Complex phenomena in pharmaceutical chemistry may have a significant impact on the performance of the dosage form. Traditionally, the concern has been with bulk product performance and stability with a focus on chemical degradation, and while this remains a serious issue over the last few decades, the focus on reproducible product performance has shifted toward considerations of physical stability.

A brief discussion of chemical considerations is followed by a more detailed presentation of the development of our understanding of important physical and surface chemical considerations.

**Chemical Reactions**

Certain chemical reactions are known to be complex phenomena. Molecular dynamics and chemical kinetics have been studied thoroughly, and they frequently appear predictable in terms of classical exponential or power functions (Billing and Mikkelsen 1996). The apparently predictable nature of chemical reactions may be an illusion of simplicity described by the Ergodic hypothesis (de Oliveira and Werlang 2007; Szasz 1994). Boltzmann originally conjectured that time-averaged behavior of microscopic components of a system gives the same outcome as the macroscopic, bulk average, where the bulk is a collection of all possible
states that molecules would reach in assembly in infinite time. Clearly depicting each of these states independently would be an enormously complex system. Attempts are being made to scrutinize reactions to more accurately depict the events that may be occurring (Nowak and Fic 2010; Bonchev et al. 1987).

**Surface and Interfacial Chemistry**

Adsorption constitutes an important area of research in which efforts to understand complex phenomena have extended for over a century. The following section begins by considering molecular association, extends to surface adsorption and models that have been proposed for nonlinear data fitting. The ability to measure surface features and energy densities at a molecular level has improved the potential to learn about the nature of interactions.

Surfactant molecules are noteworthy because of their capacity through discrete polar and nonpolar regions to align at interfaces, in particular the surfaces of solids in suspension.

The use of surfactants as coating materials requires consideration of the nature of these compounds, their interactions, and association with other substances.

Surface activity is a dynamic phenomenon, since the final state of a surface or interface represents a balance between the tendency towards adsorption and towards complete mixing due to the thermal motion of molecules.

A surface active agent (surfactant) may be described as a substance which alters the conditions prevailing at the interface. All surfactants are characterized by two structural regions, a hydrocarbon chain, which is hydrophobic, and a polar, hydrophilic group. The nature of the hydrophilic region of the surfactant enables the classification of surfactants to be subdivided into anionic, cationic, and nonionic. Examples of these are sodium dodecyl sulfate, dodecyl trimethyl ammonium bromide, and $n$-dodecyl hexaoxyethylene glycol monoether, respectively. Two further groups of surfactants exist: ampholytic surfactants which are zwitterionic and can behave as any of the aforementioned
examples depending on the pH at which they are maintained, such as alkyl betaine, and natural surfactants which usually contain a glycerol moiety, such as phosphatidylcholine. Therefore, surfactants may be described as amphiphilic.

The formation of aggregates (Kertes 1977) and micelles (Eike 1977; Ravey et al. 1984) in solutions of surfactants is well documented. The term “micelle” should designate any soluble aggregate spontaneously and reversibly formed from amphiphilic molecules or ions (Tanford 1980). The micellization processes according to the commonly used equilibrium thermodynamic descriptions, namely the multiple equilibrium model and the pseudo-phase model, are, like the micelle definition, equally well applicable to aqueous and nonpolar solutions (Mukerjee 1974). The second model best conforms to the definition of a micelle described above.

The interactions governing the formation of surfactant aggregates in apolar media are different from those in aqueous solutions, in spite of the apparently similar building principle of lipophilic and hydrophilic micelles. The differences between interactions encountered in aqueous and nonpolar surfactant solutions have been considered at a molecular level with reference to the stability or existence of micelles in apolar media (Eike 1977). It has been concluded that once equilibrium between monomers and micelles, equivalent to the pseudo-phase model, ceases to be operative and is replaced by a stepwise aggregation equilibrium, the concept of a critical micelle concentration (CMC) is inapplicable. The two models for the process of interaction between surfactant molecules, described above, are, therefore, considered to be mutually exclusive (Kertes 1977).

**Aggregation**

Inverted or reversed micelles are examples of molecular aggregation. Formation of surfactant aggregates has been referred to briefly above. The driving force for aggregation in aqueous media is the extrusion of hydrocarbon chains from solution upon micelle formation, resulting in an overall decrease in the free energy of the
Phenomena in Physical and Surface Chemistry

In nonaqueous solution, aggregation of the surfactant molecules depends upon both the solvent and the surfactant structure.

Interactions between solvent and surfactant hydrocarbon chain groups tend to minimize the size of the aggregate, while interactions between the polar groups of the surfactants promote aggregation, in polar solvent.

Kinetic treatments in both aqueous and nonaqueous micellar systems have been based on the Hartley model (Hartley 1936, 1955) of opposing hydrophobic interactions and electrostatic repulsions which are responsible for micellization in water.

Surfactant association in apolar solvents is predominantly the consequence of dipole–dipole and ion pair interactions between the amphiphiles. This differs from the Hartley model and concepts derived for surfactant association in water may not necessarily be applicable to those in apolar solvents (O’Connor and Lomax 1983).

In a nonaqueous solution of concentration, \( C \), existing as simple molecules, \( m \), and micelles composed of \( n \) molecules in equivalent concentration, \( M_n \), the mass law is as follows:

\[
KM_n = m^n = (C - nM_n)^n
\]  

(2.1)

where \( K \) is the dissociation constant of the micelles.

A phase separation model was advocated by Shinoda and Hutchinson (1962), and successfully applied by Singleterry (1955) and Fowkes (1962) to describe the aggregation of dinonylnaphthalene sulfonates in benzene. The phase separation model postulates that micellization is a phase transition. In its simplest form, it does not contain a size-limiting step and, therefore, it is of little value in accounting for the formation of the small aggregates seen in apolar media.

The mass action law can be applied to the overall aggregation process:

\[
K_n
\]

\[
nm \leftrightarrow M_n
\]

where \( K_n \) is the association constant of the process that allows a model. Thus, with the conservation of mass:
\[
\frac{[m]}{[D]} + n \left( \frac{[m]}{[D]} \right)^n [D]^{n-1} K_n = 1
\]  
(2.2)

where \([D]\) is the total molal concentration of detergent. From this equation assuming that \(K_n\) is the product of \(n-1\) individual and equal mass action constants, the following equation is obtained:

\[
\frac{[m]}{[D]} + n \left( \frac{[M_n]}{[D]} \right) = 1
\]  
(2.3)

and the CMC is then obtained:

\[
\text{CMC} = \frac{1}{k} = [D]
\]  
(2.4)

where \([D] = 1\).

This system allows for two aggregation states: monomers and micelles. This does not account for the distribution in molecular weights. Smooth transitions from monomer, dimmer, trimer, etc., with concentration-dependent growth of aggregates have been observed. These gradual physical changes have been described (Lo et al. 1975) in terms of a sequential type self-association model. Assuming all values of equilibrium concentration are the same, \(K_{12}, K_{23}, \ldots K_{ij}\) are assumed to be equal:

\[
K_{12} \quad \text{Monomer + monomer} \leftrightarrow \text{dimer}
\]

\[
K_{23} \quad \text{Dimer + monomer} \leftrightarrow \text{trimer}
\]

\[
K_{ij} \quad (n-1)\text{mer} + \text{monomer} \leftrightarrow n-\text{mer}
\]

Then the weight fraction of the monomer, \(f\), is related to the stoichiometric concentration of detergent, \([D]\), by the following equation:

\[
(1 - f^{1/2}) / f = K_{ij} [D]
\]  
(2.5)

It would be possible to modify the multiple equilibrium model to account for a critical concentration (Eike 1980). Application of the mass action law to aggregation, and conserving mass with respect to monomer yields
\[
\frac{[m]}{[D]^+} + \sum_{n=2}^{n} n([m]/[D]^n)[D]^{n-1} \prod_{n=2}^{n} k_{n-1} = 1 \quad (2.6)
\]

A size-limiting step may be introduced by requiring a functional relationship between the equilibrium constants and the association number, \(K_n = f(n)\) (Muto et al. 1974).

The number of monomers involved in most surfactant aggregates in nonpolar solvents is relatively small (typically less than 10 for alkylammonium carboxylates compared with up to 100 for aqueous micelles; Fendler and Fendler 1975); consequently, a spherical micelle structure would not provide effective shielding of the polar head groups from the solvent and its formation would be considered unlikely (Kertes and Gutmann 1976). The alternative model is that of a lamellar micelle in which the polar and hydrophobic groups are placed end to end and tail to tail, with water and organic solvents between them (Philippoff 1950; Mayer et al. 1969).

The kinetics of formation and decomposition of micelles and of the association–dissociation of the monomer to and from the micelle has rarely been studied in reversed micellar solutions (Yamashita et al. 1982). The paucity of data is attributed to: (1) the aggregation number of the micelle being very low that an abrupt change in the physico-chemical properties of the solution cannot be expected at the CMC and (2) micelle formation and monomer exchange reactions are too rapid to be observed by conventional techniques.

**Adsorption from Solution**

The method by which surfactants interact with other substances is adsorption at the interface. The interface may be a gas–liquid, liquid–liquid or solid–liquid juncture, the latter being significant in many pharmaceutical systems.

Langmuir presented a general equation for the isotherm of localized adsorption that was suitable for describing the adsorption of solutes. Langmuir’s approach was concerned with monolayer coverage (Langmuir 1917). The assumptions made for this
model were: that molecules are adsorbed at active centers on the adsorbent surface which they occupy for a finite period of time; owing to the small radius of action of adsorption forces and to their saturability, every active center while adsorbing molecules becomes incapable of further adsorption. Langmuir’s adsorption equation concerns the simplifying assumptions that the heat of adsorption is independent of surface coverage, thus ignoring adsorbate interaction and the weakening effect on the intermolecular forces by distance between the adsorbent and adsorbate. Fowler and Guggenheim (1960) adopted an approach which provides a modification for lateral interactions in the Langmuir model. Attempts have been made to generalize monolayer and multilayer concepts in order to describe the isotherms of different shapes by a single equation. Brunauer et al. (1932) developed such a generalized theory in respect to adsorption of vapors which has since become known as the BET theory. The assumption of this theory are: the adsorbent surface has a definite number of active sites which are equivalent energetically and are capable of retaining the adsorbate molecules; the interaction of the neighboring adsorbed molecules is neglected; the molecules in each layer act as an adsorption site for subsequently adsorbed molecules; it is assumed that all of the adsorbed molecules in the second and subsequent layers have the same partition function as in the liquid state, which differs from the partition function of the first layer. Brunauer (1945) has classified adsorption isotherms into five types.

The BET theory has been very useful in the interpretation of solute adsorption. This theory assumes that every molecule of a liquid has only two close neighbors, from the top and bottom chain, while the molecules of a real liquid are surrounded by many more adjacent molecules. Moreover, Giles (Giles et al. 1974a,b) has found both theoretically and experimentally the shape of some isotherms, of solute from solution, can be accounted for by postulating that adsorbate interaction does occur under particular conditions. The assumption that the adsorbent surface has a definite number of active sites which are equivalent energetically is an oversimplification (Rudzinski and Narkiewicz-Michalek 1982, Mabire et al. 1984).
The Langmuir model for adsorption assumes that while the adsorbed molecules occupy sites of energy $Q$ that they do not interact with each other. Fowler and Guggenheim (1960) have adopted an approach which accounts for lateral interaction.

The probability of a given site of energy $Q$ being occupied is $N/S$, and if each site has $z$ neighbors the probability of neighbor site being occupied is $zN/S$. So, the fraction of adsorbed molecules is $z\theta/2$, the factor one-half correcting for double counting and $\theta$ being total monolayer coverage. If the lateral interaction energy is $\omega$, the added energy of adsorption is $z\omega\theta/2$, and the added differential energy of adsorption is just $z\omega\theta$.

The modified Langmuir equation then becomes

$$\Theta = b'C(1 + b'C)^{-1} \quad (2.7)$$
$$b' = b_0 \exp(Q + Zwq) / RT = b \exp(Zwq / RT) \quad (2.8)$$

rearranging these equations

$$bC = q / (1 - q) \exp(-Zwq / RT) \quad (2.9)$$

this is equivalent to the Frumkin or Volmer (Damaskin et al. 1971) expression

$$bC = q / (1 - q) \exp(-2a) \quad (2.10)$$

therefore, $a = z\omega/2RT$, where $a$ is the interaction energy between adsorbed molecules.

The adsorption of organic substances may yield sigmoid or logarithmic isotherms (Giles et al. 1974a), depending on the interaction between the adsorbed particles being predominantly attractive or repulsive.

The forces responsible for solute adsorption may be chemical or physico-chemical and physical or mechanical (Giles 1982). The chemical or physicochemical forces may be listed as covalent bonding; hydrogen bonds and other polar forces; ion exchange attraction; van der Waals forces; and hydrophobic forces. The physical or mechanical forces are: restriction of movement of solute aggregates in micropores and facilitation of entry of solute by the progressive breakdown of the substrate structure.
Solid Surface Interaction

Figure 2.1a illustrates the classical model of molecules associating at the surface of particles. However, it has long been known that surfaces exhibit roughness and asperities that contribute fundamentally to interactions. Figure 2.1b illustrates a more realistic depiction of the surface of a crystalline particle with areas of higher energy density (Hickey et al. 2007). The potential sources of these higher energy density sites may be the presence of amorphous material, moisture, impurities, electrical charge, and sites for mechanical interlocking. It should be evident from these images that depending on the scale of the means of measuring the surface, a realistic surface may seem bigger or smaller based on the ability to penetrate into the small invaginations in the surface. Driven by knowledge of the true nature of surfaces, morphologic approaches have included Fourier analysis and fractal analysis to

Fig. 2.1  (a) Classical model of surface adsorption phenomenon (small circles represent gas or solute molecules impinging at the surface of an idealized, spherical particle) and (b) schematic of particle surface depicting surface asperities (irregularity) and high energy density sites (indicated by hatched hemispherical areas)
approximate surfaces (Kaye 1993; Beddow 1976; Meloy 1977). Briefly, Fourier analysis involves describing a particle surface by assigning a center to the image of the particle and then using polar coordinates to plot variations of the surface on a linear scale (Luerkens 1991). This image can then be subjected to harmonic analysis from which a Fourier series and the respective coordinates each corresponding with a shape, sphericity, triangularity, etc., can be derived to describe the particle based on its surface. The principle of fractal geometry is that when periphery of an object, such as a particle, is measured at different scales of scrutiny, with yardsticks of different length, it appears to be larger as the scale is smaller (Kaye 1989). There is a linear relationship between the exponent of the estimate of periphery and that of the dimension of the scale being employed. From the slope of this line the so-called fractal dimension can be derived. This is often thought of as representing dimensions between 1 and 2, for flat, 2D images and between 2 and 3 for 3D images.

Beyond the morphology of individual particles powders, composed of numerous particles, have been probed with molecules, each with a radius that establishes the scale of scrutiny to derive fractal dimensions (Avnir et al. 1984; Pfeifer and Avnir 1983; Avnir and Farin 1983; Avnir 1989). These experiments which employ inert gas molecules of different dimensions have been extended to consider the functional status of the surface. It could be argued that the use of the Scatchard interpretation of a Langmuirian adsorption but based on the specific binding capacity of proteins was an early example of a functional surface interaction (Xu et al. 2010). However, techniques such as inverse phase gas chromatography (Telko and Hickey 2007) and atomic force microscopy (Danesh et al. 2000) allow direct probing of surface features with respect to the force or energy associated with potential molecular interaction.

The recent extension of this molecule–particle interaction to particle–particle interactions may lead to greater understanding of the complex interactions of particles in pharmaceutical formulation which will be take up in great detail in Sect. 3.
Summary

Chemical reactions are typified by apparently predictable behavior which masks a complex range of underpinning states. Interest in this subject is beginning to emerge in chemistry and may ultimately be useful in considering subtleties of chemical stability of pharmaceuticals (Carstensen 1990). The nature of surfaces and their potential to interact with molecules or particles stems from a long and extensive history of attempts to model nonlinear phenomena in surface and interfacial chemistry. The strong foundation in this field gives a major opportunity for new developments as complex interpretations are employed to elucidate surface phenomena. The implications of greater understanding in this area with respect to important pharmaceutical phenomena such as deaggregation, dissolution, diffusion, and ultimately drug availability are taken up in the next section.

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