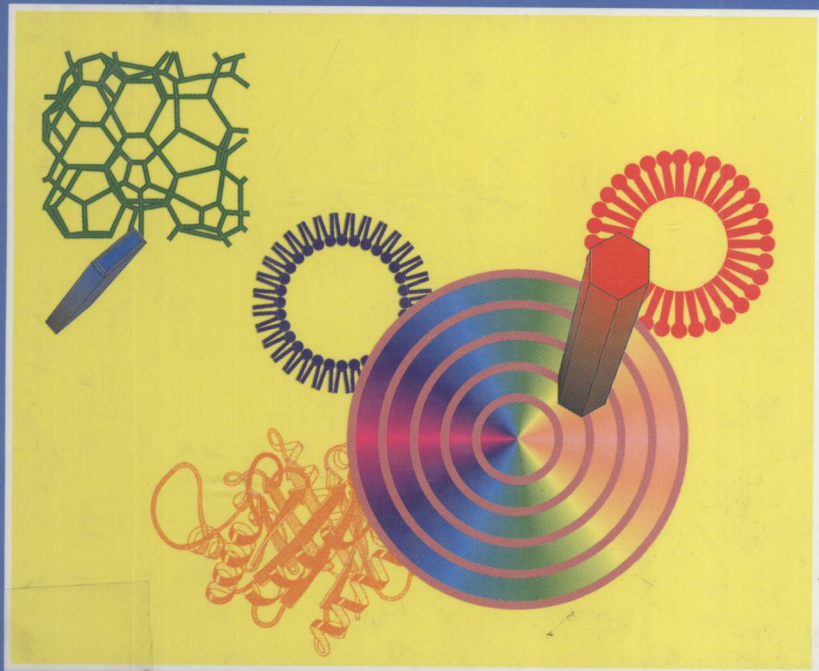Hans Mollet, Arnold Grubenmann

Formulation Technology

Emulsions, Suspensions, Solid Forms

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Translated by H. R. Payne

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Formulation Technology

⊗WILEY-VCH

① Emulsions.

② Suspensions (chemistry)

③

Preface

What do we mean by the phrase "*formulation technology*"? The word "*formulation*" has long been established as a synonym for "*recipe*". For many people, this term suggests something of a black art rather than an exact scientific discipline. The source of the oldest formulations is probably pharmacy, in which the skills associated with the development and execution of recipes has grown into an independent discipline, galenics. In other fields of chemistry, particularly industrial chemistry, formulations are amongst a company's most closely guarded trade secrets on account of their often considerable economic value. With a few exceptions, such as for pigments, foodstuffs, cosmetics, and agrochemicals, there is no general work covering the whole area of formulation technology; formulation chemists are forced to rely on widely scattered, although admittedly numerous, references in the most varied journals.

A large proportion of chemical substances, whether inorganic or organic, natural or synthetic, must be refined and formulated before they can be used in medicine, industry, agriculture, foods, cosmetics, and so on. Often this is merely a question of grinding and mixing; pure dyes and pharmaceuticals must also be combined with suitable auxiliary substances simply to permit reasonable dosage. However, a recipe alone is not usually sufficient; in addition, knowledge of the necessary raw materials, of their preparation, and of the application is required. Most important of all is the processing of the formulation into its optimal form for trade and for use. Here we should mention freeflowing, dust-free powders of optimal particle size, agglomerates and granulates, stable concentrated solutions and suspensions, emulsions, microemulsions, instant products, slow-release preparations, microcapsules, liposomes, and so on.

It has long been recognized that the application properties of a substance to be formulated can be improved by suitable measures, such as an increase in solubility, solubilization, division of solids into a colloidal form, agglomeration of the substance to be formulated, above all the use of efficient tensides – all these create numerous effects, improvements, and new possibilities for use in the field of formulation. Often the competitiveness in the marketplace of a synthetic product that is excellent of itself is determined by its commercial formulation, as has been demonstrated by vitamins formulated to flow freely or dust-free dyestuffs.

The art of formulation is thus a scientific discipline, with a pronounced inter-disciplinary character centered around physics, physical chemistry, colloid and interface chemistry, analysis, and not least process technology. Modern commercial forms and forms for application rely on many methods from process technology and on advanced modern analytical techniques. Thus the discipline of formulation has developed into formulation technology, which rests on solid scientific supports, and in which empiricism is increasingly being replaced by scientific criteria. This is not to say that creativity and inventiveness should lose their importance in the solution of problems and the creation of new or better commercial formulations.

A huge store of empirical knowledge is available to formulation chemists; this is useful, but not sufficient. The ability to diagnose current problems and, on the basis of accumulated knowledge, to relate them to solutions found earlier does indeed result in progress, but is not enough for a rapid and certain solution of problems of formulation. A more advanced method is the empirical deduction of relationships between the composition of a formulation and its properties and the expression of these in equations that correlate with the experimental data. Various computer-aided techniques common for correlation analysis are used for this purpose. Basically, these involve empirical trial-and-error schemes and regression methods. This methodology is very efficient if all the components of the formulation have already been selected by experiment or from practical requirements.

However, the soundest scientific approach is the understanding of the relationships between the components of a formulation and its properties (such as the stability of an emulsion or a suspension) in terms of molecular theory. Nowadays this is possible in simple cases, but not for complex systems. Simplifying assumptions have to be made, thus weakening the connection to the theory. So, for the time being, we cannot get by without empiricism. Nevertheless, awareness of the theoretical basis of colloid and surface chemistry, such as DLVO theory in the case of the stability of dispersions, may protect us from attempting solutions forbidden by theory. Whether formulation chemists are accustomed to approaching problems from a purely empirical angle or to seeking correlations between the components of a formulation and its application properties with the assistance of statistical computing methods, a knowledge of the physicochemical and technical basics relevant to formulation technology will be useful to them in making progress.

The present monograph is intended to fill the publication gap concerning the manufacture of optimized formulations, commercial forms, and forms for application. The aim of the book is a holistic treatment of the separate disciplines that play a role in the formulation of an active ingredient into its commercial form, in particular of colloid and surface chemistry and process technology, and the establishment of a coherent, interdisciplinary theory of formulation technology.

This general treatment of the subject, independent of individual products and of substance-specific formulation problems, makes up the heart of the book. Alongside it, the practical aspects of selected individual topics are summarized in order to provide an overview of the state of the art and the problems existing in these areas, such as pharmaceutical technology, dyestuffs and pigments, and cosmetics.

Finally, we wish to thank the many colleagues who have aided us in the realization of this project. First and foremost amongst these is Professor H. F. Eicke of Basel University, to whom we are indebted for his knowledgeable assistance and many suggestions and corrections. Amongst the many experts from industry who helped us with valuable contributions, we would like to single out Dr. U. Glor (Novartis), Dr. R. Jeanneret, Dr. E. Neuenschwander, and Dr. U. Strahm (Ciba SC), and Mr. A. Schrenk (Nestlé).

Thanks are also due to the publishers and authors who have allowed us to reproduce figures and tables. The references name the relevant sources and can be found in the literature sections of the individual chapters.

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Contents

1 Colloids, Phases, Interfaces

1.1 General Remarks

Colloid chemistry deals with systems that contain either large molecules or very small particles. With respect to particle size, they lie between solutions and coarse particulate matter; the size range is roughly 1–1000 nm, that is, 10 Å to 1 μm. This corresponds to 10^3–10^9 atoms per molecule or particle.

Interface chemistry is concerned with the phenomena and processes of heterogeneous systems, in which surface phenomena play a major role. Examples include adsorption and desorption, precipitation, crystallization, dispersion, flocculation, coagulation, wetting, formation and disruption of emulsions and foams, cleaning, lubrication, and corrosion. The specific characteristics of the interfaces which are important in such phenomena are controlled by electrochemical properties (charges) or by the use of certain organic compounds called tensides (also known as detergents or surfactants), which contain both polar and nonpolar groups in each molecule.

Table 1.1. Examples of colloidal states (s = solid, l = liquid, g = gas).

s/s	**s/l**	**s/g**
solid pharmaceutical preparations	dispersions suspensions, lime slurries	aerosols smoke
reinforced plastics	latex	
magnetic tape		
l/s	**l/l**	**l/g**
gels	emulsions	aerosols
gel permeation chromato- graphy separating gels	creams milk	fog spray
g/s	**g/l**	**g/g**
foam products	foam	–
aerogels	foam rubber	
foamed concrete, meerschaum mineral	whipped cream	

Examples of colloidal states are given in Table 1.1. This area of chemistry contrasts with the field of homogeneous-phase chemistry, which comprises the major part of synthetic chemistry. The usual training of a chemist concentrates on the homogeneous phase, and chemistry in the heterogeneous phase, interface chemistry, does not receive the attention that its great technical and biological importance merits. Exceptions that

attract notice at the level of an undergraduate course in chemistry are, for example, adsorption processes and surface tension. It is already 90 years since W. Ostwald described colloids as a "world of neglected dimensions". Very little has changed since then; colloid and interface chemistry remain neglected disciplines in education. We intend to reduce the level of such neglect with this book; we hope that the "art" of formulation, as it once was, can thus be developed into *formulation technology*, with a scientific basis and a pronounced interdisciplinary character, the emphasis being on chemistry, physical chemistry, especially interface chemistry, and process technology.

A leading interface chemist, Pradip K. Mookerjee, once wrote:
"No school teaches about mixing things together so that they do what you want and don't react with each other."

1.2 Physical Behavior of Atoms and Molecules inside Phases and at Interfaces and Surfaces

The three phases – gas, liquid, and solid – are depicted schematically in Figure 1.1.
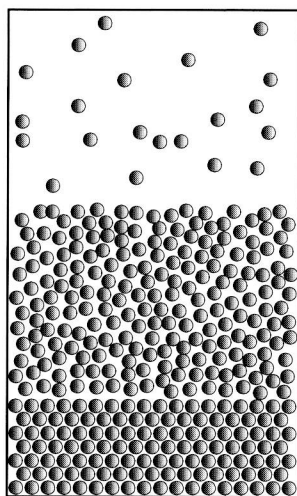
Gas: The molecules are distant from one another; little or no attraction. High mobility results in elastic collisions.

Liquid: Molecules in constant motion. Cohesive forces between the molecules influence their motion. Only in special cases are these forces sufficient to form areas of local order.

Solid: Strong forces hold the molecules in a regular arrangement.

Figure 1.1. The three phases: gas, liquid, and solid.

For a solid or a liquid to hold together, there must be strong attractive forces between its atoms. An atom inside a phase is completely surrounded by other atoms and is in a state of dynamic equilibrium (Figure 1.2).
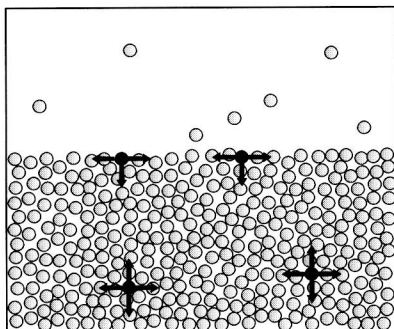
Figure 1.2. Surface forces and internal forces in a liquid.

The atoms at the surface are in a very different situation. Because of the equilibrating forces in the outer sphere, they are in a state of *surface tension*. Molecules at the surface have fewer neighbors, that is, fewer intermolecular interactions compared with the molecules in the bulk of the liquid. This leads to an attractive force normal to the surface acting to pull the surface molecules into the liquid. The surface tension γ is defined as the force necessary to counteract exactly this inward force, measured in mN (milliNewton) acting on a line of 1 m length parallel to the surface (formerly dyn acting on a line of 1 cm), and thus has the units mN/m.

$$\left[\frac{mN}{m}\right] = \left[\frac{dyn}{cm}\right] \tag{1.1}$$

The *free surface energy* of a liquid is defined as the work necessary to increase the surface by 1 cm^2; units milliJoule/m^2.

$$\left[\frac{mJ}{m^2}\right] = \left[\frac{erg}{cm^2}\right] \quad \text{(dimensionally equivalent to: } \left[\frac{mN}{m}\right] = \left[\frac{dyn}{cm}\right] \text{)} \tag{1.2}$$

(Note that m can stand for milli and for meter.)

The units of surface tension and free surface energy are therefore dimensionally equivalent! The surface energy is equal to the work that is required to bring atoms or molecules out of the interior of a liquid to the surface. Accordingly, the surface tends to contract; thus droplets form (smallest possible surface).

When two immiscible liquids are in contact, the forces of attraction acting on a molecule at the interface will be somewhat different than at a surface. There are interactions between the differing molecules at the interface (van der Waals forces; see below). Often, the interfacial tension γ_{L1L2} is somewhere between the surface tensions γ_{L1} and γ_{L2} of the two individual liquids (in contrast, the dispersion fraction γ_d and the polar fraction γ_p are always between the two individual contributions; see Section 1.7.2).

Example: The interfacial tension between hexane and water (γ_{L1L2}) lies between the surface tension of hexane ($\gamma_{L2} = 18.43$ mN/m) and that of water ($\gamma_{L1} = 72.79$ mN/m): $\gamma_{L1L2} = 51.10$ mN/m.

Table 1.2. Surface tension and interfacial tension with water of liquids at 20°C [mN/m]; water: γ_{L1} (from [1]).

Liquid	γ_{L2}	γ_{L1L2}	Liquid	γ_{L2}	γ_{L1L2}
water	72.75 (γ_{L1})	–	ethanol	22.3	–
benzene	28.88	5.0	*n*-octanol	27.5	8.5
acetone	27.6	–	*n*-hexane	18.4	51.1
acetic acid	23.7	–	*n*-octane	21.8	50.8
CCl$_4$	26.8	45.1	mercury	485	375

The attractive force between molecules in the bulk of the liquid is known as the *internal pressure* or the *cohesion energy* ΔE_v. The cohesion energy density $\Delta E_v/V$ is an important quantity; it is defined in Equation 1.3:

$$\frac{\Delta E_V}{V} = \frac{\Delta H_V - RT}{V} = \delta^2 \tag{1.3}$$

ΔH_v: enthalpy of vaporization [J·mol^{-1}]
V: molar volume [m^3·mol^{-1}]
R: gas constant = 8.314 J·K^{-1}·mol^{-1}
T: absolute temperature [K]

A quantity of great practical use is the solubility parameter $\delta = \sqrt{\delta^2}$ (cf. Chapter 8, Solubility Parameters). The quantities necessary for its calculation, ΔH and V, are easily obtained from reference books. The mutual solubility of two components can be determined from δ; the closer their δ values, the greater their mutual solubility.

Example: phenanthrene $\delta = 20.0$ MPa$^{1/2}$ [1 MPa$^{1/2} = (10^6$ N·m$^{-2})^{1/2}$]
                   carbon disulfide $\delta = 20.5$ MPa$^{1/2}$
                   n-hexane $\delta = 14.9$ MPa$^{1/2}$

Phenanthrene is therefore more soluble in carbon disulfide than in *n*-hexane. This rule applies only to nonpolar substances; for polar substances, see for example references [2] and [3].

1.2.1 Disperse Systems

Simple *colloidal dispersions* are two-phase systems consisting of a disperse phase (for example a powder) finely distributed in a dispersion medium. *Sols* and *emulsions* are the most important types of colloidal dispersions. The fine distributions of solids in a liquid formerly known as sols (the expression sol was used to distinguish colloidal from macroscopic suspensions) are now called suspensions or simply dispersions. Unlike these, emulsions consist of liquid droplets distributed in an immiscible liquid dispersion medium.

The classification of dispersions created by W. Ostwald over 80 years ago is still valid today (Figure 1.3). In principal there is always an inner, disperse or discontinuous phase that is immiscible with an outer, continuous or homogeneous phase.

disperse phase	continuous phase		
	gaseous	liquid	solid
gaseous	GAS	GAS/LIQUID foam	GAS/SOLID solid foam
liquid	LIQUID/GAS aerosol, fog	LIQUID/LIQUID emulsion	LIQUID/SOLID slurry
solid	SOLID/GAS smoke	SOLID/LIQUID suspension	SOLID/SOLID alloy

Figure 1.3. Classification of disperse systems according to W. Ostwald.

Table 1.3, which should be read as supplementary to Figure 1.3, lists a selection of typical colloidal systems.

Table 1.3. Some typical colloidal systems (from reference [4]).

Examples	Class	Disperse phase	Continuous phase
Disperse systems			
fog, spray, vapor, tobacco smoke, aerosol sprays, flue gases	liquid or solid aerosols	liquid or solid	gas
milk, butter, mayonnaise, asphalt, cosmetic creams	emulsions	liquid	liquid
inorganic colloids (gold, silver iodide, sulfur, metallic hydroxides)	sols or colloidal suspensions	solid	liquid
clay, mud, toothpaste	slurry	solid	liquid
opal, pearls, colored glass, pigmented plastics	solid dispersions	solid	solid
foam	liquid foams	gas	liquid
meerschaum mineral, foamed plastics	solid foams	gas	solid
Macromolecular colloids			
jelly, glue	gel	macromolecules	solvent
Association colloids			
soap/water, detergent/water	–	micelles	solvent
Biocolloids			
blood	–	cells	serum
Triphasic colloidal systems			
oil-bearing rocks	porous stone	oil	water/stone
mineral flotation	mineral	water	air
double emulsions	–	aqueous phase	water

Table 1.4 distinguishes between particle sizes of the colloidal dispersion state on the one hand and those of smaller molecules and of coarse heterogeneous systems on the other. These size ranges are only guidelines; in some special cases, such as suspensions and emulsions, particles of diameter greater than 1 μm are generally present. The threshold at which colloidal behavior becomes the behavior of a molecular solution lies at about 1 nm.