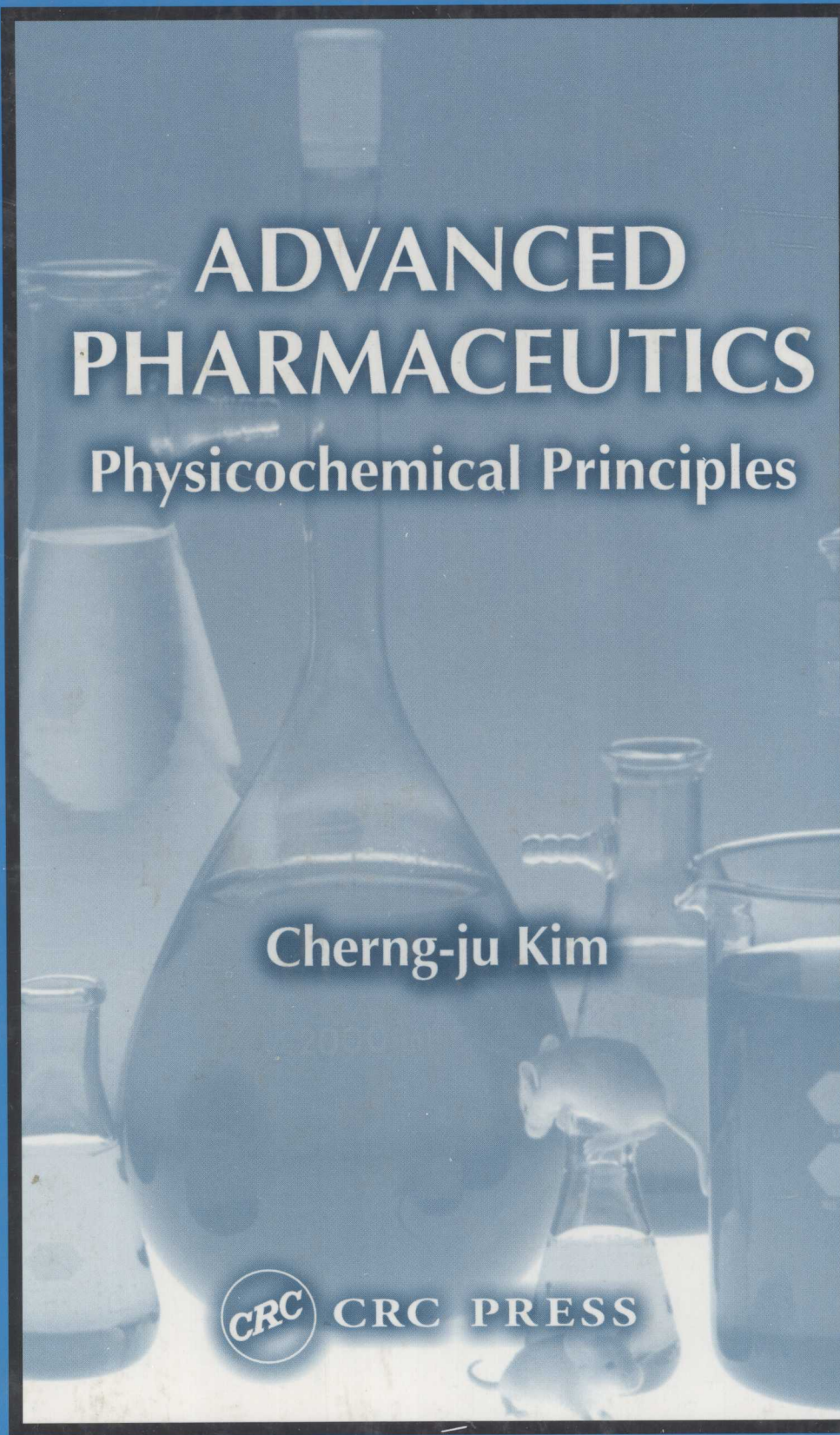




ADVANCED PHARMACEUTICS

Physicochemical Principles

Cherng-ju Kim



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Preface

This book presents, in a mechanistic, quantitative manner, many of the necessary fundamentals required for pharmaceuticals-related problems. It can be used to guide students and professionals until they understand the fundamentals well enough to focus their research areas and read articles in the literature. This book has evolved from several course notes at Temple University School of Pharmacy, particularly with the aid of books by J. R. Barrante (*Physical Chemistry for the Life Sciences*), R. Chang (*Physical Chemistry with Applications to Biological Systems*), A. T. Florence and D. Attwood (*Physicochemical Principles of Pharmacy*), A. Martin (*Physical Pharmacy*), O. Robbins, Jr. (*Ionic Reactions and Equilibria*), and Williams et al. (*Basic Physical Chemistry for the Life Sciences*). It is intended primarily for graduate students in pharmaceuticals. This book can be taught in two semesters with supplemental material: Chapters 1 to 4 for the first semester and Chapters 5 to 7 for the second semester. I hope that this book will also be useful as a reference for pharmaceutical scientists engaged in drug product development.

I acknowledge Dean Peter H. Doukas at Temple University for his support and encouragement. I owe major debts to Professor Archie E. Hamielec and Dr. Ping I. Lee who introduced me to polymer engineering and pharmaceuticals, respectively. I am grateful to graduate students who raised various questions and suggestions in diverse subject matters.

I am indebted to my wife and children for their patience, understanding, and assistance during the preparation of this book.

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1 Thermodynamics

Thermodynamics is a branch of physical chemistry that deals quantitatively with the inter-exchange of heat and work evolved in physical and chemical processes. This subject is widely utilized to explain equilibrium systems in physical pharmacy. For example, a pharmaceutical scientist may use equilibrium thermodynamics to study isotonic solutions, solubility of drugs, distributions of drugs in different phases, or ionization of weak acids and weak bases. Even though the gas laws are not usually directly related to pharmaceutical science (with some exceptions such as aerosols), these concepts must be introduced when dealing with simple thermodynamic systems of gases and the universal gas constant, R.

1.1 IDEAL GASES

Robert Boyle discovered experimentally that the volume of a gas in a J-tube apparatus at a constant temperature varied in inverse proportion to the pressure. This is known as Boyle's law. Boyle's law may be expressed mathematically as:

$$V \propto \frac{1}{P} \quad (\text{constant temperature}) \quad (1.1)$$

where V and P are the volume and pressure of the gas, respectively.

In the early 19th century, Joseph Gay-Lussac, after following the work of Alexandre Charles, established that the volume of a gas increases linearly with temperature at constant pressure. Expressed mathematically, Charles's law states that:

$$V = V_0(1 + \alpha t) \quad (\text{constant pressure}) \quad (1.2)$$

where V_0 is the volume of the gas at 0°C, α is the proportionality constant (or thermal expansion coefficient) for the gas, and t is the temperature (°C). It was found experimentally that α is independent of the nature of the gas and that it has the value of $\frac{1}{273.15} \text{ } ^\circ\text{C}^{-1}$. Substituting this value into Equation (1.2) yields:

$$V = V_0 \left(\frac{273.15 + t}{273.15} \right) \quad (1.3)$$

In Equation (1.3), the volume of the gas becomes zero when the temperature is reduced to -273.15°C, which is the absolute zero temperature. The relation between the Celsius degree and the absolute scale (called Kelvin degree) is given by:

$$T(\text{K}) = 273.15 + t \text{ (} ^\circ\text{C)} \quad (1.4)$$

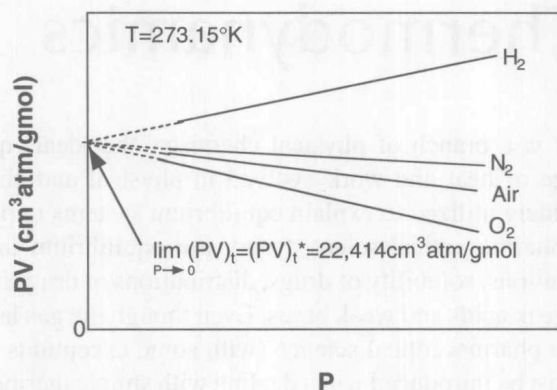


FIGURE 1.1 Variation of pressure–volume product with pressure.

The Kelvin degree scale was originally introduced by William Thomson. It is a thermodynamic temperature scale based on the second law of thermodynamics and is identical to the absolute temperature scale based on the above volume expansion arguments. Substituting Equation (1.4) into Equation (1.3) gives:

$$V = V_0 \frac{T}{T_0} \quad \text{or} \quad \frac{V}{T} = \frac{V_0}{T_0} \quad (1.5)$$

where $T_0 = 273.15 \text{ K}$.

Volume is an extensive property, which is dependent on the quantity of substance (or substances) present in the system. Therefore, the volume of a gas at constant temperature and pressure is directly proportional to the number of moles of the gas, n (Avogadro principle). Unlike volume, temperature and pressure are intensive properties and are independent of the amount of material present in the system. Combining Equation (1.1) and Equation (1.5) with the Avogadro principle gives:

$$V \propto \frac{nT}{P} \quad \text{or} \quad PV = nRT \quad (1.6)$$

where R is the proportionality constant or gas constant. Equation (1.6) is known as the ideal gas law. The proportionality constant of Equation (1.6) is determined experimentally.

As the pressure approaches zero, all gases follow the ideal gas law. Experimentally, plotting PV against P and extrapolating to zero pressure gives the gas constant, R (see Figure 1.1). Since one mole of an ideal gas occupies 22.414 L at 0°C and 1 atmospheric pressure, then, R is:

$$R = \frac{PV}{nT} = \frac{1 \text{ atm} \times 22.414 \text{ L}}{1 \text{ mole} \times 273.15 \text{ K}} = 0.08206 \text{ L} \cdot \text{atm} / \text{mole K} \quad (1.7)$$

TABLE 1.1
Values of the Ideal Gas Constant R

82.06	mL-atm K ⁻¹ mol ⁻¹
1.987	cal K ⁻¹ mol ⁻¹
8.314	J K ⁻¹ mol ⁻¹
8.314×10^7	erg K ⁻¹ mol ⁻¹
1.987	Btu (lb mol) ⁻¹ R ⁻¹

The value of R is dependent on the units used for each variable (i.e., P, V, T). The common values of R are listed in Table 1.1.

Example 1.1

Calculate the volume occupied by 23.6 g of a propellant, trifluorochloroethane, at 55°C and 720 mmHg pressure. Assume the gas follows the ideal gas law.

Solution

$$V = \frac{n RT}{P} = \frac{(23.6 \text{ g})(0.08206 \text{ L atm / mol K})(55^\circ + 273.15^\circ)}{(136 \text{ g / mole})(720 \text{ mmHg})(1 \text{ atm / 760 mmHg})} = 4.93 \text{ L}$$

In a mixture of gases in a container at constant temperature and pressure, each gas obeys the ideal gas law. The total pressure of the container is dependent on the total number of moles present in the container regardless of the nature of the gases. The individual pressures for each gas are called partial pressures (i.e., $P_1, P_2, P_3, \dots$). The sum of these partial pressures is equal to the total pressure, P_T ; this is known as Dalton's law of partial pressures. The mathematical expression for Dalton's law is as follows:

$$P_T = P_1 + P_2 + P_3 + \dots + P_N \quad (1.8)$$

where N is the number of gases in the system.

Applying the ideal gas law gives:

$$P_T = \frac{(n_1 + n_2 + n_3 + \dots) RT}{V} \quad (1.9)$$

where n_1, n_2, n_3 , etc., represent the number of moles of each gas. Equation (1.8) and Equation (1.9) give the partial pressure of each gas i as:

$$P_i = \frac{n_i RT}{V} \quad (1.10)$$

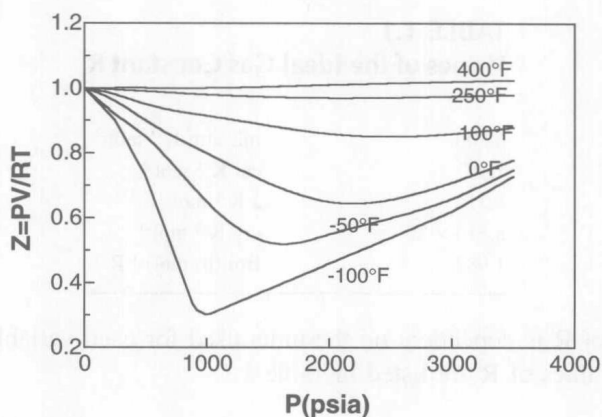


FIGURE 1.2 Compressibility factor diagram for methane.

From the ratio of Equation (1.9) to Equation (1.10), the mole fraction of the gas i , in the mixture, X_i , can be obtained by:

$$X_i = \frac{P_i}{P_T} = \frac{n_i}{n_1 + n_2 + n_3 + \dots + n_T} \quad (1.11)$$

1.2 REAL GASES

As the pressure of a gas is increased and/or its temperature is lowered, the ideal gas law is not followed because the volume of the gas is not negligible and intermolecular forces do exist. If the ratio, $z = \frac{PV}{nRT}$, referred to as the *compressibility factor* for the gas, is plotted against P at constant temperature, then the values of Z deviate from ideal behavior, which is unity for an ideal gas (see Figure 1.2). This is attributed to the pressure build-up as gas molecules collide on the walls of a container. If the gas molecules adjacent to the walls exert intermolecularly attractive forces, the momentum of the gas molecules toward the wall will be decreased. Thus, the collisions of the gas molecules will be reduced, resulting in the pressure of the gas being less than that of an ideal gas. At high pressure, the gas molecules pack the container very closely together, causing the volume of the gas molecules to be a significant part of the total volume.

Van der Waals proposed the incorporation of two additional terms into the ideal gas law to account for the deviations from ideal behavior. The ideal gas law equation then becomes:

$$\left(P + \frac{a}{V^2}\right)(V - b) = RT \quad (1.12)$$

where a and b are constants and are determined experimentally. The constant a in Equation (1.12) accounts for the cohesive forces between the gas molecules, which

TABLE 1.2
Van der Waals Constants
of Some Gases

Gas	a (L ² atm/mol ²)	b (L/mol)
He	0.0353	0.0241
H ₂	0.246	0.0267
N ₂	1.35	0.0383
O ₂	1.36	0.0319
CO ₂	3.60	0.0427
CH ₄	2.25	0.0428
H ₂ O	5.43	0.0303
NH ₃	4.19	0.0373

drag other gas molecules around a single molecule, causing the pressure of the gas to be less than that of an ideal gas. The cohesive forces are dependent on the intermolecular distances and related to the density of the gas. The term a / V^2 is called the internal pressure per mole. This internal pressure will be used to describe the solubility of the molecules in liquids in Chapter 3. The constant b in Equation (1.12) accounts for the incompressibility of the gas molecules, known as the excluded volume occupied by the gas molecules. The excluded volume is approximately four times the volume of the gas molecules. The term $(V - b)$ represents the effective volume of the gas molecules that expand freely. The van der Waals constants for typical gases are listed in Table 1.2. At low pressure, the volume of the gas molecules is so large that the contribution of the excluded volume toward the total volume is very small and the term a / V^2 becomes negligible. Thus, under these conditions, Equation (1.12) is reduced to the ideal gas law expressed by Equation (1.6).

Example 1.2

Calculate the pressure produced by 75 g of ethanol in a 5.0 L container at 80°C by the ideal gas law and van der Waals equation. The van der Waals constants a and b are 12.02 L² atm/mol² and 0.08407 L/mol, respectively.

Solution

From the ideal gas law,

$$P = \frac{n RT}{V} = \frac{(75 \text{ g})(0.08206 \text{ Latm} / \text{mol K})(353.15 \text{ K})}{(46 \text{ g} / \text{mol})(5 \text{ L})} = 9.45 \text{ atm}$$

The van der Waals equation can be rewritten as:

$$P = \frac{n RT}{V - n b} - \frac{n^2 a}{V^2} = \frac{(75 / 46)(0.08206)(353.15)}{5 - (75 / 46)(0.08407)} - \frac{(75 / 46)^2(12.02)}{5^2}$$

= 8.44 atm