A Guide to Pharmaceutical Particulate Science

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Boca Raton London New York Washington, D.C.

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Version Date: 20140730

International Standard Book Number-13: 978-0-203-00967-3 (eBook - PDF)

Dr. Norman Orr

Powder technology is the foundation of dosage form design and particle engineering is the future of efficient, reproducible, and effective drug delivery.

This was Norman's view of the justification for a book on pharmaceutical particulate science. His vision, enthusiasm, encouragement, and early contributions are its basis. This publication represents one small addition to Norman's list of achievements as a pharmaceutical scientist, educator, industrialist, colleague, family man, and friend. He is missed by all who knew him.

The Authors

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Dr. Hickey received his Ph.D. in Pharmaceutical Sciences from the University of Aston in Birmingham, United Kingdom (1984), and then worked at the University of Kentucky before joining the faculty in Parmaceutics at the University of Illinois/Chicago. In 1990, he received the Young Investigator Award in Pharmaceutics and Pharmaceutical Technology from the American Association of Pharmaceutical Scientists. He accepted a faculty position in 1993 in the School of Pharmacy at the University of North Carolina. In 2000, he was elected a Fellow of the Institute of Biology of the United Kingdom.

Dr. Hickey has published over 100 papers and chapters in the pharmaceutical and biomedical literature and co-authored a text on pharmaceutical process engineering, as well as editing two volumes on the subject of pharmaceutical inhalation aerosols.

Margaret D. Louey, Ph.D., graduated with a Bachelor of Pharmacy (Honors) and a Ph.D. in Pharmaceutics from the Victorian College of Pharmacy, Monash University (Australia). She completed a postdoctoral fellowship at the School of Pharmacy at the University of North Carolina/Chapel Hill. Her research has primarily involved particle interactions within dry powder aerosols and their formulations. Dr. Louey is a registered pharmacist with clinical experience in Australia and the United Kingdom.

Timothy M. Crowder, Ph.D., graduated with a B.S. in Physics from Davidson College, Davidson, North Carolina and a Master's in Physics from North Carolina State University. He completed his Ph.D. in Biomedical Engineering from the University of North Carolina. Dr. Crowder's research concerns the physics of powder flow and its application to dispersion in dry powder inhalers. He is a founder and the Chief Technology Officer of Oriel Therapeutics.

Contents

Preface

Numerous texts focus on aspects of powder formation and behavior, notably the contributions of Rumpf, Rietema, and Allen. In addition, the pharmaceutical application of powder technology and particle science has long been recognized. Examples of books on this subject are those by Carstensen, Groves, and Barber. In recent years, some very thorough texts have addressed pharmaceutical powders and their properties. The present volume is intended to be a guide to some key principles and their practical applications. Numerous references throughout the text are listed alphabetically at the back of the book to direct the reader to sources for greater detail on elements of this exposition.

The idea for this book was conceived in 1993 by Norman Orr, then of SmithKline Beecham; Amy Davis, formerly of Interpharm Press; and me. Norman felt strongly that this need not be a comprehensive volume because many excellent texts were already available, such as those mentioned above. Instead, he suggested, and I agreed, that the importance of particle technology in the pharmaceutical sciences was understated, and that in particular the potential for error, misuse, or abuse of data should be addressed in a guide to the field. If this initiates some debate, I am sure Norman would have been very pleased.

In the intervening years, some quite dramatic developments have occurred. Most significantly, the driving force for the production of this book was lost. Norman Orr passed away prematurely after a relatively short illness in 1997. In addition, the level of understanding of particle properties and their importance for the performance of a pharmaceutical dosage form have increased substantially. This growth in knowledge was accompanied by a variety of technological advances in particle manufacture and characterization. Fortunately, these events occurred in time for Norman to see many of his aspirations realized. In the face of these changes, the incentive to produce such a volume waned. However, through the encouragement and support of Amy Davis and Tom Waters, of Interpharm Press, I continued to muse over the possibility of finishing this project. Finally, I was fortunate in that two enthusiastic and knowledgeable colleagues, Timm Crowder and Margaret Louey, joined me in the preparation of the manuscript that was the basis for this book. Largely through their persistence and hard work, this volume was completed.

Norman's major written contribution to the text is the introduction. It includes many of his comments, and their clarity and directness convey his commitment to this subject. His overriding view, expressed in early correspondence with me, was that "there is no current text that enables the pharmaceutical scientist to sensibly exploit the power of particulate science in the design, manufacture, and control of quality medicines." To the extent that this text helps in this endeavor, the credit can be given to Norman who, without doubt, was a visionary in this field. If it deviates from this goal, I accept the responsibility because Timm and Margaret have labored under my representations of Norman's objectives without the pleasure of having known him. I hope that you, the reader, find the final product of value in your day-to-day activities.

Anthony J. Hickey
Chapel Hill, NC, 2002

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Introduction and Overview

This volume will challenge current practice in the application of particle science in formulation design, manufacturing, and control of medicines. It aims to highlight appropriate means to exploit this science for the benefit of industry. The sections of this introduction address the relevant issues in pharmaceutical particulate science.

Situation Analysis

The pharmaceutical reality is that in 90 percent of all medicines, the active ingredient is in the form of solid particles. Although the general population has a clear visual appreciation of particulate systems such as sand, gravel, stones, rocks, and boulders, and is capable of differentiating qualitatively among these, the ability to uniquely define particulate systems in a manner that suits all purposes is elusive.

Custom and practice in the pharmaceutical industry is such that particulate systems at best are poorly described and often are inadequately described to an extent that impacts the quality of the final product. Measurements need to relate to the state of the particles in

the finished product and not just the raw material. The most applicable measurement may be one derived or interpolated from a number of techniques.

Particle size provides the basis for building quality into and optimizing the design of medicine, but it is seldom fully exploited. Raw materials are very inconsistent, and how this affects the activity of the medicines is unclear.

Quality of Published Data on Particle Size in Pharmaceuticals

The following chapters review the literature with respect to the relationship of particle size to pharmaceutical parameters. The lack of rigor in the design of experiments is discussed, especially issues related to the following problems:

- Poorly prepared and even more poorly characterized size fractions
- The paucity of absolute measurements, including rigorous microscope counts or good photomicrographs
- The infrequent use of the complimentarity of particle sizing methods

The Future of Crystal Engineering

Huge opportunities surround the engineering of surfaces and morphology of crystals. The implications for formulation design and batch-to-batch uniformity are immense. This should lead, in the first decade of the twenty-first century, to consistency in secondary manufacture. Ultimately, this approach should result in cheaper, well-designed, and higher-quality medicines.

Chemistry and Pharmacy Regulatory Submissions

Increasingly, regulatory bodies such as the FDA need to be convinced that the formulation design is optimal, involving demands for

particle size data of a caliber not seen previously. Pharmacopoeia will seek data of a quality at least equal to the American Society for Testing and Materials (ASTM) or the British Standards Institute.

Misconceptions and Misunderstandings of Particulate Science

The pharmaceutical industry has an incomplete understanding of particulate science. Using tools that are not fully appreciated or understood may confuse or mislead the scientist or regulator.

Powerful Methods Complementary to Particle Sizing

A mathematical interpretation of bulk properties such as flow of powders, coalescence of emulsions, and bleeding in ointments can be developed by using approaches in complexity analysis as well as stochastic and statistical phenomena. For instance, fractal analysis of powder flow can provide numerical values that contain a specific particle size component. Experimental investigations on the powder flow of pharmaceutical systems, including raw materials, excipients, intermediate granulations, and the lubricated granulation for encapsulation and tableting processes, should provide numerical values that relate to features of the component particles. These features may be simple, such as size, or more complex, such as a combination of size, shape, asperities, interparticle forces, and environment in interparticle spaces.

Comparison of such data with that derived from the application of such conventional techniques as sieving may enhance our understanding of the fundamental interactions leading to successful granulation. A broad view of how these data and their interpretation fit into pharmaceutical development embraces a wide range of concepts, from mathematical descriptors of particle shape and molecular probes of surface energetics to numerical definitions of bulk properties. Such methods enable revolutionary approaches to understanding processes such as disintegration, which in certain biological circumstances is a key precursor to dissolution.

The argument we are proposing is that particulate systems can be described, or evaluated, in three contrasting but complementary ways:

1. Direct phenomenological characterization (e.g., bulk flow, shear cell)
2. Knowledge of component particles, their surfaces, the microenvironment in which they exist, and theoretical models that support their interpretation
3. Mathematical interpretation of discontinuities resulting in the observed phenomena (e.g., coalescence of emulsions, avalanching powder flow, bleeding in ointment, and disintegration of tablets, or the sudden disruption of the tablet from the bulk). Such knowledge may translate into an improved product.

Integration of Particle Sizing Methods with Their In-Use Situation

Powder science may be thought of as the understanding of particulate materials at a molecular level, their behavior as individual particles, and the physical and mechanical properties of collections of particles under defined conditions or in specific processes. Formulation can be defined as the transformation of a new chemical entity (NCE) into a medicine that is convenient to manufacture, distribute, and use, such that on administration the NCE is delivered in a predictable qualified and desirable manner. For the majority of medicines from the process of discovery/isolation of the NCE through production as a medicine until dissolution (e.g., in the gastrointestinal tract, or GIT), the NCE is in particulate form.

The nature of this particulate form (morphology, chemistry of the surface, and physical size) varies, depending upon its place in the transformation process. At any given time, the form of a particle may be critical to key parameters. For example, during secondary production, the shape, particle size, and surface energetics may be critical for successful granulation and subsequent compression; the solid-state stability of a capsule or tablet may well depend upon size morphology and excipient drug particle adjacencies; and the content uniformity of potent drugs depends upon both the mass of

the individual particles and the extent to which these individual particles are adequately dispersed and not agglomerated.

A desirable feature of any particulate sizing program for a given NCE in a dosage form would be to monitor the size and characteristics of that particle during the entire process, from isolation at primary manufacture through to disintegration in the GIT. This, then, is the extent of the challenge. In some circumstances, this challenge is almost met, but in the vast majority of products on the market this is not the case by default, and formulation success and final quality of the product are not guaranteed. Consequently, it may be possible to consider a measure or expression for the particle size of a powder in the absence of knowledge of its intended use.

Adjacencies and Interactions Between Particles

Particle–particle interactions do occur, and each particle must be considered in the context of its environment. Adjacencies and interactions between particles fall into two categories, advantageous and disadvantageous. The type of interactions being sought will depend upon the aspect of the design or process being considered.

As an example, when considering content uniformity and dissolution, the decision may be that particles should be <10 μm in size. These particles must be free flowing and must disperse and mix with excipients readily. If the mix is used in a direct compression process, it would be desirable that strong interaction occur between the excipient and drug but not between adjacent excipient particles (e.g., magnesium stearate when used as an excipient in tablet compression).

Technology exists to specifically assess the extent, at any processing stage, of particle adjacencies and interactions. Each of the steps is concerned with either breaking particle–particle interactions, or encouraging the formation of new particle–particle interactions, or both processes (i.e., mixing, granulation, tableting, disintegration).

Lessons from Other Industries

Other industries have studied the behavior of particulates closely. For example, the efficiency of release of energy from the combustion of coal depends to large extent on the nature of the particles

being employed. The performance of paints and polymers that consist of particulate material has been correlated with the characteristics of these particles. The modern printer utilizes a sophisticated method of depositing toner powders with unique physicochemical properties suitable for producing printed matter. These examples and others indicate the wealth of experience that can be tapped for application to pharmaceutical products.

Pharmaceutical Particulate Science as a Core Educational Requirement

Currently, particulate science for pharmaceutical systems is taught in engineering and pharmacy schools on an ad hoc basis. A convincing argument can be made for collecting all the appropriate information into a core discipline of pharmaceutical particulate science for instruction to those students intending to work in the pharmaceutical industry.

Particle Characterization and Its Impact on Regulatory Submissions from Formulation through Toxicology and Efficacy

The interface between the dosage form and the organism is the basis for the pharmacological or toxicological effects observed. The absolute amount of a drug or xenobiotic delivered by any route of administration and its rate of release, which will influence the bioavailability, must be considered since efficacy and toxicity are dose related. The nature of the particulate components of the drug delivery system will ultimately dictate the rate of release and instantaneous dose. The crystal structure, presence of polymorphs, and degree of subdivision all contribute to the solubility and dissolution rate of drugs. In general terms, these features influence the circulating concentrations of the agent, bringing it to therapeutic or toxic levels. However, in certain circumstances, specific organs may experience higher or lower concentrations of the drug than circulating levels based on intentional or unintentional targeting. Inhalation aerosol delivery, for example, deliberately targets the lungs and

achieves locally therapeutic doses while minimizing systemic side effects. Oral delivery of drugs results in absorption to a blood supply, which is delivered to the liver by the hepatic portal vein before distribution to the rest of the body. This represents unintentional targeting of an organ, which may result in local advantageous or deleterious effects.

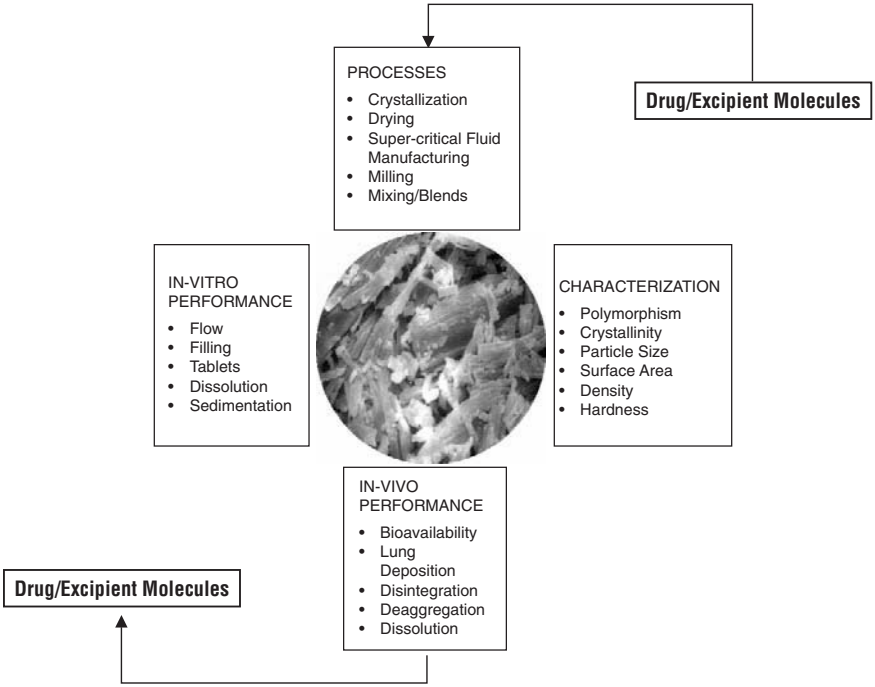
Minimally, a full characterization of the particulate nature of the product is required to ensure reproducibility of dose delivery and overall quality. If the particle size and distribution are thought to directly impact on the efficacy of a product, as is the case with inhalation aerosols, then this becomes a determinant of regulatory scrutiny.

Conclusion

The role of particulate science in the preparation of medicines is ubiquitous. The solid state is the dominant means of presentation of a drug. Once molecules have crystallized from solution or solidified from a melt, the individual form and degree of subdivision of the population must be characterized. These features directly relate to performance of the dosage form and ultimately the way in which molecules present at the site of absorption, action, and the target receptor. The impact of the particulate nature of components of the dosage form on therapeutic effect is of the utmost importance and is considered in the following chapters. For convenience, the sequence outlined in this introduction has been divided into the following topics: particulate material, its form and production (Chapter 2); sampling from bodies of powder (Chapter 3); particle size descriptors and statistics (Chapter 4); behavior of particles (Chapter 5); instrumental analysis (Chapter 6); particle size measurement and synergy of adopted techniques (Chapter 7); physical behavior of a powder (Chapter 8); and in vitro and in vivo performance criteria (Chapter 9).

Figure 1.1 illustrates the issues that must be considered without proposing a relationship between them. The general conclusion to the book draws these components of pharmaceutical particulate science into a single concise description of their integration in the context of product development.

Figure 1.1 Important factors in pharmaceutical particulate science.



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Particulate Systems: Manufacture and Characterization

As an introduction to the methods of particle production, a brief review of the fundamentals of the states of matter and crystal systems may be helpful.

States of Matter

The three states of matter—gas, liquid, and solid—each represent a different degree of molecular mobility. Gibbs first described the nature of states of matter according to the principles of thermodynamics (Rukeyser 1992; Gibbs 1993). Despite developments in the fields of quantum physics and chemistry, Gibbs' observations remain a valid description of the nature of matter.

Gas molecules are in constant vigorous, random motion according to the classical ideal gas theory of Bernoulli. Consequently, they take the shape of the container, are readily compressed, and exhibit low viscosity.

Liquids exhibit restricted random motion; the volume occupied is limited by their condensed nature resulting from intermolecular forces. Thus, liquids take the shape of a portion of the container. The liquid properties of water are within everyone's daily experience. However, to illustrate the extreme, other commonly experienced substances such as wax, pitch, and glass are highly viscous liquids, and not, as they appear to be, solids.

The last state of matter is highly constrained and is the result of a variety of forces. Solids are of great significance in the way we experience the world and are a dominant theme in the preparation of pharmaceuticals.

In broad terms, solids may be found in amorphous or crystalline states (Mullin 1993; Glusker, Lewis, and Rossi 1994). Crystallinity involves the regular arrangement of molecules or atoms into a fixed, rigid, three-dimensional pattern or lattice. Many amorphous materials exhibit some degree of crystallinity. The term "crystalline" is reserved for materials that exhibit a high degreee of internal regularity resulting in development of definite external crystal faces.

Truly amorphous solids are similar to gases and liquids in that their physical properties when measured in any direction are the same. In consequence, they are regarded as isotropic substances. Most crystals are anisotropic in that their mechanical, electrical, magnetic, and optical properties vary according to the direction of measurement. Cubic crystals are a notable exception because their highly symmetrical internal arrangement renders them optically isotropic. Anisotropy is most readily detected by refractive index measurement. Polarizing lenses may be employed to study anisotropy optically.

Liquid crystals are isotropic materials that can be induced to exhibit anisotropic behavior. Bose's swarm theory explains mesophase formation in liquid crystals by the formation of ordered regions in an otherwise randomly arranged "liquid." Molecules in these systems "swarm" into alignment. This phenomenon can be classified into smectic (soap-like), nematic (thread-like), and cholesteric. The smectic mesophase is characterized by flow of liquids in thin layers over each other. Cholesteric mesophases exhibit strong optical activity. Systems consisting of organic, often aromatic, elongated molecules form anisotropic liquids.

Crystalline Solids

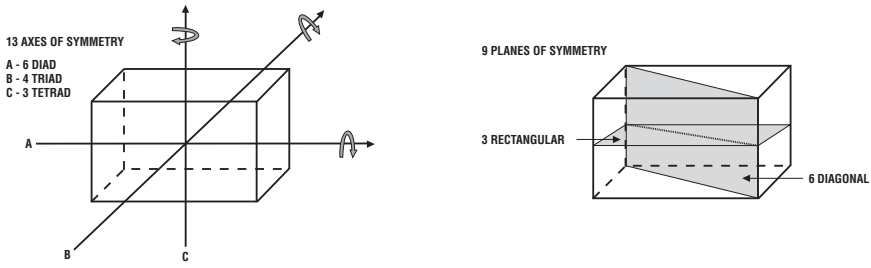
Crystals comprise a rigid lattice of molecules, atoms, or ions. The regularity of the internal structure of this solid body results in the crystal having characteristic shape (Jones and March 1973a, 1973b). The growth of most natural crystals has been restricted in one or more directions, resulting in exaggerated growth in other directions and giving rise to the so-called crystal habit (Tiwary 2001; Umprayn et al. 2001; Bennema 1992; Garekani 2001).

The apparent order exhibited by crystalline solids was once thought impossible to classify. In the late eighteenth century, however, Haüy, building on the observations of Steno from the prior century, proposed the law of constant interfacial angles, which stated that angles between corresponding faces of all crystals of a given substance are constant. Therefore, crystals may vary in size and development of various faces but the interfacial angles do not vary. A single substance can crystallize in more than one structural arrangement or form, known as polymorphism, an anomaly with regard to Haüy's law. However, the law does apply to each form, or polymorph. Modern techniques of X-ray crytallography enable lattice dimensions and interfacial angles to be measured, by the application of Bragg's law, with high precision on milligram quantities of crystalline powders (Nuffield 1966; Llacer et al. 2001; Darcy and Buckton 1998; Brittain 2001).

Crystal Symmetry

Classification of crystals can be considered in terms of the apparent order conveyed visually. This can be described in terms of the symmetries exhibited, either about a point (center), a line (axis), or a plane. A cube is a simple example of such classification, having a single point, 13 axes, and 9 planes of symmetry, totaling 23 elements of symmetry, as shown in Figure 2.1. An octahedron exhibits the same quantity or elements of symmetry as a cube. Therefore, these polygons are related despite their apparent difference in appearance. The octahedron can be transformed into a cube by passing through the intermediate forms of truncated cube and octahedron and cuboctahedron. These represent 3 of the 13 Archimedean semiregular

Figure 2.1 Classification of (a) point (center), lines (axes), and (b) planes of symmetry for a cube.



solids, which are called combination forms. Crystals frequently exhibit combination forms. The tetrahedron is also related to the cube and octahedron. These three forms belong to the five regular solids of geometry. The other two forms, the regular dodecahedron and icosohedron, do not occur in the crystalline state. However, the rhombic dodecahedron is frequently found in nature, particularly in garnet crystals.

Euler's Relationship

Euler's relationship is particularly useful for calculating the number of faces (F), edges (E), and corners (C, vertices) of any polyhedron according to the expression

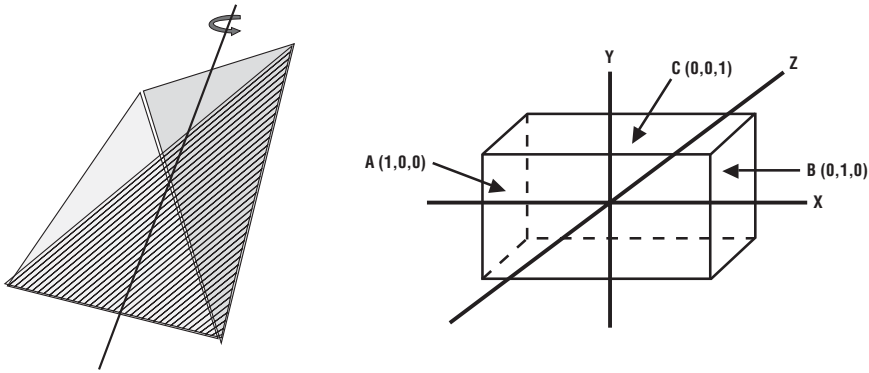
$$E = F + C - 2 \tag{2.1}$$

Intriguingly, Gibbs' phase rule, which describes the states of matter, appears to follow a similar expression in relating C, the number of components; F, the number of degrees of freedom; and P, the number of phases:

$$F = C - P + 2 \tag{2.2}$$

When rearranged, Gibbs' phase rule takes the same form as Euler's relationship:

Figure 2.2 (a) Rotary inversion symmetry and (b) cubic geometry illustrating Miller indices.



$$C = F + P - 2 \tag{2.3}$$

A fourth element of symmetry is known as compound or alternating symmetry, or, alternatively, symmetry about a rotation-reflection axis or axis of rotatory inversion. This type of symmetry comes about by performing two operations: rotation about an axis and reflection in a plane at right angles to the axis, as shown in Figure 2.2a. This is also called inversion about the center.

Crystal Systems

Only 32 combinations of the elements of symmetry are possible. These are the point groups, or classes. All but a few of these classes have been observed in crystalline bodies. These classes are grouped into seven systems based on three dimensions (x, y, and z) and angles of faces (α, β, and γ). Hexagonal crystals are unique because they have six edges in two dimensions rather than four as for the other crystal systems. Hexagonal crystals are described by invoking a third dimension in two-dimensional space with a third angle (μ). Table 2.1 describes the crystal systems.

Table 2.1 Crystal Systems, the Number of Subsidiary Classes, and Crystal Structures (Dimensions x, y, z, and Angles α, β, γ, μ)

Crystal System	(Classes)	Angles/Dimensions
Regular	(5)	$\alpha = \beta = \gamma = 90°$ / $x = y = z$
Tetragonal	(7)	$\alpha = \beta = \gamma = 90°$ / $x = y \neq z$
Orthorhombic	(3)	$\alpha = \beta = \gamma = 90°$ / $x \neq y \neq z$
Monoclinic	(3)	$\alpha = \beta = 90° \neq \gamma$ / $x \neq y \neq z$
Triclinic	(2)	$\alpha \neq \beta \neq \gamma \neq 90°$ / $x \neq y \neq z$
Trigonal	(5)	$\alpha = \beta = \gamma \neq 90°$ / $x = y = z$
Hexagonal	(7)	$\alpha = \beta = \mu = 60°$, $\gamma = 90°$

Miller Indices

An alternative visual reference technique known as Miller indices involves using a three-dimensional Cartesian coordinate system to indicate the position of crystal faces in space. In this technique, all of the faces of a crystal can be described in terms of their axial intercepts, as illustrated in Figure 2.2b.

Space Lattices

Hooke and Haüy concluded that all crystals were built up of a large number of minute units, each shaped like the larger crystal. Consequently, a space lattice is a regular arrangement of points in three dimensions. Each of the seven crystal systems identified by elements of symmetry can be classified into 14 Bravais lattices, as shown in Table 2.2. Although these are the basic lattices, interpenetration can occur in actual crystals; this interpenetration can potentially give rise to 230 possible combinations. An alternative Bravais-Donnay-Harker principle considers space groups rather than lattice types. Generally, crystals cleave along lattice planes.

Solid State Bonding

Four types of crystalline solid may be specified: ionic, covalent, molecular, and metallic. Some materials are intermediate between these types.

Table 2.2 Fourteen Bravais Lattices and Their Equivalent Symmetries and Crystal Systems

Type of Symmetry	Lattice	Crystal System
Cubic	Cube Body centered Face centered	Regular
Tetragonal	Square prism Body centered	Tetragonal
Orthorhombic	Rectangular prism Body centered Rhombic prism Body centered	Orthorhombic
Monoclinic	Monoclinic parallelepiped Clinorhombic prism	Monoclinic
Triclinic	Triclinic parallelepiped	Triclinic
Rhomboidal	Rhombohedron	Trigonal
Hexagonal	Hexagonal prism	Hexagonal

Ionic crystals (e.g., sodium chloride) consist of charged ions held in place in the lattice by electrostatic forces. Each ion is separated from oppositely charged ions by regions of negligible electron density.

Covalent crystals (e.g., diamond) consist of constituent atoms, which do not carry effective charges. A framework of covalent bonds, through which their outer electrons are shared, connects these atoms.

Molecular crystals (e.g., organic compounds) are discrete molecules held together by weak attractive forces (π-bonds, hydrogen-bonds).

Metallic crystals (e.g., copper) comprise ordered arrays of identical cations. The constituent atoms share their outer electrons, which are free to move through the crystal and confer "metallic" properties on the solid.

Pharmaceutical products are largely limited to ionic and molecular crystals. The ionic crystals are associated with additives to the products; the drug substance itself is usually a molecular