Physicochemical Principles Third Edition of Pharmacy

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PHYSICOCHEMICAL PRINCIPLES OF PHARMACY

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THIRD EDITION





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Preface

Textbooks are never completed, only abandoned, probably by readers as well as by authors. We have been intent for some time on revising the second edition of this book, published in 1988, but the work of revision took longer than anticipated. Now we are pleased that this new edition has been completed, rewritten and updated but retaining the essential character of the book which has proved successful since the book was first published 17 years ago. We have again used exclusively pharmaceutical examples to illustrate the physical chemistry which is the basis of the book.

Some material has been removed and new material added. There has been a reintroduction of some of the thermodynamics lost from the second edition. A general introduction takes the reader into the subject more gently than before, and there is a new chapter on peptides and proteins as pharmaceuticals. Solutions, the solid state and the gaseous state are discussed (the latter particularly with pressurised aerosols in mind), while ionization of drugs is considered at length as it affects so many properties of drugs in solution, as well as their absorption. Surface chemistry retains its place and the treatment of colloidal systems is enhanced with further discussion of liposomes and other colloidal carriers now used more widely in therapeutics.

The properties of soluble, insoluble and dispersible natural and synthetic polymers – elements of many delivery systems – are described. Each route used for delivering medicines is treated by considering the physiology of the route and the conditions of the route that affect the drug and dosage form, with a brief description of the factors affecting the performance of each type of delivery device. Wherever possible calculations and worked examples are included to encourage a better understanding of the equations described. We hope that the book will continue to be useful not only in undergraduate and postgraduate courses in pharmacy but those in the pharmaceutical sciences and related studies too.

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February 1998

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Mrs Maureen Lucas transcribed the text of the second edition of the book on to disk to make the task of revision easier and Mrs Gillian Patterson and Miss Barbara Grant made the many revisions that the text has gone through since work on the third edition was begun, interpreting the additions, deletions and comments. Over the years the book has been in existence, many colleagues have offered both favourable and critical comments that have spurred us on to revise the book. We thank them and encourage them also to write to us with any observations on how the present edition can be further improved.

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Introduction

Pharmacy has at its core the discipline of pharmaceutics, which is the study of drug formulations and the processes by which these are designed, manufactured and delivered to the body. In brief, the subject is about the conversion of drug substances into the medicines that patients can take or have administered to them. There are other vital component disciplines: the way drugs act in the body is the domain of pharmacology; the science of drug design and analysis is that of medicinal or pharmaceutical chemistry. Of course, there should be no clear dividing line between these subject areas. One cannot design formulations without a comprehensive knowledge of the chemistry of the drug substance, nor study how medicines behave in the laboratory or in patients without good analytical methodology. An understanding of the pharmacology of a drug is crucial not only to the proper design of an optimal delivery system, but also to the practice of pharmacy. There is certainly no dividing line in the sciences underlying these subjects, and the physical chemistry that operates in the formulation laboratory is the same that holds within the human body. The forces acting between suspension particles and the walls of the container are the same as those acting on bacteria adsorbing on to a catheter or the intestinal wall. The boundary conditions might differ, but the principles are the same. And understanding what keeps drugs in solution in an infusion fluid allows us to predict the extent to which a drug might precipitate in the renal tubules or in the blood after injection. Studying the solid-state properties of drugs should not only provide vital information for formulators but might also help us to understand the formation of crystals in joints or in the kidneys, and how to dissolve them or prevent them. There are many other examples in this book.

Physical chemistry and pharmacy

Undergraduates beginning their study of pharmacy have often been surprised at the amount of physical chemistry they are expected to absorb, when they had expected a more biological flavour to their diet. But the biological processes in the body do not operate and exist in some special non-physical world, although it is true that they are usually more complex than the processes that we control in the test tube. So in this book we not only try to give the physicochemical basis for understanding pharmaceutical formulation and drug delivery but we also stray, as we must, into areas which in the past others would have called pharmaceutical chemistry and pharmacology, biochemistry even. It is so important that the underpinning sciences are used intelligently by pharmacy graduates, and not separated into compartments. Now, it is not always possible to apply precisely the equations in this book to the complex world of multicomponent medicines, especially after their administration, but rigorous physical chemistry is the starting point for quantitative understanding. Equations describing the behaviour of drugs often apply only in extremely dilute solutions, so the caveats in the derivations of equations must be noted, but nevertheless the knowledge of the way in which the solubility of a drug increases or decreases with change in the acidity of the stomach or intestine is a useful beginning in the understanding of the complex process of drug absorption.

Although in the book we have minimised the derivation of equations, the value of appreciating the way in which an equation is derived is that one understands its limitations. Sometimes it is useful to be able to derive an equation from first principles.

2 Introduction

It would be sad if the modern pharmacist was an empiricist at a time when the science of drug development and drug therapy has become much more quantitative and predictable. There is no way that this book is a complete survey of all the physical chemistry underlying pharmacy, but we think we have selected those that are most important in pharmaceutics and biopharmaceutics, without dealing with pharmacokinetics or with many aspects of pharmaceutical production, which are covered in specialised textbooks.

Adjuvants or excipients

The drug molecule is central, whether we are dealing with its formulation, its delivery, its analysis or its activity. The formulation itself might be simply a means of delivering the dose conveniently to the patient, or it might have an influence on the site of delivery or the time course of action. Therefore it is vital that we understand the physical chemistry of materials used in formulations to control the rate of release or to solubilise insoluble molecules, to stabilise or to suspend or to form microspheres and microcapsules. These so-called adjuvants or excipients are generally regarded to be inert, but few substances are totally inert and some, such as certain surfactants, may be biologically active and indeed harmful if used inappropriately. Rational formulation requires a firm understanding of the physical mode of action of excipients in formulations.

Arrangement of the book

A brief explanation of how the book is arranged may be helpful.

In the first few chapters we examine the properties of drugs in the solid state and in solution. Gases also are treated as they are important in the design and use of therapeutic pressurised aerosols, which until recently have been derived from chlorinated fluorocarbons, but in the future will be based on volatile fluorinated hydrocarbons.

Special classes of materials are considered in separate chapters. Colloidal systems (which are those comprising particulates below and around one micrometre in diameter), including many suspensions and emulsions, are experiencing a renaissance in pharmacy because of the use of microspheres and nanospheres in drug targeting and controlled drug delivery. These have a chapter devoted to them. Polymers and macromolecules used widely in pharmaceutical formulation as excipients in many forms, as hydrogels, lipogels, viscous solutions and solid matrices or membranes are treated in one chapter; some drugs are macromolecules and are discussed in this chapter. Proteins and peptides have a new chapter which deals with this growing field of study and the attendant pharmaceutical challenges posed by these substances.

Surface activity is a phenomenon that has widespread consequences. Surface-active substances are those which adsorb at surfaces and lower surface tension; these so-called surfactant materials have a wide applicability in pharmacy, as in micellar form they can solubilise water-insoluble drugs and many at low concentrations can increase membrane permeability and aid the transport of drugs across biological barriers. Many drugs have surface-active properties and these might have consequences for their activity and behaviour. The topic is summarised in a chapter on surface activity and surfactants.

Crucial to the whole subject is the process of drug absorption, and how the physical properties of the drug and its formulation can influence the rate and extent and sometimes site of absorption. The oral route and the many alternative routes to achieving systemic levels of a drug are reviewed in a chapter which deals with the basics of the absorption process common to all routes of delivery, and then with the individual

routes of administration and the way in which the physiology of the route influences the design of formulations and the behaviour of the drugs.

Drugs are frequently given together, and some interact with clinically important consequences. Often these interactions are pharmacological but some have a basis in physical chemistry. Interactions and incompatibilities might arise from electrostatic interactions between charged drugs, or from complexation between drugs and ions or drugs and polymers, and these and a variety of other interactions are given a basic treatment in the book.

It is not always possible to predict the behaviour of drugs and formulations in the complicated environments in which they find themselves, but this should not deter us from at least attempting to rationalise events once they have become known; in this way our predictive powers will be honed, and allow us to prevent adverse events in the future. Some unwanted effects are due to the degradation of drugs and drug formulations; the examination of stability is an important part of assessing the suitability of formulations. This requires a good understanding of the chemistry of the drug substance and reaction kinetics. This too is the subject of a chapter.

Objective of this book

Almost any of the topics discussed could be the subject of a complete textbook in its own right. The objective of this textbook is to present sufficient of the physical chemistry in context to illustrate the many and varied areas of pharmacy where the subject

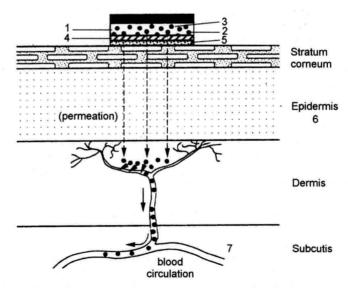


Figure 1 A typical transdermal patch system designed to deliver drug into the systemic circulation by way of the skin: (1) a reservoir containing the drug adsorbed to (2) lactose particles in (3) an oil, (4) the rate-controlling membrane, a copolymer whose thickness and composition is altered to achieve the desired rate of transport of the drug, and (5) the adhesive layer, also a polymer, although liquid, which attaches the patch to the skin; the basic structure of the skin (6) illustrates the routes of penetration of the drug through this barrier layer into the systemic circulation via the capillary blood supply (7).

4 Introduction

impinges. If we wish to understand what makes modern delivery systems work at more than a superficial level, we would advocate close reading of all the pharmaceutical sciences, of which the topic of physical chemistry forms one important part. Examination of just one such delivery system (Figure 1), a transdermal patch, can bring into focus the diversity of physical phenomena that are involved in the design, use and action of delivery systems. One could list these as adsorption, the stability of suspensions, molecular transport through polymeric membranes, adhesion, the interaction of drugs with polymers, the physicochemical properties of the skin and the diffusional characteristics of drugs in the skin, including crossing the capillary membrane into the blood.

Perhaps enough to convince us that reading the rest of the book is necessary?

1 Properties of the Solid State

The physical properties of the solid state (crystals and powders) of both drugs and pharmaceutical excipients are of interest because they can affect both the production of dosage forms and the biological behaviour of the finished product. Powders, as Pilpel¹ reminds us 'can float like a gas or flow like a solid' but when compressed can support a weight. Fine powders dispersed in liquids are used in injections and aerosol formulations. Both liquid and dry powder aerosols are available and discussed in Chapter 9. Some properties of compacted solids are dealt with in Chapter 6 but in the present chapter we will concentrate on the form and particle size of crystalline (and amorphous) drugs and the effect of these characteristics on drug behaviour, especially on drug dissolution and bioavailability.

The nature of the crystalline form of a drug substance may affect its stability in the solid state, its flow properties and its biological availability, the last mainly through the effect of the crystal size or nature on dissolution rate. It is with this topic that we start and we shall then consider other properties of the solid state important in production and formulation.

1.1 Crystal structure

Crystals contain highly ordered arrays of molecules and atoms held together by non-covalent interactions. We can consider as a simple example the unit cell of an inorganic compound, sodium chloride. In Figure 1.1 we see the ordered arrangement of Cl⁻ ions (large spheres) and Na⁺ ions (small dark spheres) which makes up the sodium chloride crystal structure. We can draw a square on one side connecting the sodium ions. Similar squares could be drawn on all the sides to form a cubic repeating unit which we call the unit cell. Within a specific crystal, each unit cell is the same size and contains the same number of molecules or ions arranged in the same way. We usually find it most convenient to think of the atoms or molecules as point sources and the crystal as a three-dimensional array of these points. We refer to this array as the crystal lattice.

For all crystals there are seven basic or primitive unit cells, which are shown in Figure 1.2. We will represent the side lengths as a, b and c and the angles as α (between sides b and c), β (between sides a and c) and γ (between sides a and b). Table 1.1 shows the characteristic side lengths and angles for these primitive unit cells.

The structures of Figure 1.2 have atoms or molecules only at each corner of the unit cell. It is also possible to find unit cells with atoms or molecules also at the centre of the top and bottom faces (end-centred), at the centre of every face (face-centred) or with a single atom in the centre of the crystal (body-centred) as in Figure 1.3.

Note that these variations do not occur with every type of unit cell: we find end-centred monoclinic and orthorhombic, face-centred cubic and orthorhombic, and body-centred, cubic, tetragonal and orthorhombic. Altogether there are, therefore, 14 possible types of unit cell and we call these the *Bravais lattices*. For drugs, however, there are only three common types of unit cell: triclinic, monoclinic and orthorhombic.

We can identify the various planes of a crystal using the system of *Miller indices*. To understand how this system is used let us consider the two-dimensional rectangular lattice formed from unit cells of sides a and b (see Figure 1.4). In the figure we are