon atom. Carbon, with its $2s^2 2p^2$ valence shell, has some interesting properties. Most notable is that carbon readily forms up to four covalent bonds with other carbon atoms and thus, from carbon, many large molecular structures are obtained. It is worth considering how one might draw such structures as a variety of methods are used. The simplest is to draw the carbon atom with four bonds from it arranged at 90°; this is easy to draw, but it is important to realize (as we will see shortly) that the molecules have a three dimensional shape. This is depicted in Figure 11-11, which shows a model of CH_4, as well as two ways in which it can be drawn on paper.

A cursory consideration of the electronic structure of the carbon atom might suggest that only two covalent bonds can be formed as the 2s orbitals are filled. However, when atoms approach each other, the atomic orbitals may become reorganized

Table 11-4. Electronegativities of Selected Elements

Element	Electronegativity
F	3.98
O	3.44
N	3.04
Cl	3.16
Br	2.96
S	2.58
C	2.55
I	2.66
P	2.19
H	2.20
B	2.04
Si	1.90
Al	1.61
Mg	1.31
Li	1.00
Ca	1.00
Na	0.93
K	0.82

(Data from Pauling, L. (1932). "The Nature of the Chemical Bond. IV. The Energy of Single Bonds and the Relative Electronegativity of Atoms". *Journal of the American Chemical Society* 54 (9): 3570–3582.)

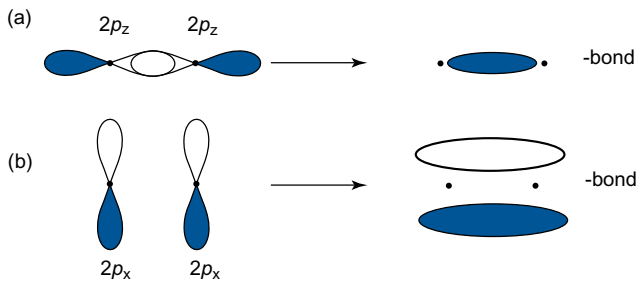

Figure 11-9. (a) Overlap of $2p_x$ orbitals to create a σ-bond, (b) Overlap of $2p_z$ orbitals to create a σ-bond.

and form hybrid orbitals. These hybrid orbitals may be considered as a combination or average of the atomic orbitals from which they are composed.

One way to think about this is that although the isolated carbon atoms may have a $2s^2 2p^2$ ground state electronic configuration, as carbon atoms approach each other, this $2s^2 2p^2$ configuration may not be the energetically favored state. In the case of diamond, which is a network of tetrahedrally bonding carbon atoms (each having four equivalent bonds), the valence shell of the atoms in this bonded state is $2s^1 2p^3$ and, more importantly, the shapes of the atomic orbitals are not maintained, and new molecular orbitals are generated. These specific orbitals are called sp^3 orbitals, and more generally this type of orbital is called a hybrid orbital because they come from a hybridization of the original atomic orbitals.

The sp^3 orbitals covalently link the carbon atom to other atoms through four σ-bonds. As each of the orbitals is equivalent, they repel each other and adopt a tetrahedral geometry. This sort of bonding is prevalent in alkane structures, that is, hydrocarbons with no double bond character. However, this is not the only way in which the valence electrons of carbon atoms may hybridize. It is possible that only three of the orbitals hybridize (the 2*s*, 2*px* and 2*py* for example) to form a sp^2 centre. The three sp^2 orbitals lie in a plane (the *xy* plane in this case) with an angle between each bond of 120°. Once again, the hybrid orbitals are as far apart as is possible. Of course, in such an arrangement there still remains a *p* orbital ($2p_z$) at right angles to the sp^2 plane. The result of this hybridization is that the carbon centre may bind through three σ-bonds, but the additional perpendicular *p* orbital can form a π-bond. In this way, one of the linkages between two sp^2 carbon atoms will have both a σ- and π-bond to give double bond character. The electrons that occupy the π-bond are often referred to as π-electrons, and they possess a number of interesting electronic properties.

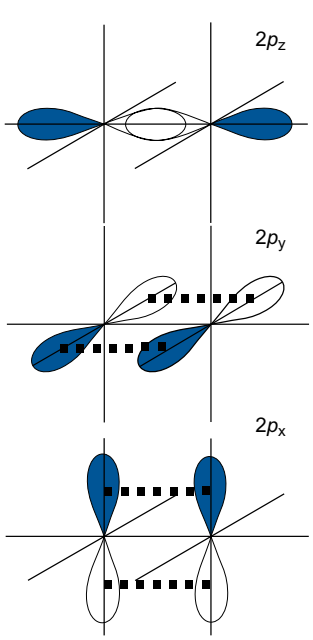

Figure 11-10. The bonding of valence orbitals in N_2, showing one σ- and two π-bonds.

Table 11-5. Dipole Moments for a Selection of Heteronuclear Diatomic Molecules

Molecule	Dipole / D[1]
CO	0.11
HCN	2.98
HCl	1.05
HBr	0.82
HI	0.38

[1]1D (one debye) corresponds to 1 D = 3.344×10^{-30} cm

We know that *sp* hybridization occurs when only one of the carbon 2*p* orbitals interacts with the 2*s*orbital; this creates two *sp* hybrid orbitals that form two σ-bonds linear to each other. However, there remain two unused *p* orbitals, each of which contains an electron, so that two π-bonds may be formed between adjacent centers. This leads to carbon–carbon triple bonded species, the alkynes.

Hybridization shows how the original atomic orbitals may change shape considerably in forming molecular structures, as depicted in Figure 11-12.

There are a number of important differences between σ- and π-bonds. The most striking of these is that π-bonds are rigid; they cannot rotate because the interaction between adjacent $2p_z$ orbitals only occurs if these orbitals are in the same plane.

Resonance and bond delocalization

Benzene and other extended sp^2 bonded structures exhibit some interesting behavior with respect to the π-electrons. The six carbon 2*pz* atomic orbitals that create the π-bonds do not have to overlap with only one adjacent 2*pz* but can share electron density with both adjacent atomic orbitals. This can happen with each of the 2*pz* atomic orbitals in the ring. This delocalization of electron density or extended conjugation imbues the benzene molecule with chemical stability because of a new series of π-molecular orbitals being created. This delocalization of electrons may be depicted by the π-molecular orbitals or by drawing single and double bonds and adding the possibility of resonance structures (Figure 11-13).

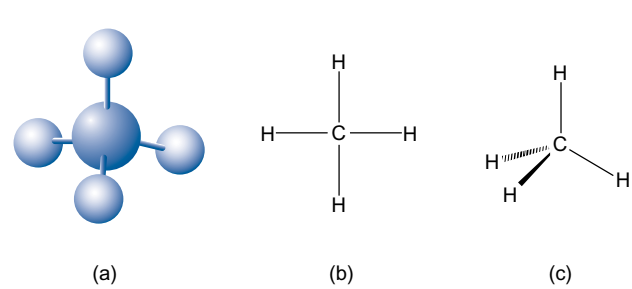

Figure 11-11. (a) Model of CH_4 and other drawing formats, (b), and (c). Note that (c) implies a three-dimensional structure with the thick wedge sticking out of the page and the dashed wedge sticking into it.

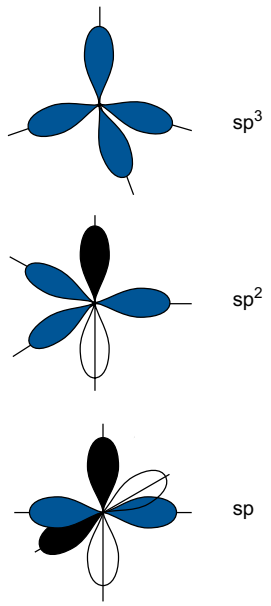

Figure 11-12. Depiction of hybrid orbitals (blue) and residual *p* orbitals (black and white).

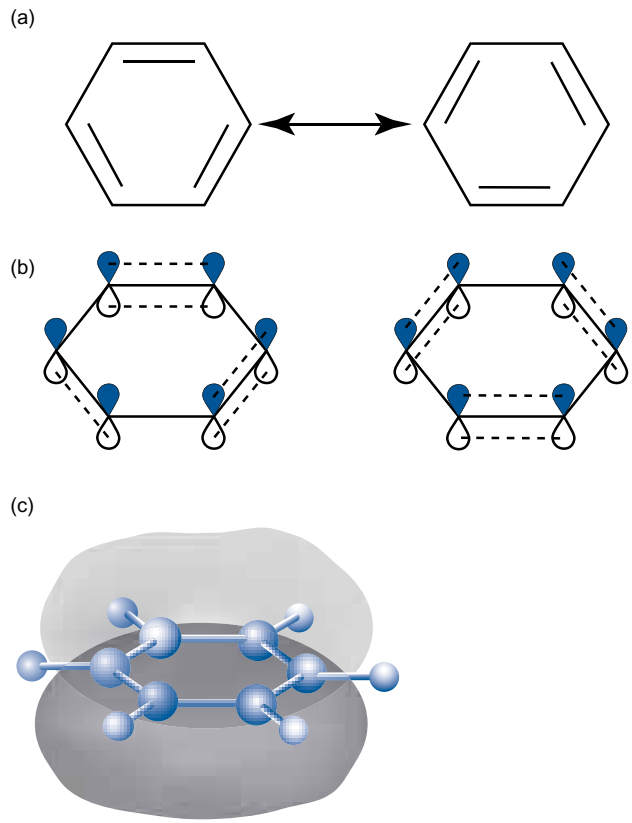

Figure 11-13. (a) Valence bond resonance structures for benzene, (b) overlap of 2*p* orbitals that results in delocalized bonds, and (c) resulting molecular orbital delocalized over the entire ring.

If one draws the structure of benzene with single and double bonds (the so-called valence bond structure), then the double bonds may be placed in different places. This is not a mere nicety: it actually implies that the structure is more complex than either one of the diagrams. This "resonance" between these two valence bond structures was first suggested by Kekulé in 1872.

Extended sp^2 systems demonstrate this delocalization in their electronic spectra, i.e., their color. The electronic spectrum can show the energy difference between the highest occupied molecular orbital (HOMO, in this case a π-orbital) and the lowest unoccupied MO (LUMO). For ethene, which has a single π-bond, the observed transition from HOMO to LUMO is at 171 nm, which corresponds to a difference in energy between HOMO and LUMO of 166 kcal mol^{-1}. For butadiene (which has two π-bonds conjugated) the transition is at 217 nm, corresponding to 131 kcal mol^{-1}. For β-carotene, which has 11 conjugated π-bonds, the transition is at 470 nm, corresponding to 60 kcal mol^{-1}. These examples demonstrate how the extending conjugation changes the electronic structure because of the delocalization of π-electrons.

Using hybridization and ideas of delocalization, it is easy to rationalize the properties of two of the allotropes of carbon, namely diamond and graphite. In the case of diamond, each carbon atom is sp^3 hybridized and diamond is an extended structure, in which each carbon has four bonds in a tetrahedral arrangement to four other carbon atoms. The rigidity of these σ-bonds creates the hardness diamond has (diamond is the hardest natural material, graded 10 on the scale of mineral hardness, the so-called Mohs scale). In the case of graphite, each carbon atom is sp^2 hybridized, which creates flat structures with delocalized electrons. Thus, the material has very low energy levels between its HOMO and LUMO – hence, it is black in color. Furthermore, graphite readily conducts electricity because of the delocalized π-bonds. The extended structure of graphite is a consequence of the $2p_z$ orbitals, which bond weakly between sheets of the sp^2 structures; this imbues graphite with its lubricating property.

Extended molecular systems that involve non-carbon atoms can also be bound through σ-bonds, as in C–Cl or π-bonds C=O, and heterocyclic systems, such as pyrrole. Because the electronegativity of atoms such as O, S, Cl, and other non-carbon atoms differs from that of C, this results in polar bonds in the molecular structure containing these systems.

Additional types of bonding

A number of other bonding types are recognized that flow from the ideas of covalent and ionic bonding.

The *coordinate covalent bond* arises when overlap between atomic orbitals creates a molecular orbital, but only one of the atoms involved has electrons. This type of bonding is commonly found in amines because the nitrogen adopts an sp^3 configuration, but since it has an extra electron (N is $2s^22p^3$) compared to carbon, only three σ-bonds are formed, leaving a lone pair (Figure 11-14). This lone pair can create a bonding interaction if it overlaps with an empty orbital of another species. Boron, which has one less electron than carbon, can bind to an amine (Figure 11-15). As the amine donates electrons, it is termed a Lewis base, and the boron, which accepts electrons, is called a Lewis acid.

Coordinate bonding may also occur in metal complexes in which the binding species, the ligand, donates electrons to form the σ-bonding, and the *d* orbitals on the metal play a secondary role in bond formation. *Cis* platin (Figure 11-16) is probably the best example of a drug that has this bonding characteristic.

Metallocenes

In 1973 Fischer and Wilkinson shared the Nobel prize in chemistry for the discovery of ferrocene.[2,3] Ferrocene is composed of two cyclopentadienyl rings with an iron in between (Figure 11-17). What is remarkable about ferrocene is that it is very stable; it can be boiled at 249°C. The compound was first reported in 1951 by Kealy and Pauson.[4] Based on the knowledge of bonding that

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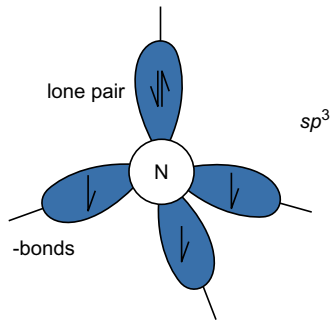

Figure 11-14. The sp^3 hybridized N atom centre.

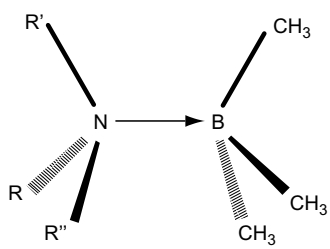

Figure 11-15. Formation of a coordinate bond between a tertiary amine and trimethylboron.

existed at that time, they proposed a σ-bonded structure. However, they did recognize that such a structure would not have great stability, and thus, that what they had made was unusual. In fact, ferrocene is bonded not by σ-bonds but rather by π-overlap.[5] The cyclopentadienyl ring in ferrocene can be thought of as having five sp^2 hybridized carbon atoms (the ligand formally carries a negative charge). The residual electrons lie in unhybridized *p* orbitals. These are able to overlap and bond with the 3*d* orbitals on the iron (which is formally Fe^{2+}), a so-called metallocene or haptic bond. This makes the compound chemically stable, and ferrocene behaves like an aromatic system, such as benzene.

ISOMERS

One of the critical issues in dealing with molecules is that they can bond to each other in different ways yet have the same formula. For example, the formula C_2H_6O corresponds to ethanol or dimethyl ether. The former is a colorless liquid, which can be tolerated and metabolized by the human body (having an LD_{50} in rats of about 7000 mg/kg). The latter is a colorless gas used in aerosol cans and is much more flammable than ethanol and more toxic (LD_{50} in rats of about 1000 mg/kg). These are examples of structural isomers in which the atoms in the molecule are the same, but they are attached in different ways.

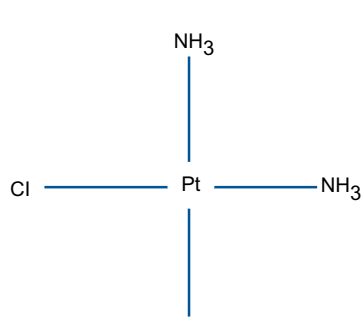

Figure 11-16. *cis* platin. The NH_3 and Cl ligands donate electrons for the four σ-bonds in this structure. The platinum actually adopts a planar structure.

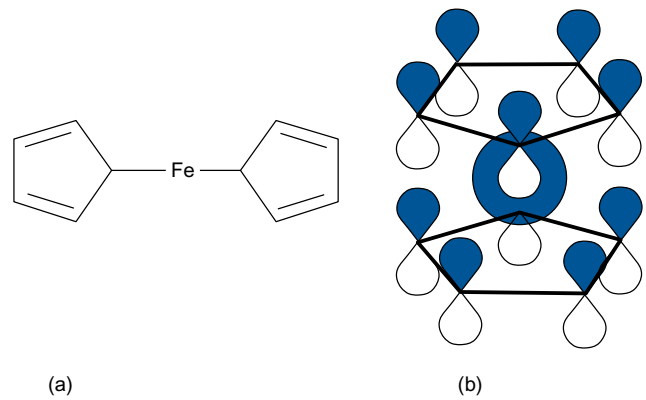

Figure 11-17. (a) The incorrect σ-bonded structure of ferrocene, and (b) the metallocene structure.

However, isomers in molecules can be more subtle than those discussed above. Geometric isomers exist where the bonding attachment between two compounds is the same, but because of the rigidity of the molecule, the atoms are not in identical positions. This is common in alkene systems because the double bond cannot rotate.

In the example shown in Figure 11-18, the compounds have identical attachments, in that each sp^2 carbon is bonded to one hydrogen, one chlorine, and another sp^2 carbon. But in one case the chlorine atoms lie on the same side of the π-bond, and in the other on opposite sides. The same-side isomer is called the *cis* isomer; the opposite-side is the *trans* isomer.

These geometric isomers are a subset of stereoisomers: compounds with the same structure but for which the atoms do not occupy the same arrangement in space. *Cis* and *trans* isomers can also exist if hydrogen bonding is present (see below the example of captopril) or in rings that restrict rotation of the bonds (Figure 11-19).

Conformations

Open chain compounds can create different conformations because of the ability to rotate the σ-bonds. If we consider C_2H_6, ethane, the rotation of the central carbon carbon bond may be such that the hydrogen atoms are *staggered* with respect to each other, or *eclipsed*. These are not isomers but different conformers, and they have different energies. They may be depicted using a Newman projection, in which the molecule is viewed down the axis of the bond that is undergoing rotation (Figure 11-20).

The situation is slightly more complicated if there are different substituents attached through the σ-bond of interest. In the case of butane, the central carbon linkage has each carbon atom bonded to two hydrogens and one methyl group (Figure 11-21). The eclipsed and staggered conformations must also consider the interaction of the methyl groups. In this case, when the methyl groups are opposite, the conformation is fully eclipsed and has the highest energy as the repulsive interactions of the methyl groups are maximized. If the methyl groups are opposite hydrogen atoms, the conformation is eclipsed. In the staggered conformations when the methyl groups are a maximum distance apart, the conformation is called anti, and when they are staggered but closer, the conformation is called gauche.

Enantiomers

These are molecules that exhibit optical activity, in that they interact with light of different handedness in differing ways. They normally possess the same atoms around a tetrahedral central, such as carbon sp^3, but they are non-superimposable, and they are called chiral centers (Figure 11-22). These enantiomers are chemically identical but interact with plane polarized light in different ways.

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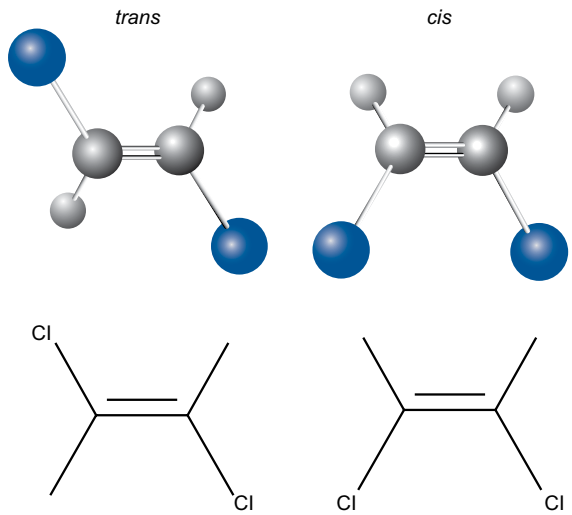

Figure 11-18. Depiction of *trans*- and *cis*-1,2-dichloroethene as a molecular model picture and as a chemical structure.

The absolute configuration of a chiral centre (termed *R* and *S* configurations) may be determined by using the following methodology.

1. Allocate substituent priorities.
2. The substituent with the atom bounded to the chiral centre with lightest mass is allocated as priority four, the next heaviest is three, and so on. In the event of equal mass bounded atoms, count down the chain until the substituents differ, and that with the lower mass is allocated the priority number up to four. In the example shown in Figure 11-22, the Cl is priority one; O is priority two; carbon, priority three; and hydrogen, priority four.
3. Rotate the sp^3 centre, such that the lowest priority substituent is pointing away from the viewer, i.e., into the page.
4. Determine if the priority labels are arranged in a clockwise or counter-clockwise fashion with regard to highest priority one to three. A clockwise orientation has an *R* absolute configuration, and a counter clockwise orientation has an *S* configuration (Figure 11-23).

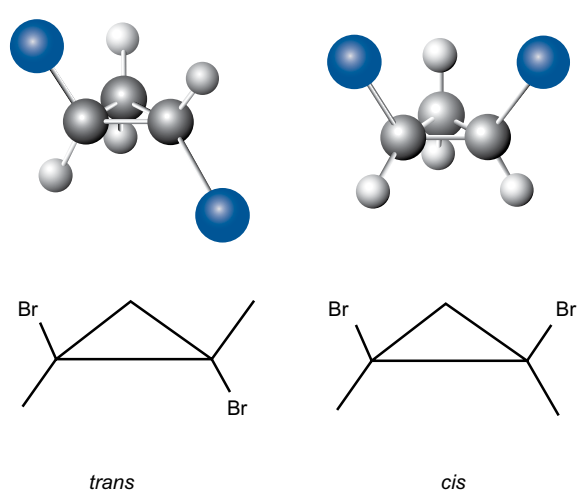

Figure 11-19. *Trans* and *cis* isomers of dibromocyclopropane; the strained ring system does not allow for bond rotation.

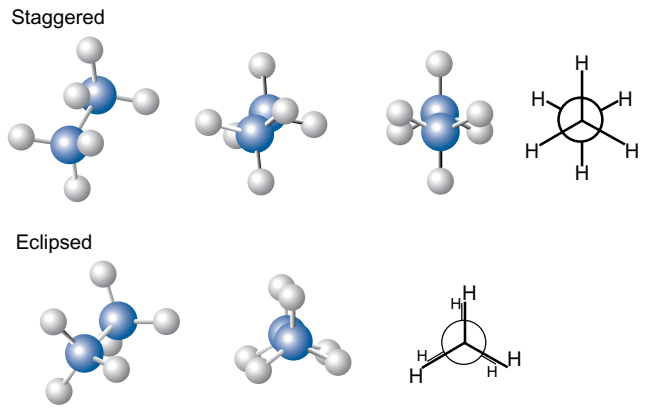

Figure 11-20. Staggered and eclipsed. Depiction of three dimensional models of the staggered and eclipsed conformers of ethane – rotated around into the orientation used in the Newman projection, shown on the right for each conformer.

Measuring optical activity

The most striking difference between two enantiomers is their interaction with light. In most other respects, such as physical properties like melting and boiling point, they are identical, but in their interaction with light, they may be differentiated.[6] In 1815 Jean-Baptiste Biot noted that some materials could rotate plane polarized light. Subsequent to this, Louis Pasteur discovered that tartrate crystals could be separated by physically picking them out under microscopic examination and

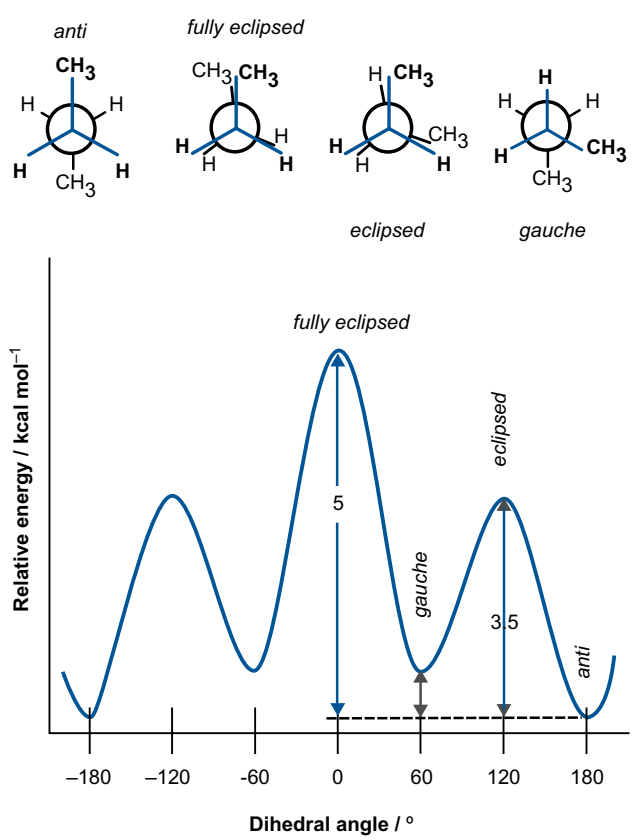

Figure 11-21. Depiction of different conformers for butane and the changes in relative energy that occur as the dihedral angle between the methyl groups is altered from 0° (fully eclipsed) to 180° (anti).

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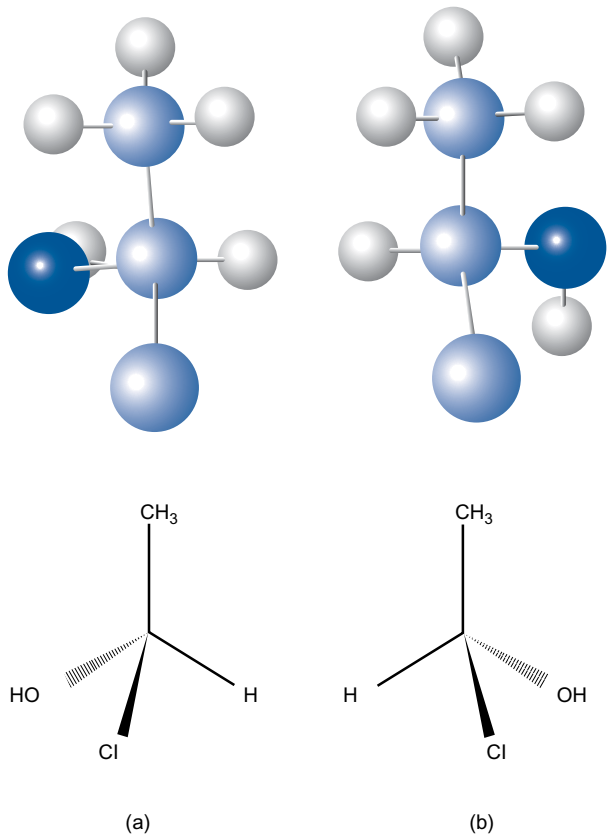

Figure 11-22. Models and chemical structures of two enantiomers.

that these two separate types of crystals rotated plane polarized light to the right or to the left in equal amounts. Yet a mixture of the two types of crystals had no effect on the polarization of light. The rotation of plane polarized light is a fairly subtle effect. To understand it, we need to consider the nature of light. We can think of light as an oscillating electromagnetic wave. The wave moves in the *z*-direction with the electric field oscillating in the *xz* plane and that of the magnetic field in *yz*. We need only concern ourselves with the electric field. The question arises, how can a chiral centre affect a plane wave? To answer this, we need to consider the plane wave as being made up of two components; each of these is a vector, but they rotate in a clockwise (E_R) and counter-clockwise (E_L) direction. When they are aligned (Figure 11-24), the electric field is at a maximum in the x axis; as they rotate, the strength of the field in the x-axis diminishes until they oppose each other, and after that the direction of the field changes until both vectors point in the -x direction. Note that at no time during the precession of the two vectors is there any electric field in the y axis because they always cancel. What is remarkable about chiral centers is that they interact differently with the E_R and E_L vectors. This can be described in a number of ways, but generally it is said that the refractive index (n) for each direction differs; that is, n_R does not equal n_L. This literally means that the speed of light differs for each of the vectors; in other words, the speed with which E_R rotates differs from that of E_L. This is depicted in Figure 11.25, in which the E_R vectors rotates more slowly than *EL*. The effect of this is that the resulting vector (E) has a component in the x-axis and thus starts to rotate. The longer the path length of the optically active medium, the more it will rotate, and furthermore, as soon as the light exits the medium, the two rotating vectors continue rotating at equal speed, and the light becomes plane polarized again just with a rotation imbued from the interaction with the optical material.

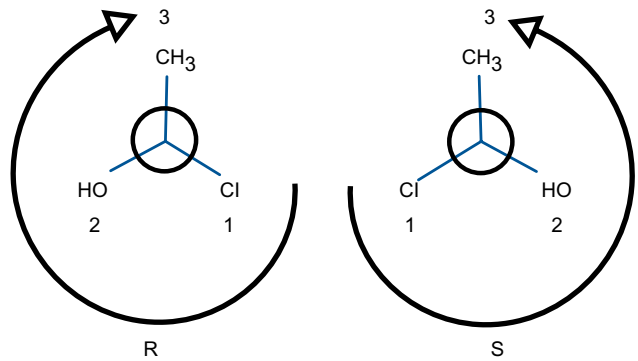

Figure 11-23. The rotated structures from Figure 11-22, showing allocation of substituent prioirties and absolute configuration.

The angle of rotation of light (α) is given by:

$$\alpha = \frac{1800}{\lambda}(n_L - n_R) \tag{11}$$

Where: α is called the angle of rotation [degrees per cm of medium]; λ is the wavelength of the polarized light [m]; and *nL* and *nR* the refractive indices of the left and right circularly polarized components of the plane polarized light.

It is very common to use the sodium D line at 589.3 nm for single wavelength determinations of angle of rotation. A more commonly used term is the specific rotation ($[\alpha]^T_\lambda$) which is given by:

$$[\alpha]^T_\lambda = \frac{\alpha}{lc} \tag{12}$$

Where: l is the pathlength of the solution of optically active material [dm]; and c the concentration [g mL^{-1}].

Both temperature (T) and wavelength (λ) need to be specified because they have a significant effect on the degree of rotation (see above). This effect is very small. For example, the angle of rotation of the optical material may be 2.00°; this corresponds to a difference in refractive indices ($nL - nR$) of about 7×10^{-8}.

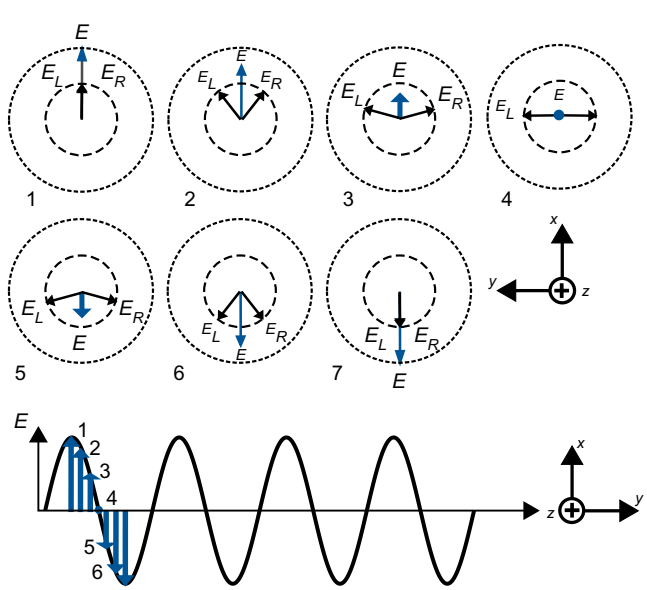

Figure 11-24. Depiction of the plane polarized light wave, made up of left-hand and right-hand rotating circular polarized vectors (*EL* and *ER*). As the vectors rotate, the amplitude of the resultant electric field goes from a maximum value at **1** through a node at position **4** to a minimum at position **7**.

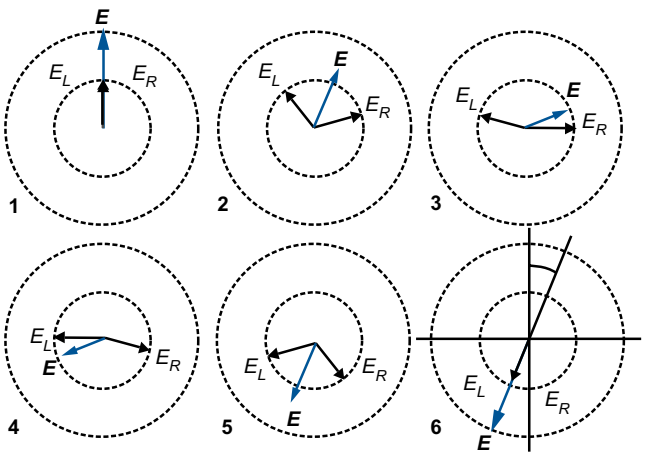

Figure 11-25. Depiction of the transmission of plane polarized light through an optically active medium (**2-5**). As the light passes through the medium, the left-handed circularly polarized light travels more slowly, and so the left and right parts get out of synch. Once the light exits, the medium both parts rotate at the same speed (**6**), and this results in a restoration of the plane polarized light field, but now it is rotated by an angle (α).

In addition to the ability of chiral centers to differentiate the circular components of plane polarized light, molecules with these centers can also absorb circularly polarized light to different extents. That is, the extinction coefficient (ε) is such that $\varepsilon R \neq \varepsilon L$. This phenomenon is referred to as circular dichroism (CD), and spectra of materials with this effect may be measured. Figure 11-26 shows the absorption, CD, and optical rotatory dispersion (ORD) spectra for a chiral molecule. The sign of the ORD response changes as the wavelength is scanned across the absorption spectrum, and the CD spectrum has a sign, depending on whether $\varepsilon R > \varepsilon L$ or vice versa. The CD plot is given by the molar ellipticity ([θ]) versus wavelength, where:

$$[\theta] = 3300(\varepsilon_L - \varepsilon_R) \quad (13)$$

Where: [θ] is measured in degrees cm–*2* per decimole and typically has values of approximately 0.08 degrees cm^{-2} per decimole.

If the light is rotated to the right, it has a positive value and is said to be dextrorotatory; if it is to the left, it has a negative value and is termed levorotatory. These terms are phenomenological only, and the reasons for the direction of rotation cannot be readily associated with the absolute configuration (*R* or *S*) of the chiral centre.

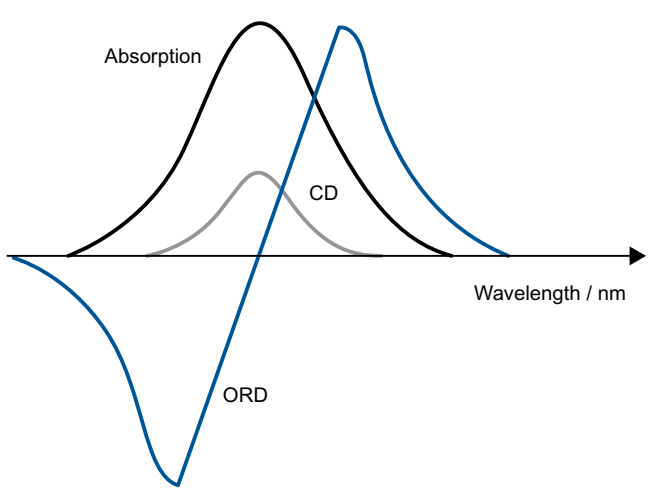

Figure 11-26. The spectral response of an optical absorption and the corresponding ORD and CD curves – note that the direction of the ORD and CD may be reversed depending of which handedness of light interacts with the optical material.

MOLECULES WITH MANY CHIRAL CENTERS

It is not uncommon that molecules with more than one chiral centre exist. These molecules are termed diastereoisomers, and they show different physical properties in addition to rotation of plane polarized light. The naming of the molecules will reflect the atom number and the chirality associated with each centre. For example, in Figure 11-27a the molecule, 2,3,4-trihydroxybutanal is shown. The particular configuration depicted is 2*S*, 3*S*, based on the fact that carbon 2 has an *S* configuration and carbon 3 an *S* configuration. A convenient way to depict such structures is to use a method invented by Fischer in 1891. This involves rotating the three dimensional structure so that the carbon–carbon bond containing the two chiral centers is vertical in the plane of the page. The residual carbon backbone is also depicted vertically, although these now point backwards into the page, and the other substituents are coming out of the page. This depiction is then "flattened" to give the so-called Fischer projection. These Fischer projections allow one to conveniently depict multiple chiral centers. The four optical isomers of 2,3,4-trihydroxybutanal may be readily drawn, using Fischer projections (Figure 11-27b). Note that not all are enantiomers of each other, and indeed, if the substituents on the carbon atoms are the same, then *meso* configurations are possible, in which two of the depicted configurations become symmetry equivalent; this occurs in tartaric acid.

Intermolecular binding forces

Up till now we have focused on the interaction and binding of atoms to molecules. A critical aspect of the behavior of

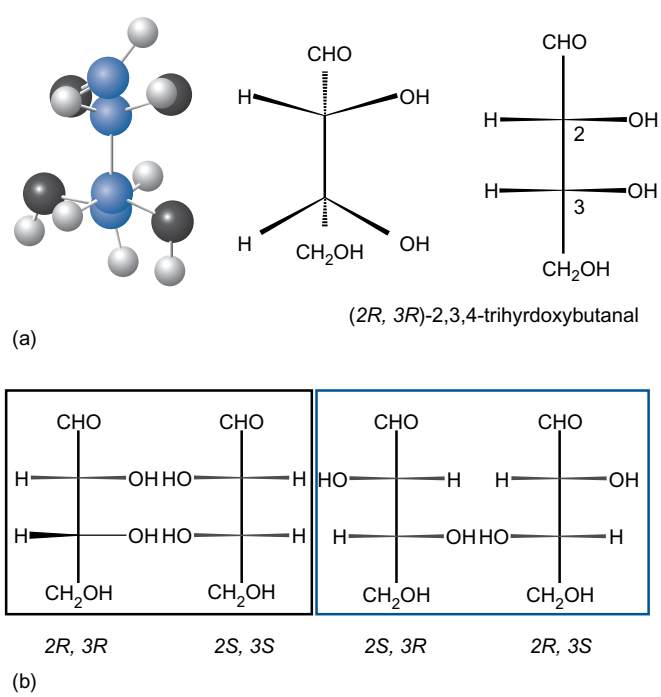

Figure 11-27. (a) Depictions of 2,3,4-trihydroxybutanal from a model structure (left) to the Fischer projection (right); the intermediate structure shows how the molecule is rotated so that the carbon backbone is in the plane of the page or behind it. (b) Fischer projections of 2,3,4-trihydroxybutanal. Absolute configurations are given, the 2*R*, 3*R* and 2*S*, 3*S* are enantiomers; the 2*S*, 3*R* and 2*R*, 3*S* are enantiomers. However, 2*R*, 3*R* and 2*S*, 3*R* are not enantiomers but diastereoisomers.

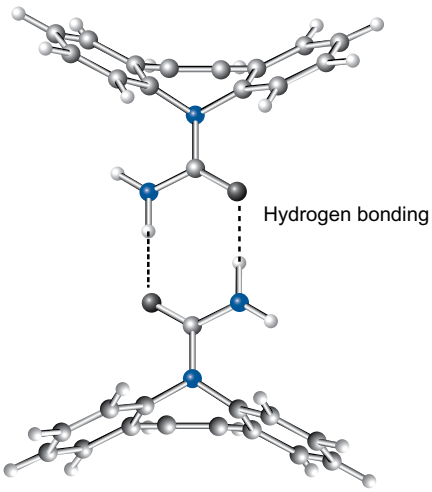

Figure 11-28. Structure of carbamazepine dimer with hydrogen bonding.

pharmaceuticals is the nature of the interactions between molecules, the intermolecular forces. The intermolecular forces may involve specific intermolecular bonds – such as hydrogen bonds – or they may involve weak attractive forces due to the electron distribution in the molecules.

Hydrogen bonding is a very important interaction, in which a pendant hydrogen interacts with the electronegative atom of a neighboring molecule. A good example of this is the anticonvulsant drug carbamazepine (CBZ), which shows distinctive hydrogen bonding between the H atom on the NH_2 group and the neighboring oxygen of the C=O linkage (Figure 11-28). The energies of these interactions are rather weak, being less than 10 kcal mol^{-1}.

Dipole–dipole interactions occur where molecules have an asymmetric distribution of electrons, i.e., they contain polar bonds. These dipoles can align to lower the energy of the assembled molecules (Figure 11-29). Typically the energy of such interactions is weak, being less than 2 kcal mol^{-1}.

Dispersion forces occur even in molecules with no discernible dipole. The electrons buzz around the nuclei, and at a particular moment there may be an asymmetric electron distribution

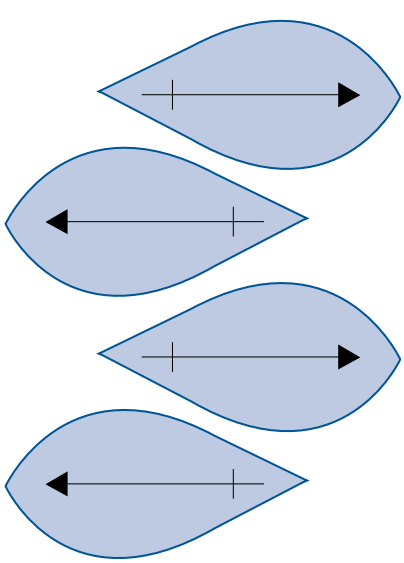

Figure 11-29. Molecules with dipole moments (depicted by arrows) align to lower energy through a dipole–dipole interaction.

and a brief temporary dipole. Despite the fleeting nature of these dipoles, an interaction does occur and may be referred to as either dispersion or London forces (after Fritz London who first described them). These are weak, being less than 1 kcal mol^{-1}, but they are present in all molecules.

Visualizing forces

It is now possible and relatively easy to calculate the structures of molecules using computational chemistry[7,8] so the forces that hold the molecules together may be evaluated. Furthermore, it is possible to measure the forces that hold molecules together using spectroscopy. The strength of bonding is associated with the potential energy curve, depicted in Figure 11.7. In the case of a covalent bond, the bond can vibrate at discrete frequencies, and this may be detected by shining light of the appropriate energy at the molecule. For covalent bonds these resonances occur in the infrared region of the electromagnetic spectrum (40 to 4000 cm^{-1}), and most materials may be characterized by their infrared spectra; as the depth and steepness of the bonding interaction decreases, so too does the energy at which the resonances or absorptions occur. In fact, the absorption frequencies may be related to the force constants (k, N m^{-1}) that hold the molecule together and the masses (the reduced mass μ, kg) involved in the various vibrations. The upshot of this is that the stronger the bonding, the higher the frequency. If lightweight atoms, e.g., hydrogen, are involved in the vibration, then the frequency of the absorption will be high. The frequency of the absorption ($\tilde{v}$, cm^{-1}) is given by

$$\tilde{v} = \frac{1}{2\pi c}\sqrt{\frac{k}{\mu}} \qquad (14)$$

Where: c is the speed of light [cm s^{-1}].

Some representative data on bond vibrations are given in Table 11.6.

The use of spectroscopy in understanding structure and bonding is well illustrated by the study of *cis* and *trans* captropil. Captopril, 1.[2(S)-3-mercapto-2-methyl-1.oxo-propyl]- L -proline, is a drug for treatment of hypertension and heart failure. It exists in an equilibrium between *cis* and *trans* forms, with the *trans* form being the active form. The ratio of *trans:cis* is approximately 6:1 at room temperature in solution. The *trans* and *cis* isomers are created by the two conformers that exist about rotation around a C–N bond, with the *trans* form being locked by a hydrogen bond (Figure 11-30).

The captropil structure contains two carbonyl bonds (C=O), and the frequencies of vibrations for these is distinct, depending on the isomer formed. This is because the *trans* isomer is hydrogen bonded, which shifts the C=O vibration from 1637 cm^{-1} down to 1591 cm^{-1}. Wang *et al.*,[9] studied this drug in the solid

Table 11-6. Vibrational Spectroscopy and Bonding Parameters for Selected Bond Types

Bond type	V/cm^{-1}	k/Nm^{-1}	μ/kg	Bond strength/ kcal mol^{-1}
C–C	1130	450	9.96×10^{-27}	90[a]
C=C	1600	900	9.96×10^{-27}	170
C≡C	1990	1400	9.96×10^{-27}	234
C–H	2880	450	1.53×10^{-27}	

[a]Estimated from the bond enthalpy for C_2H_6, C_2H_4 and C_2H_2 respectively.

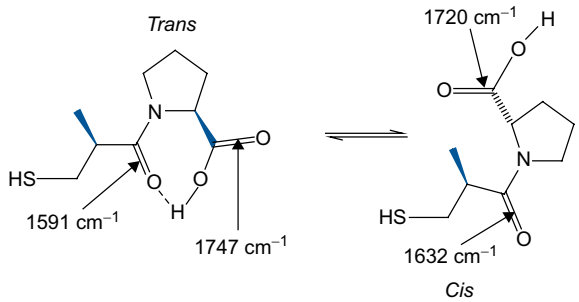

Figure 11-30. The structures of *trans* and *cis* forms of captopril and the frequencies observed for the various C=O bonds.

state and were able to determine the energetics between the two isomers.

For intramolecular interactions, the interactions are 10 to 20 times weaker than covalent bonds; thus, the interaction has very low energy infrared absorptions. These occur in the terahertz region of the spectrum (where $\tilde{\nu} < 100\,\text{cm}^{-1}$). Different polymorphs of a drug (see the section on polymorphism) will have very similar infrared spectra because the bonding interactions of the molecule that make up the pharmaceutical are virtually unchanged (unless there is hydrogen bonding), but the terahertz (THz) region of the electromagnetic spectrum is distinctive for each polymorph because the intermolecular forces differ between polymorphs. Carbamazepine shows a number of polymorphs, and these have been characterized using THz spectroscopy.[10] The spectra of the form III polymorph shows distinctive bands at 31, 44 and 52 cm^{-1} (Figure 11-31), whereas polymorph I has a band at 41 cm^{-1}.

STATES OF MATTER

INTRODUCTION

In everyday life we usually consider three states of matter: the solid state (solids), the liquid state (liquids), and the gaseous state (gases). For example, water can be differentiated into the three states: ice, liquid water, and water vapor, and at a given pressure (usually normal or atmospheric pressure, 1.013 bar) it is the temperate that decides in which state water is present; at normal pressure ice melts at 0ºC and boils at 100ºC. What we are observing at these temperatures are phase transitions from the solid state to the liquid state (melting) and from the liquid state to the gaseous state (boiling). If we lower the temperature of water vapor below 100ºC, we observe condensation (gas to liquid transition) and if we further lower the temperature below 0ºC, we observe freezing of the liquid water to ice.

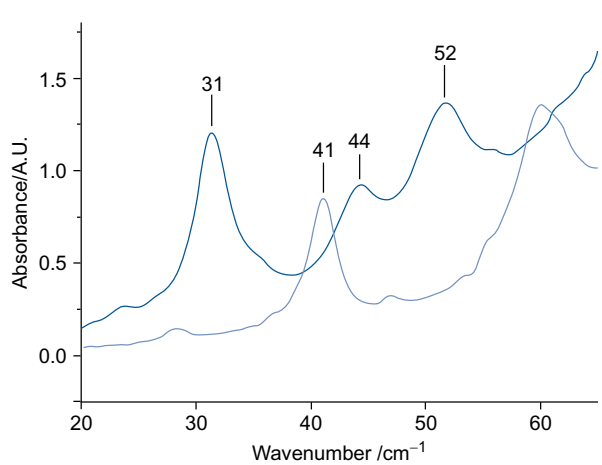

Figure 11-31. THz spectra of carbamazepine: Upper trace polymorph III, lower trace polymorph I.

In this section we will describe the different states of matter (including a few "exotic states", which nevertheless do play a role in some pharmaceutical applications) and highlight their most important characteristics. We will also discuss how we can describe the different states of matter in phase diagrams and identify a few experimental techniques that can be used to determine the characteristics of a given state of matter. Because most drugs and dosage forms used in the pharmaceutical field are solid at room temperature, we will discuss the solid state in a little more detail than the other states of matter.

SOLIDS, LIQUIDS AND GASES – A QUESTION OF INTERMOLECULAR FORCES

As outlined above, when we think about states of matter, we usually think of them in terms of solids, liquids, and gases. These distinctions are based on the interactions between the molecules (or in some cases atoms or ions) of the matter in question. Since in the pharmaceutical field we are most often dealing with molecules, the discussions below will mainly consider molecules as the components forming the various states of matter, and the reader should keep in mind that in many cases the word "molecule" could be exchanged for the words "atom" or "ion".

In the solid state of a drug, the drug molecules are held together by comparatively strong interactions, which do not allow the molecules to change their position but only to vibrate around a fixed position. These intermolecular interactions result in some important properties of solids. A given mass of a solid at a given temperature and pressure has a defined volume and keeps its shape, if no external forces (such as in milling, agglomeration or tableting operations) are acting on the solid material. Similarly, a given mass of a liquid has a defined volume at a given temperature and pressure (like solids, liquids are practically incompressible), but in contrast to a solid, its shape can vary and will take on the shape of the container it is placed in. The reasons for this are again the interactions between the molecules in the liquid state. These are still considerably strong, but the kinetic energy of the molecules is now sufficiently high to allow the molecules to change their positions (not only to vibrate around a fixed position) and to move relative to each other by diffusion or convection. This is also the reason why the density of a liquid is usually lower than that of a solid (with the most important liquid in the pharmaceutical field being the exception: water has its highest density at normal pressure at 4ºC, i.e., in the liquid state). A gas, on the other hand, does not have a defined shape or volume (in fact, gas molecules will fully occupy each volume available to them) and thus has a very low density, depending on the volume it occupies. This is due to the fact that intermolecular interactions in real gases are very weak and, in fact, are considered zero for an ideal gas. Since interactions between the molecules (or between atoms or ions) are very strong or strong in solids and liquids, these two states of matter are also summarized as condensed matter. In contrast, since the molecules in the liquid and gas state are able to change their positions, these two states of matter are summarized as fluid matter.

CHANGES BETWEEN THE STATES OF MATTER

Upon the heating (at constant pressure), for example, of a solid drug material (usually in a crystalline form, see below), the solid transforms into a liquid (melt) and further into a gas (if it is not chemically degraded in the heating process). Heat (Q, a form of energy, Unit: Joules, J) is transferred into the material during the heating process. This leads to an increase in the enthalpy ΔH [J] of the material.

$$Q = \Delta H \tag{15}$$

It follows that a gas has a higher enthalpy than a liquid and a liquid has a higher enthalpy than a solid for a given material. At the same time, the number of ways in which the molecules can be arranged with respect to each other also increases. This is known as the entropy S [J K^{-1}] of the system and is often described as the "disorder" of the system. It follows that upon a state change due to heating, both the enthalpy and the entropy of the material increase. Since every system has a tendency to exist in the lowest enthalpy and the highest entropy form, it depends on the temperature T of a given system (here considered solely as the material in question) in which form it is present. This can be summarized in form of the equation:

$$\Delta G = \Delta H - T\Delta S \tag{16}$$

Where: ΔG [J] is the free energy of the system.

If a liquid is heated, the temperature of the liquid will increase. How much the temperature increases as a function of the added heat energy depends on the heat capacity of the liquid. The heat capacity, C, can be defined as the amount of heat energy, Q, required to change the temperature, T, of a given material by a given temperate interval ΔT (measured in Kelvin, K):

$$C = Q / \Delta T \tag{17}$$

In this form C is an extensive variable, i.e., its value will depend on the mass of the material. To convert the heat capacity into an intensive variable, i.e., a variable whose value is independent of the mass of the material (measured in kg) or its amount (measured in mol), the heat capacity is usually expressed as either specific heat capacity, Csp [J K^{-1} kg^{-1}], or molar heat capacity, $Cmol$ [J K^{-1} mol^{-1}].

In any case, the result of heating the liquid for a given period of time is that the temperature of the liquid increases. However, when the liquid starts to boil, i.e., the state of the material changes from the liquid to the gaseous (vapor) state, we observe that the temperature of the material stays constant during this state transition. This temperature is the boiling point (Tb in Figure 11-32). Similarly, when a solid melts, the temperature of the material stays constant during this state transition (melting point, Tm in Figure 11-32). This is because when a substance boils, the liquid and vapor state are in equilibrium, and when a substance melts, the solid and liquid state are in equilibrium. Any heat that is applied to the system will be used to bring about the state transition until the liquid (or solid) has completely gone into the vapor state (or liquid state). Only then does the temperature rise further. The energy used for boiling the liquid is known as latent heat of vaporization (or boiling) and in the case of condensation, the energy released is known as latent heat of condensation. The amount of energy used in the vaporization process is identical to the heat of condensation released in the condensation process since these processes are reversible.

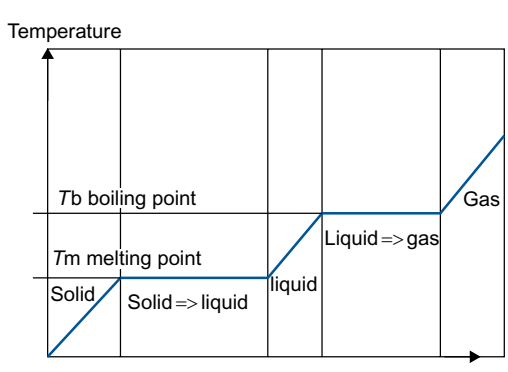

Figure 11-32. Heating curve of a material undergoing a state transition from solid to liquid and from liquid to gas. Note that the temperature stays constant during the state transitions.

During a phase transition the heat capacity of the material is infinitely high (all heat energy is used to bring about the state change), and such transitions are termed first-order phase transitions. The same holds true for the state transition from a solid to a liquid (latent heat of melting) or from a liquid to a solid (latent heat of freezing). In melting and boiling processes, the change is endothermic (the system absorbs energy), whereas in freezing and condensation processes, the change is exothermic (the system releases energy). At the melting and boiling point, the change in Gibbs free energy (ΔG) is zero. However, as discussed above, the enthalpy and the entropy of the material are increasing (i.e., ΔH and ΔS have positive values). Taking into account the relationship between the free energy and the enthalpy and entropy of the systems (see equation 16, $\Delta G = \Delta H - T\Delta S$, note the minus sign between ΔH and ΔS), we can conclude that a phase transition occurs when the free energy of the gas (or liquid) is lower than that of the liquid (or solid) at a given temperature for the material in question. At a given pressure, the temperature that denotes the boiling or melting point is the temperature at which ΔG for this process is zero, i.e., at exactly the boiling or melting point (for a given pressure), the two states can coexist.

So far we have considered the temperature as being decisive for a given material in what state of matter it is present. However, to fully describe a given state of matter, we require a second intensive variable, pressure, p. If we plot temperature on the x-axis and pressure on the y-axis of a coordinate system, and determine the state of a given material at any temperature–pressure combination, we obtain the phase diagram of the material in question. Let us again consider water.

Figure 11-33 shows the (partial) phase diagram of water as a function of pressure and temperature. We can differentiate three areas, those of solid water (ice), liquid water (water), and water vapor. To fully describe the state of water in each of these areas, we need to specify the temperature and pressure at which the material is present. For example, water exists in the liquid state at both temperature–pressure combinations indicated in the diagram by the symbol ▲ and, in fact, at an infinite possibility of other temperature–pressure combinations in the region of liquid water. The same holds true for the areas of solid water and water vapor. The different areas of the phase diagram are separated by boundary lines, known as the phase boundaries. At combinations of pressure and temperature which lie on these phase boundaries, two states of water exist in equilibrium. The curves a, b, and c in Figure 11-33 are known as the sublimation (or re-sublimation) curve (solid and gas in equilibrium), the melting (or freezing) curve (solid and liquid in equilibrium), and the boiling (or condensation) curve (liquid and gas in equilibrium). Note the orientation of the melting curve b in Figure 11-33: its slope is negative; that is, at constant temperature ice can melt if the pressure is increased (this is the principle of ice-skating). Most other compounds behave oppositely; they can solidify under pressure, so their melting curves will have a positive slope. This is termed the anomality of water and also explains the observation that ice has a lower density than liquid water.

To determine, for instance, the position of the boiling curve in the phase diagram of water, we have to determine the vapor pressure of water at various temperatures. If we place a liquid in a vacuum at a temperature T, some of the molecules of the liquid will leave the liquid phase and will go into the free space above the liquid until an equilibrium is reached, in which the same number of molecules from the free space above the liquid will go into the liquid as are leaving the liquid (this is a dynamic equilibrium). As long as there is still liquid water left (note: it is not important how much water is left), the resulting pressure is known as the vapor pressure of the liquid, and will constitute a point on the boiling curve at the temperature T. Figure 11-34 shows the temperature dependence of the vapor pressure of water. In a closed system the vapor pressure increases with increasing temperature. This is true not only for water but for

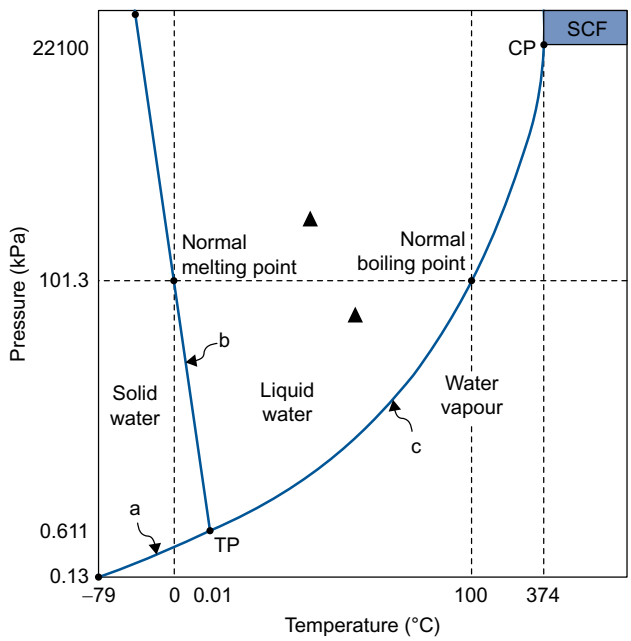

Figure 11-33. Partial phase diagram of water. The curves a, b, and c are the sublimation (or re-sublimation) curve (solid and gas in equilibrium), the melting (or freezing) curve (solid and liquid in equilibrium), and the boiling (or condensation) curve (liquid and gas in equilibrium), respectively. TP: triple point, CP: Critical point, SCF: region in which water exists as supercritical fluid. ▲shows two different pressure and temperature combinations at which water exists in the fluid state. Note that the temperature and pressure axes are not linear.

all substances, since an increase in temperature increases the likelihood for molecules to leave the condensed phase, as the increased kinetic energy of the molecules counteracts the attractive forces holding the molecules together in the condensed phase. Different liquids have different vapor pressures at given temperatures. A liquid will boil at a temperature at which its vapor pressure equals the pressure exerted onto the liquid by the surrounding pressure of the environment. Taking again the example of water, at 100°C the vapor pressure of water is 101.3 kPa, so under normal (sea level) condition of atmospheric pressure, water will boil. At 20°C, however, the vapor pressure of water is only 2.3 kPa, so it will not boil under these conditions. An interesting consequence of this is that water, for example, on a high mountain (where the atmospheric pressure is lower than at sea level) will boil at a lower temperature than 100°C.

At this point it let us make a quick stop and consider the question why drying (for example, of wet granules, to take a pharmaceutical example) occurs even if the temperature is far below 100°C at normal atmospheric conditions (i.e., below the boiling point of water). To understand this, we have to differentiate between the processes of boiling and evaporation. We have seen that, in a closed system, molecules from the liquid will leave the liquid phase until the equilibrium vapor pressure for the given temperature is reached. However, in an open system (for example, wet granules in a laboratory) some molecules from the surface of the liquid will have a sufficiently high kinetic energy to leave the liquid and are then transported away. This process takes place at any temperature also below the boiling point of the liquid, and its rate depends on factors such as

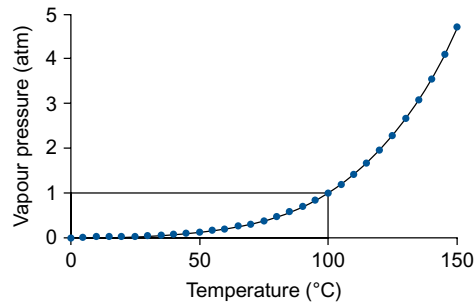

Figure 11-34. Temperature dependence of the vapor pressure of water.

- the surface area between the liquid and the air (evaporation is a surface phenomenon)
- the temperature of the liquid (the number of molecules with a sufficiently high kinetic energy to leave the liquid phase increases with increasing temperature)
- the air above the liquid (if there is an air stream, transport of the molecules away from the liquid is facilitated)
- the humidity of the air above the liquid (evaporation of water molecules from a liquid will be faster if the air is dryer), as well as other factors.

It should be noted that evaporation takes place from the surface of a liquid, whereas boiling takes place also in the liquid (that is the reason why water vapor bubbles are formed in boiling water).

We have seen how we can determine the boiling curve for a liquid to construct the phase diagram of a substance. Similarly, we can determine the sublimation curve, although experimentally this is more difficult due to the much lower vapor pressure of solids. The melting curve can be determined by thermo-analytical methods. This is usually done by determining the cooling curve of a material at various pressures as a function of time.

As we have already discussed for the boiling of a liquid, during the phase transition from the liquid to the solid, the temperature does not decrease. If we are heating a liquid in a closed container, the vapor pressure will also increase. However, since the space above the liquid is limited, further heating will increase the number of molecules in the space above the liquid, and thus the density of the gas phase will increase. At a certain, material-dependent temperature, the density of the gas phase will be equal to the density of the liquid, so that there will no longer be a phase boundary between the liquid and gas phase, and both are now indistinguishable (this is called a supercritical fluid). The temperature (critical temperature) and pressure (critical pressure) combination at which a supercritical fluid is formed is known as the critical point (CP in Figure 11-33). At temperatures above the critical temperature a liquid can no longer exist or be formed by increasing the pressure, and thus the critical point marks the end of the boiling curve. The region in the phase diagram at temperatures and pressures higher than that of the critical temperature is known as the supercritical fluid region (SCF). For water, the critical point is at approximately 374°C and 22.1 MPa, and for CO_2 the critical point is at approx. 31.1°C and 7.38 kPa. Supercritical fluids have gained pharmaceutical importance since this state of matter combines properties of gases, such as low viscosity and high diffusivity, with properties of liquids, such as a high capacity to dissolve other substances.

From Figure 11-33 we can see another critical point in the phase diagram, known as the triple point (TP in Figure 11-33). At this combination of temperature and pressure, all three states of water coexist in a dynamic equilibrium. For water the triple point is at 0.01°C and 0.61 kPa. The triple point also marks the lowest temperature at which a liquid can exist, so the temperature range for liquids to exist is between the triple

point and the critical point of the material. Similarly, sublimation and resublimation can only occur at temperatures below the triple point (see sublimation curve in Figure 11-33). Since sublimation (in the same way as boiling) occurs when the vapor pressure of the solid material equals that of the gas phase, sublimation should only occur under atmospheric conditions if the pressure at the triple point of the system is above 101.3 kPa (1 atm). For example, solid CO_2 (dry ice) sublimates at atmospheric pressure at −78.5°C since its triple point is at −56.4°C and 517 kPa. For the same reason, in the pharmaceutically relevant process of freeze drying (which at least in the primary drying phase is based on the sublimation of water), an aqueous solution or dispersion is initially frozen (below the temperature of the triple point of water) and is then subjected to a reduced pressure (below the pressure of the triple point of water). In the earlier mentioned real-life example, however, we also observe that wet clothes on a washing line (i.e., at atmospheric pressure) at or below freezing temperature (so the water in the clothes is frozen to ice) eventually will be dry. We thus observe sublimation also for substances for which the triple point has a pressure below 1 atm. The reason for this is that in an open system like that on a washing line, the partial pressure (see below) of the solid does not attain the vapor pressure of the material at the triple point. The situation is similar to the one discussed above for liquids in an open and closed system (evaporation versus boiling).

PHASES

In the examples discussed above, we have talked about states of matter, and we have considered the solid, liquid, and gaseous state. In the phase diagrams we have seen that these states of matter constitute different phases of a material. It is, however, possible and, in fact, very likely that a solid material can in its own right exist in different phases. We can define a phase as a volume element of a system, separated from other volume elements of the system by a phase boundary. The physical properties within the phase do not show abrupt changes, which means that the phase is physically homogeneous. If two phases coexist, such as at the phase boundaries in the phase diagram, the physical properties between the phases, however, are different. For example, at normal pressure and 0°C, the density of ice is approximately 920 kg/m^3; and that of liquid water is approximately 999.8 kg/m^3. Note that water makes an exception from most other materials, in that its higher density is as a liquid rather than as a solid at the equilibrium of liquid water and ice.

Let us again consider the phase diagram of water, but now have a look at a larger temperature and pressure range (Figure 11-35). We can see that different forms of ice can exist (termed ice I to ice VII). These all constitute a solid state of water but are all different in the molecular arrangement of the water molecules. They therefore have different physical properties, and these change abruptly at the phase boundary. These different solid forms of water thus constitute different water phases. While these different ice phases may not be relevant in pharmaceutical applications, they nevertheless show that molecules in the solid state can be arranged in different ways and thus give rise to the existence of different solid phases. At any given temperature and pressure, only one such solid form can be thermodynamically stable, but other forms may exist as metastable forms for considerable times at conditions where another form is the stable form. This will become important when we are considering crystalline solids in more detail later in this chapter.

The phase diagram of water in Figure 11-35 also shows that for a given chemical compound, more than one triple point can exist. In fact, in Figure 11-35 we can see six other temperature–pressure combinations at which three phases coexist in equilibrium. However, unlike the triple point between ice I, water, and water vapor, these are conditions in which either two solid phases and liquid water or three solid phases coexist.

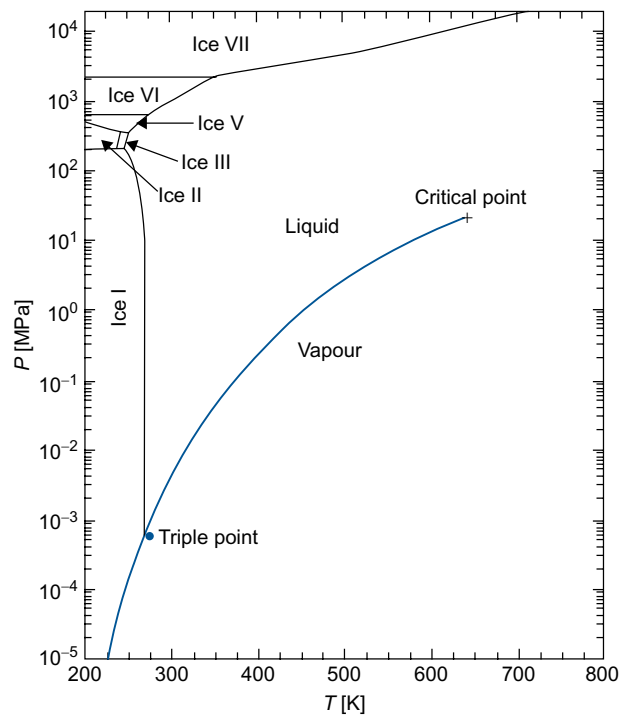

Figure 11-35. Phase diagram of water, showing several solid forms of ice (Ice I – VII). Note that the temperature is given in Kelvin [K], and the pressure axis is in shown in logarithmic form.

Earlier, we have stated that to fully describe a system in one of the areas of the phase diagram, we have to specify both its pressure and temperature. Pressure and temperature are known as the degrees of freedom of the system. The number of degrees of freedom can be defined as the least number of intensive variables (i.e., of variables that do not depend on the amount of material or its mass) of the system that are independent of other variables of the system and that can be changed without changing the number of phases that are coexisting. For any sample within an area of the phase diagram (e.g., in the area of liquid water or in the area of ice III, etc.), we can freely change pressure and temperature (until we reach a phase boundary) without changing the number of phases present (one phase).

If two phases coexist (such as for systems on the phase boundaries), the situation is different. If we change the pressure of the system, we cannot freely change the temperature but have to change the temperature to a specific value, if we don't want to change the number of phases. In the case of two phases coexisting, the system thus only has one degree of freedom. This is important, for example, in moist heat sterilization, such as sterilization in an autoclave. To have both liquid water and water vapor present in the sterilization process (this is most effective in killing microorganisms) at 106 kPa, the temperature has to be 121°C (if no air is present in the autoclave). If we raise the temperature to 134°C, we have to increase the pressure to 312 kPa to maintain the coexistence of liquid water and water vapor.

Finally, if we are at a triple point in the phase diagram, i.e., three phases are coexisting, we cannot change either pressure or temperature without getting a change in the number of phases, which means that here the system has zero degrees of freedom.

From these considerations, Gibbs' phase rule can be formulated as follows:

$$F = 3 - P \tag{18}$$

Where: F is the number of degrees of freedom; and P is the number of phases coexisting (one, two, or three).

So far, we have only considered phase diagrams of a single chemical component (e.g., H_2O). It is, however, also possible to have a single phase system which consists of more than one component. Let us now consider, for example, a salt solution. Here we have a single phase system (the salt molecules are dissolved as sodium and chloride ions in water, and the system is homogeneous). However, in this case, we can vary not only pressure and temperature without getting a phase change but also the salt concentration until we get a saturated solution of the salt in water. In this case, we have three independent variables that can be changed without changing the number of phases coexisting. Of course, as with pressure and temperature changes, this can only be done within limits, i.e., until we reach a boundary line in the phase diagram. If we, for example, increase the salt concentration above the saturation solubility of NaCl at the given pressure and temperature, the excess salt will form a second, solid phase, coexisting with the salt solution phase.

In the example of a salt solution, we have to consider two chemical entities, H_2O and the salt (e.g., NaCl). These chemical entities must be independent of each other. So even though NaCl is dissociating into Na^+ and Cl^- ions, in the current discussion these do not constitute two chemical entities because the Na^+ concentration is not independent of the Cl^- concentration. The same holds true, for example, for H_3O^+ and OH^- ions from the auto-protolysis of water. The independent chemical entities of a system are called components and are defined as the least number of chemically independent entities required to describe the composition of the system. A little tongue-in-cheek, we might say that the **p**hase is **p**hysically defined, whereas the **c**omponent is **c**hemically defined (however, note that chemically a Na^+ ion is very different to a Cl^- ion). For multicomponent systems we can formulate Gibbs' phase law as follows:

$$F = C - P + 2 \tag{19}$$

Where: C represents the number of components.

For the examples of a salt solution, $F = 2 - 1 + 2 = 3$. We can see pressure, temperature, and salt concentration here as the degrees of freedom of the system. In most cases, phase diagrams of two component systems are given at a constant pressure, usually normal atmospheric pressure (i.e., one degree of freedom is used up). In this case we can express Gibbs' phase law for a two component system as $F^* = 3 - P$, with F^* being the remaining degrees of freedom of the system. An example of such a phase diagram will be discussed later (see the section on eutectics).

CRYSTALLINE SOLIDS

The solid state of matter is perhaps the most important state in pharmaceutics since the starting material for most formulations and the majority of orally administered dosage forms are in a solid form (most often as tablets or as powders, pellets, or granules in hard gelatine capsules). We will thus consider this state of matter in some detail, whereas the properties of other states of matter will be discussed more briefly since important properties of these are explored elsewhere in this book.

Crystals are defined by a high degree of order, with a three-dimensional periodicity in position for atoms or ions and, additionally, with configurational periodicity for molecules that form the crystal. Most solid forms of drugs are used in the crystalline state, and most pharmaceutically relevant crystals are formed by organic molecules. Not all solids, however, are crystalline (this will be discussed in more detail in the section on amorphous solids).

The reason for the high degree of order of crystals lies in the strong interactions between the atoms, ions, or molecules that form the crystal. As we have seen earlier, in the case of diamond, carbon atoms form a periodic three dimensional tetrahedral network of covalently bonded *sp3* hybridized carbon atoms. Diamond is thus an example of a crystal formed by atoms through covalent bonds. Most inorganic materials form ionic crystals. A pharmaceutically relevant example is NaCl. Here the crystal is formed by sodium and chloride ions, held together by ionic interactions. In the case of NaCl, each sodium ion is surrounded by six chloride ions, and each chloride ion by six sodium ions. The number of ions (or atoms or molecules) that each ion has as its nearest neighbors is called the coordination number. The coordination number for NaCl is, therefore, six. For ionic crystals, the coordination number depends on the relative size of the cation and the anion. If the size difference is very large, the most often found coordination number is four, and if the size differences are small, a coordination number of eight is found. Higher coordination numbers are found in metal crystals (eight or twelve), and the coordination number of diamond is four.

If atoms or ions are held together by covalent or ionic interactions, the resulting crystals have very high melting points and are often hard and brittle. In metals, the crystalline structure is formed by cations, where the electrons are delocalized. This is the reason for both the high coordination numbers of metal crystals as well as the ductile behavior of many metals.

Most drugs are organic molecules. The crystals formed by these substances are held together by dipole–dipole interactions, hydrogen bonds, or London forces. Since these are at least an order of magnitude weaker than ionic or covalent interactions, the melting points of molecular crystals are lower than those of the aforementioned crystalline structures. For

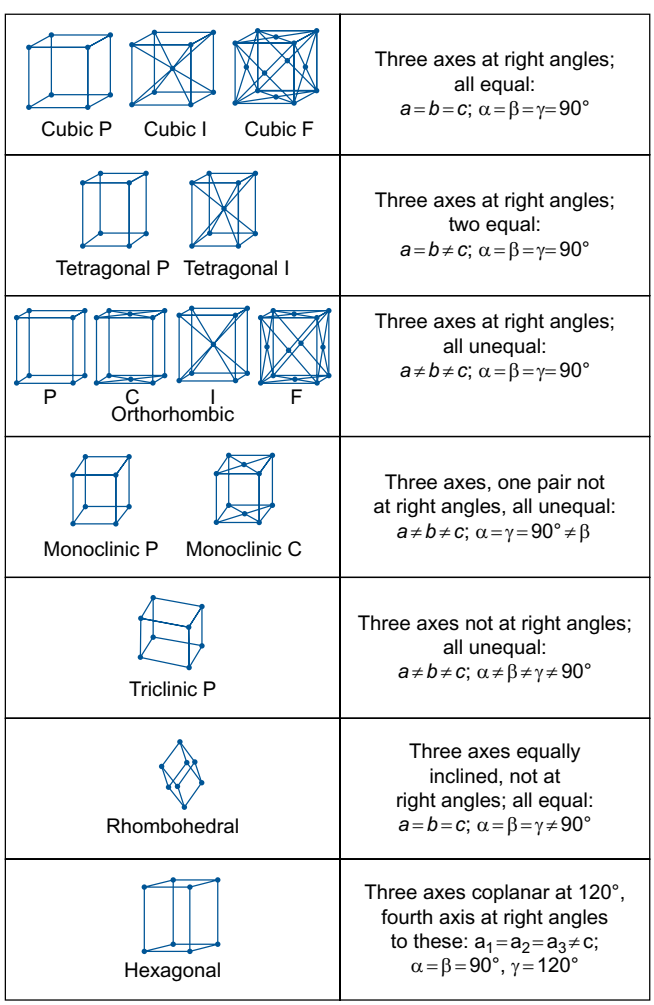

Figure 11-36. The 14 Bravais lattices.

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example, the melting points of paracetamol (molecular crystal), NaCl (ionic crystal), copper (metal crystal), and diamond (covalent crystal) are 169°C, 801°C, 1084°C, and 3550°C, respectively.

We have already seen that different types of crystals can have different coordination numbers. In fact, since crystals are periodically organized, we can define a specific unit cell characteristic for each crystal. A unit cell is defined as the smallest unit of a crystal, which, if repeated, could generate the whole crystal. For this we imagine the atoms, ions, or in the case of drug crystals, molecules, as points in a lattice, disregarding their actual shape. Within the crystal structure we now look for the smallest unit which, when endlessly repeated, forms the crystal structure. Since there may be different ways to do this, the unit cell of a given crystal is the one with the shortest dimensions, and that includes angles that deviate the least from a right angle. The unit cell is a geometric construction and does not take into account the size and shape of the crystal forming atoms, ions, or molecules, nor the type and strength of interactions between them. For this reason, it is possible to summarize the types of unit cells into only seven crystal systems, which can be understood as unique unit cell shapes and which can be differentiated with respect to the relative lengths on their axes a, b, and c and the angles α, β, and γ between the axes. These seven crystal systems are called cubic, tetragonal, orthorhombic, monoclinic, triclinic, rhombohedral (or trigonal), and hexagonal (Figure 11-36).

While there are only seven crystal systems, there are 14 Bravais lattices. This is because additional points can be present in a unit cell, other than the points at the corners of the unit cell, without changing the essential symmetry elements of the crystal system. If there is an additional point in the centre of the unit cell, these lattices are called body (or volume) centered (for example, body centered (cubic I in Figure 11-36)). If there are additional points in the centre of each side (face) of the unit cell, they are called face-centered (for example, face centered (cubic F in Figure 11-36), and if an additional point is present at the centre of two opposite faces of the unit cell, they are called base-centered (for example, base-centered (monoclinic C in Figure 11-36). Bravais lattices without extra points are called simple or primitive for example cubic P in Figure 11-36. The 14 Bravais lattices are shown in Figure 11-36.

Every crystalline material belongs to one of these Bravais lattice types but differs in their lattice parameters, and for each unit cell we can define three axes, with a length characteristic for the individual crystal, and three angles, also characteristic for this crystal. For example, NaCl crystals belong to the crystal system: cubic, Bravais lattice type: face-centered. The only lattice parameter we need is the length of one axis, a = 5.6402 Å, since for a cubic crystal the axes $a = b = c$, and the angles α = β = γ = 90°. Paracetamol (polymorphic form I) belongs to the crystal system: monoclinic, Bravais lattice type: primitive, a = 11.74 Å, b = 9.396 Å, c = 7.117 Å and β = 97.47° (α = γ = 90°, for a monoclinic unit cell).

In the above discussion, we have considered the crystalline structure as infinitely periodic. In reality most crystals, however, will show defect structures, i.e., structures in which there are packing mistakes of some kind, so the crystalline structure of a real crystal will not be perfect. Depending on the number of these defects in a crystalline material, properties of the crystalline substance may vary, for example, its behavior in a milling process. Point defects occur at a single lattice point (Figure 11-37). For example, a single lattice point may be vacant (vacancy) or occupied by a different atom, ion, or molecule from the ones that form the crystal (substitutional point defect; this would constitute a chemical impurity). It is also possible that there may be additional lattice points (interstitial point defects), either from the same or a different atom, ion, or molecule.

The dislocation is an example of a line defect, and the grain boundary is an example of a planar defect (Figure 11-38).

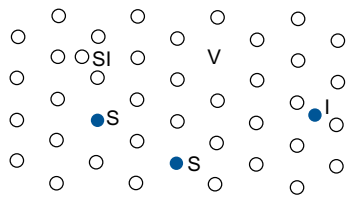

Figure 11-37. Point defects in a crystal lattice. V: vacancy, S: substitutional point defect (different atom, ion, or molecule from the ones that form the crystal), I: interstitial point defect (different atom, ion, or molecule from the ones that form the crystal), SI: self-interstitial point defect (same atom, ion, or molecule as the ones that form the crystal).

A grain boundary marks an interface between different crystalline regions, called crystallites. Such a material is termed polycrystalline and is the reality for most crystalline materials, including drug substances.

Polymorphism

An important property of many chemical entities, including most drug molecules, is that they are able to crystallize in several different crystalline forms, termed polymorphic forms. These different crystalline forms consist of the same molecules, but these are arranged in different ways. If the crystal former is an element (as we have seen in the case of carbon), different polymorphic forms are termed allotropes. For molecular crystals, the crystal is held to together by secondary forces, as outlined above. Since these interactions are fairly weak (compared to ionic, metal, or covalent crystals), and because the molecules may adopt different molecular configurations in the crystalline structures, it is not surprising that most pharmaceutical drugs show polymorphism, and are often able to crystallize in more than two, and in some case even more than ten, different crystalline forms. These different polymorphs are also termed polymorphic modifications of the substance in question. It is important to note that different modifications of a drug may not necessarily form crystals with a different type of Bravais lattice. Although this is, of course, possible, it is also possible that two polymorphic forms of a drug both have, for example, a monoclinic unit cell. In this case, however, the lattice parameters of the two polymorphic forms will be different. Also, for some polymorphic forms, for example, of drug substances, the molecules present in the lattices of the different modifications will adopt different molecular conformations (termed conformational polymorphism), while other polymorphic pairs will contain the drug molecules with the same conformation (termed packing polymorphism).

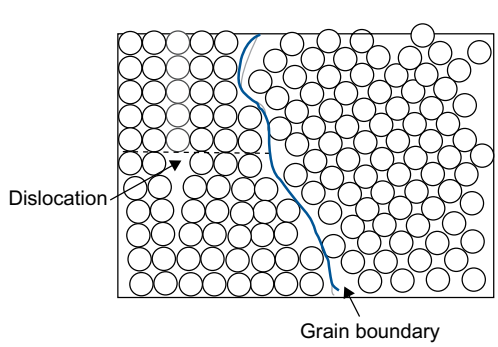

Figure 11-38. Dislocation (a line defect) and grain boundary (a planar defect).

Polymorphism is important in the pharmaceutical field, since the physical properties of different polymorphic forms are often considerably different, which can have consequences for important quality-relevant attributes of a drug substance or dosage form. Differences may be encountered in, for example, dissolution rate, solubility, flow properties, behavior under mechanical stress (for example during milling, tableting, agglomeration), hygroscopicity, etc. These differences may be sufficiently large so that different polymorphic forms may have different bioavailabilities. It is thus possible, or even common, that for a given drug regulatory approval is only given to a specific polymorphic form of the drug.

While often different polymorphic forms of a drug form macroscopically different crystals, such as needle-like versus plate-like crystals (the macroscopic appearance of a crystal is also known as the habit of the crystal), it is important to note that different polymorphic forms may not necessarily look different macroscopically, and thus it may be difficult to differentiate these by visual inspection or in the light or electron microscope alone. It is also possible that if one and the same polymorphic form of a crystal is crystallized, for example, from different solvents or from either a solution or the melt, it may adopt different crystal habits. So while the habit is important, most notably for further processing of the drug powder, it is also important to have techniques available to unambiguously identify the crystalline structure of a drug and its polymorphic form. This will be discussed in the section on methods to characterize solids, where some techniques to identify and characterize polymorphs (or indeed solid state forms in general) will be mentioned.

If a drug can crystallize in different polymorphic forms, it should be noted that at any given condition of pressure and temperature, only one polymorphic form can be the thermodynamically stable form. All other polymorphic forms that may form under these conditions will be only metastable. Metastable here means that these polymorphs can form but eventually will convert to the stable form over time if the environmental conditions are not changed. The metastable forms, on the other hand, are not unstable (in contrast to amorphous forms which will be discussed in the next section), since (sometimes considerable) activation energy is required to bring about a phase transition from the metastable to the stable polymorphic form. For some metastable polymorphs, therefore, the polymorphic transition may be very slow and may take much longer than the shelf life of the drug product containing a metastable polymorphic form. In general, if not precluded by a too low solubility of the stable form, most drugs will be manufactured in solid dosage forms in the stable polymorphic form. However the drug ranitidine-HCl, which can exist in two polymorphic forms, is manufactured using both polymorphs, i.e., the metastable polymorph is "practically" stable enough to allow safe manufacturing.[11]

It is often found that not the most stable, but a less stable (often the least stable) polymorphic form of a substance crystallizes first, for example, upon cooling of a melt. This is known as Ostwald's rule. While not universally applicable (not being a law, but rather a rule), it nevertheless highlights the importance in drug development to carefully check which polymorphic form of a drug one is indeed dealing with.

Let us consider a given set of two polymorphs of a substance. Because the solid state forms are different, their phase diagrams will also be different, and the overall phase diagram of this polymorphic substance will be the superimposed phase diagram of the two forms. This is illustrated in Figure 11-39. We can differentiate two possible scenarios, shown in Figures 11.39a and b. For the monotropic system (Figure 11-39a), the sublimation curve of form I is below the sublimation curve of form II. Since the stable polymorph is the one with the lower vapor pressure, in the case of a monotropic pair of polymorphs, one form (here form I) is always the stable form until either of the forms melts. Note that after melting there is no difference between the melts of the substance, irrespective of the polymorphic solid form.

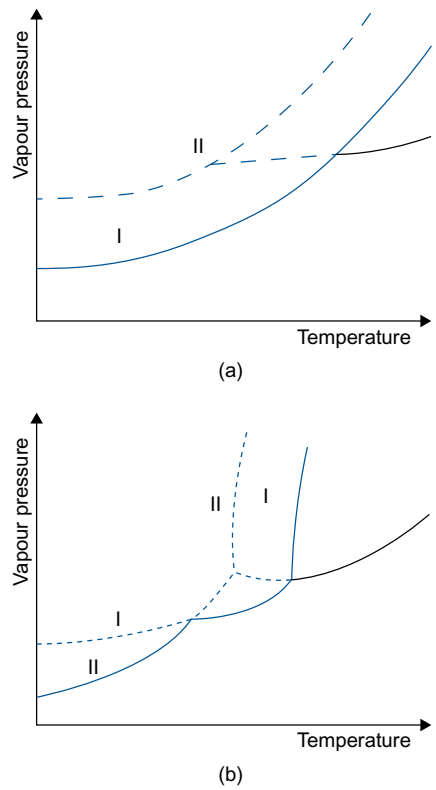

Figure 11-39. Phase diagrams of (a) a monotropic and (b) an enantiotropic polymorphic system. The solid lines represent stable states.

Should initially form II have been generated by cooling from a melt (according to Ostwald's rule this is not unlikely to happen in a practical scenario), then if conversion occurs to the stable form I, this conversion will be irreversible. The situation is different for enantiotropic systems (Figure 11-39b). Here form II has a lower vapor pressure than form I at low temperature (so it is the stable polymorph at these temperature conditions), but at higher temperatures there is a crossover in the sublimation curves of the two polymorphs before either of these forms melts. After the crossover, form I now has the lower vapor pressure and is the stable form. This means if we have form II present at low temperature, this is the stable form, but upon heating at a certain temperature, polymorphic conversion will take place and form I is the stable form. If we now cool down form I again, conversion back to form II will occur. In other words, the process is reversible.

AMORPHOUS SOLIDS

In the previous section we have seen that a crystalline solid is characterized by its long-range positional order. Amorphous solids lack the long-range order seen in crystals although short-range order over several molecular dimensions may exist. The molecular arrangement is thought to represent that of a frozen liquid with the rheological properties of a solid.

Heating of a crystalline material leads to a gradual increase in the thermodynamic properties such as enthalpy and entropy until the melting point, T_m, is reached (Figure 11.40). As we have seen, a significant increase in thermodynamic properties marks the first order transition (melting) from the solid to the liquid state. Above the melting temperature, the material exists as a molten liquid. This is a reversible process, so upon cooling, crystallization of the melt occurs whereby the molecules rearrange themselves in their crystal lattice. However, if the liquid is cooled sufficiently fast below its melting temperature, crystallization may be prevented so that a super-cooled liquid is formed, and the slope of the

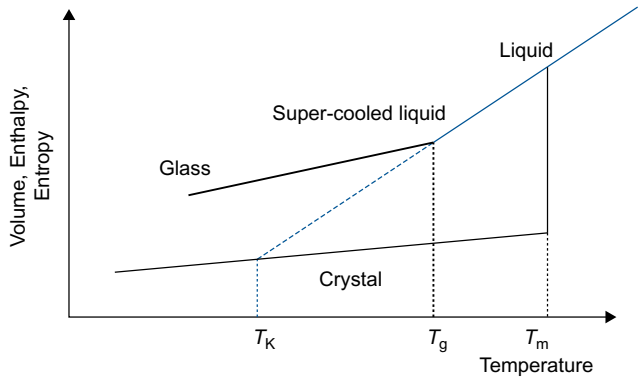

Figure 11-40. Thermodynamic relationship of crystalline and amorphous solids as a function of temperature. Shown are the melting temperature (T_m), the glass transition temperature (T_g), and the Kauzmann temperature (T_K).

equilibrium liquid line (Figure 11-40) may be followed, resulting in a gradual decrease of the thermodynamic properties below T_m.

At temperatures above the glass transition temperature (T_g, Figure 11-40) the material is said to be in the super-cooled liquid state (sometimes also called the rubbery state), the viscosity of which is typically between 10^{-3} and 10^{12} Pa s. In the super-cooled liquid state, the molecules are able to follow any further decrease of temperature to attain equilibrium conditions. However, cooling of the super-cooled liquid increases the viscosity of the system, and upon further cooling the molecules are not able to reach equilibrium any longer. At this temperature, the T_g, the molecules are "kinetically frozen in" and the super-cooled liquid solidifies into a glass. (Note that in a glass the molecules still show some mobility.) The T_g represents the temperature at which the system falls out of equilibrium. Amorphous solids are therefore non-equilibrium solids and the glass transition is a second order phase transition. Unlike melting or boiling, the heat capacity is not infinitively high at the phase transition, but jumps from one value to another. The non-equilibrium state of a glassy amorphous system has special implications: the fundamentals of thermodynamics only apply to systems in equilibrium, and therefore, the behavior of the glassy state cannot be predicted from regular thermodynamics.

Due to the high viscosity of the resulting glass (viscosity is usually greater than 10^{12} Pas), it appears as a solid. The T_g represents a characteristic thermal event for an amorphous systems, but it should be noted that the T_g is a kinetic property of the material, and its exact position depends, for example, on the cooling rate of the super-cooled liquid, i.e., on its thermal history.

In principal, the amorphous state can be produced in two ways:

1. from a liquid state, either by rapidly cooling the molten liquid or by fast evaporation of a solvent from a solution, hence "freezing in" the molecular arrangement of the liquid (vitrification), or
2. by gradually inducing and increasing defects in the crystal lattice until the amorphous state is generated (amorphization).

The vitrification process (1) is also termed the thermodynamic pathway to form amorphous materials, and the amorphization process (2) has been named the kinetic pathway. A schematic representation of the conversion from crystalline to amorphous is depicted in Figure 11-41.

If the amorphous state is produced via the thermodynamic pathway, the crystalline material has to be transferred to a liquid state, either by melting or by dissolution in an appropriate solvent. If the kinetic pathway is followed, the crystalline lattice is continuously disrupted by mechanical processing like milling, inducing crystal defects. As long as the crystal defects remain small in number, the material still exhibits crystalline properties. However, if a critical number of defects is introduced, the crystal cannot retain its structure and converts to the amorphous state. The main difference between these two approaches is that while the thermodynamic pathway abruptly destroys the long-range order of the crystal, the kinetic pathway gradually increases the number of crystal defects, thereby creating non-equilibrium crystalline states. Such materials, still crystalline but with increasing number of defects, are termed defective crystals.

While the thermodynamic pathway is commonly employed in order to deliberately generate the amorphous state, the kinetic pathway is usually associated with the unintentional amorphization of a crystalline material, for example when the actual objective of a milling process is to reduce the particle size of the crystalline material, not to change its solid state form.

It should be noted that not every preparation technique to convert a crystalline drug into its amorphous counterpart is suitable for every drug, e. g. thermolabile drugs cannot be converted to the amorphous form by using heat based methods; drugs that are insoluble in a range of organic solvents cannot easily be spray-dried to amorphize the substance, and some methods (milling) may not completely convert certain drugs into the amorphous state. We have now seen a variety of methods that can be used to generate the amorphous state of a drug. The question arises whether the amorphous state generated is the same in all cases.

Let us take a closer look at the T_g, an important feature in the amorphous state. Above the T_g the system is still in an equilibrium state; below the T_g the system has fallen out of equilibrium. Let us imagine that the T_g did not exist: in Figure 11-40 we see that the decrease of the temperature would eventually lead to the super-cooled liquid line intersecting with the crystal line. This would cause the super-cooled liquid eventually to have a lower entropy than the crystal upon further cooling. This, however, is not considered possible. The theoretical temperature at which the super-cooled liquid would attain the same properties as the crystal is known as the Kauzmann temperature, T_K (see Figure 11-40). The kinetic nature of the glass transition is evident from its dependence on the heating and cooling rates, which means that the T_g does not exist at a defined temperature. Slow cooling rates lead to a prolonged super-cooled liquid state and result in a T_g with a lower temperature, as displayed by T_g II in Figure 11-42. As the super-cooled liquid is cooled at a slower rate, the system is able to adjust to the temperature dependent increase in viscosity, resulting in a lower temperature for the glass transition. Glasses created by slower cooling rates also show lower values of enthalpy and entropy than glasses that are created by faster cooling rates. The explanation for this is that due to the lower onset of the T_g, the super-cooled liquid state is maintained at lower temperatures, therefore decreasing the value of enthalpy and entropy further.

For practical purposes, this means that for a given material an amorphous system which is prepared by one method is not identical to the amorphous system prepared by another method. Even that, if the method is the same but parameters are varied, the resulting amorphous states will not be identical, either. So, unlike "the crystalline state," which has defined properties, there is no "the amorphous state". Depending on the preparation method, sample history, geometry and mass, and the experimental heating and cooling rates, the amorphous states can differ considerably in properties, especially in physical stability (recrystallization to the crystalline state).

From Figure 11-40 we can see that the amorphous state has higher thermodynamic properties, like enthalpy and entropy, compared to the crystal. What Figure 11-40 does not show, however, is that the properties of the amorphous state are time-dependent. As time passes, we observe that the amorphous

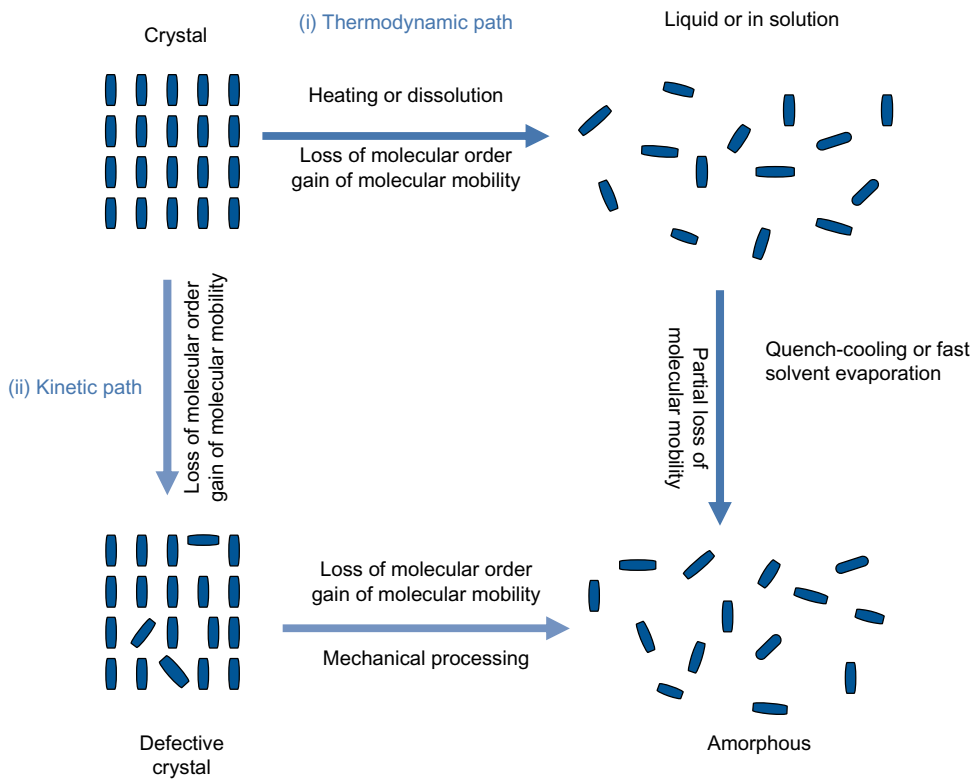

Figure 11-41. Schematic representation of the crystalline to amorphous conversion via the thermodynamic and kinetic pathways.

state decreases in properties such as enthalpy even though the temperature is kept constant. This phenomenon is called relaxation, and it has its origin in the instability of the amorphous state. The molecules may be frozen in, but they still have some molecular mobility left. This is sufficient for the molecules to relax over time and rearrange themselves in a more thermodynamically favorable way. By doing this, they decrease their enthalpy, and this is also considered an important factor in the stability of amorphous systems. This relaxation can be visualized in a DSC thermogram, in which the relaxation appears as an endothermic peak on top of the glass transition event.

In recent years the amorphous state of drugs has gained increasing interest in pharmaceutics due to its favorable solubility properties, compared to its crystalline counterpart.[12] Many new drugs show insufficient solubility for oral dosage form development. Because of its higher energy, the solubility of amorphous forms is often orders of magnitude higher than for crystals and, thus, this solid form is attractive in dosage form development. However, issues when dealing with the amorphous state, such as physical and chemical instabilities, remain. Also, to date, the prediction of physical and chemical stability of drugs in the amorphous state still proves challenging, since, for example, the application of stress tests is not straightforward for amorphous systems (they don't behave in an Arrhenius fashion).

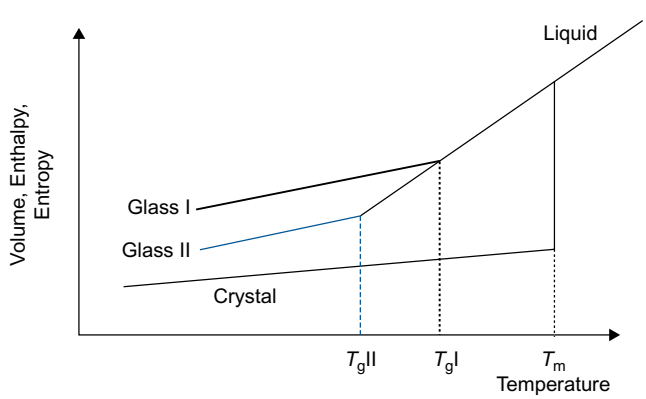

Figure 11-42. Thermodynamic relationship of glasses created by different cooling rates. Glass I has been cooled fast, and glass II has been cooled slowly.

SOLIDS WITH MORE THAN ONE COMPONENT

In the previous sections we have discussed crystalline and amorphous solids on the basis of single component systems, i.e., we were considering a single chemical entity (e.g., the drug molecules). In this section we will expand the discussion on solids by introducing a second component.

Solvates and co-crystals

Not only can most drugs crystallize in different polymorphic forms, but they can also incorporate other molecules to form crystalline structures. For example, during a crystallization process from a solvent, solvent molecules may be incorporated into the crystalline structure. This occurs if the solvent molecules can interact with the drug molecules through hydrogen bonding or other weak interactions. In this case a new crystalline structure of the drug and the solvent molecules may be formed. These crystalline structures are termed solvates. In the specific case of water as the additional molecule to be incorporated into the crystalline structure, the solvate is called a hydrate. Hydrates can also form from crystalline or amorphous non-hydrate drug substances by addition of water molecules from the air or during a dissolution process in water. Thus, hydrate formation of a drug (if the drug can indeed form hydrates, which is compound specific) may even occur during the oral administration of the drug. This is of pharmaceutical significance, for in most cases the resulting hydrate will have lower water solubility than the respective non-hydrate, which may even result in a lower bioavailability. For example, partial hydrate formation has been made responsible for erratic bioavailability

of carbamazepine and theophylline after administration of the drug in a non-hydrate form.[13,14]

Since the water molecules (or other solvent molecules) are incorporated into the crystalline lattice in a regular structure, the molar ratio of drug to solvent molecules will take on fixed ratios (stoichiometric hydrates). However, this molar ratio does not have to be 1:1 (monohydrates), and for example hemihydrates (the molar ratio of drug to water molecules in a hemihydrate is 2:1) or dihydrates (the molar ratio of drug to water molecules is 1:2) are not uncommon. Some drugs can form different hydrates (for example, mono- and dihydrates) and even within one group of hydrates, polymorphism may occur, further increasing the possibilities of a given material to crystallize in many different forms, with different physico-chemical properties.

Not all hydrates, however, have a fixed stoichiometric ratio between the drug and the water molecules. If the water molecules can be incorporated into channels that may be present in a non-hydrate crystalline structure, many different ratios of water to drug molecules are possible, depending, for example, on the relative humidity of the air surrounding the hydrate. These types of hydrates are called channel hydrates.

If a stoichiometric hydrate loses its water (for example, by heating), the water in most cases will leave the crystal at a defined temperature. If we are measuring the weight loss of a hydrate as a function of temperature (these types of measurements are called thermogravimetric measurements), typical weight loss curves, as shown in Figure 11-43, are obtained for stoichiometric hydrates. In case of a dihydrate, for example, water may be leaving the crystal initially to form a monohydrate

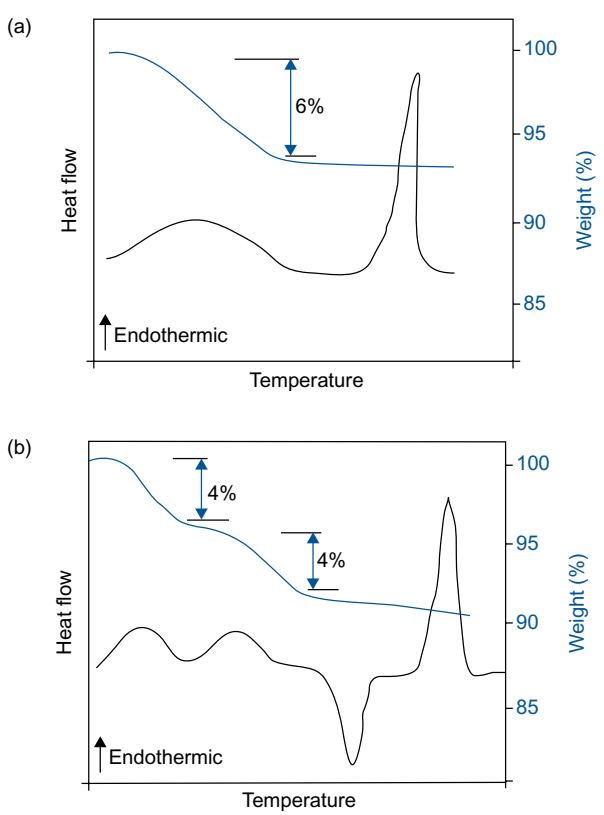

Figure 11-43. Thermogravimetric weight loss curves (——) and corresponding DSC curves (——) of (a) a hypothetical monohydrate and (b) a hypothetical dihydrate. Note that the water loss also appears as an endothermic event in the DSC thermogram. Other thermal events in the DSC curves (e.g., a polymorphic conversion, or melting) are not accompanied by a weight loss in the thermogravimetric curves. For more information on DSC, see the section Methods to characterize solids.

that is then losing the remaining water at a higher temperature, so two steps in the weight loss curve may be observed (Figure 11-43b). For a given mass of material, if the molecular weights of the drug and the solvate molecule (18 g/mol in case of water) are known, the stoichiometric ratio of drug to solvate molecules can be determined by these measurements. In some cases the water only leaves the crystal upon melting of the material. In contrast, for channel hydrates the water molecules are leaving the crystalline structure often before melting and over a broader temperature range. If the water in a stoichiometric hydrate leaves the crystal before melting this may result in a collapse of the crystalline structure altogether, leading to the formation of an amorphous material. In the case of channel hydrates, the result of water leaving the crystal may be a non-hydrate with almost the same crystalline structure as the hydrate (same crystal lattice type and similar, but not identical, lattice parameters), sometimes called a vacant hydrate, before further polymorphic conversion to the stable non-hydrate form occurs.

Of recently increasing pharmaceutical interest are co-crystals.[15] Unlike salts, in which the drug (as an anion or cation, depending on the nature of the drug) is bound by ionic interaction to the counter ion, in a co-crystal the drug and the co-crystal former (see below) are interacting via weaker interactions, in most cases by hydrogen bonding, as is the case for solvates. However, in contrast to solvates, both components of the co-crystal are solid at room temperature. If the hydrogen bond between the two molecules is formed by similar molecular moieties (for example, two carboxylic acid groups), this is known as a supramolecular homosynthon, whereas a hydrogen bond between two different moieties of the two components (for example, a phenol group and an amide group) is known as a supramolecular heterosynthon. Generally, the formation of a heterosynthon leads to a higher likelihood of formation of a stable co-crystal. Typical co-crystal formers used in the pharmaceutical field include maleic acid, tartaric acid, nicotinamide, saccharin, and many others. Since co-crystals have other properties, including solubility, hygroscopicity, and pharmaceutical processability, they offer interesting possibilities in drug development. Co-crystals (for example, the carbamzepine-nicotinamide co-crystal and the carbamazepine-saccharin co-crystals) can also show polymorphism.[16]

Eutectics

Above we have considered solid state materials containing two components but forming a single phase. Eutectics are an important example of a solid mixture of crystals (in contrast to co-crystals, which are "mixed crystals", rather than a "crystalline mixture"). Eutectics thus contain two phases. However, in eutectic mixtures the two phases (two materials) are intimately mixed and thus often show different properties from simple physical mixtures of the two components.

Let us consider two crystalline materials, A and B, with meeting points Tm_A and Tm_B, that are miscible in the molten state, i.e., they form a single liquid phase. This is shown in form of a phase diagram in Figure 11-44. If we have a mixture of the two materials at the mixing ratio R1, at a temperature where both materials are molten (so we are in the liquid area of the phase diagram), and we now reduce the temperature of this melt, at the intersection with the melting curve, we will observe crystallization of compound A. As A will crystallize, but not B, this means that the composition of the remaining melt will change and it will become more B-rich. We thus follow the melting curve upon further lowering of the temperature until we reach the lowest point of the melting curve of A. If we lower the temperature further, now B will also crystallize. Similarly, if we have a B-rich mixture, B will crystallize when the temperature is lowered to the melting curve of B. This, in turn, will lead to the remaining melt having relatively more A than the original melt, and we follow the melting curve of B until we reach its lowest point, which is the same as for an A-rich system. The ratio of A and B at this point is called the eutectic mixture for these

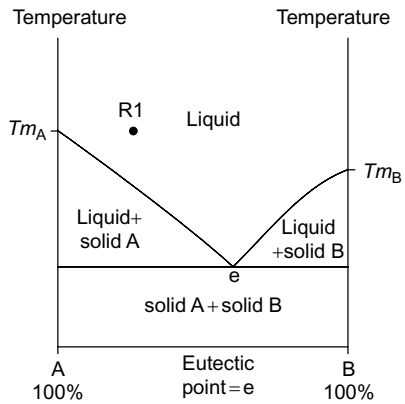

Figure 11-44. Phase diagram of two materials, A and B.

two compounds, and the temperature in the phase diagram is known as the eutectic temperature (e), the lowest temperature at which both compounds crystallize together. In other words, at the eutectic point both crystalline A and B and the melt are in equilibrium. For the eutectic mixture of sodium chloride and water, this occurs at a salt concentration of 22.4 percent and a eutectic temperature of –22°C.

For a given two compound system, the ratio of the compounds at the eutectic mixture can be estimated from the theoretical melting curves of the two compounds, using a simplified form of the Schröder–Van Laar equation:

$$\ln x = \frac{\Delta H_0}{R}\left(\frac{1}{T_0} - \frac{1}{T}\right) \tag{20}$$

Where: x is the mole fraction of one compound in the mixture; ΔH_0 and T_0 are the corresponding heat of fusion [J mol^{-1}] and melting temperature [K] of the pure compound, respectively; T is the melting point of the binary mixture at x; and R is the gas constant [8.314 J K^{-1} mol^{-1}].

However, it should be noted that for this approach to be valid, a number of assumptions are made: there is no solid solution formation between the two compounds (see below), the melt has to be an ideal mixture, and the heat capacities of the pure compounds in the melt and as a solid should be fairly similar.

In the phase diagram shown above, we did not consider the possible formation of a solid solution between the two compounds. If this occurs, then there will be partial miscibility between the compounds in the solid state, and rather than pure compound A and pure compound B crystallizing together at the eutectic point, we will have the crystallization of an A-rich and a B-rich phase of the two corresponding solid solutions. This plays a major role in the formation of metal alloys.

Amorphous mixtures

We have discussed above that the amorphous form of a solid is thermodynamically unstable and tends to crystallize back to the stable crystalline form or a metastable polymorphic form. In order to make use of the advantages, including a higher dissolution rate and solubility that amorphous solids offer, especially for poorly water soluble drugs, it is therefore often necessary to stabilize the amorphous form. One way of achieving this is to use two components (for example, a drug and an excipient) in the formation of a solid amorphous material. In most cases this will be an amorphous, hydrophilic polymer. If an amorphous polymer (such as, for example, polyvinypyrrolidone (PVP), PVP-vinylacetate copolymer (PVPVA), hydroxypropylmethylcellulose (HPMC), HPMC-acetatesuccinate (HPMCAS), and various polymethacrylates) is melted together with the drug to form a single phase melt, this can be cooled down rapidly to form a single phase amorphous material, known as a glass solution (do not confuse the amorphous glass solution with the crystalline solid solution, mentioned above). In this solid form the drug and the polymer are molecularly mixed with each other. For this to be successful, it is required that the two compounds show mutual solubility, for example, have similar solubility parameters. It is often advantageous for the physical stability of glass solutions if some interactions between the drug and polymer occur (usually hydrogen bonding), since this will lower the molecular mobility (especially of the low molecular weight drug) and thus will slow down the processes of nucleation and crystal growth, which lead to the crystallization of the amorphous material. The polymers used for the formation of glass solutions often have a high glass transition temperature (T^g) so that the resulting glass transition temperature of the glass solution will be higher than the T_g of the pure amorphous drug, further stabilizing the drug against crystallization. If the glass transition temperatures of the two pure amorphous components are known, the resulting glass transition temperature of the glass solution in various mixing ratios of the two compounds can be estimated based on the Gordon Taylor equation:

$$T_{g12} = \frac{w_1 \cdot T_{g1} + K \cdot w_2 \cdot T_{g2}}{w_1 + K \cdot w_2} \tag{21}$$

Where: T_{g12} is the glass transition temperature [K] of the mixture; T_{g1} and T_{g2} are the glass transition temperatures [K] of the single amorphous compounds (e.g., the drug and the polymer); w_1 and w_2 are the weight fractions of each compound in the mixture; and K is a constant, depending on the glass transition temperatures and amorphous densities of the single compounds:

$$K = \frac{T_{g1} \cdot \rho_1}{T_{g2} \cdot \rho_2} \tag{22}$$

Where: ρ_1 and ρ_2 are the densities of the single amorphous components.

It should be noted, though, that this equation assumes volume additivity, i.e., the absence of specific molecular interactions and, as such, can often only be used as an estimate for the actual glass transition temperature of the glass solution.

In most cases the T_g of the glass solution is predicted by using the T_g of the drug and polymer. However, in real situations a third component can be present: moisture. It is known that moisture can accelerate crystallization from the amorphous state, and this effect can be explained by the plasticizing effect of water. The T_g of water is approx. 139 K, which is significantly lower than the T_g of commonly used pharmaceutical materials. In the same way that a high T_g polymer is added for stability, a low T_g compound can lower the T_g of the system. If the Gordon-Taylor equation is extended to a third component, it is obvious that even small amounts of a low Tg compound can have a significant effect on the T_g and, hence, on stability. Therefore, moisture should be excluded during manufacturing and storage of amorphous systems.

If the two components (for example, the drug and the polymer) are not miscible on a molecular level, the formation of a solid suspension may occur upon cooling of a melt of the two components. These systems will show two glass transition temperatures, one for the drug (or possibly a drug rich phase, if there is partial miscibility) and one for the polymer (or the polymer rich phase).

METHODS TO CHARACTERIZE SOLIDS

It is beyond the scope of this chapter to provide a detailed description of the various methods that have been developed to characterize the properties of solids. However, in a brief fashion we will have a look at several important techniques that allow the characterization of the many forms in which the solid state of matter, for example, of a given drug may manifest itself.

We have seen that a pharmaceutical solid can be present during development or in a final dosage form in various polymorphic forms. It can also be present in form of hydrates or

other solvates. Salt formation is possible, as is the formation of a co-crystal. Solvates, salts and co-crystals in their own right can show polymorphism. The drug may also be partly or fully amorphous, either on its own or in form of a glass solution or amorphous suspension. All of these solid state forms will differ in many of their physical properties, and this can be relevant for the drug and dosage form if, for example, solubility, dissolution rate, and chemical and physical stability are affected. It is thus obvious that we require a thorough identification and, in many cases quantification, of the various solid state forms of a drug that we may encounter in preformulation, formulation, during storage and upon administration of the dosage form. It is also obvious that this task is more complex for solids than, for example, if the drug is present in liquid form or in a solution, for in these cases all differences of the solid state forms disappear.

The list of analytical techniques that are useful to investigate solid state properties is almost endless, and it is convenient to differentiate the techniques available to the pharmaceutical scientist according to the different levels at which they probe the solid material. Most spectroscopic techniques, such as Raman and infrared spectroscopy, but also solid state NMR, near infrared spectroscopy and others are probing predominately molecular properties. If a drug, for example, can crystallize in different polymorphic forms, these forms still contain the same molecules, and as such, the resulting spectra should be identical. Indeed, that is (almost) the case. However, the fingerprint regions of the resulting spectra will also be influenced by the neighboring molecules, for example, by the unit cell of the crystalline forms. Because these are different between different polymorphic forms, the resulting spectra, for example, for IR and Raman measurements, will also (subtly) be different. If the polymorphic pair shows configurational differences between the molecules, the differences in the resulting spectra will be larger than if the configuration of the drug molecules is the same in both polymorphs. It is often necessary to use multivariate data analytical tools, such as principal components analysis or partial least squares analysis, to identify the different solid state forms using IR or Raman spectroscopy. It is advisable, in any case, to use such techniques if a quantification of different solid state forms that are present at the same time is desired. Generally, differences in the spectra between a non-solvate and a solvate form are larger than between two polymorphic forms, and differences between the spectra of a crystalline and an amorphous form may be even larger, with the spectra in IR

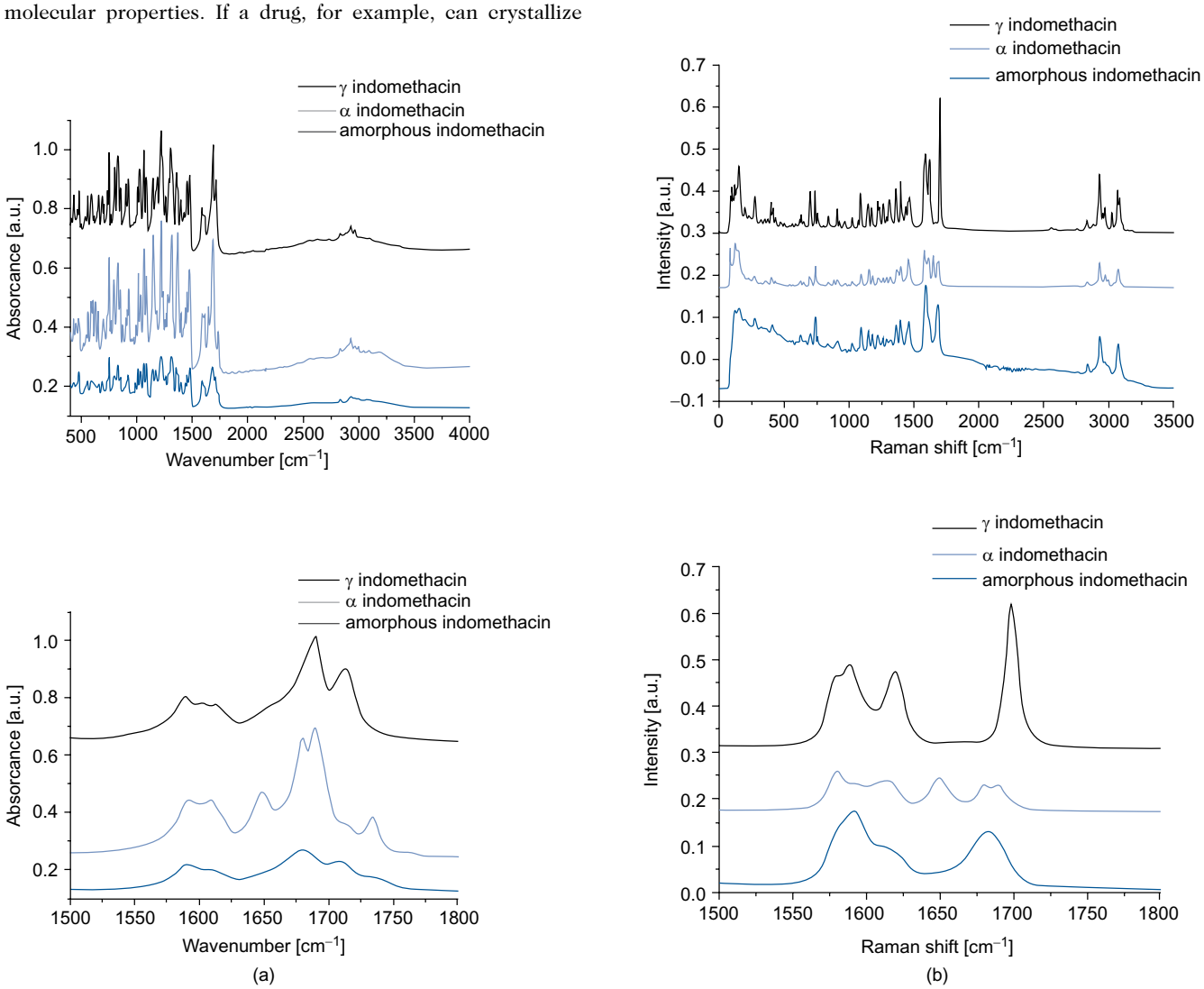

Figure 11-45. (a), Infrared spectra of amorphous indomethacin, and the α- and γ- polymorphic crystalline forms of indomethacin. The lower figure shows the wavenumber region of 1500–1800 cm^{-1} (C=O stretch), where differences between the different solid state forms can be clearly visualised. Individual traces are offset for clarity. (b), Raman spectra of amorphous indomethacin, and the α- and γ- polymorphic crystalline forms of indomethacin. The lower figure shows the wavenumber region of 1500–1800 cm^{-1} (C=O stretch), where differences between the different solid state forms can be clearly visualised. Individual traces are offset for clarity.

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and Raman measurements being less well defined (peak broadening and peak merging) for amorphous forms, compared to their crystalline counterparts. Figure 11-45 shows example IR spectra (Figure 11-45a) and Raman spectra (Figure 11-45b) of different solid state forms of the drug indomethacin.

The next level of analytical techniques, and in many ways the "gold standard" techniques to characterize and quantify different solid state forms of a drug, are the techniques that probe an assembly of molecules. These techniques have been termed "particulate level techniques," and include X-ray diffraction (mostly used in the forms of X-ray powder diffraction, XRPD), and various thermal analytical techniques (of which differential scanning calorimetry, DSC, plays the largest role in pharmaceutical analysis). These will be described briefly below. It should be noted, however, that also terahertz spectroscopy, probing the phonon modes of solids, is a particulate level technique, as are the various microscopic and electron microscopic techniques.

X-ray powder diffraction is one of the most important analytical techniques used in solid-state analysis. An X-ray powder pattern is the result of scattering of an incident monochromatic X-ray beam by the lattice of the crystalline material.The resulting diffractogram is based on constructive and destructive interference of the diffracted X-ray beams. This phenomenon is described by Bragg's law:

$$n\lambda = 2d\sin\theta \tag{23}$$

Where: n is the order of reflection (an integer); λ is wavelength of the incident beam [Å]; d is distance between the planes in the crystal [Å]; and θ is angle of beam diffraction.

Constructive interference takes place when the scattered X-rays are in phase, i.e., the phase difference that the scattered X-rays reflected from two neighboring planes of the crystal lattice is an integer (Figure 11–46). Each crystalline material will exhibit a diffractogram, which is unique to the specific compound and its solid state form, and individual peaks may be attributed to the crystalline structure. As amorphous solids do not possess an ordered lattice, no diffraction occurs and no diffraction pattern is obtained. Rather, a diffuse "amorphous halo," showing one or several broad maxima, is observed. XRPD is particularly useful to detect small amounts of crystallinity in an amorphous sample, for the residual crystallinity results in small diffraction peaks on an amorphous halo. However, the technique is of limited use for the detection of low levels of amorphous content since the halo will be obscured by the stronger crystalline diffraction peaks.

XRPD is one of the most commonly used techniques in the pharmaceutical industry for solid-state analysis because it may be used for the identification and quantification of polymorphs, solvates, hydrates and amorphous forms, based on their unique diffraction patterns. It does not require large sample sizes, and unlike thermal methods, it is a non-destructive technique. This is potentially advantageous in the early stages of pharmaceutical development, and despite its limitations in detecting low levels of amorphous material, XRPD has been used both qualitatively and quantitatively in the characterization of partially crystalline systems. Quantification of the crystalline content can be achieved by measuring the area or the height of the main peaks in the diffractogram and of the amorphous content by measuring the amorphous scattering in the diffractogram. However, quantitative analysis using XRPD has to be carried out carefully, for physical characteristics such as sample height, surface character and shape, and the presence of microcrystallinity may influence the outcome of the measurements. Figure 11-47 shows example diffractograms of different solid state forms of the drug indomethacin.

DSC is used in the study of both crystalline and amorphous materials. Two types of DSC instruments are available: power-compensated DSC and heat-flux DSC. In power-compensated DSC a reference and a sample pans are placed on two individual furnaces, and the temperature difference between them is maintained at zero by varying the heat that is required to keep both pans at the same temperature. The parameter recorded is the difference in energy input which is required to maintain the samples at the same temperature, for example, during a melting process. In heat-flux DSC one heating element is used for sample and reference. Heat is applied to both via an electrically heated thermoelectric disc, and the temperature difference between sample and reference is monitored. The obtained signal is converted to heat flow [mW] via the following relationship:

$$\Delta Q = \frac{T_s - T_r}{R_\gamma} \tag{24}$$

Where: Q is heat energy [J]; $R\gamma$ is the thermal resistance [KJ^{-1}]; T_s is the sample temperature [K]; and T_r is the reference temperature [K].

In DSC, thermal events connected to the sample are presented in a thermogram, in which endothermic and exothermic energy deviations from the reference pan are recorded as a function of time or temperature. Endothermic events include processes such as evaporation, melting, and some solid–solid transitions. In contrast, the recrystallization of an amorphous form and other solid–solid transitions are exothermic. It is possible to use DSC not only to determine the temperature of these events but also to calculate the heat of the respective reaction.

As we have seen above, any change in the enthalpy of a system at constant pressure can be described by the change in heat. Hence, the area under a DSC peak is directly proportional to the heat absorbed or released by the thermal event if the sample mass is known.

The determination of the heat capacity, C_p, for the amorphous state is of particular interest, for the glassy and the super-cooled liquid state exhibit different values for their respective C_ps, and

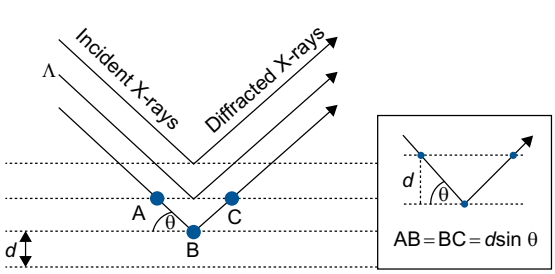

Figure 11-46. Diffraction of X-ray beams by planes of a crystal lattice. A, B, and C are points in the crystal planes. d is the distance between two planes.

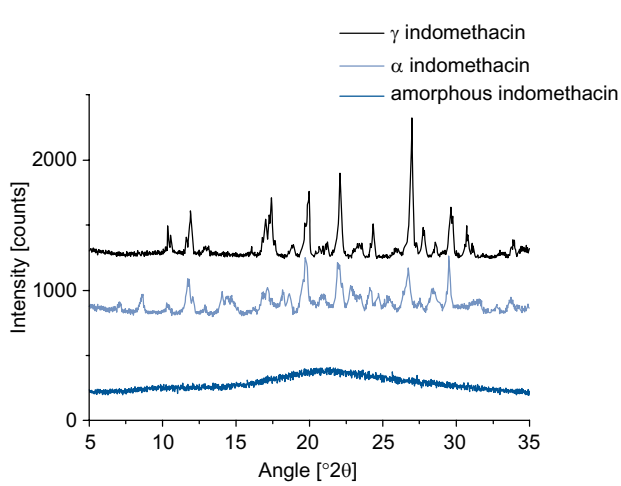

Figure 11-47. X-ray powder diffraction patterns of amorphous indomethacin, and the α- and γ- polymorphic crystalline forms of indomethacin. Individual traces are offset for clarity.

the heat capacity will change in a stepwise fashion at the glass transition temperature. The extent of the difference in heat capacity (ΔC_p) is an important characteristic for amorphous materials. The enthalpy of a system increases as its temperature is increased. The heat capacity can be obtained as the slope of a plot of enthalpy versus temperature at constant pressure:

$$C_p = \left(\frac{\delta h}{\delta T}\right)_p \tag{25}$$

The advantages of DSC for analytical purposes lie in the requirement of only small sample sizes (typically 2–6 mg), the broad temperature range, and in the speed of the experiments (heating rates of 5–20 K/min are typically employed). DSC can be used to analyze both crystalline and amorphous materials, and unlike XRPD, it is possible to directly detect the amorphous content through the presence of a T_g.

The thermal behavior of a solid sample may be analyzed, for example, in terms of

- melting point and melting enthalpy of polymorphic crystalline materials
- conversion temperature of two enantiotropic polymorphic forms
- enthalpy and temperature of the loss of solvate molecules from solvates
- heat capacity difference and temperature of the glass transition of amorphous material
- enthalpy and temperature of any crystallization events of amorphous material
- temperature of decomposition
- extent of interactions in mixtures (e.g., with excipients).

Quantification, for example, of amorphous content in a sample is also possible. However, despite the many advantages that make DSC one of the most widely used techniques, it has to be considered that the analyzed sample is subjected to thermal treatment, which destroys or at least changes the sample and may induce thermal artifacts. Therefore, care has to be taken in the interpretation of thermograms to avoid misleading conclusions. Moreover, DSC thermograms are often difficult to interpret if multiple overlapping thermal processes are involved. Every DSC thermogram is a compromise between sensitivity and resolution as both are dependent on the heating rate, but in opposite ways. To increase the sensitivity, the scan rate may be increased; however, this may lead to decreased resolution, for the scan rate may be too rapid to separate close thermal events. Figure 11-48 shows example DSC thermograms of different solid state forms of the drug indomethacin.

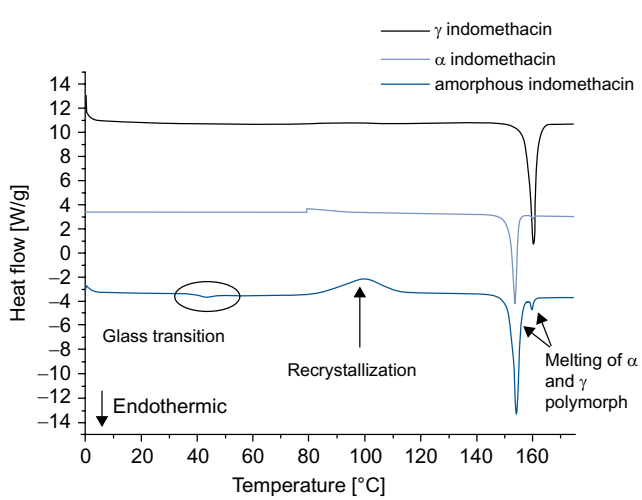

Figure 11-48. DSC thermograms of amorphous indomethacin, and the α- and γ- polymorphic crystalline forms of indomethacin. The thermogram of the amorphous form shows a glass transition and recrystallization event, in addition to the melting. Individual traces are offset for clarity.

Modulated temperature DSC (MTDSC) is an alternative to conventional DSC.[17] In MTDSC a sine wave modulation is applied to a linear temperature program. The obtained heat flow signal is analyzed by applying a discrete Fourier Transform algorithm, which results in the deconvolution of the measured heat flow signal into reversing and non-reversing components. The non-reversing signal comprises the kinetically controlled events that are dependent on the absolute temperature alone, and the reversing signal is a function of the samples' heat capacity and rate of temperature change. The heat flow signal of a sample will be a combination of these two components. The total heat flow signal may, therefore, be expressed as

$$\frac{dQ}{dt} = \frac{Cp}{dT} + f(t,T) \tag{26}$$

Where: dQ/dT is the heat change over time (heat flow) [J s^{-1} or W]; C_p is the "thermodynamic" heat capacity [J K^{-1}]; T is the temperature [K]; and $f(t,T)$ is the kinetic response.

Conventional DSC records the reversing and non-reversing heat flow simultaneously and is not able to resolve them. MTDSC is able to separate the heat capacity (reversing) and kinetic (non-reversing) components, due to their different responses to the underlying and modulated heating rates. Processes that occur at defined temperatures, such as crystallization, evaporation, relaxation, and decomposition will appear in the non-reversing heat flow signal. As the reversing component is related to the samples' heat capacity, for example, the glass transition event is visible in the reversing signal. This enables the separation of the glass transition event from any endothermic relaxation.

LIQUID CRYSTALS

We have seen that crystalline solids are defined by long range order in three dimensions. In contrast, liquids lack long-range order (as do amorphous solids). When some solid materials are heated, they do not directly show a phase transition to the liquid state but instead enter into a different state of matter, between the solid and the liquid state. This state of matter is called the liquid crystalline state. Liquid crystals (also called mesophases) show structural properties which are intermediate between those of crystalline solids and liquids. It should be noted, however, that liquid crystals are not simply a mixture of solids and liquids but, indeed, a separate state of matter. Also, it is important to note that not every organic material is able to exist in a liquid crystalline state. We will discuss a few structural considerations of molecules that can exist in the liquid crystalline state below. These molecules are termed mesogens and usually are anisotropic organic molecules, mostly of rod-like shape.

In a thermogram we observe a first order phase transition, when we, for example, cool a melt that at a certain temperature transforms into a liquid crystal. Similarly the transition from a solid to a liquid crystal is a first order transition. Being situated between the solid and the liquid state of matter, liquid crystals also are a condensed state of matter.

There are two principal types of liquid crystals: thermotropic liquid crystals (TLC) and lyotropic liquid crystals (LLC). TLCs are formed by heating a crystalline solid. In contrast, LLCs are formed by the addition of a liquid (in most pharmaceutical cases, water), to a usually solid mesogen. If we are applying Gibbs' phase law, we can say that the minimum number of components in a TLC is one and in a LLC is two, if a single phase liquid crystal is formed. The degrees of freedom to describe a TLC is two (temperature and pressure) and for a LLC is three (temperature, pressure, and the concentration of the mesogen).

Lyotropic liquid crystals

LLCs can be understood as associations of differently shaped micelles. Micelles are colloidal assemblies of amphiphilic

molecules, e.g., surfactant molecules and phospholipids, i.e., molecules that have a polar head group and a lipophilic, non-polar tail group. We can differentiate the following types of LLC, shown in Figure 11-49:

Lamellar phase (Figure 11.49a): This is pharmaceutically perhaps the most important liquid crystalline phase and consists of a layered packing of indefinitely extended disc-like micelles, leading to a bilayer structure as repetition unit. As such, the lamellar phase has a one-dimensional, long-range, positional order (from layer to layer) but only long-range orientational order within the layers. It is also possible that a lamellar liquid crystalline phase may be dispersed in excess water (so that we get a two phase system). The resulting lamellar liquid crystalline particles form concentric bilayers and are termed liposomes. Phospholipids are pharmaceutically relevant examples of lamellar liquid crystal forming molecules.

Hexagonal phase (Figure 11.49b): This type of LLC consists of hexagonally packed rod-like micelles. As such, the hexagonal phase has a two-dimensional, long-range, positional order (normal to the symmetry axis of the rods) but only long-range, orientational order within the rods. Depending on the nature of the solvent (polar or non-polar), hexagonal phases can exist in a normal and in a reversed form. In the normal form the polar head groups of the mesogens are pointing outwards, and in the reversed form inwards into the rod-like micelles that are forming the hexagonal phase. As we have just discussed for the lamellar phase, also the hexagonal phase of some amphiphilic molecules may be dispersed into colloidal particles, known as hexosomes.

Cubic phase (Figure 11.49c): This type of LLC consists, in the simplest case, of a cubic packing of spherical micelles. As such, the cubic phase has a three-dimensional, long-range, positional order, like a crystalline solid. In contrast to a solid crystal, however, the mesogens in the micelles forming the cubic phase show rotational–diffusional motion and not merely vibrations, as in the case of crystals. Micellar cubic phases can also exist in a normal and in a reverse form, depending on the nature of the solvent. Moreover, bicontinuous cubic phases exist, which cannot simply be interpreted as assemblies of spherical micelles, and some bicontinuous cubic phases may also be dispersed into particles called cubosomes.

Lyotropic nematic phase (Figure 11.49d): This LLC is composed of rod-like micelles and shows a long-range orientational order with respect to the symmetry axis of the micelle. There is no long-range positional order in this type of LLC.

As we could expect from the increasing degree of order, the viscosity of the liquid crystals increases as we go from lyotropic nematic to lamellar, hexagonal, and cubic liquid crystals. Many surfactant and phospholipid mesogens may also show liquid crystalline polymorphism, i.e., they are able to self-assemble into different LLCs, depending on the concentration of the mesogens and temperature.

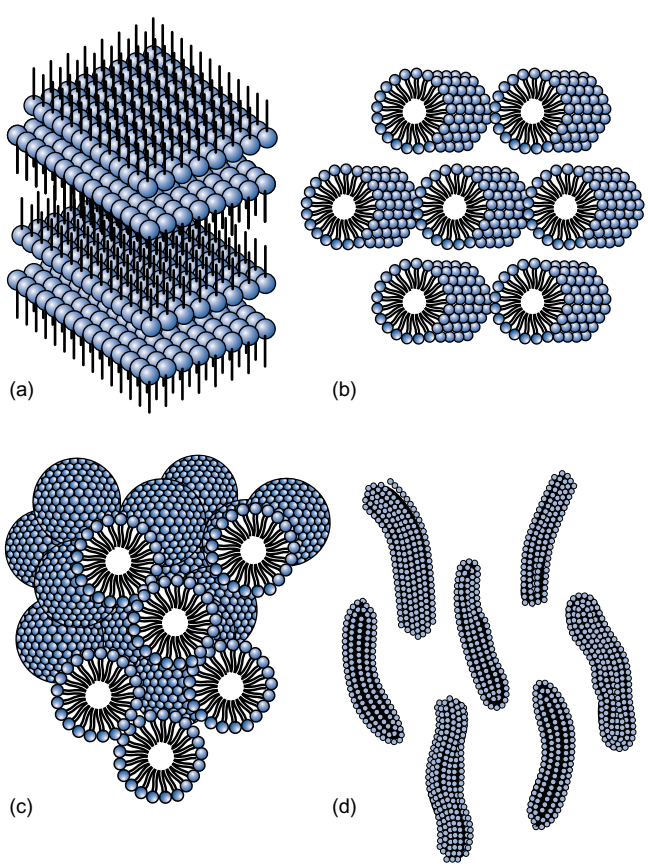

Figure 11-49. Schematic representation of several types of lyotropic liquid crystals. (a) lamellar phase, (b) hexagonal phase, (c) cubic phase, and (d) lyotropic nematic phase.

Thermotropic liquid crystals

The typical structure of a rod-like mesogen able to exist in a thermotropic liquid crystalline state is

$$\begin{array}{ccccccccc} T_1 & - & R_1 & - & C & - & R_2 & - & T_2 \\ & & | & & & & | & & \\ & & LS_1 & & & & LS_2 & & \end{array}$$

The rod-like shape of the mesogen is usually formed by two ring systems (R_1 and R_2, which can be aromatic or aliphatic and may also consist of condensed ring systems). These ring systems are connected by a polar central group (C) and linked to two terminal groups (T_1 and T_2), of which at least one usually is an alkyl chain. However, not all these structural elements necessarily have to be present in a mesogen. Additionally, lateral substituent groups may be present in the mesogen molecular structure (LS_1 and LS_2).

As was the case for LLC, several types of TLC can be differentiated. It is beyond the scope of this chapter to give a detailed description of all TLC types that have been described in the literature (there are over 20 different types of smectic TLC alone). We will thus restrict the description of different TLCs here to three types: nematic phases, chiral nematic phases (cholesteric phases), and fluid smectic phases (including smectic A and smectic C). Schematic representations of these TLCs are shown in Figure 11-50.

Above, we have already described a lyotropic nematic phase, formed by elongated micelles. In case of a thermotropic nematic phase, individual rod-like molecules (not micelles) show an orientational long-range order, again in the absence of any positional long-range order. The orientation of the long axes of the rod-like molecules, however, is not the same for all molecules and varies around a preferred orientation, known as the director of the nematic phase (n ▲ This can be expressed using the order parameter S:

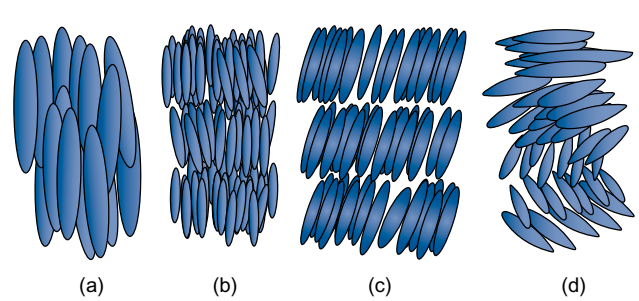

Figure 11-50. Schematic representation of several types of thermotropic liquid crystals: (a) nematic, (b) smectic A, (c) smectic C, and (d) chiral nematic (cholesteric) phase.

$$S = 0.5 < 3\cos^2\Theta - 1> \quad (27)$$

Where: Θ is the angle between the director and the orientation of the molecular length axis of the molecule (see Figure 11.51).

This is, of course, an average value, depending, for example, on the temperature. In the ideal case of complete parallel arrangement of the molecules, S would have the value of 1.

The chiral nematic phase can be regarded as a special form of a nematic phase. If the mesogen is chiral (see above), the director field may adopt a helical superstructure, so that we have nematic layers whose directors are shifted by a constant angle from layer to layer. The distance between two nematic layers with the same director is known as the pitch of the chiral nematic phase. Since the pitch height of some cholesteric mesophases is in the order of the wave length of visible light, they may be colored, and since the pitch height is sensitive to temperature, such liquid crystals may be used as sensitive thermometers, with a specific color indicating a specific temperature.

Smectic phases have a layered structure, similar to the lamellar structure of LLCs. However, in contrast to the lamellar phase, the smectic phase usually does not form a bilayer structure. Depending on the angle the rod-like molecules have with respect to the layer, we can differentiate the smectic A phase (in which the molecules are oriented perpendicular to the layers) from the smectic C phase (in which the molecules are tilted with respect to the layers).

Several drugs have been identified to be able to exist as thermotropic liquid crystals at elevated temperatures,[18] including fenoprofen sodium, fenoprofen calcium, [19] and itraconazole.[20]

Both LLC and TLC can be identified by characteristic appearances (textures) in the polarizing light microscope, as well as by electron microscopic investigation. Also, the liquid crystals show characteristic peak sequences when investigated by X-ray diffraction. Since the distances between the repetition units in liquid crystals are larger than in crystals, the diffraction angles are smaller and, therefore, small angle X-ray diffraction is usually used as an analytical technique, in contrast to wide angle X-ray diffraction, which is usually used in powder diffractometry of crystalline solids.

LIQUIDS

The liquid state of matter is an intermediate state between the solid (and potentially the liquid crystalline state) and the gaseous state of matter. It is thus not surprising that the liquid state of matter shares some commonalities with both solids and gases. As for solids, liquids are practically incompressible under pressure (except if very high pressures are used) and have a high density. This is the reason that solids and liquids are summarized as condensed states of matter. Usually, however, the density of liquids is lower than that of solids for a given material, with water being an important exception, as we have discussed above. Unlike solids, however, the molecules in a liquid can move and change places by diffusing under the influence of heat energy (diffusion). This is a property that liquids have in common with gases and the reason that gases and liquids are summarized as fluid states of matter. While liquids show in general a much higher tendency to be miscible with each other than solids, not all liquids are miscible (unlike gases, which are always completely miscible with each other), and in many cases mixing two liquids will lead to the formation of a two phase system of the two immiscible liquids or a two phase system of a liquid A-rich phase and a liquid B-rich phase if the liquids show partial miscibility. In these cases the two liquids will form an interface with a corresponding interfacial tension. Since the interfacial tension γ is the intensive variable of the interfacial free energy G_S (with the interfacial area A being the extensive variable; $G_S = \gamma A$), two phase liquid systems have a higher energy if the interfacial area between the liquids is increased. An example for this is an emulsion, in which one liquid phase is dispersed in the form of droplets in the other. The system will try to minimize its free energy, and thus the dispersed droplets will fuse together (coalescence) over time to reduce the interfacial energy by reducing the interfacial area. To reduce the surface free energy of emulsions and thereby to stabilize the dispersed nature of the emulsion, surfactants can be added to the emulsion to reduce the interfacial tension between the two liquid phases.

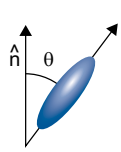

Figure 11-51. Schematic showing the angle Θ between the director (n̂) and the orientation of the molecular length axis of a molecule in a nematic liquid crystal.

Generally, the principle "like dissolves like" can be applied, and liquids with similar polarity (for example, water and ethanol, or benzene and cyclohexane) will be miscible, whereas liquids with different polarities (for example, water and benzene) will be immiscible or show partial miscibility.

Another property liquids have in common with gases is that they are isotropic. This means their physical properties are uniform in all directions or orientations. This is not the case for crystalline solids and liquid crystals, which are anisotropic (with the exception of cubic crystals and liquid crystals). The anisotropic nature of most crystals (and liquid crystals) is also the reason for their optical birefringence, making them visible in the polarized light microscope. Conversely, liquids will be invisible in the polarized light microscope under cross polarization.

If we investigate a liquid with X-ray diffraction, we only measure the characteristic halo we have already discussed in the context of amorphous solid materials (amorphous materials are also isotropic and show no long-range order, which would give rise to peaks in a diffractogram). However, also like amorphous materials, liquids are not without near order, and certain distances between the molecules of a liquid may be preferred over others, due to intermolecular interactions. This can also be determined from X-ray diffraction measurements, by calculating the radial distribution function $g(r)$, which can be generated by a Fourier transformation of the diffraction pattern, and presents the average spatial distribution in a liquid (or in a amorphous solid).

An important property relevant for many pharmaceutical applications of liquids is their viscosity. Viscosity is the resistance to flow or, in other words, the resistance of the liquid to be deformed under a shear stress (due to the intermolecular interactions of molecules in a liquid). If a shear stress (a force F [N] applied parallel to the fluid's surface A [m^2], F/A [N/m^2]) is applied to a liquid, this will result in a velocity gradient in the liquid (dv/dx [s^{-1}]). The ratio between the two is called viscosity η [Pa s]

$$\eta = (F/A)/(dv/dx) \quad (28)$$

This equation is usually rearranged to give Newton's law of viscosity:

$$F/A = \eta dv/dx \quad (29)$$

Liquids can be differentiated by their viscosities and the type of viscosity they have. A Newtonian liquid (ideal viscosity) is a liquid in which η remains constant if the shear stress or shear rate is increased. Water and ethanol are examples of Newtonian liquids. Not all liquids, however, show ideal flow behavior, and these liquids are called non-Newtonian liquids. Many pharmaceutically relevant liquids are non-Newtonian. If the viscosity decreases with increasing shear stress, the liquid shows pseudoplastic flow behavior (also called shear thinning), and in the opposite case, when the viscosity increases as shear stress is increased, the liquid shows dilatant flow behavior (also called shear thickening). Time, however, does not change the viscosity for a given shear stress for pseudoplastic and dilatant liquids (nor for Newtonian liquids). This is, however, not always the case. A pseudoplastic liquid shows a certain viscosity for a certain shear stress. If the stress is kept constant, for

some liquids a further decrease in viscosity can be observed. When the shear stress is removed, the system does not immediately return to its original state, but the viscosity gradually increases. This behavior is termed thixotropy. For pharmaceutical suspensions this is advantageous, for the suspension can be homogenized by shaking and can be poured easily. After some time, the viscosity increases again, stabilizing the suspension against sedimentation.

While many polymer solutions used in pharmaceutical applications are pseudoplastic liquids, concentrated pastes may show dilatant flow behavior, and many suspensions and "semisolids", such as creams and ointments, show thixotropy. Note that a semisolid is a pharmaceutical term used to describe creams, ointments, etc. These are solids at rest, but they start to flow (become liquid) at low shear stresses.

To describe pseudoplastic and dilatant liquids, we can extend Newton's viscosity equation to a power law, known as the Ostwald–de Waele equation:

$$F / A = K(\mathrm{d}v / \mathrm{d}x)^n \tag{30}$$

Where: K is the flow consistency index [Pa s^n]; and n is the flow behavior index [no unit]. $n = 1$ for a Newtonian liquid, $n < 1$ for a pseudoplastic liquid and $n > 1$ for a dilatant liquid.

The viscosity of liquids decreases with increasing temperature, due to the higher molecular mobility. Gases, in contrast, not only have much lower viscosities than liquids but also show an increase in viscosity as temperature is increased (due to higher collision rates of the gas molecules at elevated temperatures). For example, water has a viscosity of 1.002×10^{-3} Pa s at room temperature and 0.35×10^{-3} Pa s at 80°C. Air, on the other hand, has a viscosity 1.79×10^{-5} Pa s at room temperature. Amorphous solids in the glassy state have viscosities in the order of 10^{12} Pa s or higher.

GASES

Gases play an important role in the pharmaceutical field, for example, in the use of medical gases (e.g., oxygen, nitrous oxide, carbon dioxide, compressed air, etc.), as functional excipients in aerosols and inhalers, and in quality control of drugs and dosage forms. Further, oxygen from the air may contribute to oxidative degradation of drugs, and water molecules from air can initiate hydrolytic degradation. Water molecules in air (especially at high relative humidity) may also decrease the physical stability of amorphous drugs or glass solutions, as we have seen, since water is a potent plasticizer, lowering the glass transition temperature of amorphous materials and thus increasing the likelihood of crystallization.

The gaseous state of matter is characterized by very weak interactions between the molecules (for real gases), which in fact are assumed to be completely absent for ideal gases (see below). The consequence of this is that in gases the molecules constantly change their positions by diffusion or convection and have a very low viscosity and density. This makes gases easily compressible under pressure (in contrast to liquids and solids). Also, in contrast to solids and liquids, different gases are always completely miscible with each other. For example, air is a mixture of several gases: approximately 78.1 percent nitrogen, 20.9 percent oxygen, 0.9 percent argon, 0.03 percent carbon dioxide, and small concentrations of neon, helium, methane, and other gases.

If we are completely disregarding the weak interactions between gas molecules, we can fully describe the behavior of gas by the ideal gas law. Historically, the properties of gases have been described in a set of laws, which we will have a quick look at first:

Boyle's law states that the product of absolute pressure (p) and volume (V) is constant (K_1) at constant temperature:

$$pV = K_1 \tag{31}$$

Charles' law states that if a given mass of a gas is heated at constant pressure, the volume of the gas is directly proportional (K_2) to its absolute temperature (T):

$$V / T = K_2 \tag{32}$$

Avogadro's law states that equal volumes of pure gases at constant temperature and pressure contain the same number of particles (n):

$$V / n = K_3 \tag{33}$$

The volume that one mole of gas molecules occupies (the molar volume) is 22.4 L at 0°C and a pressure of 1 atm. The number of molecules in a mol of gas is: 6.022×10^{23} mol^{-1}.

These three laws can be regarded as special cases of the ideal gas law:

$$pV = nRT \tag{34}$$

Where: R is the ideal gas constant [8.314 J/(mol K)]. Note that K_1 in Boyle's law is nRT, K_2 in Charles' law is nR/p, and K_3 in Avogadro's law is RT/p in the ideal gas law.

Finally, if we take into account the ideal gas law (which assumes no interactions between the molecules forming the gas), we arrive at Dalton's law, which states that the total pressure (p_t) of a mixture of gases equals the sum of their partial pressures (p_1 to p_n):

$$p_t = p_1 + p_2 + \ldots + p_n \tag{35}$$

Related to Dalton's law is Henry's law, which states that at constant temperature the amount of a gas (n) that dissolves in a given volume V ($c = n/V$) of a given liquid is directly proportional (K_4) to the partial pressure of that gas in equilibrium with the liquid (p_1).

$$c / p_1 = K_4 \tag{36}$$

While all the above laws hold true for many gases over reasonable temperature and pressure ranges, and thus can be used fairly well to describe the behavior of gases, they do not take into account the fact that interactions between the gas molecules do take place and that the gas molecules occupy a part of the total volume of the gas (albeit usually a very small part). Deviations of the behavior of gases from the ideal situation become more important as, for example, pressure is increased or temperature is decreased. We can also understand this by the fact that gases can be liquefied if the temperature is lowered (this would not be possible if the gas molecules did not interact with each other). On the other hand, many gases behave very closely to ideal gases, and this can be seen, for example, if we determine the molar volumes of some gases. For the gases that make up more than 99 percent of air, we find that nitrogen, oxygen, and the noble gases indeed have molar volumes of 22.4 L. Other gases, though, already at 0°C and a pressure of 1 atm, have molar volumes that differ slightly from that of ideal gases. Methane and carbon dioxide, for example, have molar volumes of 22.3 L and ammonia of 22.1 L.

As stated above, for real gases we have to take into account that the gas molecules occupy a certain volume in the given volume of a gas and that interactions between the gas molecules can occur. These interactions, for example, could be dipole–dipole interactions if the gas molecules contain polar bonds (these interactions are termed Keesom forces). Even in the absence of permanent dipoles in the gas molecules, interaction can occur through transiently induced dipoles (London forces). Note that in the literature the expression "van der Waals force" is sometimes used to describe Keesom and London forces and sometimes specifically for London forces.

The van der Waals equation is one model that takes into account the non-zero volume of the gas molecules and the possible interactions between the gas molecules:

$$nRT = (p + an^2 / V_m^2)(V_m - b) \tag{37}$$

For one mol of gas the equation simplifies to

$$RT = (p + a / V_m^2)(V_m - b) \tag{38}$$

Where: p is the pressure; T is the temperature; R is the ideal gas constant; V_m is the molar volume; and n is the number of molecules.

The parameters a and b are parameters that have to be empirically determined for each gas. The parameter a appears in the pressure term of the equation and relates to intermolecular interactions, whereas the parameter b appears in the volume term of the equation and relates to the fact that the gas molecules themselves occupy a certain volume of the gas.

It should be noted that the van der Waals equation is just one of many models that have been developed to better describe the behavior of gases, especially at extreme conditions, and that many other models exists. This is, perhaps, an opportune moment to remind us that a model is a mathematical description of a physical reality, and not the physical reality itself. It is up to the given situation (and possibly the required precision) as to which model is best used in a particular situation.

PLASMA

We will finally briefly discuss the plasma state of matter. Plasma is actually the most common state of matter in the universe (for example, stars are matter in the plasma state). Plasma is formed by a phase transition from gases if these are heated to very high temperatures. At a certain temperature the electrons of the gas molecules or atoms leave the atoms, leading to an ionization of the gas. Plasma thus contains charged molecules or atoms and free electrons and conducts electricity (unlike gases). Due to the very high temperature of plasma, it is not particularly useful in the pharmaceutical field. Not all atoms however, need to be ionized for plasma to gain its typical properties. So most plasma consist of ions, electrons, and neutral molecules, which nevertheless are in an activated state, e.g., in the form of radicals (molecules containing one or more unpaired electrons).

It is also possible to create the plasma state from gases by electric discharge under reduced pressure, leading to "cold plasma". Cold plasma created in this way has found medical applications [21] and, for example, cold plasma from argon or oxygen has been used to irradiate polymer coats of tablets and granules.[22,23] This plasma irradiation leads to the emission of intensive UV radiation, which can lead to changes in the polymer structure, influencing, for example, drug release kinetics from these tablets or creating gastro-retentive, floating drug delivery systems.[24]

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Chapter 30

Oral Solid Dosage Forms

Ahmed Adel Sakr, PhD and Fars K. Alanazi, PhD

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Medicinal substances are most frequently administered orally, by means of solid dosage forms, such as tablets and capsules. Large scale production methods used for their manufacture, as is described in this chapter, require the incorporation of other materials, in addition to the active ingredients. These additives are usually included in the formulation to facilitate handling, enhance the physical appearance, improve stability, and aid in the delivery of the medicament to the blood stream after administration. These materials, as well as the employed production methods, have been shown to potentially influence the absorption and /or bioavailability of the drugs.[1] In addition, the physicochemical characteristics of the drug substances may influence the physiological bioavailability from solid dosage forms.[2]

TABLETS

According to the USP, tablets are solid dosage forms, containing medicinal substances with or without suitable diluents. They may be classed, according to the method of manufacture, as compressed tablets or molded tablets. The vast majority of all tablets manufactured today are made by compression, and compressed tablets are the most widely used dosage form. Compressed tablets are prepared by the application of high pressures, utilizing steel punches and dies, to powders or granulations. Recently, punching of laminated sheets, electronic deposition methods, and three-dimensional printing methods have been used to make tablets. Tablets have been in widespread use, since the latter part of the 19th century, and their popularity continues. The term "compressed tablet" is believed to have been first used by John Wyeth and Brother, Inc. of Philadelphia. During this same period, molded tablets were introduced for use as hypodermic tablets, for the extemporaneous preparation of solutions for injection. Tablets remain popular as a dosage form, due to the advantages afforded both to the manufacturer (e.g., simplicity and economy of preparation, stability, and convenience in packaging, shipping, and dispensing) and to the patient (e.g., accuracy of dosage, compactness, portability, blandness of taste, and ease of administration). Although the basic mechanical approach for most tablet manufacture has remained the same, tablet technology has undergone great improvement and experimentation. Efforts are continually made to understand more clearly the physical characteristics of powder compaction and the factors affecting the availability of the drug substance from the dosage form after oral administration. Tableting equipment continues to improve in both production speed and the uniformity of tablets. Recent advances in tablet technology have been reviewed.[3,4]

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

COMPRESSED TABLET (CT)

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

Sugar-Coated Tablets (SCT)

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

Film-Coated Tablets (FCT)

Film-coated tablets are compressed tablets covered with a thin layer or film of a water-soluble material. A number of polymeric substances with film-forming properties may be used. Film coating imparts the same general characteristics as sugar coating with the added advantage of the greatly reduced time required for the coating operation. Advances in material science and polymer chemistry have made these coatings the first-choice of formulators.

Enteric-Coated Tablets (ECT)

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

Multiple Compressed Tablets (MCT)

Multi-compressed tablets are compressed tablets made by more than one compression cycle. This process is best used when separation of active ingredients is needed for stability purposes or if the mixing process is inadequate to guarantee uniform distribution of two or more active ingredients.

Layered Tablets

Layered tablets are prepared by compressing additional tablet granulation on a previously compressed granulation. The operation may be repeated to produce multilayered tablets of two or more layers.

Press-Coated Tablets

Press coated tablets, also referred to as dry-coated tablets, are prepared by feeding previously compressed tablets into a special tableting machine and compressing another granulation layer around the preformed tablets. They have all the advantages of compressed tablets (i.e., slotting, monogramming, speed of disintegration), while retaining the attributes of sugar-coated tablets in masking the taste of the drug substance in the core tablets. An example of a press-coated tablet press is

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the Manesty Drycota. Press-coated tablets can also be used to separate incompatible drug substances; in addition, they can provide a means of giving an enteric coating to the core tablets. Both types of multiple-compressed tablets have been widely used in the design of prolonged-action dosage forms.

Controlled-Release Tablets (CRT)

Compressed tablets can be formulated to release the drug slowly over a prolonged period of time. Hence, these dosage forms have been referred to as "prolonged-release" or "sustained-release" dosage forms as well. These tablets, as well as capsule versions, can be categorized into three types: 1) those that respond to some physiological condition to release the drug, such as enteric coatings; 2) those that release the drug in a relatively steady, controlled manner; and 3) those that combine combinations of mechanisms to release pulses of drug, such as repeat-action tablets. Chapter 32 describes the performance of these systems in more detail. Other names for these types of tablets are; Extended Release, Sustained Release, Prolonged Release, Delayed Release, and, in the case of pulsatile tablets, Repeat Action, Pulsatile Release, or Pulse Release.

Tablets for Solution (CTS)

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

Effervescent Tablets

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

Compressed Suppositories or Inserts

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

Buccal and Sublingual Tablets

Buccal and sublingual tablets are small, flat, oval tablets. Tablets intended for buccal administration by inserting into the buccal pouch (the space between the lip and gum in the mouth) may dissolve or erode slowly; therefore, they are formulated and compressed with sufficient pressure to give a hard tablet. Progesterone tablets may be administered in this way. Some newer approaches have employed materials that act as bioadhesives to increase absorption of the drug. Other approaches use tablets that melt at body temperatures. The matrix of the tablet is solidified, while the drug is in solution. After melting, the drug is automatically in solution and available for absorption, thus, eliminating dissolution as a rate-limiting step in the absorption of poorly soluble compounds. Sublingual tablets, such as those containing nitroglycerin, isoproterenol hydrochloride, or erythrityl tetranitrate, are placed under the tongue. Sublingual tablets dissolve rapidly, and the drug substances are absorbed readily by this form of administration.

MOLDED TABLETS OR TABLET TRITURATES (TT)

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

Dispensing Tablets (DT)

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

Hypodermic Tablets (BT)

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

COMPRESSED TABLETS (CT)

For medicinal substances, with or without diluents, to be made into solid dosage forms with pressure, using available equipment, it is necessary that the material, either in crystalline or powdered form, possess a number of physical characteristics. These characteristics include the ability to flow freely, cohesiveness, and lubrication. The ingredients, such as disintegrants designed to break the tablet up in gastrointestinal (GI) fluids and controlled-release polymers designed to slow drug release, ideally, should possess these characteristics or not interfere with the desirable performance traits of the other excipients. Since most materials have none or only some of these properties, methods of tablet formulation and preparation have been developed to impart these desirable characteristics to the material that is to be compressed into tablets. The basic mechanical unit in all tablet-compression equipment includes a lower punch that fits into a die from the bottom and an upper punch, with a head of the same shape and dimensions, which enters the die cavity from the top, after the tableting material fills the die cavity (Fig. 30-1). The tablet is formed by pressure applied on the punches and, subsequently, is ejected from the die. The weight of the tablet is determined by the volume of the material that fills the die cavity. Therefore, the ability of the granulation to flow freely into the die is important in ensuring a uniform fill, as well as the continuous movement of the granulation from the source of supply or feed hopper. If the tablet granulation does not possess cohesive properties, the tablet, after compression, will crumble and fall apart on handling. As the punches must move

Figure 30-1. Multi-tip punches and die. (Courtesy of Natoli.)

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freely within the die and the tablet must be ejected readily from the punch faces, the material must have a degree of lubrication to minimize friction and allow the removal of the compressed tablets. There are three general methods typically used for commercial tablet preparation: the wet-granulation method, the dry granulation method, and direct compression. The method of preparation and the added ingredients are selected to give the tablet formulation the desirable physical characteristics, allowing the rapid compression of tablets. After compression, the tablets must have a number of additional attributes, such as appearance, hardness, disintegration ability, appropriate dissolution characteristics, and uniformity, which are also influenced by both the method of preparation and the added materials present in the formulation. In the preparation of compressed tablets, the formulator must also be cognizant of the effect that the ingredients and methods of preparation may have on the availability of the active ingredients and, hence, the therapeutic efficacy of the dosage form. In response to a request by physicians to change a dicumarol tablet, so it might be broken more easily, a Canadian company reformulated to make a large tablet with a score. Subsequent use of the tablet, containing the same amount of drug substance as the previous tablet, resulted in complaints that larger-than-usual doses were needed to produce the same therapeutic response. Conversely, literature reports indicate that the reformulation of a commercial digoxin tablet resulted in a tablet that, although containing the same quantity of drug substance, gave the desired clinical response at half its original dose. Methods and principles that can be used to assess the effects of excipients and additives on drug absorption have been reviewed.[5–7]

TABLET INGREDIENTS

In addition to the active or therapeutic ingredient, tablets contain a number of inert materials. The latter are known as additives or excipients. They may be classified according to the part they play in the finished tablet. The first group contains those that help to impart satisfactory processing and compression characteristics to the formulation. These include diluents, binders, glidants, and lubricants. The second group of added substances helps to give additional desirable physical characteristics to the finished tablet. Included in this group are disintegrants, surfactants, colors, and, in the case of chewable tablets, flavors and sweetening agents, and, in the case of controlled-release tablets, polymers or hydrophobic materials, such as waxes or other solubility-retarding materials. In some cases, antioxidants or other materials can be added to improve stability and shelf-life. Although the term "inert" has been applied to these added materials, it has become apparent that there is an important relationship between the properties of the excipients and the dosage forms containing them.[8] Preformulation studies demonstrate their influence on stability, bioavailability, and the processes by which the dosage forms are prepared. The need for acquiring more information and use standards for excipients has been recognized in a joint venture of the Academy of Pharmaceutical Sciences and the Council of the Pharmaceutical Society of Great Britain. The result is called the *Handbook of Pharmaceutical Excipients.* This reference work is now distributed widely throughout the world.[9]

Diluents

Frequently, the single dose of the active ingredient is small, and an inert substance is added to increase the bulk to make the tablet a practical size for compression. Compressed tablets of dexamethasone contain 0.75 mg steroid per tablet; hence, it is obvious that another material must be added to make tableting possible. Diluents used for this purpose include dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such tablets are commonly called chewable tablets. Upon chewing, properly prepared tablets disintegrate smoothly at a satisfactory rate, have a pleasant taste and feel, and leave no unpleasant aftertaste in the mouth. Diluents used as excipients for direct compression formulas have been subjected to prior processing to give them flow ability and compressibility. These are discussed in the section Direct Compression. Most formulators of immediate-release tablets tend to consistently use only one or two diluents selected from the listed group in their tablet formulations. Usually, these are selected on the basis of experience and cost factors. However, in the formulation of new therapeutic agents, the compatibility of the diluents with the drug must be considered (e.g., calcium salts used as diluents for the broad-spectrum antibiotic tetracycline) have been shown to interfere with the drug's absorption from the GI tract. When drug substances have low water solubility, it is recommended that water-soluble diluents be used to avoid possible bioavailability problems. Highly adsorbent substances (e.g., bentonite and kaolin) are avoided in making tablets of drugs used clinically in small dosage, such as the cardiac glycosides, alkaloids, and synthetic estrogens. These drug substances may be adsorbed after administration. The combination of amine bases with lactose or alkaline salts with lactose in the presence of alkaline lubricant results in tablets that discolor on aging.

Microcrystalline cellulose (Avicel) is usually used as an excipient in direct-compression formulas. However, its presence in 5–15% concentrations in wet granulations has been shown beneficial in the granulation and drying processes in minimizing case-hardening of the tablets and in reducing tablet mottling. Many ingredients are used for several different purposes, even within the same formulation (e.g., cornstarch can be used in paste form as a binder). When added in drug or suspension form, it is a good disintegrant. Even though these uses are to achieve opposite goals, some tablet formulas use cornstarch in both ways. In some controlled-release formulas, the polymer hydroxypropyl methylcellulose (HPMC) is used both as an aid to prolong the release from the tablet, as well as a film-former in the tablet coating. Therefore, most excipients used in formulating tablets and capsules have many uses, and a thorough understanding of their properties and limitations is necessary to use them rationally.

Binders

Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators. They impart cohesiveness to the tablet formulation that ensures the tablet remain intact after compression, as well as improve the free-flowing qualities by the formulation of granules of desired hardness and size. Materials commonly used as binders include starch, gelatin, and sugars, such as sucrose, glucose, dextrose, molasses, and lactose. Natural and synthetic gums that have been used include acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, Veegum, and larch arabogalactan. Other agents considered binders under certain circumstances are polyethylene glycol, ethylcellulose, waxes, water, and alcohol. Synthetic binders, such as polyvinylpyrrolidone and HPMC are becoming more popular. The quantity of binder used has considerable influence on the characteristics of the compressed tablets. The use of too much binder or too strong a binder will make a hard tablet that will not disintegrate easily and will cause excessive wear of punches and dies. Differences in binders used for CT Tolbutamide resulted in differences in hypoglycemic effects observed clinically. Materials that have no cohesive qualities of their own require a stronger binder than those with these qualities. Alcohol and water are not binders in the true sense of the word, but, due to their solvent action on some ingredients, such as lactose, starch, and celluloses, they change the powdered material to granules, and the residual moisture retained enables the materials to adhere together when compressed. Binders are used both as a solution and in a dry form, depending on the other ingredients in the formulation and the method of preparation. However, several pregelatinized starches available are intended

to be added in the dry form, so water alone can be used as the granulating solution. The same amount of binder in solution will be more effective than if it were dispersed in a dry form and moistened with the solvent. By the latter procedure, the binding agent is not as effective in reaching and wetting each of the particles within the mass of powders. Each of the particles in a powder blend has a coating of adsorbed air on its surface, and it is this film that must be penetrated before the powders can be wetted by the binder solution. After wetting, a certain period of time is necessary to dissolve the binder completely and make it completely available for use. Since powders differ with respect to the ease with which they can be wetted and their rate of solubilization, it is preferable to incorporate the binding agent in solution. By this technique, it is often possible to gain effective binding with a lower concentration of binder. The direct-compression method for preparing tablets requires a material that is not only free-flowing but also sufficiently cohesive to act as a binder. This use has been described for a number of materials, including microcrystalline cellulose, microcrystalline dextrose, amylose, and polyvinylpyrrolidone. It has been postulated that microcrystalline cellulose is a special form of cellulose fibril in which the individual crystallites are held together largely by hydrogen bonding. The disintegration of tablets containing the cellulose occurs by breaking the intercrystallite bonds by the disintegrating medium.

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

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

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

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

Polyvinylpyrrolidone–(PVP) can be used as an aqueous or alcoholic solution, and this versatility has increased its popularity. Concentrations range from 2% and vary considerably. It should be noted that binder solutions are usually made up to Weight, rather than volume. This is to enable the formulator to determine the weight of the solids that have been added to the tablet granulation in the binding solution. This becomes part of the total weight of the granulation and must be taken into consideration in determining the weight of the compressed tablet, which will contain the stated amount of the therapeutic agent. As can be seen by the list of binders in this chapter, most modern binders used in solution are polymeric. Because of this, the flow or spreadability of these solutions becomes important, when selecting the appropriate granulating equipment. The rheology of polymeric solutions is a fascinating subject in and of itself and should be considered for these materials.

Lubricants

Lubricants have a number of functions in tablet manufacture. They prevent adhesion of the tablet material to the surface of the dies and punches, reduce interparticle friction, facilitate the ejection of the tablets from the die cavity, and may improve the rate of flow of the tablet granulation. Commonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid, glyceryl behanate, hydrogenated vegetable oils, and polyethylene glycol (PEG). Most lubricants, with the exception of talc, are used in concentrations below 1%. When used alone, talc may require concentrations as high as 5%. Lubricants are, in most cases, hydrophobic materials. Poor selection or excessive amounts can result in waterproofing the tablets, resulting in poor tablet disintegration and/or delayed dissolution of the drug substance. The addition of the proper lubricant is highly desirable, if the material to be tableted tends to stick to the punches and dies. Immediately after compression, most tablets have the tendency to expand and will bind and stick to the side of the die. The choice of the proper lubricant will overcome this effectively. The method of adding a lubricant to a granulation is important, if the material is to perform its function satisfactorily. The lubricant should be divided finely by passing it through a 60- to 100-mesh nylon cloth onto the granulation. In production, this is called "bolting" the lubricant. After adding the lubricant, the granulation is tumbled or mixed gently to distribute the lubricant without coating the particles too well or breaking them down to finer particles. Some research has concluded that the order of mixing of lubricants and other excipients can have a profound effect on the performance of the final dosage form. Thus, attention to the mixing process itself is just as important as the selection of lubricant materials. These process variables can be seen in the prolonged blending of a lubricant in a granulation. Overblending materially can affect the hardness, disintegration time, and dissolution performance of the resultant tablets. The quantity of lubricant varies, being as low as 0.1% and, in some cases, as high as 5%. Lubricants have been added to the granulating agents in the form of suspensions or emulsions. This technique serves to reduce the number of operational procedures and, thus, reduce the processing time. In selecting a lubricant, proper attention must be given to its compatibility with the drug agent. Perhaps the most widely investigated drug is acetylsalicylic acid. Different talcs varied the stability of aspirin significantly. Talc, with a high calcium content and a high loss on ignition, was associated with increased aspirin decomposition. From a stability standpoint, the relative acceptability of tablet lubricants for combination with aspirin was found to decrease in the following order: hydrogenated vegetable oil, stearic acid, talc, and aluminum stearate. The primary problem in the preparation of a water-soluble tablet is the selection of a satisfactory lubricant. Soluble lubricants reported to be effective include sodium benzoate, a mixture of sodium benzoate and sodium acetate, sodium chloride, leucine, and polyethylene glycol/Carbowax 4000. However, it has been suggested that formulations used to prepare water soluble tablets may represent a number of compromises between compression efficiency and water solubility. Although magnesium stearate is one of the most widely used lubricants, its hydrophobic properties can retard disintegration and dissolution. To overcome these waterproofing characteristics, sodium lauryl sulfate is sometimes included. One compound found to have the lubricating properties of magnesium stearate, without their disadvantage, is magnesium lauryl sulfate. Its safety for use in pharmaceuticals has not been established.

Glidants

A glidant is a substance that improves the flow characteristics of a powder mixture. These materials always are added in the dry state just prior to compression (i.e., during the lubrication step). Colloidal silicon dioxide Cab-o-sil (Cabot) is the most commonly used glidant and is used in low concentrations of

1% or less. Talc (asbestos-free) is also used and may serve the dual purpose of lubricant glidant. It is especially important to optimize the order of addition and the mixing process for these materials, to maximize their effect and to make sure their influence on the lubricant(s) is minimized.

Disintegrants

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

Starch has a great affinity for water and swells when moistened, thus, facilitating the rupture of the tablet matrix. However, others have suggested that its disintegrating action in tablets is due to capillary action, rather than swelling; the spherical shape of the starch grains increases the porosity of the tablet, thus, promoting capillary action. Starch, 5%, is suggested, but, if more rapid disintegration is desired, this amount may be increased to 10% or 15%. Although it might be expected that disintegration time would decrease as the percentage of starch in the tablet increased, this does not appear to be the case for tolbutamide tablets. In this instance, there appears to be a critical starch concentration for different granulations of the chemical. When their disintegration effect is desired, starches are added to the powder blends in the dry state. A group of materials known as "super disintegrants" have gained in popularity as disintegrating agents. The name comes from the low levels (1–4%) at which they are completely effective. Croscarmellose, crospovidone, and sodium starch glycolate represent examples of a cross-linked cellulose, a cross-linked polymer, and a cross-linked starch, respectively. The development of these disintegrants fostered new theories about the various mechanisms by which disintegrants work. Sodium starch glycolate swells 7- to 12-fold in less than 30 seconds. Croscarmellose swells 4- to 8-fold in less than 10 seconds. The starch swells equally in all three dimensions, whereas the cellulose swells only in two dimensions, leaving fiber length essentially the same. It is postulated that the rate, force, and extent of swelling play an important role in those disintegrants that work by swelling. Cross-linked PVP swells little but returns to its original boundaries quickly after compression. Wicking, or capillary action, is also postulated to be a major factor in the ability of cross-linked PVP to function.10–13 In addition to the starches, large varieties of materials have been used and are reported to be effective as disintegrants. This group includes Veegum HV, methylcellulose, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp, and carboxymethylcellulose. Sodium lauryl sulfate, in combination with starch, has also been demonstrated to be an effective disintegrant. In some cases, the apparent effectiveness of surfactants in improving tablet disintegration is postulated as due to an increase in the rate of wetting. The disintegrating agent is usually mixed with the active ingredients and diluents after granulation. In some cases, it may be advantageous to divide the disintegrant into two portions: one part is added to the powdered formula prior to granulation, and the remainder is mixed with the lubricant and added prior to compression. Incorporated in this manner, the disintegrant serves a double purpose: the portion added to the lubricant rapidly breaks down the tablet to granules, and the disintegrant mixed with the active ingredients disintegrates the granules into smaller particles.[12] Veegum has been shown more effective as a disintegrator in sulfathiazole tablets, when most of the quantity is added after granulation and only a small amount before granulation. Likewise, the montmorillonite clays were found to be good tablet disintegrants, when added to prepared granulations as powder. They are much less effective as disintegrants, when incorporated within the granules.

Factors other than the presence of disintegrants can affect the disintegration time of compressed tablets significantly. The binder, tablet hardness, and the lubricant have been shown to influence the disintegration time. Thus, when the formulator is faced with a problem concerning the disintegration of a compressed tablet, the answer may not lie in the selection and quantity of the disintegrating agent alone. The evolution of carbon dioxide is also an effective way to cause the disintegration of compressed tablets. Tablets containing a mixture of sodium bicarbonate and an acidulant, such as tartaric or citric acid, will effervesce when added to water. Sufficient acid is added to produce a neutral or slightly acidic reaction when disintegration in water is rapid and complete.

One drawback to the use of the effervescent type of disintegrator is that such tablets must be kept in a dry atmosphere at all times during manufacture, storage, and packaging. Soluble, effervescent tablets provide a popular form for dispensing aspirin and noncaloric sweetening agents.

Coloring Agents

Colors in compressed tablets serve functions other than making the dosage form more esthetic in appearance. Color helps the manufacturer control the product during its preparation, as well as serves as a means of identification to the user. The wide diversity in the use of colors in solid dosage forms makes it possible to use color as an important category in the identification code developed by the AMA to establish the identity of an unknown, compressed tablet in situations arising from poisoning. All colorants used in pharmaceuticals must be approved and certified by the FDA. For several decades, colorants have been subjected to rigid toxicity standards, and, as a result, a number of colorants have been removed from an approved list of Food, Drug and Cosmetic Act (FD&C) colors, or "delisted." Several have been listed as well. Table 30-1 lists the colorants currently approved in the United States. Each country has its own list of approved colorants, and formulators must consider this in designing products for the international market. Any of the approved, certified, water-soluble FD&C dyes, mixtures of the same, or their corresponding lakes may be used to color tablets. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. In some instances, multiple dyes are used to give a purposefully heterogeneous coloring in the form of speckling to compressed tablets. The dyes available do not meet all the criteria required for the ideal pharmaceutical colorants. The photosensitivity of several of the commonly used colorants and their lakes has been investigated, as well as the protection afforded by a number of glasses used in packaging tablets. Another approach for improving the photostability of dyes has been in the use of ultraviolet-absorbing chemicals in the tablet formulations with the dyes. The Di-Pac line (Amstar) is a series of commercially available colored, direct-compression sugars. The most common method of adding color to a tablet formulation is to dissolve the dye in the binding solution prior to the granulating process. Another approach is to adsorb the dye on starch or calcium sulfate from its aqueous solution; the resultant powder is dried and blended with the other ingredients. If the insoluble lakes are used, they may be blended with the other dry ingredients. Frequently, during drying, colors in wet granulations migrate, resulting in an uneven distribution of the color in the granulation. After compression, the tablets have a mottled appearance, due to the uneven distribution of the color. Migration of colors may be reduced by drying the granulation slowly at low temperatures and stirring the granulation, while it is drying. The affinity of several water-soluble, anionic, certified dyes for natural starches has been demonstrated; in these cases, this affinity should aid in preventing color migration. Other additives have been shown to act as dye-migration inhibitors. Tragacanth (1%), acacia (3%),

Table 30-1. Color Additives Approved for Use in Drugs

Part 74, Subpart B: Color additives subject to batch certification			
21 CFR Section	**Straight Color**	**Year [2] Approved**	**Uses and Restrictions**
§74.1101	FD&C Blue No. 1	1969	Ingested drugs generally [5]
§74.1102	FD&C Blue No. 2	1987	Ingested drugs
§74.1203	FD&C Green No. 3	1982	Drugs generally [5]
§74.1205	D&C Green No. 5	1982	Drugs generally [5]
§74.1303	FD&C Red No. 3	1969	Ingested drugs
§74.1306	D&C Red No. 6	1983	Drugs such that total with D&C Red No. 7 NTE [7] 5 mg/daily dose of drug
§74.1307	D&C Red No. 7	1983	Drugs such that total with D&C Red No. 6 NTE [7] 5 mg/daily dose of drug
§74.1321	D&C Red No. 21	1983	Drugs generally [5]
§74.1322	D&C Red No. 22	1983	Drugs generally [5]
§74.1327	D&C Red No. 27	1982	Drugs generally [5]
§74.1328	D&C Red No. 28	1982	Drugs generally [5]
§74.1330	D&C Red No. 30	1982	Drugs generally [5]
§74.1333	D&C Red No. 33	1988	Ingested drugs, other than mouthwashes and dentifrices (NTE [7] 0.75 mg/daily dose of drug)
§74.1336	D&C Red No. 36	1989	Ingested drugs, other than mouthwashes and dentifrices, NTE [7] 1.7 mg/daily dose for drugs taken less than 1 yr; NTE [7] 1.0 mg/daily dose for drugs taken more than 1 yr
§74.1340	FD&C Red No. 40(3)	1971	Drugs generally [5]
§74.1705	FD&C Yellow No. 5	1969	Ingested drugs generally [5]
§74.1706	FD&C Yellow No. 6	1986	Drugs generally [5]
§74.1710	D&C Yellow No. 10	1983	Drugs generally [5]
		1984.	Modification of uses and restrictions

[2] The year approved is based on the date listed in the "Confirmation of Effective Date" notice for the action as published in the Federal Register.
[5] Color additives permitted for general use may not be used in the area of the eye, in injections or in surgical sutures, unless such use is specified in the color additive listing regulation. Currently, no color additives are listed for use in injected products, such as tattoos or permanent makeup.
[7] NTE—not to exceed

attapulgite (5%), and talc (7%) were effective in inhibiting the migration of FD&C Blue Nolin lactose. In using dye lakes, the problem of color migration is avoided, since the lakes are insoluble. Prevention of mottling can also be helped, by the use of lubricants and other additives that have been colored similarly to the granulation prior to their use. The problem of mottling becomes more pronounced as the concentration of colorants increases. Color mottling is an undesirable characteristic common to many commercial tablets.

Flavoring Agents

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

POWDER COMPACTION

Compressed tablets became a commercially viable and efficient dosage form with the invention of tablet machines. In 1843, William Brockendon, a British inventor, author, artist, and watchmaker, received British Patent #9977 for *Shaping Pills, Lozenges, and Black Lead by Pressure in Dies.* In over 150 years of tablet manufacture, the basic process has not changed. Surprisingly, improvements have been made only with regards to speed of manufacture and quality control. The process of compaction has several identifiable phases. As can be seen in Figure 30-2, when powders undergo compression (a reduction in volume), the first process to occur is a consolidation of the powders. During this consolidation phase, the powder particles adopt a more efficient packing order. The second phase of the compaction process is elastic, or reversible deformation. If the force were removed during this phase, the powder would completely recover to the efficiently packed state. For most pharmaceutical powders, this phase is very short in duration and very difficult to identify on most instrumented tablet presses. The third phase of compaction is plastic, or irreversible, deformation of the powder bed. It is this phase that is the most critical in tablet

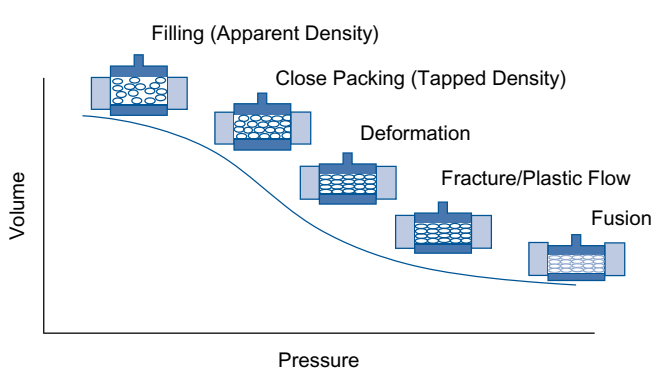

Figure 30-2. The stages of powder compaction.

formation. If too much force is applied to the powder, brittle fracture occurs. If the force is applied too quickly, fracture and de-bonding during stress relaxation can occur. In 1950, Stewart reported on the importance of plastic flow and suggested that, if a material has significant plastic flow under compression, it will be more likely to form a compact. Stress-relaxation data, using the Maxwell model of viscoelastic behavior, were evaluated, in an attempt to quantify the rate of plastic deformation of some direct compression excipients. The term "contact time" was used to describe the total time for which a moving punch applies a detectable force to the die contents during the compression and decompression event, excluding ejection.

Tablet Strength-Compression Pressure Profile

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

Tablet Friability

There have been many suggestions about how tablet friability tests should be performed. Many formulators believe this is an important indicator of cohesiveness but is of limited value in predicting failure in the field.

Changes in Bed Density During Compression

As applied stress (force) increases, elastic and plastic deformation of the particles occurs, which results in plastic flow and a reduction in inter- and intraparticulate void spaces. This lowers the overall compact density. For highly cohesive systems, the reduction in void space may yield a compact of sufficient strength for insertion into a capsules shell. However, the inherent cohesiveness for most drugs and excipients is not suitable alone for tablet manufacture. The Heckel equation is subsequently given; K can be considered equal to the reciprocal of the mean yield pressure, and A is a function of the original compact volume and is related to the densification and particle rearrangement prior to bonding:

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

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

Changes in Surface Area During Compression

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

Stress Relaxation

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

Stress Transmissions during Compression

If the stresses in the upper punch, lower punch, and die wall are monitored, a general plot can be constructed, showing the relationship between these forces.

GRANULATION METHODS

Wet Granulation

The most widely used and most general method of tablet preparation is the wet-granulation method. Its popularity is due to the greater probability that the granulation will meet all the physical requirements for the compression of good tablets. Its chief disadvantages are the number of separate steps involved, as well as the time and labor necessary to carry out the procedure, especially on a large scale. The steps in the wet method are weighing, mixing, wet massing, screening the damp mass, drying, dry screening, lubrication, and compression. The equipment involved depends on the quantity or size of the batch and the percent active ingredient per total weight of the tablets. Wet massing can be performed by:

1. Low Shear mixers/granulators,
2. High Shear mixers/granulators,
3. Fluid-Bed granulators/dryers,
4. Spray Dryers, or
5. Extruders and Spheronizers.

Low shear mixers include the barrel, cube, twin shell, double cone, slated double cone, ribbon, sigma blade, planetary mixers, etc. (Fig. 30-3). Although these mixers continue to be used in some older pharmaceutical factories, they are replaced, now, by the high shear mixers/granulators. High shear mixers are stationary shell mixers with a large mixer scraper blade, which mixes the ingredients, eliminates dead spots, and presents the ingredients with a high speed chopper blade, which intimately

Figure 30-3. Twin Shell Blender with Intensifier Bars. (Courtesy of Patterson Kelly Buflovak LLC.)

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mixes the ingredients and breaks the lumps. The advantages of the high shear mixers/granulators are: simple, robust technology, production of high density granules, rapid and efficient mixing, low liquid requirements, and equipped for drying.

There are many models/trade names of high shear mixers in the pharmaceutical market, such as the Loedige, Littleford MGT, Diosna, Fiedler, Vector, Glatt, GEA, and Hüttlin Gentlewing. Figure 30-4 shows a typical high shear mixer granulator from Vector, and Figure 30-5 shows a typical Glatt high shear mixer. A relatively new high shear mixer from Hüttlin is the Gentlewing High Shear Mixer, which is available in laboratory and large scale sizes, either top driven or bottom driven. The Gentlewing technology applies the principle of a positive displacement impeller for blending a non-Newtonian medium. The impeller shape matches the contour of the mixing container, and its angled impeller plate ensures a forced mixing of the product. Rather than using the impulse of an impeller for mixing, the Gentlewing's uniform presence throughout the product container distributes the mixing energy, at lower speeds but higher torque, evenly throughout the product, reducing segregation issues typically caused by high dynamic forces (Fig. 30-6 and Fig. 30-7).

The active ingredient, diluent, and part of the disintegrant are mixed or blended well. Solutions of the binding agent are added or sprayed to the mixed powders with stirring. The powder mass is wetted with the binding solution, until the mass has the consistency of damp snow or brown sugar. If the granulation is over-wetted, the granules will be hard, requiring considerable pressure to form the tablets, and the resultant tablets may have a mottled appearance. If the powder mixture is not wetted sufficiently, the resulting granules will be too soft, breaking down during lubrication and causing difficulty during compression. In modern high shear mixers, the end point of wet granulation is no more dependent on the experience of the operator and the "hand" feeling of the wet mass, but is measured accurately by a built in torque meter. This consistency and reproducibility from batch to batch are assured. The wet granulation mass is then forced through a 6- or 8-mesh screen. Small batches can be forced through by hand, using a manual screen. For larger quantities, one of several comminuting mills suitable for wet screening can be used. These include the Stokes oscillator, Colton rotary granulator, Fitzpatrick comminuting mill, Cone Mill, or Stokes tornado mill. In comminuting mills, the granulation is forced through the sieving device by rotating hammers, knives, or oscillating bars (Fig. 30-8–30-10). Most high-speed mixers are equipped with a chopper blade that operates independently of the main mixing blades and can replace the wet milling step (i.e., can obviate the need for a separate operation). For tablet

Figure 30-5. High Shear Mixer. (Courtesy of GLATT.)

Figure 30-4. Vector High Shear Mixer.

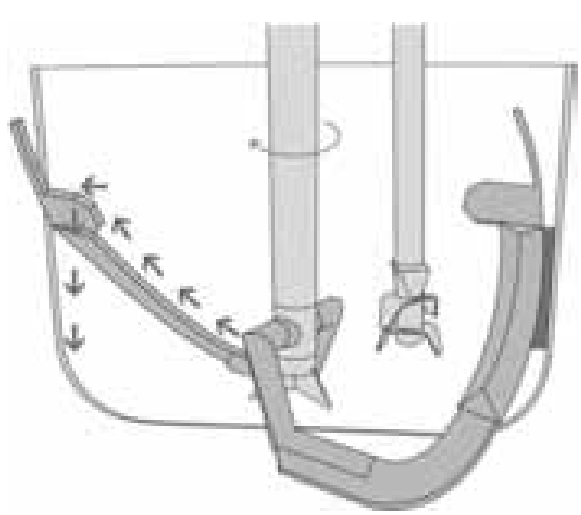

Figure 30-6. Gentlewing High Shear Mixer, diagram. (Courtesy of Hüttlin GmbH, A Bosch Packaging Technology Company.)

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Figure 30-7. Gentlewing High Shear Mixer. (Courtesy of Hüttlin GmbH, A Bosch Packaging Technology Company.)

Figure 30-8. Fitzmill Comminutor. (Courtesy of Fitzpatrick Co.)

formulations in which continuous production is justified, extruders, such as the Reitz extruder, have been adapted for the wet-granulation process. Moist material from the wet milling step, traditionally, was placed on large sheets of paper on shallow wire trays and placed in drying cabinets with a circulating air current and thermostatic heat control. Although tray drying was the most widely used method of drying tablet granulations in the past, fluid-bed drying is now considered the standard. In drying tablet granulation by fluidization, the material is suspended and agitated in a warm air stream, while the granulation is maintained in motion. Drying tests comparing the fluidized bed and a tray dryer for a number of tablet granulations indicated that the former was 15 times faster than the conventional method of tray drying. In addition to the decreased drying time, the fluidization method is claimed to have other advantages, such as better control of drying temperatures, decreased handling costs, and the opportunity to blend lubricants and other materials into the dry granulation directly in the fluidized bed (Fig. 30-11). The application of microwave drying and infrared drying to tablet granulations has been reported as successful for most granulations tried. These methods readily lend themselves to continuous granulation operations. The study of drying methods for tablet granulations led to the development of the Rovac dryer system by Ciba Novartis pharmacists and engineers. The dryer is similar in appearance to the cone blender, except for the heating jacket and vacuum connections. By excluding oxygen and using the lower drying temperatures made possible by drying in a vacuum, opportunities for degradation of the ingredients during the drying cycle are minimized. A greater uniformity of residual moisture content is achieved, due to the moving bed, controlled temperature, and controlled time period of the drying cycle. Particle-size distribution can be controlled by varying the speed of rotation and drying temperature, as well as by comminuting the granulation to the desired granule size after drying. Recently, many machine manufacturers, such as Hüttlin, GEA, and Glatt, introduced the single pot technology in which the drying process can also take place in a vertical granulator specially equipped for this purpose. The drying is assisted by suitable measures, according to the product and the process, such as heated wall surfaces, gas stripping, and vacuum (Fig. 30-12).

In drying granulations, it is desirable to maintain a residual amount of moisture in the granulation. This is necessary to maintain the various granulation ingredients, such as gums, in a hydrated state. Also, the residual moisture contributes to the reduction of the static electric charges on the particles. In the selection of any drying process, an effort is made to obtain uniform moisture content. In addition to the importance of moisture content of the granulation in its handling, during the manufacturing steps, the stability of the products containing moisture-sensitive active ingredients may be related to the moisture content of the products. Previously, it was indicated that water-soluble colorants can migrate toward the surface of the granulation during the drying process, resulting in mottled tablets after compression. This is also true for water-soluble drug substances, resulting in tablets unsatisfactory as to content uniformity. Migration can be reduced by drying the granulation slowly at low temperatures or using a granulation in which the major diluent is present as granules of large particle size. The presence of microcrystalline cellulose in wet granulations also reduces migration tendencies. After drying, the granulation is reduced in particle size, by passing it through a smaller-mesh screen. Following dry screening, the granule size tends to be more uniform. For dry granulations, the screen size selected depends on the diameter of the punch. The following sizes are suggested:

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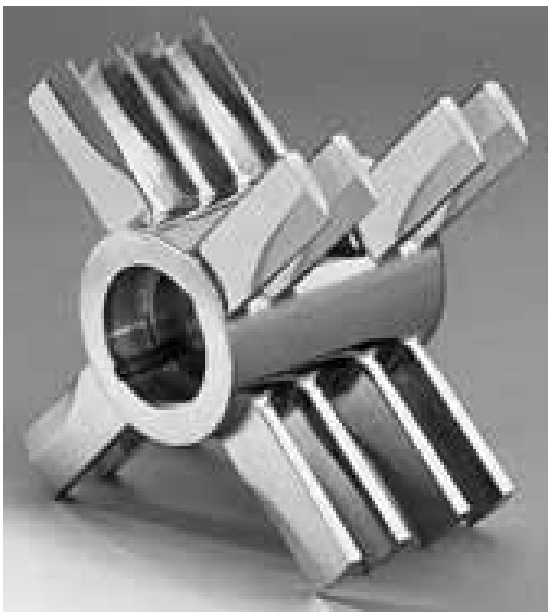

Figure 30-9. Hammers. (Courtesy of Fitzpatrick Co.)

1. Tablets up to 3/16 inch diameter, use 20-mesh
2. Tablets 7/32 to 5/16 inch, use 16-mesh
3. Tablets 11/32 to 13/32 inch, use 14-mesh
4. Tablets7/16 inch and larger, use 12-mesh

For small amounts of granulation, hand screens may be used and the material passed through with the aid of a stainless steel spatula. With larger quantities, any of the comminuting mills with screens corresponding to those just mentioned may be used. Note that the smaller the tablet, the finer the dry granulation to enable more uniform filling of the die cavity; large granules give an irregular fill to a comparatively small die cavity. With compressed tablets of sodium bicarbonate, lactose, and magnesium trisilicate, a relationship has been demonstrated between the particle size of the granulated material and the disintegration time and capping of the resultant tablets. For a sulfathiazole granulation, however, the particle-size distribution did not appear to influence hardness or disintegration. After dry granulation, the lubricant is added as a fine powder.

Figure 30-10. Screens. (Courtesy of Fitzpatrick Co.)

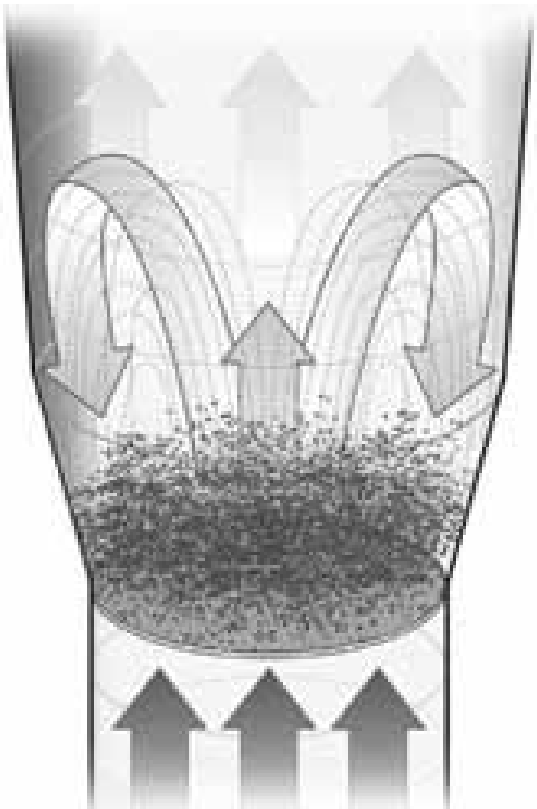

Figure 30-11. Schematic Fluid bed Dryer. (Courtesy of Glatt.)

It is screened onto the granulation through 60- or 100-mesh nylon cloth to eliminate small lumps, as well as to increase the covering power of the lubricant. As it is desirable for each granule to be covered with the lubricant, the lubricant is blended with the granulation very gently, preferably in a blender using a tumbling action, such as the Patterson Kelly Twin Shell Blender (Fig. 30-3). Gentle action is desired to maintain the uniform granule size, resulting from the granulation step. It has been claimed that too much fine powder is not desirable, because fine powder may not feed into the die evenly; consequently, variations in weight and density result. Fine powders, commonly designated as "fines," also blowout around the upper punch and down past the lower punch, making it necessary to clean the machine frequently. Fines, however, at a level of 10–20%, are, traditionally, sought by the tablet formulator. The presence of some fines is necessary for the proper filling of the die cavity. Now, even higher concentrations of fines are used successfully in tablet manufacture. Most investigators agree that no general limits exist for the amount of fines that can be present in a granulation; it must be determined for each specific formula. Many formulators once believed (and some still believe) that over blending resulted in an increased amount of fines and, hence, caused air entrapment in the formula. The capping and laminating of tablets associated with over blending lubricants was thought to be caused by these air pockets. Most scientists now recognize that a more plausible explanation has to do with the function of the lubricants themselves. Since the very nature of a lubricant tends to make surfaces less susceptible to adhesion, over blending prevents the intergranular bonding that takes place during compaction.

Fluid-Bed Granulation

A relatively new method for granulating evolved from the fluid-bed drying technology previously described. The concept was to spray a granulating solution onto the suspended particles,

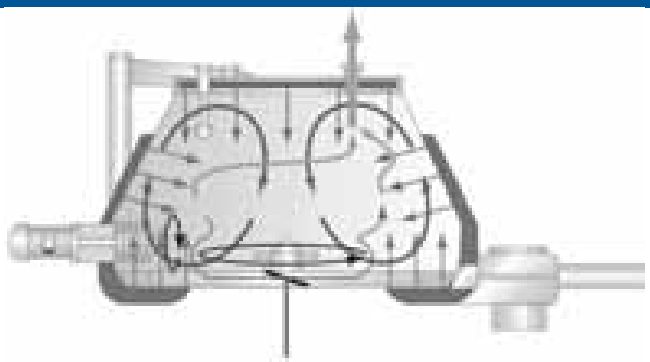

Figure 30-12. Single Pot Vertical Granulator. (Courtesy of Glatt.)

which then would be dried rapidly in the suspending air. The main benefit from this system is the rapid granulation and drying of a batch. The main firms that developed this technology are Glatt, Aeromatic (now GEA), Vector, and Hüttlin. The general design of these systems is the same with most companies (Fig. 30-13–30-16). In this method, particles of an inert material or the active drug are suspended in a vertical column with a rising air stream; while the particles are suspended, the common granulating materials in solution are sprayed into the column. There is a gradual particle buildup under a controlled set of conditions, resulting in a tablet granulation ready for compression after the addition of the lubricant. An obvious advantage exists, since granulating and drying can take place in a single piece of equipment. It should be noted, however, that many of the mixers discussed previously can be supplied with a steam jacket and vacuum and can provide the same advantage. In these systems, a granulating solution or solvent is sprayed into or onto the bed of suspended particles. The rate of addition of the binder, temperature in the bed of particles, temperature of the air, volume, and moisture of the air all play an important role in the quality and performance of the final product. Many scientists feel that this method is an extension of the wet-granulation method, as it incorporates many of its concepts. However, anyone who has developed a formulation in

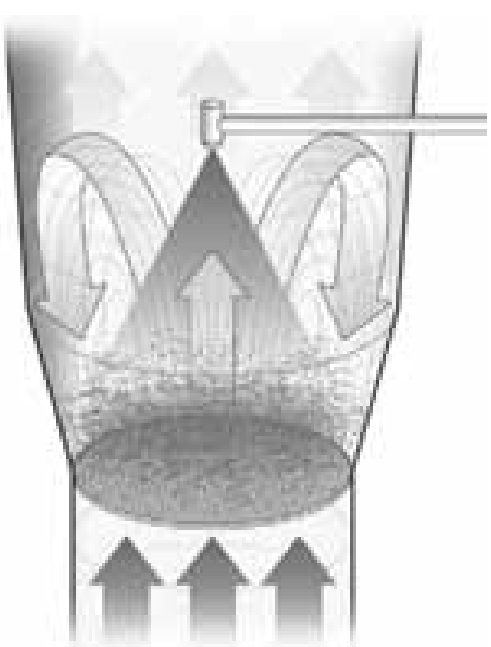

Figure 30-13. Fluid Bed Top Spray Granulator. (Courtesy of Glatt.)

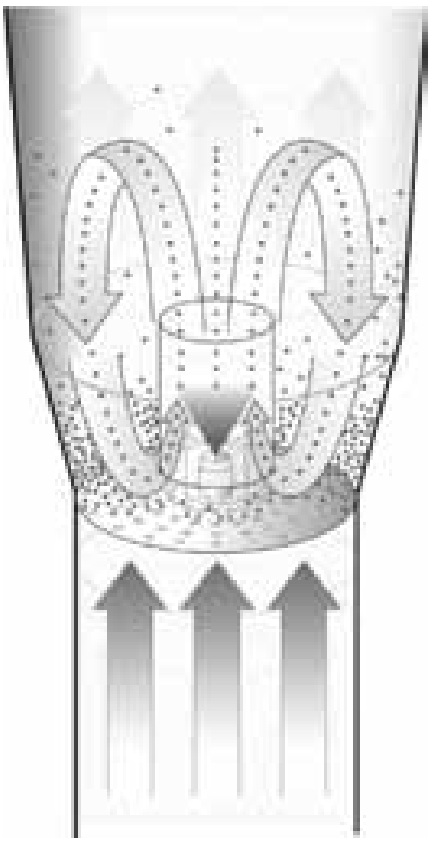

Figure 30-14. Bottom Spray Fluid Bed. (Courtesy of Glatt.)

a fluid-bed system knows that the many operating parameters involved make it somewhat more complex. In addition to its use for the preparation of tablet granulations, this technique has also been proposed for the coating of solid particles, as a means of improving the flow properties of small particles. Researchers have observed that, in general, fluid-bed granulation yields a less dense particle than conventional methods, and this can affect subsequent compression behavior. The Merck facility at Elkton, VA, was the first completely automated tablet production facility in the world. The entire tablet-manufacturing process, based on a wet-granulation method, was computer-controlled. The system weighed the ingredients, blended, granulated, dried, and lubricated to prepare a uniform granulation of specified particle size and particle-size distribution. The computer directed the compression of the material into tablets with exacting specifications for thickness, weight, and hardness. After compression, the tablets were coated with a water-based film coating. The computer controlled and monitored all flow of material. The plant represented the first totally automated pharmaceutical manufacturing facility. However, due to shifting market trends, the burdens of process validation, and changes to processes, totally automated processes are, generally, not used today. Instead, many production operations focus on computer-controlled and monitored unit operations, such as seen in various tableting machines and granulators. Equipment suppliers work closely with individual pharmaceutical companies in designing specialized and unique systems. Newer developments from the machine manufacturing industries improved the process efficiency by modifying the air distribution plate and introducing the new Diskjet with a tangential air exit, which ensures optimum exchange of materials and energy, as well as reduced process time for drying, granulating, and coating (Fig. 30-17). Total containment systems are available from Glatt, GEA, and Hüttlin. Thus, a high

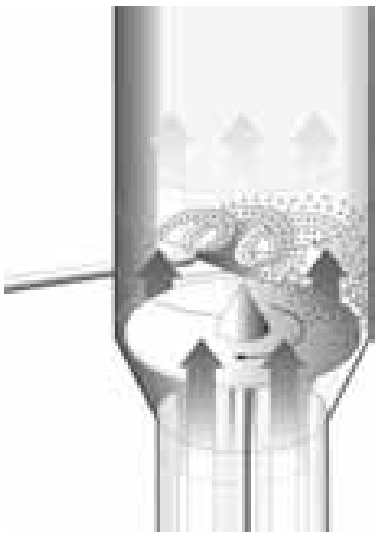

Figure 30-15. Tangential Spray Fluid Bed. (Courtesy of Glatt.)

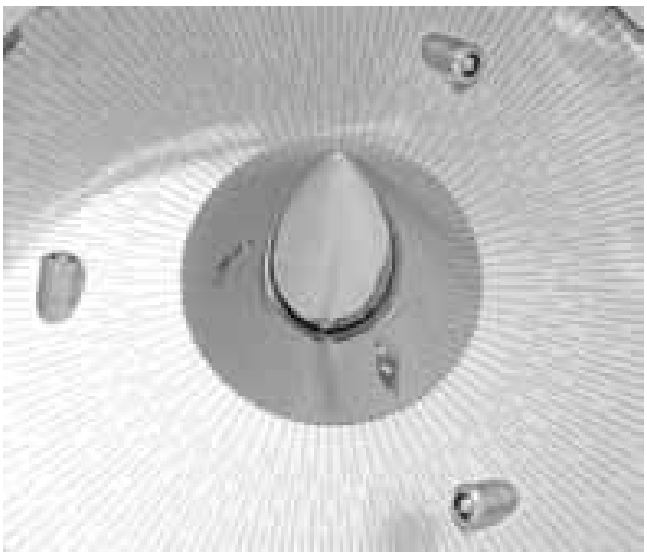

Figure 30-17. Disk Jet. (Courtesy of Hüttlin GmbH, A Bosch Packaging Technology Company.)

shear mixer is connected to a cone mill and then a fluid bed dryer. Charging and discharging take place under totally dust and contamination free conditions (Fig. 30-18).

Dry Granulation

When tablet ingredients are sensitive to moisture or are unable to withstand elevated temperatures during drying and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules. This method is referred to as dry granulation, precompression, or double-compression. It eliminates a number of steps but still includes weighing, mixing, slugging, dry screening, lubrication, and compression. The active ingredient, diluent (if required), and part of the lubricant are blended. One of the constituents, either the active ingredient or the diluent, must have cohesive properties. Powdered material contains a considerable amount of air; under pressure, this air is expelled, and a fairly dense piece is formed. The more time allowed for this air to escape, the better the tablet or slug. When slugging is used, large tablets are made as slugs, because fine powders flow better into large cavities. Also, producing large slugs decreases production time: 7/8-1 in are the most practical sizes for slugs. Sometimes, to obtain the pressure desired, the slug sizes are reduced to 3/4 in. The punches should be flat-faced. The compressed slugs are comminuted through the desirable mesh screen either by hand or, for larger quantities, through the Fitzpatrick or similar comminuting mill. The lubricant remaining is added to the granulation and blended gently, and the material is compressed into tablets. Aspirin is a good example of where slugging is satisfactory. Other materials, such as aspirin combinations, acetaminophen, thiamine hydrochloride, ascorbic acid, magnesium hydroxide, and other antacid compounds, may be treated similarly. Results comparable to those accomplished by the slugging process are also obtained with compacting mills. In the compaction method, the powder densified passes between high-pressure rollers that compress the powder and remove the air. The densified material is reduced to a uniform granule size and compressed into tablets after the addition of a lubricant. Excessive pressures that may be required to obtain cohesion of certain materials may result in a prolonged dissolution rate. Compaction mills available include the Chilsonator (Fitzpatrick), Roller Compactor (Vector), and the Compactor Mill (Allis-Chalmers; Fig. 30-19).

Figure 30-16. Fluid-Bed. (Courtesy of Hüttlin GmbH, A Bosch Packaging Technology Company.)

Direct Compression

As its name implies, direct compression consists of compressing tablets directly from component materials, without modifying the physical nature of the materials themselves. Formerly, direct compression, as a method of tablet manufacture, was reserved for a small group of crystalline chemicals having all the physical characteristics required for the formation of a good tablet. This group includes chemicals, such as potassium salts (chlorate, chloride, bromide, iodide, nitrate, and permanganate), ammonium chloride, and methenamine. These materials possess cohesive and flow properties that make direct compression possible. Since the pharmaceutical industry is constantly making efforts to increase the efficiency of tableting operations and reducing costs by using the smallest amount of floor space and labor as possible for a given operation, increasing attention is given to this method of tablet preparation. Approaches used to make this method more universally applicable include the introduction of formulation additives capable of imparting the characteristics required for compression and the use of force-feeding devices to improve the flow of powder blends.

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

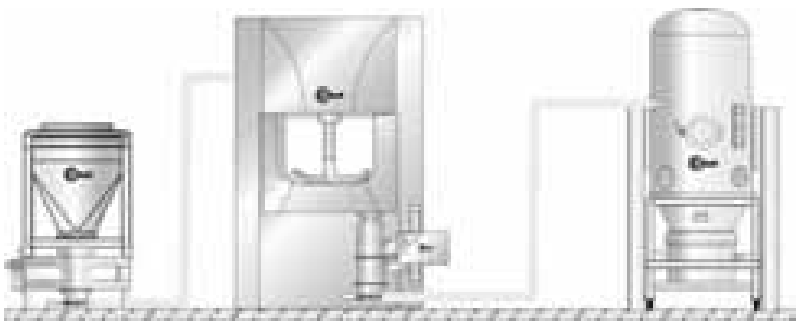

Figure 30-18. Horizontal granulation line consisting of a Top Driven Granulator and a Fluid bed Dryer. (Courtesy of Glatt.)

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

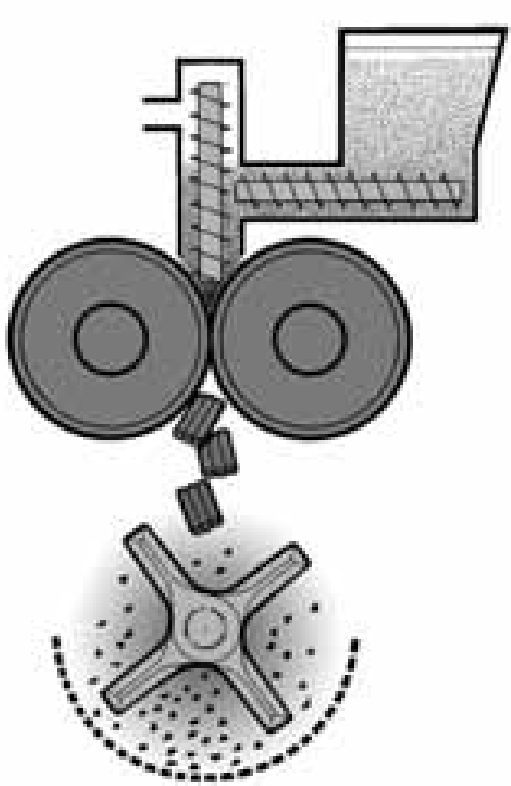

Figure 30-19. Roller Compactor Granulator. (Courtesy of Fitzpatrick Co.)

to have properties suitable for direct compression. It also may contain small quantities of dextrin, starch, or invert sugar. It is a white crystalline powder with a sweet taste and complete water solubility. It requires the incorporation of a suitable lubricant at normal levels for lubricity. The sugar is used widely for chewable vitamin tablets because of its natural sweetness. One commercial source is Di-Pac (Amstar), prepared by the co crystallization of 97% sucrose and 3% dextrins. Some forms of lactose meet the requirements for a direct-compression vehicle. Hydrous lactose does not flow, and its use is limited to tablet formulations prepared by the wet-granulation method. Both anhydrous lactose and spray-dried lactose have good flowability and compressibility and can be used in direct compression, provided a suitable disintegrant and lubricant are present. Mannitol is a popular diluent for chewable tablets, due to its pleasant taste and mouth feel, resulting from its negative heat of solution. In its granular form (lCI Americas), it has good flow and compressible qualities. It has low moisture content and is not hygroscopic. The excipient that has been studied extensively as a direct compression vehicle is microcrystalline cellulose (Avicel, FMC). This non-fibrous form of cellulose is obtained by spray-drying washed, acid-treated cellulose and is available in several grades, ranginge in average particle size from 20 to 250 um. It is water-insoluble, but the material has the ability to draw fluid into a tablet by capillary action; it swells on contact and, thus, acts as a disintegrating agent. The material flows well and has a degree of self-lubricating qualities, thus, requiring a lower level of lubricant than other excipients. Recently, FMC introduced Avicel DG, which occurs as a white, odorless powder, containing 75% of microcrystalline cellulose and 25% anhydrous dibasic calcium phosphate. The wet dispersion and spray-drying of microcrystalline cellulose and anhydrous dibasic calcium phosphate results in an intimate physical combination, which cannot be achieved by traditional dry blending. JRS PHRMA introduced PROSOLV, which is coprocessed silicified microcrystalline cellulose. JRS PHARMA also introduced to the pharmaceutical excipient market PROSOLV EASY TAB, which is composed of coprocessed microcrystalline cellulose, colloidal silicon dioxide, sodium starch Glycolate, and sodium stearyl fumarate, which is claimed to be the ideal direct compression complete excipient. Forced-flow feeders are mechanical devices, available from pharmaceutical equipment manufacturers, designed to deaerate light and bulky material. Mechanically, they maintain a steady flow of powder moving into the die cavities under moderate pressure. By increasing the density of the powder, higher uniformity in tablet weights is obtained (Fig. 30-20, 30-21). Recently, many companies have reversed their optimism for some direct-compression systems. Some formulations made by direct compression were not as forgiving as the older, wet-granulated products were. As raw material variations occurred, especially with the drug, many companies found themselves with poorly compactable formulations. Interest in direct compression is also stimulating basic research on the flowability of powders with and without additives.

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Figure 30-20. Forced Flow Feeder. (Courtesy of Fette.)

Figure 30-21. Forced Flow Feeder. (Courtesay of Courtesy of Bosch Packaging Technology Ltd., Manesty.)

Related Granulation Processes

Spheronization–Spheronization, a form of pelletization, refers to the formation of spherical particles from wet granulations. Since the particles are round, they have good flow properties when dried. They can be formulated to contain sufficient binder to impart cohesiveness for tableting. Spheronization equipment, such as the Marumerizer (Luwa) and the CFGranulator (Vector), are commercially available for small-scale manufacture, on up to commercial sized equipment. A wet granulation containing the drug substance, diluent (if required), and binder is passed, first, through an extruding machine to form rod-shaped cylindrical segments, ranging in diameter from 0.5 to 12 mm. The segment diameter and the size of the final spherical particle depend on the extruder screen size. After extrusion, the segments are placed into the Marumerizer, where they are shaped into spheres by centrifugal and frictional forces on a rotating plate. The pellets are then dried by conventional methods, mixed with suitable lubricants, and compressed into tablets or used as capsule- fill material. Microcrystalline cellulose has been shown to be an effective diluent and binder in granulations to be spheronized. The advantages of the process include the production of granules, regular in shape, size, and surface characteristics; low friability, resulting in fewer fines and less dust; and the ability to regulate the size of the spheres within a narrow particle-size distribution. Spheres can also be produced by fluid-bed granulation techniques and other specialized equipment, such as the CFGranulator (Vector). These processes, however, must begin with crystals or nonpareil seeds followed by buildup. Exact results, such as sphere density, are different for the various methods and could be important in product performance. These processes can be run as batches or continuously.

Spray-Drying–A number of tableting additives suitable for direct compression have been prepared by the drying process known as spray-drying. The method consists of bringing together a highly dispersed liquid and a sufficient volume of hot air to produce evaporation and drying of the liquid droplets. The feed liquid may be a solution, slurry, emulsion, gel, or paste, provided it is pumpable and capable of being atomized.

The feed is sprayed into a current of warm filtered air. The air supplies the heat for evaporation and conveys the dried product to the collector; the air is then exhausted with the moisture. As the liquid droplets present a large surface area to the warm air, local heat and transfer coefficients are high. The spray-dried powder particles are homogeneous, approximately spherical in shape, nearly uniform in size, and frequently hollow. The latter characteristic results in low bulk density, with a rapid rate of solution. Being uniform in size and spherical, the particles possess good flowability. The design and operation of the spray-dryer can vary many characteristics of the final product, such as particle size and size distribution, bulk and particle densities, porosity, moisture content, flowability, and friability. Among the spray-dried materials available for direct compression formulas are lactose, mannitol, and flour. Another application of the process in tableting is spray-drying the combination of tablet additives as the diluent, disintegrant, and binder. The spray-dried material is then blended with the active ingredient or drug, lubricated, and compressed directly into tablets. Since atomization of the feed results in a high surface area, the moisture evaporates rapidly. The evaporation keeps the product cool and, as a result, the method is applicable for drying heat-sensitive materials. Among heat-sensitive pharmaceuticals successfully spray-dried are the amino acids; antibiotics, such as aureomycin, bacitracin, penicillin, and streptomycin; ascorbic acid, cascara extracts, and liver extracts; pepsin and similar enzymes; protein hydrolysates; and thiamin. Frequently, spray-drying is more economical than other processes, since it produces a dry powder directly from a liquid and eliminates other processing steps as crystallization, precipitation, filtering or drying, particle-size reduction, and particle classifying. By the elimination of these steps, labor, equipment costs, space requirements and possible contamination of the product are reduced. Intrinsic factor concentrate obtained from hog mucosa was previously prepared by Lederle / American Home Products, using a salt-precipitation process, followed by freeze-drying. By using spray-drying, it was possible to manufacture a high-grade material by a continuous process. The spherical particles of the product facilitated its subsequent blending with vitamin B12. Similar efficiencies have been found in processes producing magnesium trisilicate and dihydroxyaluminum sodium carbonate; both chemicals are used widely in antacid preparations. Encapsulation of chemicals can also be achieved using spray-drying equipment. The process is useful in coating one material on another to protect the interior substance or to control the rate of its release. The substance to be coated can be either liquid or solid, but must be insoluble in a solution of the coating material. The oil-soluble vitamins A and D can be coated with a variety of materials, such as acacia gum to prevent their deterioration. Flavoring oils and synthetic flavors are coated to give the so-called dry flavors.

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Spray-Congealing–Also called spray-chilling, spray-congealing is a technique similar to spray-drying. It consists of melting solids and reducing them to beads or powder, by spraying the molten feed into a stream of air or other gas. The same basic equipment is used as with spray-drying, although no source of heat is required. Either ambient or cooled air is used, depending on the freezing point of the product. For example, monoglycerides and similar materials are spray-congealed with air at 50°F. A closed-loop system with refrigeration cools and recycles the air. Using this process, drugs can be dissolved or suspended in a molten wax and spray-congealed; the resultant material can then be adapted for a prolonged-release form of the drug. Among the carbohydrates used in compressed tablets, mannitol is the only one that possesses high heat stability. Mannitol melts at 167 and, either alone or in combination with other carbohydrates, can be fused and spray-congealed. Selected drugs have been shown to be soluble in these fused mixtures, and the resultant spray-congealed material possesses excellent flow and compression characteristics.

TABLET MACHINES

As mentioned previously, the basic mechanical unit in tablet compression involves the operation of two steel punches within a steel die cavity. The tablet is formed by the pressure exerted on the granulation by the punches within the die cavity or cell. The tablet assumes the size and shape of the punches and dies used. Although round tablets are used more generally, oval, square, triangular or other irregular shapes and capsule-form may be used (Fig. 30-22). Likewise, the curvature of the faces of the punches determines the curvature of the tablets. Punch faces with ridges are used for compressed tablets scored for breaking into halves or fourths, although it has been indicated that variation among tablet halves is significantly greater than among intact tablets. However, a patented formulation for a tablet scored to form a groove that is one-third to two-thirds the depth of the total tablet thickness is claimed to give equal parts containing substantially equal amounts of the drug substance. Tablets, engraved or embossed with symbols or initials, require punches with faces embossed or engraved with the corresponding designs. The use of the tablet, sometimes, determines its shape; effervescent tablets are usually large, round, and flat, whereas vitamin tablets are frequently prepared in capsule-shaped forms. Tablets prepared using deep-cup punches are round and, when coated, take on the appearance of pills. Veterinary tablets often have a bolus shape and are much larger than those used in medical practice. The quality-control program for punches and dies, frequently referred to as tooling, instituted by large pharmaceutical companies, emphasizes the importance of their care in modern pharmaceutical production. To produce physically perfect, compressed tablets, an efficient punch-and-die program must be set up. Provisions for inspection of tooling, parameters for cost-per-product determination, product identification, and tooling specifications must all be considered. A committee of the Industrial and Pharmaceutical Technology Section of the American Pharmacists Association established a set of dimensional specifications and tolerances for standard punches and dies. Regardless of the size of the tableting operation, the attention that must be given to the proper care of punches and dies should be noted. They must be highly polished and kept free from rust and imperfections. In cases in which the material pits or abrades the dies, chromium-plated dies have been used. Dropping the punches on hard surfaces chips their fine edges. When the punches are in the machine, the upper and lower punches should not be allowed to contact each other; otherwise, a curling or flattening of the edges that is one of the causes of capping results. This is especially necessary to observe in the case of deep-cup punches. When the punches are removed from the machine, they should be washed thoroughly in warm, soapy water and dried well with a clean cloth. A coating of grease or oil should be rubbed over all parts of the dies and punches to protect them from the atmosphere. They should be stored carefully in boxes or paper tubes. Natoli wrote an excellent review on tooling for pharmaceutical processing in which he addressed tooling options, standards, configurations, recent innovations, and production problems due to tooling. A significantly important part of the review is the listing of possible causes and corrective actions for tablet problems related to tooling.[14]

Figure 30-22. Punches and Dies with various shapes. (Courtesy of NATOLI.)

Single-Punch Machines

The simplest tableting machines available are those having the single-punch design. A number of models are available. Although most of these are power-driven, several hand-operated models are available. Compression is accomplished on a single-punch machine. The feed shoe filled with the granulation is positioned over the die cavity, which then fills. The feed shoe retracts and scrapes all excess granulation away from the die cavity. The upper punch lowers to compress the granulation within the die cavity. The upper punch retracts, and the lower punch rises to eject the tablet. As the feed shoe returns to fill the die cavity, it pushes the compressed tablet from the die platform. The weight of the tablet is determined by the volume of the die cavity; the lower punch is adjustable to increase or decrease the volume of granulation, thus, increasing or decreasing the weight of the tablet (Figs. 30-23, 30-24). For tablets having diameters larger than 1/2 inch, sturdier models are required. This is also true for tablets requiring a high degree of hardness, as in the case of compressed lozenges. The heavier models are capable of much higher pressures and are suitable for slugging.

Operation of Single-Punch Machines—In installing punches and dies in a single-punch machine, insert the lower punch first, by lining up the notched groove on the punch with the lower punch set screw and slipping it into the smaller bore in the die table; the setscrew is not tightened yet. The lower punch is differentiated from the upper punch in that it has a collar

Figure 30-23. Manufacture of 1, 2 or 3 layer tablets (Courtesy of Bosch Packaging Technology Ltd., Manesty.)

around the punch head. Slip the die over the punch head so the notched groove (with the widest area at the top) lines up with the die setscrew. Tighten the lower punch setscrew after seating the lower punch, by pressing on the punch with the thumb. Tighten the die setscrew, making certain the surface of the die is flush with the die table. Insert the upper punch, again lining up the grooved notch with the upper punch setscrew. To be certain that the upper punch is seated securely, turn the machine over by hand, with a block of soft wood or wad of cloth between the upper and lower punches. When the punch is seated, tighten the upper punch setscrew. Adjust the pressure so the upper and lower punches will not come in contact with each other when the machine is turned over. Adjust the lower punch so it is flush with the die table at the ejection point. Install the feed shoe and hopper. After adding a small amount of granulation to the hopper, turn the machine over by hand and adjust the pressure until a tablet is formed. Adjust the tablet weight until the desired weight is obtained. The pressure will have to be altered concurrently with the weight adjustments. Remembered, as the fill is increased, the lower punch moves farther away from the upper punch, and more pressure has to be applied to obtain comparable hardness. Conversely, when the fill is decreased, the pressure has to be decreased. When all the adjustments have been made, fill the hopper with granulation and turn on the motor. Hardness and weight should be checked immediately, and suitable adjustments made if necessary. Periodic checks should be made on the tablet hardness and weight during the running of the batch, at 15- to 30-minute intervals. When the batch has been run off, turn off the power and remove loose dust and granulation with the vacuum cleaner. Release the pressure from the punches. Remove the feed hopper and the feed shoe. Remove the upper punch, the lower punch, and the die. Clean all surfaces of the tablet machine, and dry well with clean cloth. Cover surfaces with thin coating of grease or oil prior to storage. As tablets are ejected from the machine, after compression, they are usually accompanied by powder and uncompressed granulation. To remove this loose dust, the tablets are passed over a screen, which may be vibrating, and cleaned with a vacuum line.

Rotary Tablet Machines

For increased production, rotary machines offer great advantages. A head carrying a number of sets of punches and dies revolves continuously, while the tablet granulation runs from the hopper, through a feed frame, and into the dies placed in a large, steel plate revolving under it. This method promotes a uniform fill of the die and, therefore, an accurate weight for the tablet. Compression takes place as the upper and lower punches pass between a pair of rollers, as can be seen in Figure 30-25. This action produces a slow squeezing effect on the material in the

Figure 30-24. Modern Single Punch Tablet Press. (Courtesay of Courtesy of Bosch Packaging Technology Ltd., Manesty.)

die cavity from the top and bottom, and so gives a chance for the entrapped air to escape. The lower punch lifts up and ejects the tablet. Adjustments for tablet weight and hardness can be made, without the use of tools, while the machine is in operation. One of the factors that contributes to the variation in tablet weight and hardness during compression is the internal flow of the granulation within the feed hopper. On most rotary machine models, there is an excess pressure release that cushions each compression and relieves the machine of all shocks and undue strain. The punches and dies can be readily removed for inspection, cleaning, and to insert different sets to produce a great variety of sizes and shapes. Most rotary tablet presses measure a tablet's weight either by measuring its variation in tablet height at precompression or by the force at main compression. They compress a volume of granules, captured in a die, between two rollers, using an upper and lower punch. By changing the distance between the rollers, one adjusts the force used to compress tablets. Once the distance between the rollers is set, the compression force will stay the same. Several factors affect the precise amount of granules captured within each die. For example, granule size, size distribution, and variation in punch length can have an effect. In addition, an excessively high rotational speed allows the granules insufficient time to fall into the die. Variations in the amount of granules in each die result in tablets of different weights and densities. An inconsistency in the maximum compression force can result in inconsistent tablet properties, thus, affecting the efficacy of the dosage form.

Compression to equal force (EF) is a new concept that allows tablets to be compressed at the same peak compression force, independent of tablet weight. This method relies on the use of an air piston (Fig. 30-26). The air piston is installed at the precompression and main compression station and allows the pre- and main compression rollers to be floating rather than fixed. The piston moves vertically in a cylinder filled with compressed air. The air pressure in the cylinder is preset and

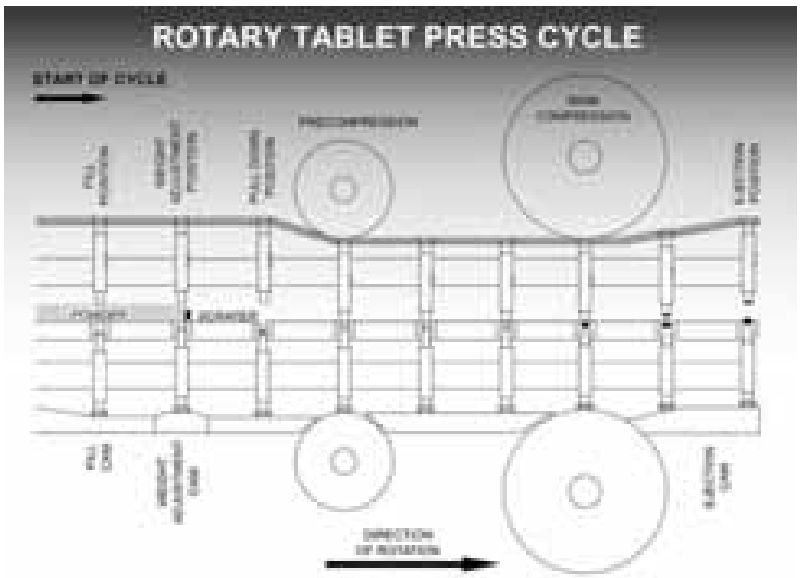

Figure 30-25. Rotary Tablet Press Cycle. (Courtesy of Natoli.)

kept constant by a pressure-regulating valve and an expansion chamber. Because the surface of the cylinder and the air pressure are constant, the force is also constant, irrespectively of the position of the floating roller. If the air pressure in the cylinder is such that this maximum compression force is higher than the actual compression force, the system compresses tablets to equal thickness, leading to high variation in tablet hardness. Conversely, the press can be set to make the compression roller move up at each compression. In this arrangement, all tablets are compressed at the same peak force, providing a much reduced variation in tablet hardness. The tablet press is equipped with a linear variable displacement transducer sensor that measures compression-roller movement accurately. A heavy tablet causes the compression roller to move more, and a light tablet causes less movement. This provides a tablet weight control method, called "tablet weight control by displacement," with a linear relationship between tablet weight and displacement. Accordingly, more accurate tablet weight for smaller tablets than the conventional tablet weight control by force is assured. Floating compression rollers also provide an effective means to increase dwell at high turret revolutions. Increasing the dwell time at pre- and main compression and at high turret speed is necessary to improve deaeration and uniform distribution of compaction stress in the die prior to final compaction at high tablet output. This provides reduced risk of capping, better bonding of layers, in the case of bilayer tablets, and improved tablet tensile strength. When compressed to equal force, variations in tablet weight do not affect tensile strength. Therefore, tablets maintain a consistent clinical efficacy. Equal force tableting is also of interest when compacting coated pellets or when producing of Orally Disintegrating Tablets.

Operation of Rotary Machines—Before inserting punches and dies, make certain the pressure has been released from the pressure wheel. The die holes should be cleaned thoroughly, making certain the die seat is completely free of any foreign materials. Back off all die locks, and loosely insert dies into the die holes, then tap each die securely into place, with a fiber of soft metal rod through the upper punch holes. After all the dies have been tapped into place, tighten each die locks crew progressively and securely. As each screw is tightened, the die is checked to see it does not project above the die table. Insert the lower punches through the hole made available, by removing the punch head. Turn the machine by hand until the punch bore coincides with the plug hole. Insert each lower punch in its place progressively. Insert the upper punches by dropping them into place in the head. Each punch (upper and lower) should be coated with a thin film of mineral oil before insertion into the machine. Adjust the ejection cam, so the lower punch is flush with the die table at the ejection point. After insertion of the punches and dies, adjust the machine for the tablet weight and hardness. The feed frame should be attached to the machine along with the feed hopper. Add a small amount of the granulation through the hopper and turn the machine over by hand. Increase the pressure by rotating the pressure wheel until a tablet is formed. Check the weight of the tablet, and adjust the fill to provide the desired tablet weight. Most likely, more than one adjustment of the fill will be necessary before obtaining the acceptable weight. When the fill is decreased, the pressure must be decreased to provide the same hardness in the tablet. Conversely, when the fill is increased, the pressure must be increased to obtain comparable hardness. Fill the hopper with the granulation and turn on the power. Check tablet weight and hardness immediately after the mechanical operation begins, and make suitable adjustments, if necessary. Check these properties routinely and regularly at 15- to 30-minute intervals, while the machine is in operation. When the batch has been run, turn off the power. Remove the hopper and feed frame from the machine. Remove loose granulation and dust with a vacuum line. Remove all pressure from the wheel. Remove the punches and dies in the reverse order of that used in setting up the machine. First, remove the upper punches individually, then the lower punches, and finally the dies. Wash each punch and die in alcohol, and brush with a soft brush to remove adhering material. Dry them with a clean cloth, and cover them with a thin coating of grease or oil before storing.

High-Speed Rotary Tablet Machines

The rotary tablet machine has evolved, gradually, into models capable of compressing tablets at high production rates (see Figs. 30-27, 30-28). This has been accomplished by increasing the number of stations (i.e., sets of punches and dies) in each revolution of the machine head, improving feeding devices, and on some models installing dual compression points. Rotary machines with dual compression points are referred to as double rotary machines, and those with one compression point, single rotary. One-half of the tablets are produced 180° from the tablet chute. They travel outside the perimeter and

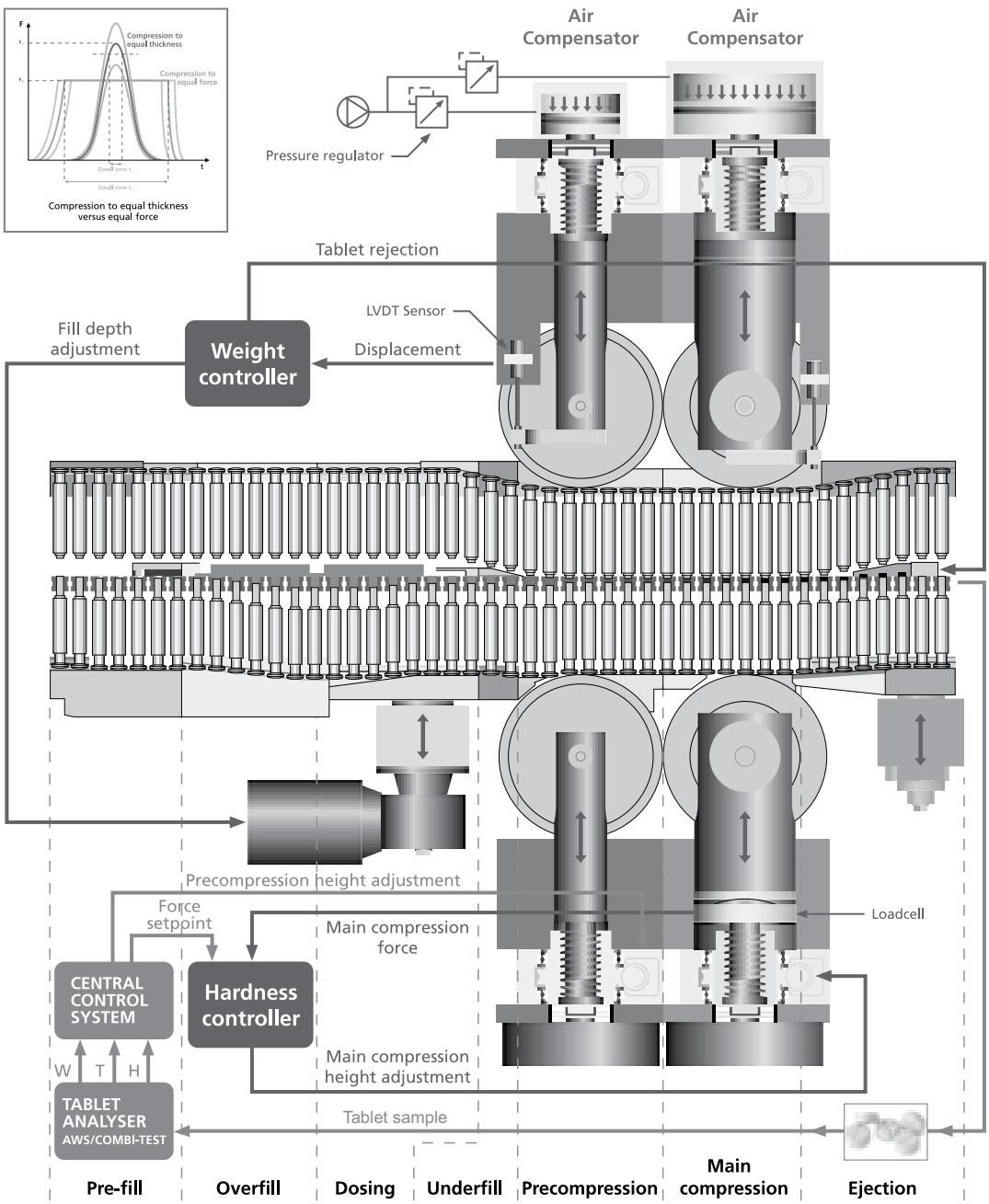

Figure 30-26. Rotary Tablet Compression Cycle. (Courtesy of Courtoy.)

discharge with the second tablet production. Although these models are mechanically capable of operating at production rates of more than 5000 tablets per minute, the actual speed still depends on the physical characteristics of the tablet granulation and the rate that is consistent with compressed tablets having satisfactory physical characteristics. The main difficulty in rapid machine operation is ensuring adequate filling of the dies. With rapid filling, dwell time of the die cavity beneath the feed frame is insufficient to ensure the requirements of uniform flow and packing of the dies. Various methods of force-feeding the granulation into the dies have been devised to refill the dies in the very short dwell time permitted on the high-speed machine. Presses with pre-compression rollers permit the partial compaction of material before final compaction. This provides for partial deaeration and particle orientation of material before final compression. This helps in the direct compacting of materials and reduces laminating and capping due to entrapped air.

Multilayer Rotary Tablet Machines

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

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Figure 30-27. Modern Rotary Tablet Press. (Courtesy of Courtoy.)

with the different granulations in successive layers, and the tablet was formed by a single compression stroke. The separation lines of the tablets prepared by this method tended to be irregular. In the machines now available for multilayer production, the granulation receives a precompression stroke after the first and second fill, which lightly compacts the granulation and maintains a well-defined surface of separation between each layer. The operator is able to eject either precompressed layer, with the machine running, at any desired speed, for periodic weight and analysis checks. Other multiple-compression presses can receive previously compressed tablets and compress another granulation around the preformed tablet. An example of a press with this capability is the Manesty Drycota (Oystar Manesty). Pressure coated tablets can be used to separate incompatible drug substances and to give an enteric coating to the core tablets.

Figure 30-28. Modern Tablet Press. (Courtesy of FETTE.)

Capping and Splitting of Tablets

The splitting or capping of tablets is one of great concern and annoyance in tablet making. It is quite difficult to detect, while the tablets are processed, but can be detected easily by vigorously shaking a few in the cupped hands. A slightly chipped tablet does not necessarily mean that the tablet will cap or split. There are many factors that may cause a tablet to cap or split: excess fines or powder, which traps air in the tablet mixture; deep markings on tablet punches. Many designs or "scores" on punches are too broad and deep. Hairline markings are just as appropriate as deep, heavy markings: worn and imperfect punches. Punches should be smooth and buffed. Nicked punches often cause capping. The development of fine feather edges on tablets indicates wear on punches: worn dies. Dies should be replaced or reversed. Dies that are chrome plated or have tungsten carbide inserts wear longer and give better results than ordinary steel dies; too much pressure. By reducing the pressure on the machines, the condition may be corrected; unsuitable formula. It may be necessary to change the formula; moist and soft granulation. This type of granulation will not flow freely into the dies, thus, giving uneven weights and soft or capped tablets; poorly machined punches. Uneven punches are detrimental to the tablet machine itself and will not produce tablets of accurate weight. One punch out of alignment may cause one tablet to split or cap on every revolution.

Instrumented Tablet Presses

Compressional and ejectional forces involved in tablet compression can be studied by attaching strain gauges to the punches and other press components involved in compression. The electrical output of the gauges has been monitored by telemetry or use of a dual-beam oscilloscope equipped with camera. Instrumentation permits a study of the compaction characteristics of granulations, their flowabilities, and the effect of formulation additives, such as lubricants, as well as differences in tablet press design. Physical characteristics of tablets, such as hardness, friability, disintegration time, and dissolution rate, are influenced not only by the nature of the formulation, but by the compressional force as well. The rate and duration of compaction forces can be quantified. The rate of force application has a profound effect on powder consolidation within the die and, hence, efficiency of packing and powder compaction. The rate of release of force, or decompression, has a direct effect on the ability of the tablet to withstand relaxation. A prominent hypothesis, fostered by suggestion that capping and laminating of tablets is caused by too-rapid stress relaxation or decompression. This explains why slowing a tablet press and using tapered dies is useful in such situations. Most prominent pharmaceutical scientists have embraced this theory and have largely discounted air entrapment as a cause of capping and laminating. As compaction force rises, the steel tooling actually compresses in accommodation to the forces applied. The forces used to produce a tablet are considerable and should be monitored and understood. Therefore, definition of the compressional force and duration of force (dwell time), giving a satisfactory tablet for a formulation, provides an in-process control for obtaining both tablet-to-tablet and lot-to-lot uniformity. Instrumentation

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has led to the development of on-line, automatic, electromechanical tablet weight-control systems capable of continuously monitoring the weights of tablets as they are produced. Most commercial presses today can be delivered with some sort of instrumentation attached. When tablet weights vary from preset limits, the monitor will automatically adjust the weight control mechanism to re-establish 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. 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.[15]

Contamination

Although 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. 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 modern presses, shown in Figures 30-27 and 30-28, 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 micro-organisms 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 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 micro-organisms, when present in oral products, include *Salmonella* spp, *Escherichia coli*, and certain *Pseudomonas* spp, such as *P aeruginosa*, and *Staphylococcus aureus.* The compendia have microbial limits on raw materials, such as aluminum hydroxide gel, cornstarch, thyroid, acacia, and gelatin. These represent examples of the industry's efforts to conform to the intent of current good manufacturing practice, as defined by the FDA.

Molded Tablets or Tablet Triturates (TT)

Tablet triturates are small, discoid masses of molded powders weighing 30–250 mg each. The base consists of lactose, B 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, due to 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 used as the source of the drug in compounding other formulations or solutions. Narcotics, in the form of hypodermic tablets, were originally 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 are currently 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 50–500 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. In some hand molds, the pegs are forced down onto the plate holding the moist trituration.

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. The tablets may be scored in halves or quadrants to facilitate breaking, if a smaller dose are 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

Figure 30-29. Electric Tablet Hardness Tester. (Courtesy of Erweka.)

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Figure 30-30. Electric Hardness Tester. (Courtesy of Key.)

Figure 30-32. Tablet Thickness Tester. (Courtesy of Starrett.)

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 or Crushing Strength

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 second and third 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. 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. 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 expressed in either kilograms or pounds of force. Currently, the most widely used apparatuses to measure tablet hardness or crushing strength are the electrically operated equipment, which eliminates the operator variability. Newer equipment are also available with printers. Manufacturers, such as SOTAX, Key, Van Kel, Erweka, Dr. Schleuniger Pharmatron, and others, make electrically driven hardness testers (Figs. 30-29, 30-30). 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 handling during subsequent processing, such as coating or packaging and shipping operations.

Figure 30-31. Tablet Friability Testers. (Courtesy of Erweka.)

Friability

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 free-falls 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. 30-31). The friability test is now included in the USP.

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, due to difference in the density of the granulation and the pressure applied to the tablets, as well as the speed

of tablet compression. Not only is the tablet thickness important in reproducing tablets identical in appearance, but also to ensure that every production lot will be usable with selected packaging components. If the tablets are thicker than specified, a given number no may longer 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, due to 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 Standard Operating Procedures (Fig. 30-32).

UNIFORMITY OF DOSAGE UNITS

Over the past 40 years, the limits for uniformity of dosage units have been upgraded and made stricter. The reader is advised to refer to the most recent Pharmacopeia for complying with the regulations where the test is done.

The term "uniformity of dosage unit" is defined as the degree of uniformity in the amount of the drug substance in a tablet. The uniformity of dosage units can be demonstrated by either one of two methods, Content Uniformity (CU) or Weight Variation. The most recent USP 34 is harmonized with the Japanese and European Pharmacopoeias.[16]

CU testing was developed to ensure the content consistency of active pharmaceutical ingredients (API) within a narrow range around the label claim in dosage units. CU is related to efficacy, especially for low drug content where manufacturing loss is the dominant problem; whereas, for potent and narrow therapeutic indexed drugs, CU is also associated with safety.

By default, all tablets and capsules, as dosage units, are requested to pass the CU acceptance criteria, by direct individual analysis of each sampled unit, otherwise weight variation (WV) procedure is to be applied, if dosage units contain 25.0 mg or 25.0% *W/W* of API or more, or when the process development and validation data support its application. CU by WV is determined by multiplying the composite assay results by the ratio of each individual unit weight to the average weight of the sample.

Current CU testing has a confirmatory nature and is based on calculation of acceptance value (AV) of two stage sampling plan by applying the following equation:

$$\mathrm{AV} = (|\, M - \bar{x} \,| + ks)$$

The multiplier k is either 2.4 or 2.0, for sample sizes of 10 or 30, respectively. s is the standard deviation. The reference value M takes different values, according to the sample mean () and the target content per dosage unit at the time of manufacturing (T).The calculated AV should be less than 15.0 (L_1), and no single unit deviates by more than L_2 % (generally, 25%) from the reference value M. Theoretically, this new concept aims to assure dosage units to have drug content not critically (within ±15%) deviating from the nominal dose value.

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 dosage forms. In the present disintegration test, the particles are those that pass

Figure 30-33. USP Disintegration Tester. (Courtesy of SOTAX.)

through a 10-mesh screen. 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, in as much as a change in the apparatus can cause a change in the results of the test. The USP apparatus consists of a basket-rack assembly, a 1000-mL, low-form beaker, 138–160 mm in height and having an inside diameter of 97–115 mm for the immersion fluid, a thermostatic arrangement for heating the fluid between 35°C and 39°C, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than 53 mm and not more than 57 mm. The volume of the fluid in the vessel is such that, at the highest point of the upward stroke, the wire mesh remains at least 15 mm below the surface of the fluid and descends to not less than 25 mm from the bottom of the vessel on the downward stroke. At no time should the top of the basket-rack assembly become submerged. The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition, rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

Basket-Rack Assembly—The basket-rack assembly consists of six open-ended transparent tubes, each 77.5 ± 2.5 mm long and having an inside diameter of 20.7–23 mm and a wall 1.0–2.8 mm thick; the tubes are held in a vertical position by two plates, each 88–92 mm in diameter and 5–8.5 mm in thickness, with six holes, each 22–26 mm in diameter, equidistant from

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the center of the plate and equally spaced from one another. Attached to the under surface of the lower plate is a woven stainless steel wire cloth, which has a plain square weave with 1.8- to 2.2-mm apertures and with a wire diameter of 0.57-0.66 mm. The parts of the apparatus are assembled and rigidly held by means of three bolts passing through the two plates. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device, using a point on its axis (Fig. 30-33).

The design of the basket-rack assembly may be varied somewhat, provided the specifications for the glass tubes and the screen mesh size are maintained. The use of disks is permitted only where specified or allowed in the monograph. If specified in the individual monograph, each tube is provided with a cylindrical disk 9.5 ± 0.15 mm thick and 20.7 ± 0.15 mm in diameter. More details about disk design are in the USP. The endpoint of the test is indicated when any residue remaining is a soft mass with no palpably soft core. The plastic discs help force any soft mass that forms through the screen. For compressed, uncoated tablets the testing fluid is usually purified water USP at 37°C, 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 repeated using 12 tablets. Of the 18 tablets then tested, 16 must have disintegrated within the given period of time. The conditions of the test are varied somewhat for coated tablets, buccal tablets, and sublingual tablets. Disintegration times are included in the individual tablet monograph. For most uncoated tablets, the period is 30 minutes, although the time for some uncoated tablets varies greatly from this. For coated tablets up to 2 hours may be required, whereas, for sublingual tablets, such as CT Isoproterenol Hydrochloride, the disintegration time is 3 minutes. This is harmonized with the corresponding texts of the European Pharmacopoeia and/or the Japanese Pharmacopoeia. (For the exact conditions of the test, consult the USP.)

Dissolution Test

Currently, for most 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 important properties 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

Figure 30-34. USP Dissolution Tester, Paddle Method. (Courtesy of Erweka.)

Figure 30-35. USP Dissolution Tester, Flow Through. (Courtesy of SOTAX.)

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 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. Figures 30-34 and 30-35 show some popular commercial dissolution testers. (Refer to Chapter 6 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 are that the validation activity must begin in Research and Development 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.[17]

PROCESS ANALYTICAL TECHNOLOGY (PAT)

One definition for PAT is the "systems for continuous analysis and control of manufacturing processes based on real-time measurements, or rapid measurements during processing, of quality and performance attributes of raw and in-process materials and processes to assure acceptable end product quality at the completion of the process."[18] This requires a synergy of multiple systems, including process analytical chemistry tools, information management tools, feedback process control strategies, and strategies for product/process design and optimization. The PAT initiative in pharmaceuticals began in the 1990s. In 1993, an AOAC International Symposium was held entitled "Pharmaceutical Process Control and Quality

Assessment by Non-Traditional Means." Then, in 2001, an Advisory Committee for Pharmaceutical Science (ACPS) meeting was held and discussed PAT. This meeting prompted 20/FDA Science Board endorsement of the formation of a PAT subcommittee within ACPS.[18] The PAT subcommittee is comprised of four working groups: 1) benefits, technology, definitions/terminology, 2) process and analytical validation, 3) chemometrics, and 4) product/process development. These working groups are composed of people from the FDA, industry, and academia. In addition, a new journal was published to address the expanding role of PAT in the pharmaceutical industry, *The Journal of Process Analytical Technology* with its first issue in September/October 2004. It is apparent that PAT will become an important part of the pharmaceutical industry, as it has in other industries. The reason is that PAT can improve efficiency and capability of pharmaceutical processes, while verifying and improving product quality. Results the pharmaceutical industry anticipates from optimal application of PAT include reduced risk of scrap and recalls, improved process understanding with quality "by design," improved capacity utilization and reduced cycle times, and eventual reduction in product development time. The current methods to verify product quality, final product testing at the end of manufacturing and some process operation ranges, cause low manufacturing efficiency and require a very high level of regulatory scrutiny.[18] For example, if a batch fails final product release testing for product quality control, these results are not known until weeks after the batch was manufactured. In that time period, multiple batches could have been manufactured with the same problems and would have to be rejected. In contrast, PAT allows for rapid identification of out of the ordinary situations, when the critical product properties are defined up front. Therefore, the time to respond to problems is greatly reduced, and much time and money can be saved. PAT also allows for statistical process control analysis (trending) of critical in-process product attributes.[19]

CAPSULES

Capsules are solid dosage forms in which the drug substance is enclosed in either a hard or soft, soluble container or shell of gelatin or other suitable material. 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. More recently, capsule shells made from hydroxypropyl methylcellulose have become available commercially. These capsules contain less residual moisture than gelatin capsules and thus may have applications in filling hydrolytic drugs. In addition, these capsules offer an excellent alternative for strict vegetarians. Gelatin, however, due to 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.

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 products in capsule form, even though the products have already been produced in tablet form.

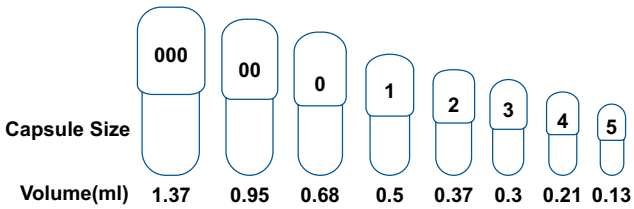

Figure 30-36. Hard gelatin capsules showing relative size.

Although 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 indicated a consumer preference of 44.2% for soft elastic capsules, 39.6% for tablets, and 19.4% for hard gelatin capsules.[20]

HARD GELATIN CAPSULES

The hard gelatin capsule consists of two sections, one slipping over the other, thus, completely surrounding the drug formulation. Figure 30-36 illustrates the classic capsule shape and size. 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 from gelatin and other materials used either to enable capsule formation or to improve their performance (see Table 30-2).[21] Hard gelatin capsules contain 12–16% water, but the water content can vary, depending on the storage conditions. When the humidity is low, the capsules can become brittle; if stored at high humidities, the capsules can become flaccid, sticky, and lose their shape. Storage in high-temperature areas can also affect the quality of hard gelatin capsules. Gelatin capsules do not protect the fill materials from atmospheric water vapor, as moisture can readily diffuse through the gelatin wall.

Companies having equipment for preparing empty hard gelatin capsules include Lilly, Parke-Davis, Scherer, and Smith-Kline. The latter's production is mainly for its own use; the others are suppliers to the industry. With this equipment, stainless steel pins, set in plates, are dipped into the gelatin solution, which must be maintained at a uniform temperature and an exact degree of fluidity. If the gelatin solution varies in viscosity, it will correspondingly 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 removed from the pins, trimmed to uniform length, and joined, the entire process being mechanical.

Table 30-2. Gelatin Capsule Additives

Additives	Function and Examples
Coloring Agent	Aesthetic, Identification, Psychological effect and Light protection (e.g., E122, E127, E171)
Process Aids	Surfactants: help in gelatin to take the shape of the moulds Silicon Fluid: assistant in enteric coating
Performance Aids	Flavoring agent: improve patient acceptability
Preservative	Gelatin is good medium for bacterial and fungal growth (e.g., Sulfur dioxide)
Gelatin Extenders	To reduce the quantity of gelatin needed per capsule (e.g., hydroxylalkylstarch)
Protective Coating	To improve the capsule stability (i.e., moisture resistance and prevent capsule sticking)

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Capsules are supplied in a variety of sizes. The hard, empty capsules (Fig. 30-36) 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, depending on the densities of the powdered drug materials. FDA issued a draft guidance for the industry in January 2011 about the maximum capsule bead size, which is 2.0 mm. This is based on approved product information and human studies that demonstrate food is chewed to approximately 2 mm in median particle size before swallowing.[22]

Commercially filled capsules have the conventional oblong shape illustrated above, with the exception of capsule products from Lilly and SmithKline. For Lilly products, capsules are tapered at the base of the body to give the capsule a bullet-like shape; products encapsulated in this shape of capsule are called Pulvules. The SmithKline capsules differ in ends of both the cap and body are angular.

After hard gelatin capsules are filled and the cap applied, there are a number of methods used to ensure 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 applied around the joint. 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 the Snap-Fit and Coni-Snap capsules that use a pair of matched locking rings in 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, pharmaceutical companies now use a number of locking and sealing technologies in addition to tamper-resistant packaging.

For extemporaneous compounding, the pharmacist must determine the size of the capsule needed for a given prescription. The correct capsule size can be determined from the volume of the material to be held by a single capsule. For powdered materials, the body of the capsule is filled with the desired weight of powder and the cap replaced. Weight checks of the compounded capsules should be done to verify the correct amount of powder has been filled in each 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 a 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. Commercial prescription products must be given further identification by markings with special numbers 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 23. 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 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.

The powder is placed on paper and flattened with a spatula, so the layer of powder is not greater than about 1/3 the length of the capsule being filled. This helps 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 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 an excess or a shortage of material, when the specified number of capsules have been packed.

Today, many manual and automatic capsule filling machines are available for increasing the speed of the capsule filling operation. Figure 30-37 illustrates a capsule-filling machine that is supplied by Torpac Inc. (ProFiller ® 100). Many community pharmacists find this a useful apparatus, and some pharmaceutical manufacturers use it for small-scale production of specialty items. It is a 100-hole, hand-held capsule filling system available in all capsule sizes from 000 to 5, including el sizes. Production rates of 2000–3200 capsules per hour, within 1–2% of target capsule weight, are possible. Entire capsules (cap and body) are placed in the machine; the lower plate holds the capsule bodies in place and makes it possible to remove the caps. The powder is filled in the bodies; the accuracy of the fill depends on the selection of capsule size and the amount of pressure applied during filling. The capsule caps are then rejoined with the bodies. For large batches, the hand-operated machine (ProFiller ® 3800) can be used, as illustrated in Figure 30-38. It is a bench-top filler with a bench-top Orienter (loader) that

Figure 30-37. Hand operated capsule machine. (Courtesy of Torpac Inc.)

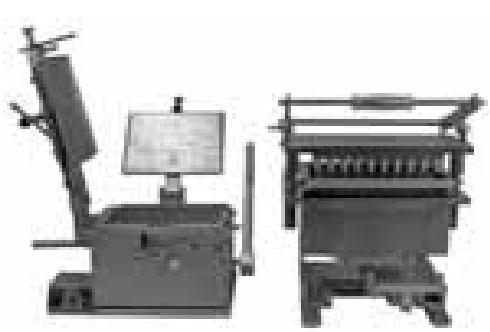

Figure 30-38 Hand operated capsule machine, Model 3008-bs. (Courtesy of Torpac Inc.)

fills 300 capsules per try with an output of up to 7200 to 9000 capsules/hr.

Machine Filling Methods

Large-scale capsule filling equipment operates on the same principle as the manual machines described above, namely the filling of the body of the capsule. Compared with tablets, powders for filling into hard gelatin capsules require a minimum of formulation efforts. The active ingredient is mixed with a sufficient volume of a diluent to fill the body with the desired amount of drug. Since powder flow is of great importance in the rapid and accurate filling of the capsule bodies, glidants, such as silica derivatives or the stearates, are also used frequently. As is true with tablets, additives present in the capsule formulation can influence drug release. 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.[23] The manner of operation of the machine can influence the volume of powder filled into the base of the capsule; therefore, the weights of the capsules must be checked routinely as they are filled (see Table 30-3).

Hard capsules are usually filled with active ingredient in dry powder from, yet other preparation may also be filled in capsules, including tablets, pellets, and even certain types of liquids. If liquids are filled in hard gelatin capsule, a banding step is generally necessary to prevent leakage of the fill. The filling of capsules is carried out in four steps: 1) separating the cap from the capsule body, 2) filling the body, 3) rejoining the capsule cap and body, and 4) discharge of the filled capsules. Filling the hard capsules with powders varies greatly from one manufacturer to another. The following are the four methods for filling the powder into hard capsules:

The Plate Method—The plate method is consider the basic and traditional filling method and is probably the oldest system used to fill hard gelatin capsules. It depends on overlaying the powder or granules over the capsule body in the dosing disc and then a using tamping device for dose punching and filling. The excess material is removed before replacing the caps. H Höfliger has developed a method, dependent on using free flowing material combined with a tamping punch (Fig. 30-39). In this method, the powder is compressed and tamped against the base plate of the dosage disc, which is designed to give a certain fill-weight in the capsule.

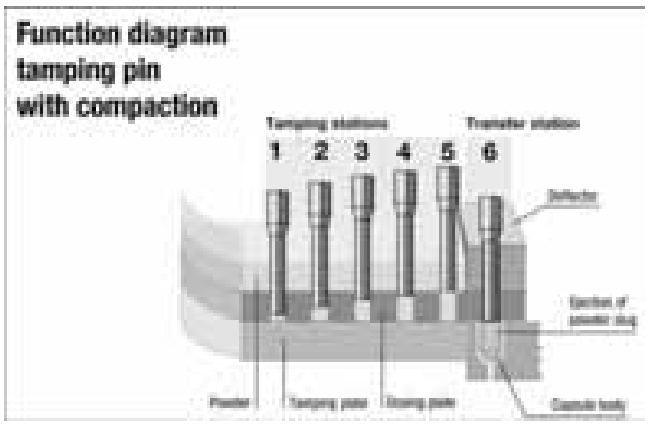

Figure 30-39. Filling capsule by tamping method. (Courtesy of Harro Hofliger Verpackungsmachinen GmbH.)

Although the filling weight can be adjusted slightly, by changing the tamping force, the dosing amount is more or less defined by the thickness of the dosing discs. Height adjustable dosing discs are on the market, but tests have shown that, due to the nature of the design, only easy to fill powders can be processed on this type of device. Furthermore, the constancy of the powder bed height influences the fill weight. Without extra measures, the tamp filling principle is not suitable for dosages below 30 mg. Powders that tend to segregate are problematic when dosing discs are above a certain diameter.

In comparison to the vacuum drum filler, there is more residual powder in the powder bowl at the end of a production run. Thus, this filling method, as well as the dosator nozzle principle, is usually not first choice, if the powder is expensive and batch sizes are small. Irrespective of these limitations, the tamp filling method is a very robust and easy to maintain system.

Intermittent Compression Filling—This method is used by Zanasi and other companies. In this method the powder is fed into the dosage hopper, and then the dosage tube enters the powder bed. This leads to form a unit mass inside the tube, which is lifted by the dosator and ejected into the capsule body

Table 30-3. Capsule Fill Chart

CAPSULE FILL WEIGHTS (MG) BASED ON SIZE AND DENSITY										
	CAPSULE VOLUME (ML)									
	0.95	0.78	0.68	0.54	0.5	0.37	0.3	0.25	0.21	0.13
POWDER DENSITY (g/ml)	CAPSULE SIZE 00	0el	0	1el	1	2	3	4el	4	5
0.3	285	234	204	162	150	111	90	75	63	39
0.4	380	312	272	216	200	148	120	100	84	52
0.5	475	390	340	270	250	185	150	125	105	65
0.6	570	468	408	324	300	222	180	150	126	78
0.7	665	546	476	378	350	259	210	175	147	91
0.8	760	624	544	432	400	296	240	200	168	104
0.9	855	702	612	486	450	333	270	225	189	117
1	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	168
1.4	1330	1092	952	756	700	518	420	350	294	182
1.5	1425	1170	1020	810	750	555	450	375	315	159

(Fig. 30-40). One of the important factors that should be considered in this method is producing sufficient compression force to form an united mass and perfectly transferring it to the capsule body.

The dosator procedure is suitable for powder dosing quantities of ≥20 mg; however, it has only limited usage with very cohesive powders, with a high level of fine particles. Dosator pins can be manufactured with coated front surfaces or from materials to which the respective powders are less likely to adhere (e.g., certain polymers, which are certified by the FDA as product-contact materials.)

Continuous Compression Filling—This method was first developed by mG2 company. It is similar to the intermittent method in principle, yet it differs in application of high filling speeds. In this method, the dosator dips into the powder, and then fills the capsule body. The movement is rapid and continuous.

Vacuum Filling—This method was developed first by Perry Industries Inc. In this filling process the dosator draws the powder by suction, not like the previous process (i.e., punch). Some compression takes place by suction, allowing the material to stay in the dosator by vacuum pressure. The dosator then delivers the powder into the capsule body, after releasing the vacuum and applying positive pressure. One important technique of vacuum filling is called vacuum-drum dosing.

The principle construction of such a dosing system is represented in Figure 30-41. In the center is the rotating dosing drum, which consists of a core with a connection to the vacuum/pressure system and an outer casing with one or more rows of holes, which form the dosing chambers. Each dosing chamber is positioned over a cross drilled hole in the core that is connected with the air system. The openings turned toward the core of the chamber are closed by a suitable filter membrane. The filter material forms the separation of the chamber to the vacuum/pressure system and prevents the powder particles from being drawn off during dosing.

The filling cycle starts when the dosing cavities are positioned beneath the powder bed and vacuum is applied. The powder is forced into the cavities in the stationary or slowly rotating drum. By maintaining the vacuum, the drum is rotated for 180° above the target, the vacuum is turned off, and the powder slug is ejected by means of a short pulse of compressed air. Finally, the drum is rotated to the exhaust channel to remove residual powder adhering to the filter membrane or the walls of the dosing cavity.

There are many new capsule filling machines that work with one or more of the mentioned processes of capsule filling. Figure 30-42 shows a Modular capsule filling machine (Modu-C LS), produced by H Höfliger. Figure 30-43 shows another new capsule filling machine, produced by PharmaLand (PCF 1200 Model).

All capsules, whether filled by hand or by machine, will require cleaning. Small quantities of capsules may be wiped individually with cloth. Larger quantities are generally processed through a capsule deduster/polisher.

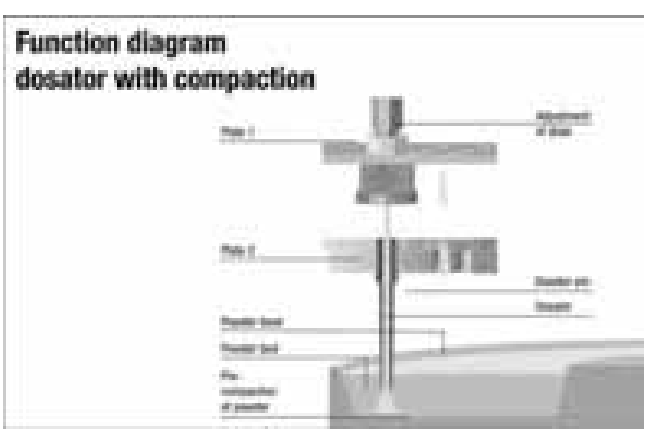

Figure 30-40. Intermittent compression filling of capsules. (Courtesy of Harro Hofliger Verpackungsmachinen GmbH.)

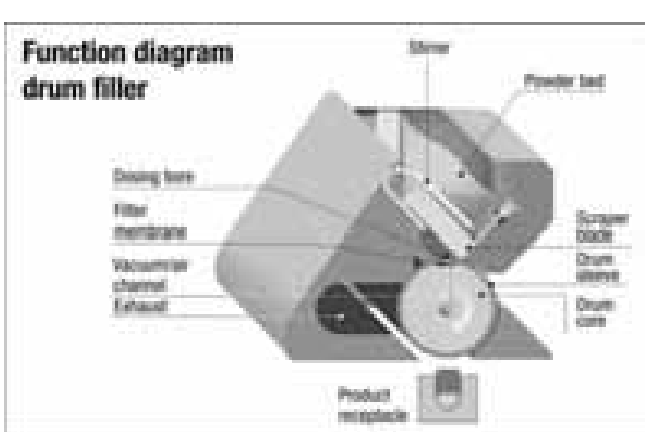

Figure 30-41. Filling capsule by Vacuum-Drum Method. (Courtesy of Harro Hofliger Verpackungsmachinen GmbH.)

Uniformity of Dosage Units

Uniformity of dosage units is defined as the degree of uniformity in the amount of the drug substance among dosage units, USP 34[24]. The uniformity of dosage units of capsules can be demonstrated by either of two methods: Content Uniformity or Weight Variation (Table 30-4).

Disintegration tests are not usually 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.

SOFT ELASTIC CAPSULES

Soft elastic capsules, also known as soft gelatin capsules or softgels, differ from hard gelatin capsules in several ways. First, the capsule shells are typically made and filled simultaneously. Commercially filled soft gelatin capsules are available in a wide variety of shapes (e.g. round, oblong, tubular). The gelatin is plasticized by the addition of glycerin, sorbitol, or other suitable material, which gives the shell its characteristic flexibility. Preservatives are often included in the capsule shell formulation to prevent microbial or fungal growth.

Figure 30-42. Automated capsule filling machine, Modu-C LS. (Courtesy of Harro Hofliger Verpackungsmachinen GmbH.)

Figure 30-43. Automated capsule filling machine, Modu-PCF 1200. (Courtesy of PharmaLand.)

Soft gelatin capsules are generally filled with liquids, where the drug is dissolved or dispersed in a solvent. The oral bioavailability of poorly water soluble drugs can be enhanced when the drug is dissolved in the fill liquid. Selection of the fill liquid (solvent) depends on the physicochemical properties of the drug, presence of other additives, and weight or volume of the content. Product stability is dependent on the properties of the capsule shell, storage conditions, and fill content[25]. For example, water vapor migration from the atmosphere can migrate through the capsule shell into the fill liquid and potentially cause precipitation of the drug.

Manufacturing Methods

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, followed by the top plate of the mold. The set is placed under a press where pressure is applied to form the capsules. Filled capsules are then washed off with a volatile solvent to remove any traces of oil from the exterior. The sheets of gelatin may have the same or different colors.

Rotary-Die Process—In 1933, the rotary-die process for soft gelatin capsules was perfected by Robert P Scherer.[26] 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 30-44 (see also Fig. 30-45).

By this process, the content of each capsule is measured individually by a single stroke of a pump, so accurately constructed that a plunger travel of 0.025 in will deliver 1 <minim> (apoth). The Scherer machine contains banks of pumps arranged so that many capsules are 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 3% from theory, depending on the materials used.

The rotary-die process makes it possible to encapsulate viscous 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 ideally suited.

The modern and well-equipped capsule plant is completely air-conditioned with a high-quality water source, a practical necessity for 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 have also been used in the capsule shell to exclude light wavelengths 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, a process 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 can successfully 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.

Seamless Process (Bubble Method)—The seamless technique produces soft gelatin capsules without requirement of dies. In this process, a molten gelatin stream runs through an outer nozzle of a concentric tube at a constant rate. The medicated liquid formulation is dispensed through the inner orifice by means of a pump. The emerging stream is broken up into an intermittent but steady flow of uniform sized by a pulsating mechanism, leading to the formation of droplets enveloped in molten gelatin. The formed capsules are quickly removed from the nozzle, slowly congealed, and automatically ejected from the system.

Table 30-4. Application of Content Uniformity (CU) and Weight Variation (WV) Tests for Capsule Dosage Forms

Dosage type	Subtype	Dose and ratio drug substance	
		≥25 mg	<25 mg
Hard gelatin capsule	Powder or others	WV	CU
Soft gelatin capsule	Suspension, emulsion or gel	CU	CU
	Solutions	WV	WV

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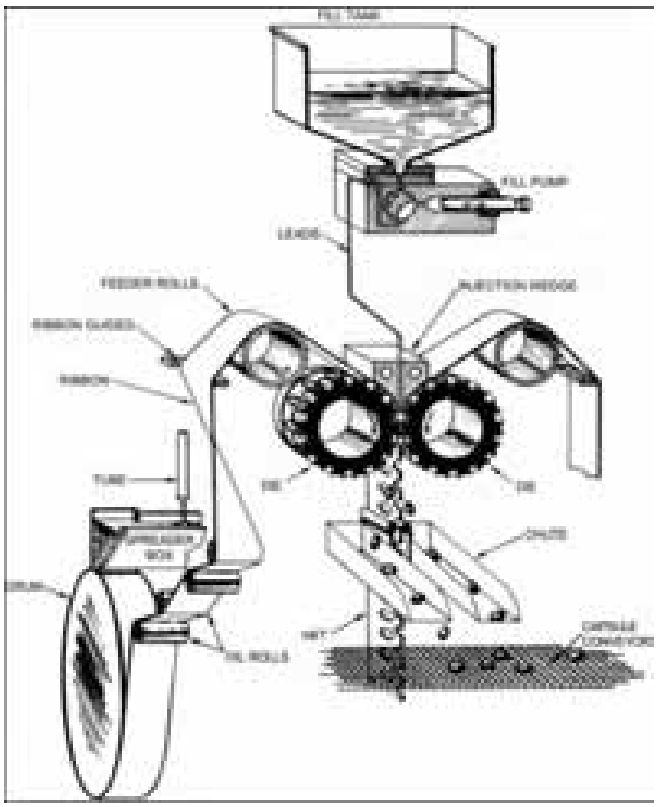

Figure 30-44. Schematic drawing of a rotary-die soft gelatin capsule filler. (Courtesy of R.P. Scherer: Detroit, MI.)

Figure 30-45. Rotary-die soft gelatin capsule filler. (Courtesy of Pharmagel Engineering SPA: Milan, Italy.)

Microencapsulation— 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 to about 5000 micrometers in size. As a technology, microencapsulation is placed in the section on capsules only because of the relationship in terminology to mechanical encapsulation previously described. The topic is also discussed in Chapter 32.

A number of microencapsulation processes have been disclosed in the literature, some based on chemical processes involving a chemical or phase change and others are mechanical in nature, requiring specialized equipment.[27,28] A number of coating materials have been used successfully to microencapsulate materials; examples of these include gelatin, polyvinyl alcohol, ethylcellulose, cellulose acetate phthalate, and styrene maleic anhydride. Film thickness can be varied considerably, depending on the surface area of the material 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. Microencapsulation has applications for masking the taste of bitter drugs, but can also be used as a means of formulating prolonged-action dosage forms, protecting chemicals against moisture or oxidation, and modifying a material's physical characteristics for ease of handling in formulation and manufacture.

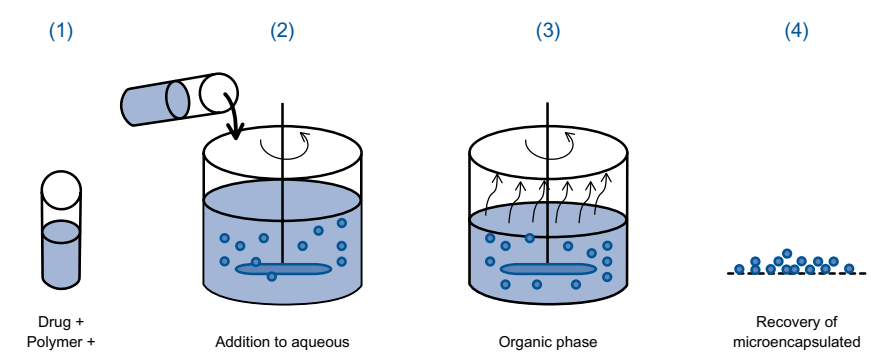

Figure 30-46 Basic steps of microencapsulation by solvent evaporation.

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The technique of microencapsulation by solvent evaporation is widely applied in pharmaceutical industries to obtain the controlled release of drug (Fig. 30-46). The basic steps of microencapsulation by solvent evaporation include: 1) dissolving of the hydrophobic drug in an organic solvent containing the polymer; 2) emulsification of this organic phase in an aqueous phase; 3) extraction of the solvent from the organic phase, by the aqueous phase, accompanied by solvent evaporation, transforming droplets of dispersed phase into solid particles; and 4) recovery and drying of microencapsulation particles to eliminate the residual solvent. For insoluble or poorly water-soluble drugs, the oil-in-water (o/w) method is frequently used.

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