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Modern Pharmaceutics

Volume 1
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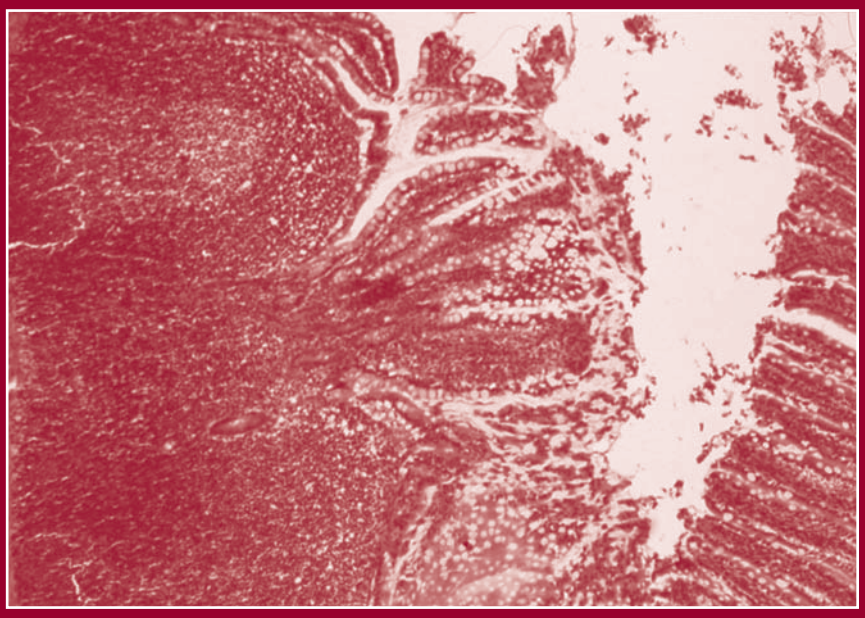

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Modern Pharmaceutics

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FIFTH EDITION

Modern Pharmaceutics

Volume 1
Basic Principles and Systems

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Preface

Modern Pharmaceutics edited by Gilbert Banker and Christopher Rhodes has become a classic in the field. It is well known and has been well received on an international basis, necessitating the publication of this fifth edition. The present editors took on the difficult task of following in the footsteps of the founding editors and their associates with some trepidation. It has been several years since the last edition, and on realizing that Dr. Banker and Dr. Rhodes wanted to pass on the editorship, we accepted the mantle.

Given the passage of time and the growth and change in the field, the book has been divided into two volumes: *Basic Principles and Systems* and *Applications and Advances*. There have been so many exciting developments which impinge on pharmaceutics that it was time to reconsider the content of the book.

Basic Principles and Systems is principally a textbook and advanced reference source of pharmaceutics, which focus on the core of the subject that is key to pharmacy. We define pharmaceutics as encompassing the design, formulation, manufacture, assessment and determination of the quality of pharmaceutical products, and also the quality of effect in patients as the guiding principles. We have therefore continued only with chapters that fall within these criteria.

We have added chapters on in vivo imaging of dosage forms, surfactant systems, and the solid state. In each of these fields there have been significant advances. In vivo imaging is a powerful adjunct to biopharmaceutical studies, providing evidence of the spatial distribution of dose forms, which is vital in site-specific therapies. Surfactant systems, aspects of nanotechnology before this became a vogue, are now used with more sophistication than in the past and provide a wide variety of means of administration of drugs. Techniques for investigating the solid state have become more abundant and shed more light on crystal forms, key to the optimal design of delivery systems and choice of drug salt or form.

This volume opens with an essay on new challenges and paradigms in pharmaceutics and follows with updated chapters on drug absorption, pharmacokinetics, bioavailability, and route of administration, the starting points for the design of systems. Chemical kinetics and drug stability, excipient design and characterization as well as preformulation along with a chapter on optimization techniques further treat these fundamentals of pharmaceutics. Chapters on disperse systems, tablets, hard and soft capsules, and parenteral products complete *Basic Principles and Systems*.

Many of these chapters are written by their original authors. We are grateful for their enterprise, enthusiasm, and time and also thank those authors who wished to stand down. They have allowed the new authors to draw heavily on their original material,

which has eased the process and has allowed us to retain the essence of the earlier volumes.

We thank Sandra Beberman of Informa Healthcare USA for her patience with new editors and her encouragement, and all the staff at Informa Healthcare USA who have nursed these two volumes through to press. We also thank of course all who have devoted time in preparing material for this new edition of *Modern Pharmaceutics*.

We trust that *Basic Principles and Systems* and its companion *Applications and Advances* will satisfy the needs of a wide range of colleagues who have an interest or indeed passion for pharmaceutics. If there are lacunae, perhaps this will lead readers to research these areas.

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Juergen Siepmann

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1

Pharmaceutics: New Challenges, New Paradigms

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INTRODUCTION

Background

The essence of pharmaceutics, as many of the chapters in the two volumes of this book illustrate, is the amalgamation of physical science (physical pharmacy) with aspects of biological science. It is a distinct discipline quite different from biophysics or chemical biology because at its center is not only the dosage form with its active and inactive ingredients but also the behavior of the ensemble in the environment in which these medicines are used, generally in human subjects. Pharmaceutics has existed as a discipline within pharmacy and the pharmaceutical sciences for a long time. It is difficult to discern the origins of the term, although one can deduce from the evolution of textbooks of pharmaceutics something about its development. From the early days of the 20th century to the mid-1950s, it was concerned primarily with the science and practice of the manufacture of medicines (dosage forms) on small and large scales and the preparation of galenicals. It was viewed sometimes as a discipline without much regard to the fate of the dosage form in vivo. However, this is not really the case. For example, the 1924 edition of Martindale and Wescott's *The Extra Pharmacopeia* (1) discusses enteric coating of tablets to minimize the effects of drugs on the intestinal mucosa in the following words:

> Various substances have been proposed for the coating of pills, tablets and capsules to render them insoluble in the stomach but soluble in the intestines, i.e. on reaching the duodenum. Drugs, for example, which irritate the mucous membrane and the administration of which is liable to induce vomiting, and substances intended to act solely on the intestines and the anthelmintic drugs, have been so given. Keratin, as usually employed, seldom brings about the desired effect.

Here there is clear concern for the usefulness of formulations and the therapeutic consequences of their composition. The use of keratin-coated pills is reported in a Lancet paper in 1893 (2), but the process is accredited to a German, Dr Unna, who first marketed such products (3). There were concerns about the quality of such systems, particularly product ageing, and it is interesting that as early as 1938, an X-ray study was carried out on the disintegration in vivo of keratin-coated systems (4). The first commercial sustained-release preparations emerged in the late 1940s with the Spansule™, which contained wax-coated beads with different release properties in a soluble capsule, thus controlling release of the drug in the GI tract.

The term *biopharmaceutics* was an invention of the 1960s. The nature of the dosage form was from then on inextricably linked with its performance in patients. Microencapsulation of drugs, encouraged by the National Cash Register Company (NCR) patents on carbonless copy paper at the time (5), was adapted to the development of controlled- or sustained-release products, and this has more recently evolved into nanotechnological approaches. Nanotechnology began in the pharmaceutical domain, much before the current vogue for all things "nano," with Peter Speiser and his coworkers in the 1970s in Zurich developing "nanoparts" and nanocapsules (6). Pharmaceutical nanotechnology, therefore, is not as new as some of its proponents would have us to believe. Table 1 is a brief summary of just some of the key events in pharmaceutical technology.

Table 1 Key Development of Controlled-Release Systems[a]

Date	System	Remark
1867	Collodion coating	Delayed-release coating for pills
1884	Keratin coating	Enteric-coated pills prepared with keratin (Unna)
1887	Salol coating	As an enteric coating material (Ceppi)
1929	Coacervation	Bungenberg de Jong and Kruyt
1936	Stearic acid coating	Stearic acid and waxes and mixtures for release control
1945	CAP	Cellulose acetate phthalate as enteric coating material
1945	Spansule™	Wax-coated and uncoated drug beads in a capsule (SKF)
1950	Lontab™	Lontab tablets (Ciba)
1953	Microencapsulation	NCR patent for carbonless copy paper
1959	Duplex™	Film-coated tablet between the core and external layer
1959	Duretter™	Plastic matrix dosage forms (Durules)
1962	Liposomes	Bangham's discovery
1973	Nanoparticles	Nanoencapsulation (Speiser et al., ETH Zurich)
1974	Ocusert™	Delivery to conjunctival sac (Alza)
1975	Silicone implants	Silicone implants for slow release (Folkman)
1975	Oros™	Oral osmotic pump (Alza)
1979	Transdermal patch	Scopolamine patch approved by the FDA
1981	Zoladex™	Poly(lactide) implants for polypeptide delivery (ICI)
1982	Dendrimers	Synthesized by Tomalia
1988	Stealth liposomes	Gabizon and Papahadjopolous; Allen et al., 1989
1989	Lupron Depot™	TAP launches leuprorelin PLGA microsphere SR product
1990	Liposome	First liposome product to gain approval (Ireland)
1994	Stealth liposome	LTI seeks approval of doxorubicin stealth liposome (Caelyx)
2003	Drug-eluting stents	First FDA approval (Cypher™ sirolimus)
2006	Dendrimer product	First dendrimer pharmaceutical (VivaGel™ Star Pharma)

[a]Dates are approximate.

Abbreviations: CAP, Cellulose acetate phthalate; SKF, SmithKline French; NCR, National Cash register Company; ICI, Imperial Chemical Industries; TAP, Takeda Abbot Pharmaceutical Company; SR, Sustained release; LTI, Liposome Technology Incorporated.

Means for the production and the design of refined controlled-release systems was advanced by the development of biodegradable polymers, the three archetypal polymers being poly(lactic acid–glycolic acid) (PLGA), poly(lactic acid) (PLA), and poly (glycolic acid) (PGA). Now there are many other polymers and copolymers that act as carriers for drugs. Lipid-based delivery systems, most notably liposomes, discovered by Bangham in the 1960s, led to the marketing, some 20 to 25 years later, of liposome-based doxorubicin and amphotericin products. The list of liposomal products is now impressive, but the gestation time was long as more was learned about the behavior of dosage forms in the body and about their stability, their interaction with proteins, uptake by the reticuloendothelial system, and extravasation, not to mention diffusion and uptake into diseased sites. Dendrimers, spherical or starburst polymers first synthesized by Tomalia and coworkers (7) in the early 1980s, are also now finding their niche along with a variety of other nanoconstructs, but the period from the first concept to the clinic is still proving tortuous. Many polymer micro- and nanoparticles have random polymeric internal and surface structures. So, in theory, the ability to synthesize dendrimers with their precise architectures and controlled arrangement of surface groups allows the practice of true molecular pharmaceutics, with precisely positioned ligands and other agents.

In a relatively short period of time, pharmaceutics has moved from the macroscopic through the microscopic to the nanoscopic domain and from the more empiric to the more quantitative. It has long been intertwined with colloid science typically in relation to the formulation of micellar-solubilized products and the stabilization of suspensions and emulsions; the application of colloid science to nanosystems is more vital than ever, as discussed in chapter 12, volume 2.

In many experimental systems, for example, with dendrimers (2.5 to 10 nm in diameter) and carbon nanotubes as vehicles for delivery, the drug has dimensions in the same range as these putative carriers. This is an inevitable consequence of the fact that not only have such dosage forms become smaller but also the average size of therapeutic molecules has grown with the use of more biologicals. New or reinvented approaches to the interactions between a carrier and a drug need to be applied. A deal of effort has been addressed to the topic of carrier-mediated drug targeting, perhaps at the expense of the physical, pharmaceutical, and technological aspects of the task, but there is a growing realization that the neglect of the fundamental physical aspects of pharmaceutics is a mistake. Particulate delivery systems once administered are placed in new thermodynamic situations, which we must model and predict and thus design products that are colloidally stable yet labile enough to deliver their loads and be excreted.

NEW PARADIGMS

According to one dictionary, a paradigm is “a philosophical and theoretical framework of a scientific school of discipline within which theories, laws and generalizations and the experiments performed in support of them are formulated,” but a simpler definition of “a generally accepted perspective of a particular discipline at a given time” is apposite too. Pharmaceutics is espousing new paradigms. The concept of the carrier system, traditionally tablets, capsules, suppositories, or the like with the drug internalized, has changed as the actives such as DNA and other macromolecules may not be internalized but may be intertwined with the complexing molecules, as hinted above, to form the delivery vector, usually leading to condensation. Active molecules may be adsorbed to the

surface of nanoparticles. Products such as drug-releasing coated stents present new challenges, not least in quality control.

A More Predictive Science?

Reflecting on past decades of research in pharmaceutics, drug delivery, and drug targeting, one can detect a certain lack of an overall ability to predict the ultimate behavior of systems, not only but especially at the early formulation stage, and with behavior in vivo. Is pharmaceutics still too empirical, a shadow that has held the subject back for many years? There has been success in drug solubility prediction, as the work of Peterson (8) and others (9) has demonstrated, but in a related field, that of the micellar solubilization of drugs by surfactants, in spite of decades of research, it is not an easy task to predict the solubilization potential of a given surfactant system for a given drug molecule. In the same way, more recent research in gene delivery employing cationic complexing polymers, lipids or dendrimers to condense the DNA, has led to transfection of cells in culture with varying degrees of success, but there is no consensus yet as to the optimum size, shape, charge, or other characteristics of the gene construct to achieve maximal cell penetration, nor has it been possible to predict a priori the effectiveness of a given construct on a particular cell line.

Pharmaceutics has come a long way since its focus mainly on physical systems, but there must be a fresh look at the type of research problems that are tackled if we are to achieve a more predictive science. Not only this, but it seems a long time since new equations entered pharmaceutics' basic pantheon. It is several decades since Takeru Higuchi developed the equations for the diffusion of drugs in, and release from, complex systems (10). There is a need to explore new areas of pharmaceutics, to explain phenomena that otherwise will not be treated theoretically. Issues of adhesion, including mucoadhesion, film coating, tack, and cracking in films, are but some of the areas that require a greater theoretical approach after considerable amounts of phenomenological research has been published.

The study of the behavior of dosage forms in vivo, not least of nanosystems, is desperately short of a comprehensive theoretical base, which will relate properties, both physical and biological, not only to the size of particulate systems but also to their surface characteristics. On the other hand, while pharmaceutics must continue to reinvent itself, all those involved in medicines development and drug delivery and targeting must be acquainted and absorb the canon of pharmaceutics that already exists. This centers around the quality, pharmacy, and standards of products, modes of production and sterilization and characterization, their reproducibility, their quality (both intrinsic and quality related to activity), as well as studies of the potential of products themselves to cause harm. All this is a unified holistic approach. It is little use concentrating on the fabrication of physical devices if these are not able to be manufactured, or are not stable and not safe. This must be balanced by the imperative to carry out research that explores new materials and ideas whether or not we have all the requisite information that might be required ultimately for their conversion to dosage forms.

In drug targeting, much effort goes into the design of nanoparticles (although here again the approach is often necessarily empirical when there should be a more comprehensive understanding of, say, drug- or protein-polymer interactions), but little attention is paid, other than in a descriptive sense, to the issues surrounding the flow and movement of nanoparticles toward their distant targets and destinations. The nature of the flow of nanoparticles in vivo has been largely neglected, yet it is a branch of pharmaceutical engineering science. Flow, interactions between particles, and interactions

of particles with blood components, erythrocytes, and proteins must be addressed in a unified manner before there can be any major advance in the predictability or, indeed, the reality of targeting, especially with nanoparticles decorated with ligands intended to interact with epithelial receptors. The flow of asymmetric carbon nanotubes in blood can be predicted to an extent by extant equations linking viscosity to axial ratio, but experimental proof is required.

This introductory chapter explores some areas of pharmaceutics and also the academic and educational aspects of the discipline. If we are to attract the best scientists into the field, the subject must be presented at undergraduate levels in an exciting and relevant manner. It must show the promise of controlling drug and therapeutic agents and the fact that that there is still much to do. Above all, it must demonstrate connections to avoid insularity and isolation as a discipline while remembering its heartland.

Connections

Connections between research in pharmaceutics and education in pharmacy are vital, but so too are the connections not only between the different types of research but also between different disciplines that can underpin pharmaceutics. Perhaps pharmaceutics could benefit from more research for its own sake, with less directed research aimed at the production of marketable dosage forms. Research on phenomena that are interesting in themselves, research into potential situations (what if?), and research into real systems and situations to answer the question "How does this work?" or "What causes this system to behave as it does?" are all legitimate. Some of these connections are illustrated in Figure 1, some being vital in the educational process.

Pharmaceutics as such is a distinct subject professed within schools of pharmacy worldwide. With the increasing trend toward a more clinical orientation of pharmacy graduates, as already has been achieved in the United States, there may be diminished attention paid to the teaching of pharmaceutics. As in research, there must be a greater effort to present the subject not only in its physicochemical envelope but to demonstrate the importance of the subject matter ultimately in the clinic. As examples, consider the

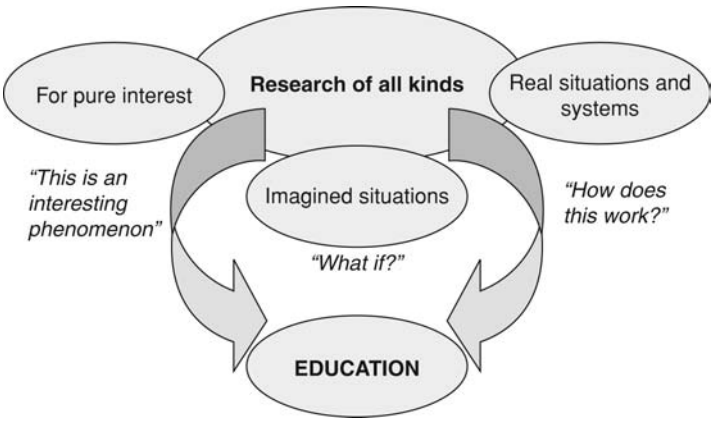

Figure 1 The connections between research of all types in pharmaceutics from the real to the imagined and the link to education. Education must inspire a questioning attitude in students and stimulate them about a subject, pharmaceutics, that continues to adapt and to evolve.

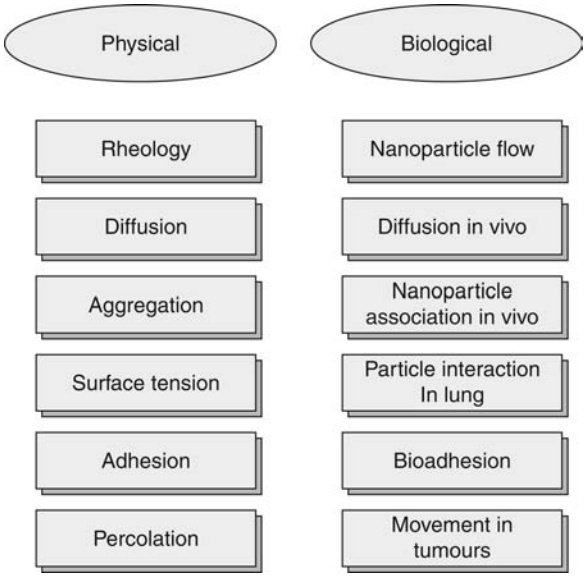

Figure 2 Examples of the connections between phenomena known in physical pharmacy and biological events using the examples of rheology, diffusion, aggregation, surface tension, adhesion, and percolation, and their biological importance in particulate systems as an example.

connections in Figure 2 between the physical phenomena of rheology, diffusion, aggregation, surface tension, adhesion, and percolation, some of the staples of physical pharmacy, to the behavior of systems in vivo.

These topics might be thought of as biopharmaceutics, but they are more than this. They are about the relevance of physicochemical phenomena in all aspects of therapy: rheology relating to blood flow and joint lubrication, crystallization as relevant to crystalluria and drug precipitation from formulations, surface tension and lung surfactant expansion and solubilization of drugs, colloidal interactions and interactions between nanoparticles and surfaces in vivo, and so on. This is what we might call *clinical pharmaceutics.* Clinical pharmaceutics also deals with the adverse effects of dose forms, induced by their excipients and by colors, flavors, tonicifiers, or impurities (11). It also concerns the beneficial influence of dose forms and modes of delivery on clinical outcomes.

Pharmaceutics faces two challenges in schools of pharmacy, one from the clinical impetus that exists and one from the need to maintain the basic and fundamental science in the subject, one which is distinctively pharmaceutics. The latter is not for its own sake, but because the combination of physical, chemical, and biological knowledge that the subject encompasses is vital for improved therapy and the development of safe and novel systems. It could be argued that while there has been progress in the subject in controlled-release technologies with direct patient benefit, pharmaceutical nanotechnology, and aspects of drug targeting, the study of basic phenomena perhaps deserves reinforcement. In particular, we require the application of physical pharmacy concepts to delivery and targeting issues. One example would be the interaction between a nanoparticle and a cell surface as characterized by Sun and Wirtz (12) in Figure 3A. This has clear analogies to, say, indentation testing of pharmaceutical materials shown in Figure 3B, two widely separated topics. Such connections or analogies are intriguing as well as useful.

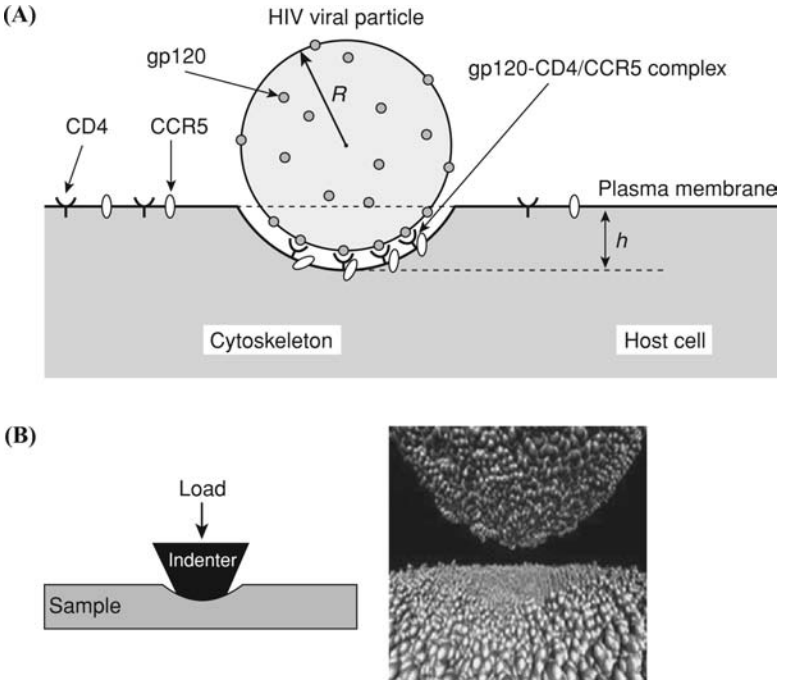

Figure 3 Analogies I. (**A**) Comparison between a diagram from Sun and Wirtz (12) on the interaction of a viral particle with a plasma membrane and (**B**) an illustration demonstrating an indentation measurement on a solid. (**A**) R = radius of the particle and h = the depth of "indentation" of the viral particle. Various receptor and ligand molecules are denoted in addition to ligand-receptor complexes. Sun and Wirtz invoke Young's modulus and other physical terms to describe the interaction. Hiestand and Smith (13) cite Tabor's (14, 15) equation for indentation hardness P, obtained using a pendulum indenter (which actually might be a relevant model for particle-receptor interactions during flow):

$$P = \left[\frac{4mgrh_r}{\pi a^4}\right]\left[\frac{h_i}{h_r} - \frac{3}{8}\right]$$

where m is the mass of the indenter, g is the gravitational constant, r is the radius of the spherical indenter, a is the chordal radius of the dent produced on impact, and h_i is the initial height of the indenter, whereas h_r is the rebound height of the indenter.

NEEDS

There are still urgent needs in the field of pharmaceutical nanotechnology, which are posited below (16), but these might also be suitably modified for many delivery systems.

1. The relevance to the whole animal of in vitro tests of activity, selectivity, uptake, and toxicity of nanoparticulate carrier systems.

   In vitro systems are generally static, whereas most interactions between particles and ligands on cell surfaces occur under dynamic conditions. Flow of blood in which nanosystems move generally decreases the interaction between

carrier and target, through shear forces at surfaces. Laminar and nonlaminar flow in vessels and other tubules is determined by the variable velocity and velocity gradients in blood vessels (17). Dilution effects and the propensity of nanoparticles to interact with proteins in the blood affect the translation from cell culture to living animal.

2. Scaling factors in animal models and the extrapolation of results to human subjects.

   The relevance to the human subject of animal studies, which form the greatest number of sources of data to date, is obscure. Does a 100-nm particle behave in the same way in a mouse and in a human? What is the importance of the distance traveled between the point of entry and the point of interaction with target? How does the physiology of various species influence interpretation of data? Kararli (18) reviewed aspects of the physiological differences between a variety of experimental animals and human subjects in relation to drug absorption. A similar exercise is necessary to determine the influence of species differences on nanocarrier behavior and fate.

3. The causes of the differential uptake and transport of particles in different cell lines in vitro and tissues in vivo.

   Studies of transfection of a variety of cell lines with a particular DNA-complexing agent have frequently shown very marked differences in effectiveness. For example, in the case of dendriplexes (dendrimer-DNA complexes), Bayele et al. (19) have shown 1000-fold differences in transfection. These variations have been confirmed by many researchers. Is this due to cell size (i.e., the distance to be traveled), membrane differences, cell culture media, differences in cell division rate, or the nature of the nucleus and cytoplasm of each cell type? Is there a physical cause, rather than a fundamental biological problem? Diffusion in the cytoplasm is, in part, a purely physical phenomenon; the process is akin to diffusion in a complex gel, strongly dependent on the radius of the particle and the "pore size" of the gel as well as the volume fraction of the gelator. Both obstruction effects and adsorption can occur, so that diffusion is slow, and above critical particle radius ceases altogether. With biological therapeutics, their size often controls their release from delivery systems and certainly their escape into and diffusion in tissue.

4. The influence of the nature of the polymer or other construction material in the manufacture of nanosystems on their biological and colloidal behavior.

   It is one thing to formulate a protein in a polymeric carrier and another to be able to *predict* the miscibility of that protein with the polymer and its potential distribution within the matrix of the polymer. Does phase separation occur as the mixing of two macromolecules is not a simple process thermodynamically? Phase separation can lead to rapid release of active. There has been significant concentration on the effect of the size of nanoparticles on physical and biological behavior but perhaps less on the nature of the polymer in as far as this affects the capacity of the system to encapsulate therapeutic agents or the potential to influence particle flocculation and the vital interactions at close approach of the nanoparticles and cell surface receptors. The Hamaker constants (see chap. 11) are fundamental for assessing the attractive forces between surfaces, and for different polymeric materials can be quite different (20,21), as shown in Table 2.

Table 2 Hamaker Constants (in vacuo) for Some Polymers

Polymer	A ($\times 10^{20}$ J)
Polyvinyl chloride	10.8, 7.5
Polyethylene	10.0
Polystyrene	9.8, 6.6, 6.4, 7.8
PVAc	8.9
PVA	8.8
Polyethylene oxide	7.5
PMMA	6.3
PDMS	6.3
PTFE	3.8

van der Waals attraction between two particles at a distance S
(*i*) for two spheres of equal radius r is $-Ar/12S$, and
(*ii*) for two spheres of unequal radii r_1 and r_2 is $-Ar_1r_2/6S(r_1+r_2)$.
Source: Adapted from Refs. 20 and 21.

5. Analysis of the colloidal behavior of nanoparticles and especially the influence of surface ligands on this behavior.

   As suggested above, the addition of specific ligands to the surface of nanoparticles, whether by covalent attachment or by adsorption, does not always lead to improved targeting in animals. Thus, the manner in which the ligands affect the physical stability and interactions of nanosystems is a worthy goal to elucidate the optimal conformation and configuration of adsorbed ligands.
6. Nanoparticle navigation in complex biological networks.

   A better understanding of the movement of nanoparticles in the complex environment in which they are deposited in tissues, in tumors, and in blood, lymph, and the extracellular matrix is essential for prediction of behavior. The influence of particle size, shape, and flexibility on such movement is key (22). Does shape matter? If flow matters, then asymmetric particle flow is clearly different from the flow of spherical particles. Hence, there is a need for better comprehension of such behavior, particularly with the advent of carbon nanotubes whose rheological and diffusional properties will differ from those of spherical systems.
7. Analysis of published data to move pharmaceutical nanotechnology toward greater predictability of nanoparticle behavior.

   Targeting activity is essential in the design of many delivery systems, vaccines, and gene delivery vectors, hence collating the already voluminous material that has been published and finding common threads to improve predictive powers are important. One of the difficulties here is the variation in size measurement techniques and their interpretation, as has been emphasized in two recent publications (23,24), one going so far as to suggest that 90% of published measurements are faulty. Accurate size measurements are essential. If size is key to access to targets or interactions with receptors, then the width of the particle size distribution must be known. Figure 4 illustrates this in a general way. If the optimal size range is as shown, then particles in region A will no doubt have access but will have different flow characteristics, particles in B will be in the desired range, while those in C will not access the target. It may be that particles in category D will, in fact, exhibit toxicity. It is perhaps

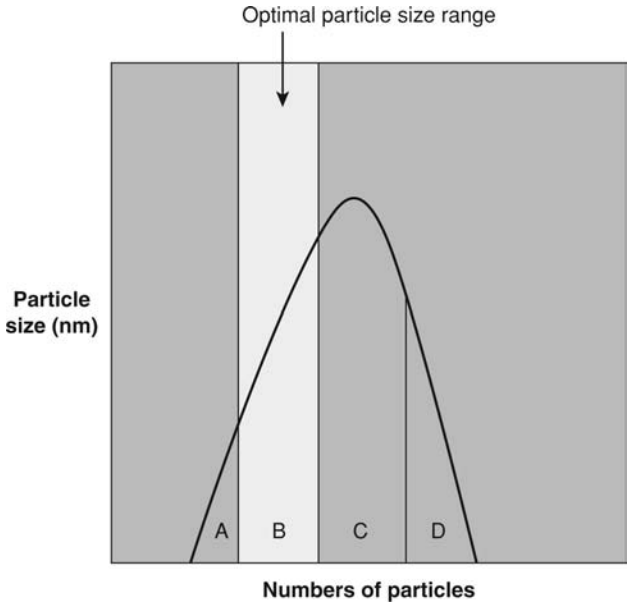

Figure 4 A diagrammatic particle size distribution with a hypothetical optimum-size band for biological activity, extravasation, transport, and receptor interactions. Zones A to D are discussed in the text.

timely to explore a "gold standard" for particle sizing so that all laboratories routinely use and cite the values they obtain with their equipment using a standard material, for example, a gold sol. After all, this is a common practice in surface science, where the surface tension of water is routinely cited as a marker of accuracy and precision.

8. Pharmaceutical aspects of nanotoxicology or nanosafety.

   The study of nanotoxicology has been referred to by the Oberdösters in a review (25), which will repay reading as a discipline emerging from studies of ultrafine particles. Nanoparticles, unlike the majority of microparticles, can penetrate the body in a variety of ways and can be absorbed and translocated to organs such as the liver and spleen. It is clear that we must have more specific information on the safety of nanosystems, the influence of the nature of their surfaces and the material of which they are composed, and the influence of porosity, size, and shape.

9. Pharmacokinetics of drugs and other agents encapsulated in nanosystems and more studies on the kinetics of distribution of carriers in vivo.

   This is a fairly self-evident need. It is important that we distinguish between the pharmacokinetics of drug that is released from the carrier and the biokinetics of the carriers themselves (i.e., carrier kinetics). It is wrong etymologically to discuss the pharmacokinetics of vectors.

10. The physical chemistry of peptide, protein, or macromolecule—polymer miscibility in relation to the incorporation of these molecules in polymer nanoparticles, microparticles, and implants, their stability, and release.

    Given sometimes overwhelming biological interests, the pharmaceutical and physicochemical issues in formulation must not be underestimated. One lack seems to be a systematic study of the interactions between peptides,

proteins, and DNA and the variety of polymers used in the construction of nanosystems. The basic thermodynamics of mixing under the conditions of preparation will yield valuable data. Gander et al. (26) have approached this subject in relation to the microencapsulation of proteins by PLGA spheres by spray drying and sought correlations between Hildebrand constants, partial Hansen solubility parameters, and other thermodynamic measures. They were able to conclude that encapsulation efficiency is increased and burst release reduced if polymer-drug interactions are dominant and polymer-solvent and drug-solvent interactions are reduced. The same authors also studied the thermodynamics of interactions in the preparation of microcapsules (27). More studies of this kind are important especially when polymer mixtures are used and polymer-polymer interactions turn out to be complex. Figure 5 illustrates a study of protein-polysaccharide interactions (28), which points out regions of compatibility and incompatibility in the phase diagram.

The above subject areas are possibly an idiosyncratic and certainly an incomplete list of topics in nanotechnology. They arise from the need to counteract the exaggerated claims for nanosystems in drug delivery and targeting by addressing the core factors which prevent quantitative delivery of therapeutic agents to complex targets such as tumors and sites of inflammation.

Some phenomena are extremely difficult, if not impossible, at present to investigate in vivo; hence, there needs to be a theoretical approach to many of the phenomena we invoke to explain delivery and targeting with nanoparticles. The stochastic nature of many interactions must be incorporated into predictions. While we are studying the biological barriers to delivery and targeting, we should devise new systems, which are better able to

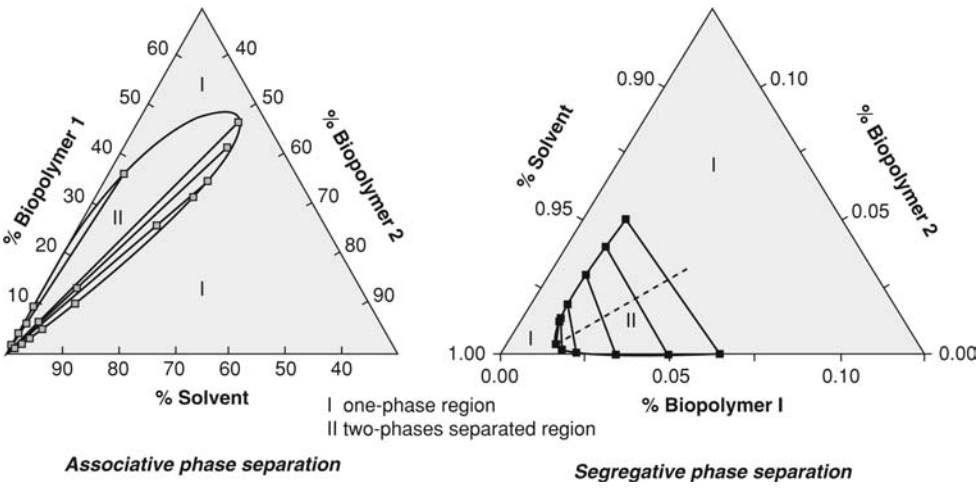

Figure 5 Phase diagrams for biopolymer 1–biopolymer 2 solvent systems from Doublier et al. (28). Not shown is the Flory-Huggins lattice model for predicting experimental tie lines, whose equations exhibit enthalpic and entropic terms. The diagram on the right illustrates the most common form of thermodynamic incompatibility or "segregative phase separation" where solvent–biopolymer 1 interactions are favored over biopolymer 1–biopolymer 2 interactions and solvent-solvent interactions, hence demixing. In the associative phases separation, interactions between the two biopolymers are favored (e.g., because of interactions between a positively and a negatively charged molecule).

take their load quantitatively to their targets yet release them in a predictable manner when and only when they reach their site of action. A tall order.

Nanotechnology offers the opportunity not only to enhance delivery and targeting but also to produce new material and devices: in the formation of fine membranes, meshes, lubricant material for fine valves, and so on. There is also the recognition of the potential of the toxicity of materials such as titanium dioxide, used not as a carrier but as an excipient in tablets. Titanium dioxide is absorbed from the GI tract in the form of rutile, some 50 nm in diameter (29), and particles of 2 to 5 nm after inhalation (30). The ever present possibility of aggregation and its influence on interpretation of nanoparticle toxicity has been discussed (31).

Fundamental Topics

The late Nobel laureate in physics Pierre-Gilles de Gennes, for much of his research career, worked in the field of soft matter, which has so much significance in pharmaceutical systems. In his 1994 Dirac Memorial Lecture (32) given in Cambridge, he ranged widely over topics such as the dynamics of partial and complete wetting, principles of adhesion and tack, and polymer/polymer welding. "Compared to the giants of quantum physics," de Gennes wrote modestly, "we soft-matter theorists look like the dwarfs of German folk tales. These dwarfs were often miners or craft-workers: we, also, are strongly motivated by industrial purposes. *We see fundamental problems emerging from practical questions*." It is this last sentence that is especially relevant to pharmaceutics, where the issues of compaction, flow, film formation, wetting, and adhesion and tack can be of industrial relevance but are incompletely understood. Yet there are pressing issues raised by the necessity to formulate and deliver drugs that are macromolecules or labile and which possess the "wrong" physical and chemical characteristics as drug molecules. The objective de Gennes proposes is that we need to obtain "simple impressionistic visions of complex phenomena, ignoring many details, actually in many cases operating only at the level of scaling laws."

Pharmaceutical formulations and systems are frequently, and possibly usually, extremely complex. We use multicomponent systems, polymers of varied molecular weight, surfactants, products of polymerization processes, which are impure, particles of a wide distribution of sizes and shapes, and processes that are themselves often complex and ill defined at a molecular level. Then we administer these systems to a complex biological environment. We are a long way from a pharmaceutical theory of everything. To return to an earlier theme, we need the theoretical bases on which to become less empirical. This present book contains a chapter by Frenning and Alderborn (chap. 11, vol. 2) on aspects of pharmaceutical physics, written to illustrate the approaches that can be made to complex fields in pharmacy. Some of the topics once of great interest in pharmaceutics laboratories, say in the domain of powder technology, are still pursued elsewhere, for example, in physics. As an example, a paper on the wet granular pile stability recently tackled problems of spherical and nonspherical particle mixing and agglomeration (33).

Other Topics

Aqueous Interaction with Solids: Wetting and Dewetting

Water repellency (34) is relevant to pharmaceutical systems. With porous dosage forms, there is generally a desire to *avoid* water repellency to allow ingress of water. A

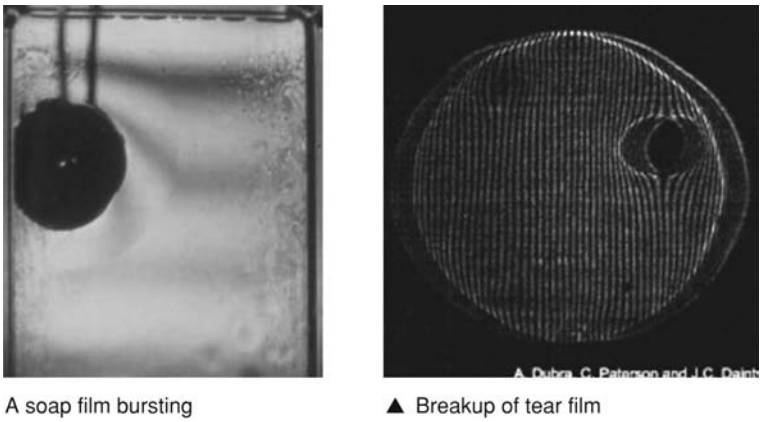

Figure 6 Analogies II. (*Left*) A film of sodium dodecyl sulfate in air a few microseconds after a spark bursts the film and causes rapid contraction of the surfactant layers with thickening in the so-called aureole region around the hole. (*Right*) An image of tear film rupture on a solid surface. *Source*: Left figure from A. T. Florence and K. J. Mysels, 1967 (unpublished photograph); right figure from the laboratory of A. Dubra (38), Imperial College London.

possibility of reversible repellency might be of advantage in controlling release of drugs by first inhibiting uptake of water and then allowing it. Indeed, the wettability of textured materials can be tuned rapidly with an electric field, for example (35), leading to the possibility of pulsed release from dose forms as the systems are tuned and detuned. Dewetting is also related to issues of water repellency and is important in some biological situations. In xerophthalmia (dry eye), the dewetting of the cornea through the breakup of the tear film leads to dry spots. Studies on dewetting of polymer films on mica or viscous fluids or surfactant films or solutions can lead to understanding of many physical and biological processes. Photographs of thin surfactant film breakup obtained many years ago (36,37) in the late Karol Mysels' laboratory (Fig. 6) bear a remarkable similarity to recent work by Dubra et al. (38) on tear film breakup.

Flow of Complex Liquids

In Balaz's paper on the flow of complex liquids (such as binary fluids) through heterogeneous channels (39), it is argued that the dynamic behavior of complex fluids in confined geometries is vital if we are to understand a range of topics from the processing of polymeric materials to the flow of blood in confined spaces. Not least, the work has provided basic information and the optimal configurations for the production of emulsions having well-controlled structures. The molecular dynamics of sorbed fluids in mesoporous materials (40) are relevant to the understanding of hysteresis in porous systems, important in some pulsatile hydrogel delivery systems, which display considerable hysteresis, which may only be in part due to the mechanics of the polymer chains.

The chapter by Anthony Hickey (chap. 5, vol. 2) on inhalational delivery of drugs exemplifies the theory that has been derived to understand the processes of lung deposition so far. Nanoparticulate interaction with the lung surfactant layer has been discussed and a three-dimensional cellular model devised to study these processes (41).

Boundary Lubrication, Splashes, and Turbulence

Boundary lubrication under water discussed by Briscoe et al. (42) is relevant to particles with surfactant layers. They state,

> Boundary lubrication, in which the rubbing surfaces are coated with molecular monolayers, has been studied extensively for over half a century. Such monolayers generally consist of amphiphilic surfactants anchored by their polar headgroups; sliding occurs at the interface between the layers, greatly reducing friction and especially wear of the underlying substrates. This process, widespread in engineering applications, is also predicted to occur in biological lubrication via phospholipid films, though few systematic studies on friction between surfactant layers in aqueous environments have been carried out. Here we show that the frictional stress between two sliding surfaces bearing surfactant monolayers may decrease, when immersed in water, to as little as one per cent or less of its value in air (or oil). We attribute this to the shift of the slip plane from between the surfactant layers, to the surfactant/substrate interface. The low friction would then be due to the fluid hydration layers surrounding the polar head groups attached to the substrate. These results may have implications for future technological and biomedical applications.

Investigation of splashes (43,44) might seem abstruse pharmaceutically, but such work would be of relevance to the nature of micro- and nanoparticle interaction with alveolar fluids from the airways: hydrophilic spheres have been shown to enter liquid surfaces without commotion, while hydrophobic particles cause a splash. Problems of turbulence (45), aspects of mixing (46), and the nature of complex liquids, inter alia, are studies on apparently nonpharmaceutical systems which nevertheless have or may have relevance to a theoretically based approach to pharmaceutical design and manufacture and thus a deeper understanding of product performance.

The Pharmaceutics of Cell Therapy

Pharmaceutics has progressed as drugs have developed first from natural product extracts, through synthetic and generally small molecules to peptides, proteins, and oligonucleotides and DNA itself, into the beginning era of cell-based therapies. Cell therapy, whether with stem cells, dendritic cells, or pancreatic cells, involves a host of pharmaceutical issues: of dose, of quality, of consistency, and of accurate delivery to specific sites. Several means of delivery cells have been explored, including direct intramuscular injection (e.g., into cardiac muscle) (47) and intravenous administration. It has been reported that stem cells when injected directly into the blood are able to locate myocardial infarctions by the process of cell homing (48). Cell-collagen composites have been employed (by implantation) for the repair of tendon injuries (49), biodegradable alginate beads for delivery of bone cells and antibiotics (50), and PEGylated fibrin patches for mesenchymal stem cell delivery (51). Clearly, the route of administration is key to determining the distribution of injected dendritic cells (52): intravenously administered cells accumulate in the spleen, whereas intramuscularly injected cells accumulate in the T-cell regions of lymph nodes, results confirmed by Morse et al. (53), who found intravenously administered dendritic cells localized first in the lungs and then distributed to liver, spleen, and bone marrow. Data on the biodistribution of nanoparticles are relevant to an understanding of some of the issues in cell-based therapeutics, while efficient delivery matrices are also key.

Guidelines of human somatic cell therapy developed by the FDA in the United States and by the EU's Committee for Medicinal Products for Human Use (CHMP) both address the triad of safety, quality, and efficacy that have been applied routinely to conventional therapeutic agents (54).

MATHEMATICAL MODELING

To be a more predictive science, pharmaceutics needs to embrace mathematical modeling of systems, however complex they may be. Mathematical modeling is one area that holds much promise for estimating the behavior of dose forms, such as in the release and diffusion of drugs in brain tissue (55). A thorough theoretical analysis can provide major benefits, including the following:

1. It can help to *understand how the dose forms work*, for example, why the drug is released at a particular rate from a controlled delivery system (56–58). The underlying mass transport mechanisms can be elucidated, and most importantly, the dominant physicochemical processes can be identified (59). Often a significant number of phenomena are involved, such as the wetting of a device's surface, water penetration into the dose form, drug dissolution, swelling of polymeric excipients, glassy to rubbery phase transitions, drug and excipient diffusion out of the dose form, polymer dissolution and/or degradation, and drug-polymer interactions, to mention just a few. Chapter 11 in volume 2 gives a detailed description of a number of these phenomena. If several of these processes occur in sequence and significantly differ in velocity, the much faster ones can be neglected. In the case where certain processes in the sequence are much slower than all the others, then these are release rate limiting.

   It is valuable to know which phenomena are dominant in a particular system, because this knowledge simplifies device optimization and trouble-shooting during product development, scale-up, and production. It has to be pointed out that the type of dose form, type and amount of drug and excipients, and even the type of preparation technique can significantly alter the relative importance of the involved physicochemical phenomena. Chapter 1 in volume 2 on sustained- and controlled-release drug delivery systems provides an overview on the most frequently used control mechanisms in advanced drug delivery systems, including matrix tablets for oral administration and biodegradable microparticles for parenteral use. Furthermore, a theoretical analysis based on comprehensive experimental in vivo results can give valuable insight into the phenomena that are governing the fate of the drug once it released into the human body. Obviously, this knowledge—the thorough understanding of the processes occurring within the dose form as well as within the living organism—provides the basis for an efficient improvement of the safety of the respective drug treatment, especially in the case of highly potent drugs with narrow therapeutic windows.
2. Mathematical modeling can significantly *facilitate the development of new products* and the optimization of existing ones. An appropriate mathematical theory allows for a quantitative prediction of the effects of different formulation and processing parameters on the resulting properties of the dose form, for example, the release rate of an incorporated drug. Figure 7 shows an example for such a simulation: the effects of the initial radius of propranolol HCl–loaded, hydroxypropyl methylcellulose (HPMC)-based

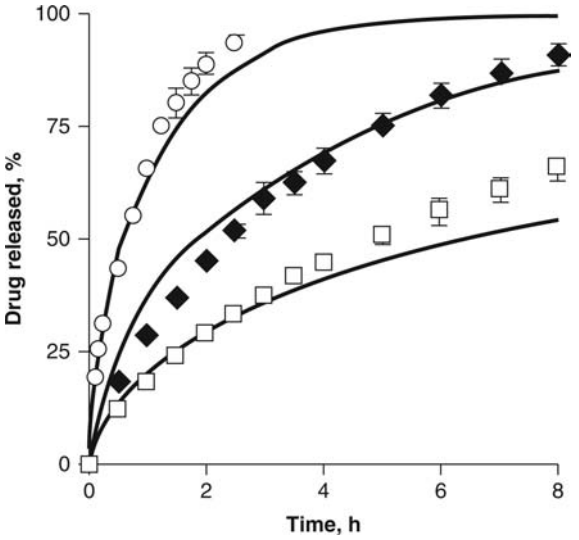

Figure 7 Theoretical prediction (*curves*) of the effects of the initial radius of hydroxypropyl methylcellulose–based matrix tablets containing 5% propranolol HCl on the resulting drug release kinetics in phosphate buffer pH 7.4. The symbols represent independent experimental results, confirming the theoretical calculations. The initial tablet height is 2.6 mm, the initial tablet radius is varied from 1.0 to 2.5 to 6.5 mm (corresponding to the *upper curve—open circles*; *middle curve—filled diamonds*; and *lower curve—open squares*). *Source*: From Ref. 60.

matrix tablets on the resulting drug release kinetics in phosphate buffer pH 7.4 are shown (curves) (60). The initial tablet height was constant (2.6 mm), whereas the initial tablet radius was varied from 1.0 to 6.5 mm (corresponding to the curves at the top to the bottom). Clearly, the resulting relative release rate significantly decreases when increasing the initial tablet radius, which can at least partially be attributed to the decreasing "surface area:volume ratio" of the system (and thus decreased relative surface area available for diffusion). The symbols in Figure 7 represent the independently determined experimental drug release kinetics from these matrix tablets. The good agreement between theory and experiment serves as an indication for the validity of this model for this type of drug delivery system. But also, the effects of other formulation and processing parameters on the resulting system properties can be theoretically predicted, including the initial drug and polymer content, type and amount of plasticizer, as well as size and shape of the dose form (61,62).

In silico simulations can, thus, be used to effectively replace or minimize the series of cost- and time-intensive "trial-and-error" experiments during product development. This is particularly useful in the case of controlled drug delivery systems with long-term release kinetics, for example, implants that are intended to provide appropriate drug levels during several months or years.

Two types of mathematical theories can be distinguished: *empirical models* and *mechanistic realistic models*. Empirical models are purely descriptive and do not allow for a better understanding of the underlying physical, chemical, and/or biological phenomena. Furthermore, they cannot be used to quantitatively predict the effects of formulation and processing parameters on the resulting system properties. In contrast,

mechanistic theories are based on real phenomena, such as diffusion, dissolution, swelling, and/or dissolution/erosion. They allow for the determination of realistic parameters characterizing the respective dose form, for example, the diffusion coefficient of the drug within a matrix former or the degradation rate constant of a polymeric excipient. On the basis of these parameters, further insight into the underlying mass transport phenomena can be gained. For instance, the relative importance of the involved processes can be determined.

Because of the large variety of drugs, excipients, and dose forms that are used, there is no universal mathematical theory valid for all types of systems. In each particular case, it must be determined which processes are involved and—if possible—which of them are dominant. This type of analysis must be based on comprehensive experimental results, otherwise, no reliable conclusions can be drawn. It has to be pointed out that obtaining good agreement between a *fitted* theory and a set of experimental results is not a proof for the validity of a mathematical theory. Fitting a model to experimental results implies that one or more model parameters are adjusted to obtain the least-deviations "theory-experiment." Especially if a significant number of parameters are simultaneously fitted to the same set of experimental data, caution has to be paid when drawing conclusions. To evaluate the validity of a mathematical model for a particular type of drug-loaded dose form, the theory should be used to predict the effects of different formulation and/or processing parameters on the resulting system properties and these theoretical predictions should be compared with independent experimental results. Also, care should be taken when applying a mathematical theory to a specific dose form so that no major assumptions on which the model is based are violated. As an example, the famous Higuchi equation (10) is unfortunately often misused and applied to drug delivery systems for which it is not valid.

Yet, there is a significant lack of mechanistic realistic mathematical theories, which appropriately describe both the physicochemical phenomena occurring within the dose form and the subsequent fate of the drug within the human body (55). This can at least partially be explained by the complexity of the resulting set of mathematical equations considering all the involved physical, chemical, and biological processes (63). Also, a large variety of phenomena can be of importance in vivo for the fate of the drug, including diffusion and convection within the extra- and intracellular space, reversible and irreversible binding to extracellular matrix, drug metabolism, passive and active uptake into living cells (e.g., by "simple" diffusion and/or by receptor-mediated internalization), release from endolysosomes into the cytosol of the cells, uptake into the cell nuclei, and uptake/elimination/distribution from/into the blood stream and/or lymphatic system. Figure 8 shows as an example some of the processes that can be decisive for the drug upon direct administration into brain tissue. Importantly, drug transport in vivo can be highly anisotropic (direction dependent), because the human organism is not one homogeneous mass. Major advances in this research area allowing for a better understanding of the underlying drug transport mechanisms have been achieved by the working groups of Nicholson (64) and of Haller and Saltzman (65,66). However, there is a significant need for comprehensive and mechanistic mathematical theories relating formulation and processing parameters of dose forms to the resulting drug concentrations at the site of action and the pharmacodynamic effects of the treatment.

An often underestimated aspect when characterizing dose forms in vitro is the importance of the type of environment the systems are exposed to. This includes, for instance, the physical state of the medium (liquid or gel), degree of agitation, pH and ionic strength of the medium, the maintenance or absence of sink conditions, the presence/absence of enzymes and/or macrophages, etc. For example, the drug release patterns from PLGA parenteral controlled drug delivery systems can strongly depend on the pH of the surrounding environment, because ester hydrolysis is catalyzed by

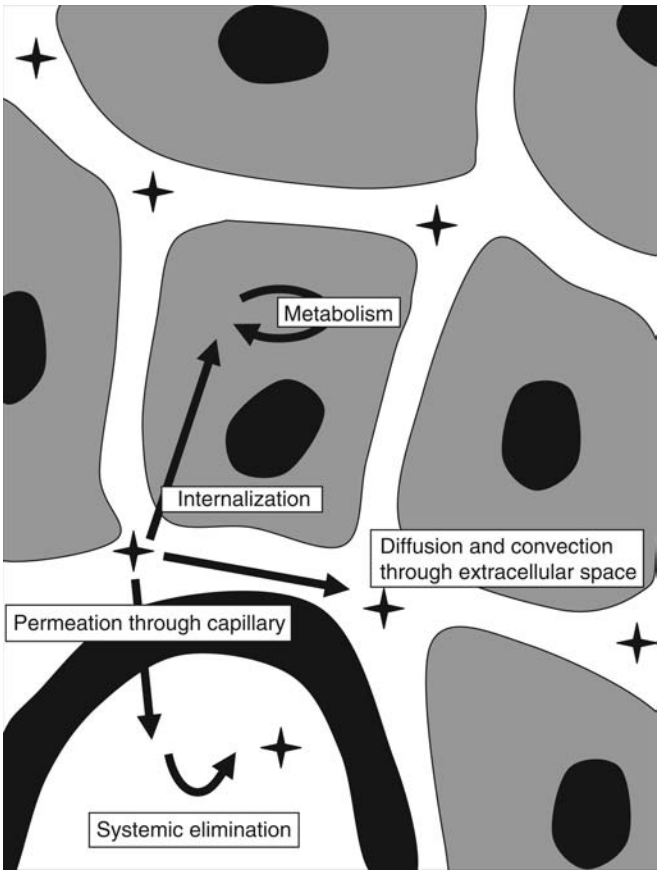

Figure 8 Schematic presentation of some of the processes that can be involved in drug transport within human brain tissue, including diffusion and convection through the extracellular spaces, permeation through capillaries, systemic elimination, internalization, and metabolism. The black circles represent drug molecules in the interstitial space. *Source*: From Ref. 63.

protons (67). Also, the osmotic pressure of the release medium can be of crucial importance for the drug release patterns from oral coated dose forms, in which crack formation is mandatory to allow for drug release. Appropriate mathematical modeling can be of great help in this perspective if the theory adequately takes into account the effects of the environmental conditions on the systems' properties. This allows for an appropriate correlation of the in vitro and in vivo results and thus for a significantly facilitated product development and improved safety of the drug treatment.

CONCLUSIONS

There can be no conclusions, only new challenges. This chapter, while it has not covered the whole gamut of possible topics or even all those described in this book, has attempted to show the connections between topics in a range of disciplines. It has always been the strength of pharmaceutics that perhaps it could not be defined, but we believe in its integrity and its ability to evolve and to have an important holistic view of medicines. This edition of *Modern Pharmaceutics*, following on from four editions edited by Gilbert

Banker and Christopher Rhodes, reflects the continual change and refinement in the subject and points the way to, and we hope encourages, further research, both applied and basic for the ultimate benefit of the patient.

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2
Principles of Drug Absorption

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INTRODUCTION

Drug dosing most often involves the oral route of administration. The vast majority of drug dosage forms are designed for oral ingestion, primarily for ease of administration. It should be recognized, however, that this route may result in inefficient and erratic drug therapy. Whenever a drug is ingested orally (or by any nonvascular route), one would like it to have rapid and complete absorption into the bloodstream for the following reasons:

1. Assuming that there is some relationship between drug concentration in the body and the magnitude of the therapeutic response (which is often the case), the greater the concentration achieved, the larger the magnitude of response.
2. In addition to desiring therapeutic concentrations, one would like to obtain these concentrations rapidly. The more rapidly the drug is absorbed, in general, the sooner the pharmacological response is achieved.
3. In general, one finds that the more rapid and complete the absorption, the more uniform and reproducible the pharmacological response becomes.
4. The more rapidly the drug is absorbed, the less chance there is of drug degradation or interactions with other materials present in the gastrointestinal tract (GIT).

In a broad sense, one can divide the primary factors that influence oral drug absorption and thus govern the efficacy of drug therapy into the following variables: physicochemical, physiological, and dosage form. For the most part, these variables will determine the clinical response to any drug administered by an extravascular route. Although often the total response to a drug given orally is a complex function of the aforementioned variables interacting together, the present discussion is limited primarily to the first two categories involving physicochemical and physiological factors. Dosage form variables influencing the response to a drug and the effect of route of administration are discussed in chapters 4, 5 and 6.

The vast majority of drugs in current use and those under development are relatively simple organic molecules obtained from either natural sources or by synthetic methods. It

is important to note, however, the virtual revolution in development of new therapeutic entities; those based upon the incredible advances being made in the application of molecular biology and biotechnology. These new drugs, especially peptides, proteins, and monoclonal antibodies are not the traditional small organic molecules stressed in this chapter. Indeed, those compounds have unique physicochemical properties, which are quite different from those of small organic molecules, and they offer remarkable challenges for drug delivery. As a result, new and more complex physical delivery systems are being designed in conjunction with an examination of other, less traditional routes of administration (e.g., nasal, pulmonary, transdermal). Because of issues of instability in the GIT and poor intrinsic membrane permeability, it appears unlikely that these new biologically-based drugs will employ the oral route for administration. Numerous strategies are being explored, but to date relatively little success has been achieved (1). One approach that shows promise involves conjugating a poorly absorbed compound to a so-called molecular transporter. The latter are oligomers of arginine that undergo active cellular uptake (2,3).

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS OF THE GASTROINTESTINAL TRACT

The GIT is a highly specialized region of the body whose primary functions involve the processes of secretion, digestion, and absorption. Since all nutrients needed by the body, with the exception of oxygen, must first be ingested orally, then processed by the GIT, and then made available for absorption into the bloodstream, the GIT represents a significant barrier and interface with the environment. The primary defense mechanisms employed by the gut to rid it of noxious or irritating materials are vomiting and diarrhea. In fact, emesis is often a first approach to the treatment of oral poisoning. Diarrhea conditions, initiated by either a pathological state or a physiological mechanism, will result in the flushing away of toxins or bacteria or will represent the response to a stressful condition. Indeed, the GIT is often the first site of the body's response to stress, a fact readily appreciated by students taking a final exam! The nearly instinctive gut response to stress may be particularly pertinent to patients needing oral drug therapy. Since stress is a fact of our daily lives, and since any illness requiring drug therapy may to some degree be considered stressful, the implications of the body's response to stress and the resulting influence on drug absorption from the gut may be particularly pertinent.

Figure 1 illustrates the gross functional regions of the GIT (4). The liver, gallbladder, and pancreas secrete materials vital to the digestive and certain absorptive functions of the gut. The lengths of various regions of the GIT are presented in Table 1. The small intestine, comprising the duodenum, jejunum, and ileum, represents greater than 60% of the length of the GIT, which is consistent with its primary digestive and absorptive functions. In addition to daily food and fluid intake ($\sim$1–2 L), the GIT and associated organs secrete about 8 L of fluid per day. Of this, only 100 to 200 mL of stool water is lost per day, indicating efficient absorption of water throughout the tract.

Stomach

After oral ingestion, materials are presented to the stomach, whose primary functions are storage, mixing, and reducing all components to a slurry with the aid of gastric secretions and then emptying these contents in a controlled manner into the upper small intestine (duodenum). All these functions are accomplished by complex neural, muscular, and hormonal processes. Anatomically, the stomach has classically been divided into three

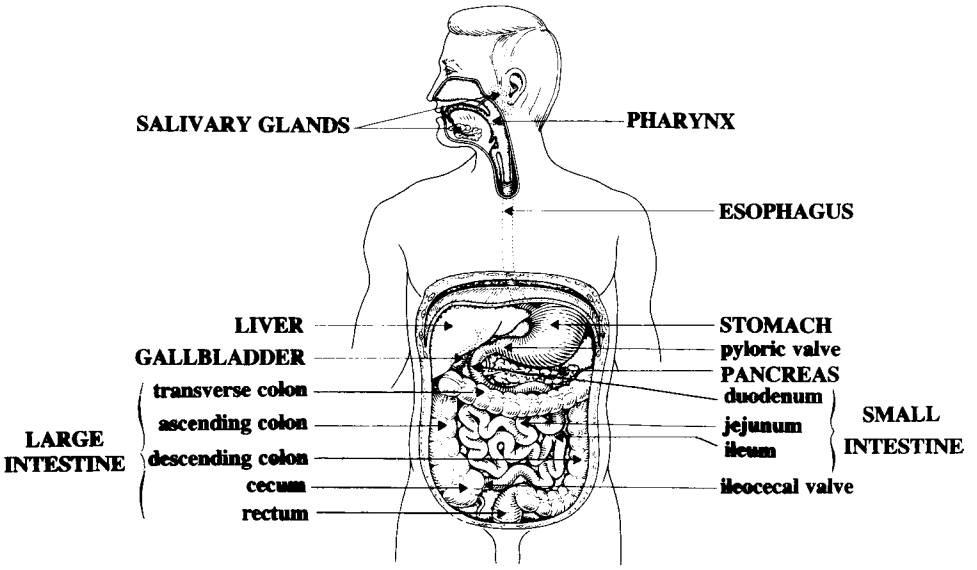


Figure 1 Diagrammatic sketch of the gastrointestinal tract (and subdivisions of the small and large intestines) along with associated organs. *Source*: Modified from Ref. 4.

Table 1 Approximate Lengths of Various Regions of the Human Gastrointestinal Tract

Region	Length (m)
Duodenum	0.3
Jejunum	2.4
Ileum	3.6
Large intestine	0.9–1.5

parts: fundus, body, and antrum (or pyloric part), as illustrated in Figure 2 (5). Although there are no sharp distinctions among these regions, the proximal stomach, made up of the fundus and body, serves as a reservoir for ingested material and secretes acid, while the distal region (antrum), which secretes gastrin, is the major site of mixing motions and acts as a pump to accomplish gastric emptying. The fundus and body regions of the stomach have relatively little tone in their muscular wall and, as a result, can distend outward to accommodate a meal of up to 1 L.

A common anatomical feature of the entire GIT is its four concentric layers. Beginning with the luminal (i.e., inner or absorbing) surface these are the mucosa, submucosa, muscularis mucosa, and serosa. The three outer layers are similar throughout most of the tract; however, the mucosa has distinctive structural and functional characteristics. The mucosal surface of the stomach is lined by an epithelial layer of columnar cells, the surface mucous cells, which secrete mucous (mucopolysaccharides) that protects the epithelial surface from acid, enzymes, and pathogens. Covering the epithelial cell surface is a layer of mucous 1.0 to 1.5 mm thick. Along this surface are many tubular invaginations, referred to as gastric pits, at the bottom of which are found specialized gastric secretory cells. These secretory (parietal) cells form part of an

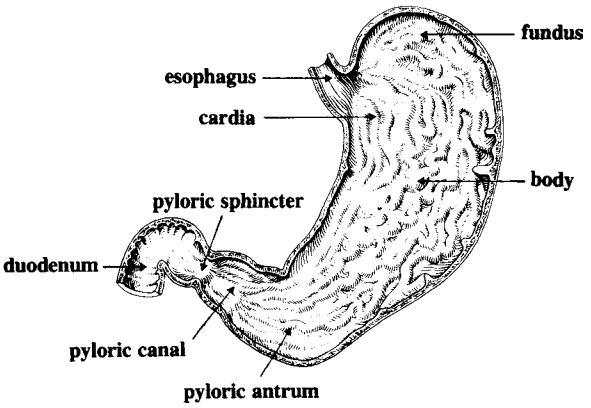


Figure 2 Diagrammatic sketch of the stomach and anatomical regions. *Source*: Modified from Ref. 5.

extensive network of gastric glands, which produce and secrete about 2 L of gastric fluid daily. The epithelial cells of the gastric mucosa represent one of the most rapidly proliferating epithelial tissues, being shed by the normal stomach at the rate of about a half-million cells per minute. As a result, the surface epithelial layer is renewed every one to three days.

The next region, the muscularis mucosa, consists of an inner circular and an outer longitudinal layer of smooth muscle. This area is responsible for the muscular contractions of the stomach wall needed to accommodate a meal by stretching and for the mixing and propulsive movements of gastric contents. An area known as the lamina propria lies below the muscularis mucosa and contains a variety of tissue types, including connective and smooth muscles, nerve fibers, and the blood and lymph vessels. It is the blood flow to this region and to the muscularis mucosa that delivers nutrients to the gastric mucosa. The major vessels providing a vascular supply to the GIT are the celiac and the inferior and superior mesenteric arteries. Venous return from the GIT is through the splenic and the inferior and superior mesenteric veins. The outermost region of the stomach wall provides structural support for the organ.

Small Intestine

The small intestine has the shape of a convoluted tube and represents the major length of the GIT. The small intestine, comprising the duodenum, jejunum, and ileum, has a unique surface structure, making it ideally suited for its primary role of digestion and absorption. The most important structural aspect of the small intestine is the means by which it greatly increases its effective luminal surface area. The initial increase in surface area, compared with the area of a smooth cylinder, is due to the projection within the lumen of folds of mucosa, referred to as the folds of Kerckring. Lining the entire epithelial surface are fingerlike projections, the villi, extending into the lumen. These villi range in length from 0.5 to 1.5 mm, and it has been estimated that there are about 10 to 40 villi/mm^2 of mucosal surface. Projecting from the villi surface are fine structures, the microvilli (average length 1 mm), which represent the final large increase in the surface area of the small intestine. There are approximately 600 microvilli protruding from each absorptive cell lining the villi. Relative to the surface of a smooth cylinder, the folds, villi, and microvilli increase the effective surface area by factors of 3, 30, and 600, respectively.

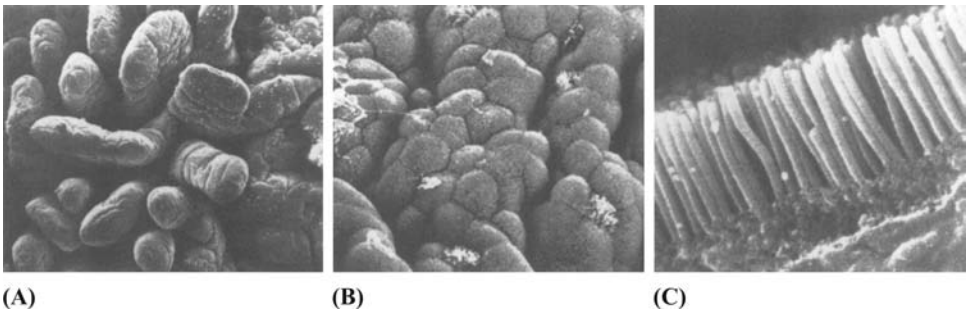


Figure 3 (**A**) Photomicrograph of the human duodenal surface illustrating the projection of villi into the lumen (magnification 75×). The goblet cells appear as white dots on the villus surface. (**B**) Photomicrograph of a single human duodenal villus illustrating surface coverage by microvilli and the presence of goblet cells (*white areas*) (magnification 2400×). (**C**) Photomicrograph illustrating the microvilli of the small intestine of the dog (magnification 33,000×). *Source*: From Ref. 6.

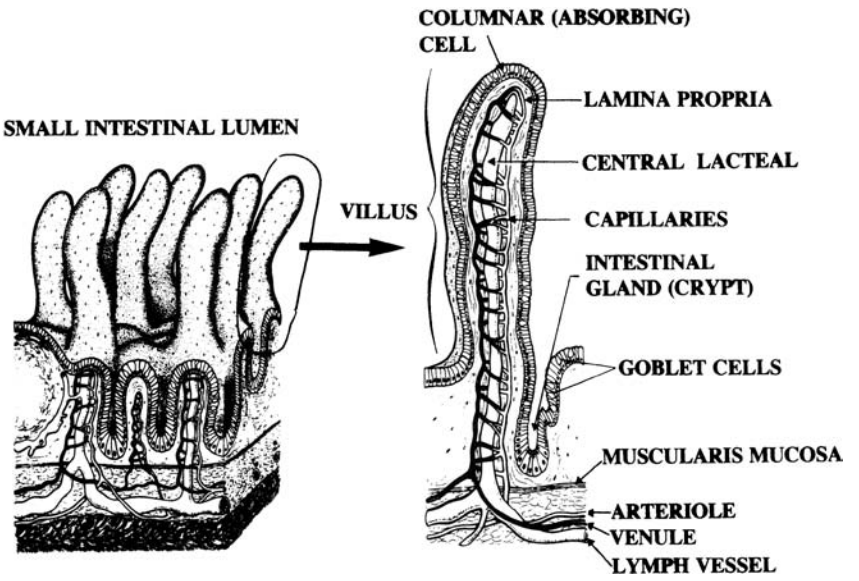


Figure 4 Diagrammatic sketch of the small intestine illustrating the projection of the villi into the lumen (*left*) and the anatomic features of a single villus (*right*). *Source*: Modified from Ref. 4 (see p. 439).

The resulting area represents a surface equal to about two-thirds of a regulation tennis court! These structural features are clearly indicated in the photomicrographs shown in Figure 3. A diagrammatic sketch of the villus is shown in Figure 4.

The mucosa of the small intestine can be divided into three distinct layers. The muscularis mucosa, the deepest layer, consists of a thin sheet of smooth muscle 3 to 10 cells thick and separates the mucosa from the submucosa. The lamina propria, the section between the muscularis mucosa and the intestinal epithelia, represents the subepithelial connective tissue space and together with the surface epithelium forms the villi structure. The lamina propria contains a variety of cell types, including blood and lymph vessels and nerve fibers. Molecules to be absorbed must penetrate into this region to gain access to the bloodstream.

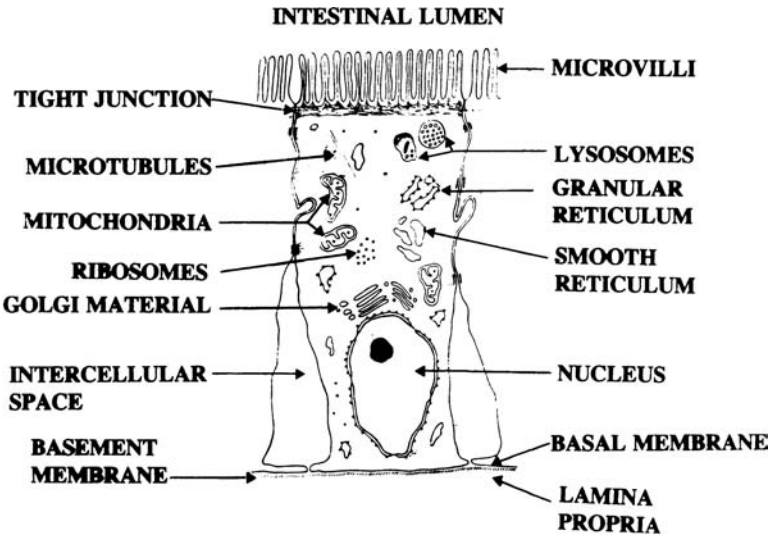


Figure 5 Diagrammatic sketch of the intestinal absorptive cell. *Source*: Modified from Ref. 7.

The third mucosal layer is that lining the entire length of the small intestine and which represents a continuous sheet of epithelial cells. These epithelial cells (or enterocytes) are columnar in shape, and the luminal cell membrane, upon which the microvilli reside, is called the apical cell membrane. Opposite this membrane is the basal (or basolateral) plasma membrane, which is separated from the lamina propria by a basement membrane. A sketch of this cell is shown in Figure 5. The primary function of the villi is absorption.

The microvilli region has also been referred to as the striated or "brush" border. It is in this region where the process of absorption is initiated. In close contact with the microvilli is a coating of fine filaments composed of weakly acidic sulfated mucopolysaccharides. It has been suggested that this region may serve as a relatively impermeable barrier to substances within the gut such as bacteria and other foreign materials. In addition to increasing the effective luminal surface area, the microvilli region appears to be an area of important biochemical activity.

Consistent with the absorptive function of the GIT and, in addition to its large surface area, the enterocyte membrane contains proteins that are responsible for specialized (i.e., nonpassive) transport (influx) of certain molecules. In direct contrast with such processes but consistent with the GIT function as a barrier to the environment, there are also efflux transporters that move absorbed molecules back into the gut lumen. Complementing the efflux transporters is the metabolic activity of the enterocytes reflecting the high concentrations of cytochrome (phase I) and conjugating (phase II) enzymes. These enzymes are known to metabolize many drugs and form the basis for numerous drug-drug and drug-nutrient interactions. These factors are discussed in a later section.

The surface epithelial cells of the small intestine are renewed rapidly and regularly. It takes about two days for the cells of the duodenum to be renewed completely. As a result of its rapid renewal rate, the intestinal epithelium is susceptible to various factors that may influence proliferation. Exposure of the intestine to ionizing radiation and cytotoxic drugs (such as folic acid antagonists and colchicine) reduce the cell renewal rate.

Large Intestine

The large intestine, often referred to as the colon, has two primary functions: the absorption of water and electrolytes and the storage and elimination of fecal material. The large intestine, which has a greater diameter than the small intestine ($\sim$6 cm), is connected to the latter at the ileocecal junction. The wall of the ileum at this point has a thickened muscular coat called the ileocecal sphincter, which forms the ileocecal valve, whose principal function is to prevent backflow of fecal material from the colon into the small intestine. From a functional point of view the large intestine may be divided into two parts. The proximal half, concerned primarily with absorption, includes the cecum, ascending colon, and portions of the transverse colon. The distal half, concerned with storage and mass movement of fecal matter, includes part of the transverse and descending colon, the rectum, and anal regions, terminating at the internal anal sphincter (Fig. 1).

In humans, the large intestine usually receives about 500 mL of fluid-like food material (chyme) per day. As this material moves distally through the large intestine, water is absorbed, producing a viscous and finally a solid mass of matter. Because of efficient water absorption, of the 500 mL normally reaching the large intestine, approximately 80 mL are eliminated from the gut as fecal material.

Structurally, the large intestine is similar to the small intestine, although the luminal surface epithelium of the former lacks villi. The muscularis mucosa, as in the small intestine, consists of inner circular and outer longitudinal layers. Figure 6 (8) illustrates a photomicrograph and diagrammatic sketches of this region.

Pathways of Drug Absorption

Once a drug molecule is in solution, it has the potential to be absorbed. Whether or not it is in a form available for absorption depends on the physicochemical characteristics of the drug (i.e., its inherent absorbability) and the characteristics of its immediate environment (e.g., pH, the presence of interacting materials, and the local properties of the absorbing membrane). Assuming that there are no interfering substances present to impede absorption, the drug molecule must come in contact with the absorbing membrane. To accomplish this, the drug molecule must diffuse from the gastrointestinal (GI) fluids to the membrane surface. The most appropriate definition of drug absorption is the penetration of the drug across the intestinal "membrane" and the appearance of the unchanged form in the blood draining the GIT. The latter blood flow will drain into the portal circulation on the way to the liver. A clear distinction must be made between *absorbed* drug and *bioavailable* drug. The former was defined above; the latter refers to the appearance of unaltered drug in the systemic circulation (i.e., beyond the liver). There are two important points to this definition. First, it is often assumed that drug disappearance from the GI fluids represents absorption. This is true only if disappearance from the gut represents appearance in the blood stream. This may not be the case, for example, if the drug degrades in GI fluids or if it is metabolized within the intestinal cells. Second, the term intestinal membrane is rather misleading, since this membrane is not a unicellular structure but a number of unicellular membranes parallel to one another. In fact, relative to the molecular size of most drug molecules, the compound must diffuse a considerable distance. Thus, for a drug molecule to reach the blood, it must penetrate the mucous layer and brush border covering the GI lumen, the apical cell surface, the fluids within this cell, the basal membrane, the basement membrane, the tissue region of the lamina propria, the external capillary membrane, the cytoplasm of the capillary cell, and finally, the inner

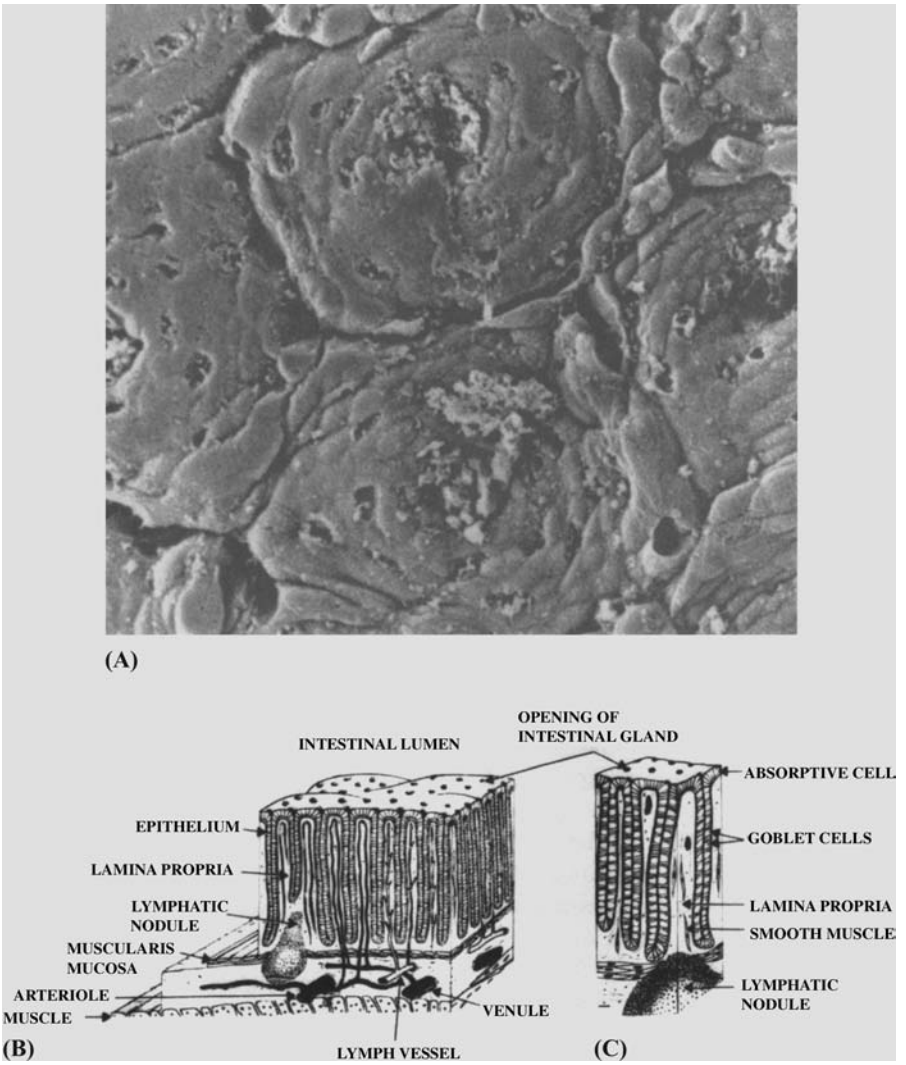


Figure 6 (**A**) Scanning electron micrograph of the luminal surface of the large intestine (transverse colon; magnification 60×). (**B**) Schematic diagram showing a longitudinal cross-section of the large intestine. (**C**) Enlargement of cross-section shown in (**B**). *Source*: Part A from Ref. 6 (see p. 135) and parts B and C modified from Ref. 8.

capillary membrane. Therefore, when the expression "intestinal membrane" is used, we are discussing a barrier to absorption consisting of several distinct unicellular membranes and fluid regions bounded by these membranes. Throughout this chapter the term intestinal membrane will be used in that sense.

For a drug molecule to be absorbed from the GIT and gain access to the portal circulation (on its way to the liver), it must effectively penetrate all the regions of the intestine just cited. There are primarily three factors governing this absorption process once a drug is in solution: the physicochemical characteristics of the molecule, the properties and components of the GI fluids, and the nature of the absorbing membrane. Although penetration of the intestinal membrane is obviously the first part of absorption, the factors controlling penetration are discussed in the following section. At this point,

assume that the drug molecule has penetrated most of the barriers in the intestine and has reached the lamina propria region. Once in this region the drug may either diffuse through the blood capillary membrane and be carried away in the bloodstream or penetrate the central lacteal and reach the lymph. These functional units of the villi are illustrated in Figure 4. Most drugs reach the systemic circulation via the bloodstream of the capillary network in the villi. The primary reason for this route being dominant over lymphatic penetration is the fact that the villi are highly and rapidly perfused by the bloodstream. Blood flow to the GIT in humans is approximately 500 to 1000 times greater than lymph flow. Thus, although the lymphatic system is a potential route for drug absorption from the intestine, under normal circumstances it will account for only a small fraction of the total amount absorbed. The major exception to this rule will be drugs (and environmental toxicants, such as insecticides) that have extremely large oil/water partition coefficients ($K_{o/w}$ greater than about 10^5 or log partition of 5). By increasing lymph flow or, alternatively, reducing blood flow, drug absorption via the lymphatic system may become more important. The capillary and lymphatic vessels are rather permeable to most low-molecular-weight and lipid-soluble compounds. The capillary membrane, however, represents a more substantial barrier than the central lacteal to the penetration of very large molecules or combinations of molecules as a result of frequent separations of cells along the lacteal surface. The lymphatic route of movement is important, for example, for the absorption of triglycerides or emulsified fats in the form of chylomicrons, which are rather large ($\sim$0.5 μm in diameter). A recent study has concluded that effective lymphatic absorption of a drug depends not only on $K_{o/w}$ but also on the ability to partition into chylomicrons and long-chain triglycerides (9).

PHYSICOCHEMICAL FACTORS GOVERNING DRUG ABSORPTION

Oil/Water Partition Coefficient and Chemical Structure

As a result of extensive experimentation done in the early 1900s, it has been found that the primary physicochemical properties of a drug influencing its passive absorption into and across biological membranes are its $K_{o/w}$, extent of ionization in biological fluids determined by its pK_a value and pH of the fluid in which it is dissolved, and its molecular weight or volume. Passive absorption refers to a first-order kinetic process not having any membrane involvement (i.e., no energy is required or expended for transport to occur). The fact that these variables govern drug absorption is a direct reflection of the nature of biological membranes. The cell surface of biological membranes (including those lining the entire GIT) is lipid in nature; as a result, one may view penetration into the intestinal cells as a competition for drug molecules between the aqueous environment on one hand and the lipid-like materials of the membrane on the other. To a large extent, then, the principles of solution chemistry and the molecular attractive forces to which the drug molecules are exposed will govern movement from an aqueous phase to the lipid-like phase of the membrane.

At the turn of the last century, Overton examined the osmotic behavior of the frog sartorius muscle soaked in a buffer solution containing various dissolved organic compounds. He reasoned that, if the solute entered the tissue, the weight of the muscle would remain essentially unchanged, whereas, loss of weight would indicate an osmotic withdrawal of fluid and hence impermeability to the solute in solution. He noted that, in general, the tissue was most readily penetrated by lipid-soluble compounds and poorly penetrated by lipid-insoluble substances. Overton was one of the first investigators to

illustrate that compounds penetrate cells in the same relative order as their $K_{o/w}$, suggesting the lipid-like nature of cell membranes. Using animal or plant cells, other workers provided data in support of Overton's observations. The only exception to this general rule was the observation that very small molecules penetrate cell membranes faster than would be expected based on their $K_{o/w}$ values. To explain the rapid penetration of these small molecules (e.g., urea, methanol, formamide), it was suggested that cell membranes, although lipid in nature, were not continuous but interrupted by small water-filled channels or "pores"; such membranes are best described as being lipid-sieve membranes. As a result, one could imagine lipid-soluble molecules readily penetrating the lipid regions of the membrane while small water-soluble molecules pass through the aqueous pores. Fordtran et al. (10) estimated the effective pore radius to be 7 to 8.5 and 3 to 3.8 Å in human jejunum and ileum, respectively. There may be a continuous distribution of pore sizes, a smaller fraction of larger ones and a greater fraction of smaller pores.

Our knowledge of biological membrane ultrastructure is the result of rapid advances in instrumentation. Although some controversy remains over the most correct biological membrane model, the concept of membrane structure presented by Davson and Danielli of a lipid bilayer is perhaps the one best accepted (11,12). The most current version of that basic model is illustrated in Figure 7 and is referred to as the "fluid mosaic" model of membrane structure (13). That model is consistent with what we have learned about the existence of specific ion channels and receptors within and along surface membranes.

Table 2 summarizes some literature data supporting the general dependence of the rate of absorption on $K_{o/w}$, as measured in the rat intestine (14,15). As with numerous other examples, as $K_{o/w}$ increases, the rate of absorption increases. However, note that this is seldom a simple linear relationship. For example, secobarbital has a value for absorption that is about three-times that of barbital; however, $K_{o/w}$ differs by 70-fold. One very extensive study (16–18) has examined in depth the physicochemical factors governing nonelectrolyte permeability for several hundred compounds. This study employed an in vitro rabbit gallbladder preparation, an organ whose mucosal surface is lined by epithelial cells. The method used to assess solute permeability is based upon

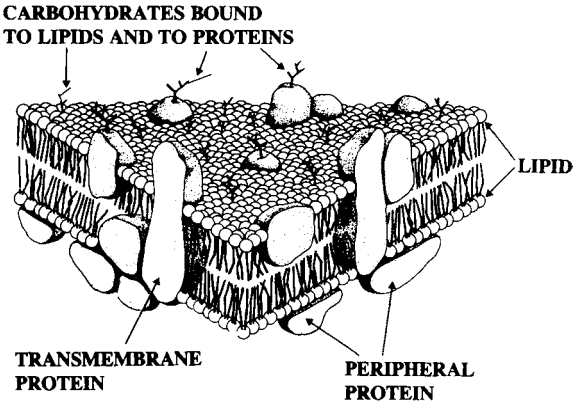


Figure 7 Diagrammatic representation of the fluid mosaic model of the cell membrane. The basic structure of the membrane is that of a lipid bilayer in which the lipid portion (*long tails*) points inward and the polar portion (*round "head"*) points outward. The membrane is penetrated by transmembrane (or integral) proteins. Attached to the surface of the membrane are peripheral proteins (*inner surface*) and carbohydrates that bind to lipid and protein molecules (*outer surface*). *Source*: Modified from Ref. 13.

Table 2 Influence of $K_{o/w}$ on Absorption from Rat Intestine

Compound	$K_{o/w}$	Percentage absorbed
Olive oil/water		
Valeramide	0.023	85
Lactamide	0.00058	67
Malonamide	0.00008	27
Chloroform/water		
Hexethal	>100	44
Secobarbital	50.7	40
Pentobarbital	28.0	30
Cyclobarbital	13.9	24
Butethal	11.7	24
Allybarbituric acid	10.5	23
Phenobarbital	4.8	20
Aprobarbital	4.9	17
Barbital	0.7	12

Abbreviation: $K_{o/w}$, oil/water partition coefficient.

measurement of differences in electrical potential (streaming potentials) across the membrane. The more permeable the compound, the smaller the osmotic pressure it exerts and the smaller the osmotic fluid flow it produces in the opposite direction; this results in a small potential difference. If the compound is impermeable, it produces a large osmotic pressure and osmotic fluid flow, resulting in a large potential difference. Experimentally, one exposes the mucosal membrane surface to a buffer solution containing a reference compound to which the membrane is completely impermeable (e.g., mannitol) and measures the resulting potential difference. This is followed by exposing the same membrane to a solution of a test compound and again measuring the resulting potential difference. The ratio of the potential difference of the test compound to that of the reference compound is referred to as the reflection coefficient (σ). The σ is a measure of the permeability of the test compound relative to a reference solute with the particular membrane being used. The less permeable the test compound, the closer the σ approaches 1 ($\sigma = 1$); the more permeable the test compound, the closer the σ approaches 0 ($\sigma = 0$).

By using this method, Wright and Diamond were able to reach a number of important conclusions concerning patterns of nonelectrolyte permeability. In general, membrane permeability of a solute increases with $K_{o/w}$, supporting previous findings mentioned earlier. The two classes of exceptions to this pattern are highly branched compounds, which penetrate the membrane more slowly than would be expected on the basis of their $K_{o/w}$, and smaller polar molecules, which penetrate the membrane more readily than would be expected on the basis of their $K_{o/w}$. The latter observation has been reported by other workers, and, as noted earlier, it has resulted in the development of the lipid-sieve membrane concept whereby one envisions aqueous pores in the membrane surface. The authors postulate that these small, polar, relatively lipid-insoluble compounds penetrate the membrane by following a route lined by the polar groupings of membrane constituents (i.e., localized polar regions). This concept is an attractive structural explanation of what have been referred to as pores. The accessibility of this route would be limited primarily by the molecular size of the compound as a result of steric hindrance. In fact, it is the first one or two members of a homologous series of compounds that are readily permeable, but beyond these members, it is primarily $K_{o/w}$ that dictates permeability. Table 3 illustrates this effect for several members of various

Table 3 Influence of Chain Length on Membrane Permeability Within Several Homologous Series

Compound	Reflection coefficient, σ
Urea	0.29 ↑
Methyl urea	0.54 |
Ethyl urea	0.92 |
Propyl urea	0.93 -
Butyl urea	0.70 ↓
Malononitrile	0.09 ↑
Succinonitrile	0.30 -
Glutaronitrile	0.21 ↓
Methylformamide	0.28 ↑
Methylacetamide	0.51 -
Methylproprionamide	0.22 ↓

The reflection coefficient σ is defined in the text. The direction of the arrows indicates an increase in permeability from the least permeable member of the series.

homologous series. Recall that the smaller the σ, the more permeable the compound. In each instance, permeability decreases after the first member, reaches a minimum, and then increases again.

The other anomalous behavior was the smaller-than-expected permeability of highly branched compounds. This deviation has been explained on the basis that membrane lipids are subject to a more highly constrained orientation (probably a parallel configuration of hydrocarbon chains of fatty acids) than are those in a bulk lipid solvent. As a result, branched compounds must disrupt this local lipid structure of the membrane and will encounter greater steric hindrance than will a straight-chain molecule. This effect with branched compounds is not adequately reflected in simple aqueous lipid-partitioning studies (i.e., in the $K_{o/w}$ value).

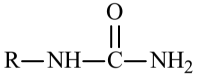
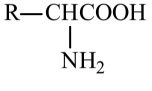
With the exception of rather small polar molecules, the majority of compounds, including drugs, appear to penetrate biological membranes via a lipid route. As a result the membrane permeability of most compounds is dependent on $K_{o/w}$. The physicochemical interpretation of this general relationship is based on the atomic and molecular forces to which the solute molecules are exposed in the aqueous and lipid phases. Thus, the ability of a compound to partition from an aqueous to a lipid phase of a membrane involves the balance between solute-water and solute-membrane intermolecular forces. If the attractive forces of the solute-water interaction are greater than those of the solute-membrane interaction, membrane permeability will be relatively poor and vice versa. In examining the permeability of a homologous series of compounds and, therefore, the influence of substitution or chain length on permeability, one must recognize the influence of the substituted group on the intermolecular forces in aqueous and membrane phases (e.g., dipole-dipole, dipole-induced dipole, or van der Waals forces). The membrane permeabilities of the nonelectrolytes studied appear to be largely determined by the number and strength of hydrogen bonds the solute can form with water. Thus, nonelectrolyte permeation is largely a question of physical organic chemistry in aqueous solution. Table 4 summarizes some of the interesting findings of Diamond and Wright with respect to the influence of substituent groups on membrane permeation. These data have been interpreted on the basis of the solutes' ability to form hydrogen bonds with water.

Table 4 Influence of Chemical Substitution on the Membrane Permeability of Several Series of Nonelectrolytes

Substituent group	Influence on membrane permeability	Compound	Example	σ[a]
Oxygen and nitrogen functional groups				
Alcoholic hydroxyl group (−OH)	(a) At any given chain length, permeability decreases as the number of −OH groups increases	*n*-Propanol	$CH_3CH_2CH_2OH$	0.02
		1,2-Propanediol	$CH_3CHOHCH_2OH$	0.84
		Glycerol	$CH_2OHCHOHCH_2OH$	0.95
	(b) Intramolecular H-bonds formed between adjacent −OH groups result in greater permeability compared with the same compound with nonadjacent −OH groups because of decreased H-bond formation with water	2,3-Butanediol	$CH_3CHOHCHOHCH_3$	0.74
		1,3-Butanediol	$CH_3CHOHCH_2CH_2OH$	0.77
		1,4-Butanediol	$Ch_2OHCH_2CH_2CH_2OH$	0.86
Ether group (−O−)	Has less of an influence than an −OH group in decreasing permeability	*n*-Propanol	$CH_3CH_2CH_2OH$	0.02
		Ethyleneglycol-methyl ether	$CH_3-O-CH_2CH_2OH$	0.15
		1,2-Propanediol	$CH_3CHOHCH_2OH$	0.84
Carbonyl group Ketone (−C=O) Aldehyde (−HC=O)	Has less of an influence than an −OH group in decreasing permeability; difficulty in measuring permeability of these compounds per se as many are unstable in solution-forming diols and enolic tautomers	Acetone	CH_3CCH_3 (O)	0.01
		2-Propanol	$CH_3CHOHCH_3$	0.10
		2-5-Hexanedione	$CH_3CCH_2CH_2CCH_3$ (O, O)	0.00
		2,5-Hexanediol	$CH_3CHOHCH_2CH_2CHOHCH_3$	0.59
Ester group (O ‖ (—C—O—))	Has less of an influence than an −OH group in decreasing permeability	1,2-Propanediol-1-acetate	$CH_3C(=O)-O-CH_2CHOHCH_3$	0.31
		1,5-Pentanediol	$CH_2OH(CH_2)_3CH_2OH$	0.71

(*Continued*)

Table 4 Influence of Chemical Substitution on the Membrane Permeability of Several Series of Nonelectrolytes (*Continued*)

Substituent group	Influence on membrane permeability	Compound	Example	σ[a]
Oxygen and nitrogen functional groups				
Amide group 	Causes a greater decrease in permeability than any of the above groups	*n*-Propanol	$CH_3CH_2CH_2OH$	0.02
		Acetone	$CH_3\overset{\overset{O}{\|\|}}{C}CH_3$	0.08
		Ethyleneglycol-methyl ether	$CH_3—O—CH_2CH_2OH$	0.15
		Proprionamide	$CH_3CH_2\overset{\overset{O}{\|\|}}{C}NH_2$	0.66
Urea derivatives 	These compounds have lower permeability than amides with the same number of carbons and are about as impermeable as the corresponding dihydroxyl alcohols	*n*-Butanl	$CH_3CH_2CH_2CH_2OH$	0.01
		n-Butryamide	$CH_3CH_2CH_2\overset{\overset{O}{\|\|}}{C}— NH_2$	0.42
		1,4-Butanediol	$CH_2OHCH_2CH_2CH_2OH$	0.86
		n-Propyl urea	$CH_3CH_2CH_2NH\overset{\overset{O}{\|\|}}{C}NH_2$	0.89
α-Amino acids 	These compounds have the lowest $K_{o/w}$ values of all organic molecules and are essentially impermeable due to large dipole-dipole interactions with water	Proprionamide	$CH_3CH_2\overset{\overset{O}{\|\|}}{C}NH_2$	0.66
		1-Amino-2-propanol	$CH_3CHOHCH_2NH_2$	0.89
		1,3-Propanediol	$CH_2OHCH_2CH_2OH$	0.92
		Alanine	$CH_3\overset{H_2N}{\overset{\|}{C}}H\overset{\overset{O}{\|\|}}{C}—OH$	0.06