



Voigt's Pharmaceutical Technology

Alfred Fahr

WILEY

A Comprehensive and Comprehensible Textbook that Offers Easy, Scientifically Sound, Reading to Both Students and Professionals

Now in its 12th edition in its native German, *Voigt's Pharmaceutical Technology* is an interdisciplinary textbook covering the fundamental principles of pharmaceutical technology. Available for the first time in English, this edition is produced in full colour throughout, with a concise, clear structure developed after consultation with students, instructors and researchers.

- Features clear chapter layouts and easily digestible content
- Presents novel trends, devices and processes
- Discusses classical and modern manufacturing processes
- Covers all formulation principles including tablets, ointments, capsules, nanosystems and biopharmaceutics
- Takes account of legal requirements for both qualitative and quantitative composition
- Addresses quality assurance considerations
- Relates contrasting international pharmacopeia from EU, US and Japan to formulation principles
- Includes examples and text boxes for quicker data assimilation

Written for both students studying pharmacy and industry professionals in the field as well as toxicologists, biochemists, medical lab technicians, *Voigt's Pharmaceutical Technology* is the essential resource for understanding the various aspects of pharmaceutical technology.

Prof. Dr. Alfred Fahr is Professor Emeritus in Pharmaceutical Technology at the Institute of Pharmacy, Friedrich-Schiller University of Jena, Germany. He was Head of laboratory at Sandoz Pharma (now Novartis) between 1986 and 1996 responsible for Biopharmaceutics, Human Pharmacology and Drug Delivery Systems, and spent six years at Philipps-Universität Marburg in the Faculty of Pharmacy and Food Chemistry before joining Friedrich-Schiller University of Jena in 2002. His research interests include biophysics of modern formulations, mechanisms of skin penetration and non-viral gene therapy, nanotechnological formulations in pharmacy and formulations of poorly soluble active substances.


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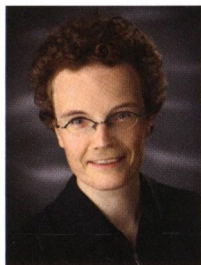
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Foreword

During my studies in Oxford, I had to follow a class in electrochemistry, and in the Bodleian library I found an excellent textbook on this topic. Comfortably stretched out on the perfectly trimmed lawn of my college, I started to read it. To my surprise, I quickly discovered that I was able to easily grasp the meaning of all the statements and formulas, which had given me so much trouble years before in Germany when I was following a similar class using a German textbook. I considered that, rather than due to my increased wisdom, this was due to the difference in style of textbook writing between German and Anglo-Saxon countries. In other words, “A German author likes to emphasize the complexity of matters that only he understands.”

At the end of my studies, I decided that, whenever I would have the opportunity to write my own textbook, I would bring into practice the ideas and recommendations that famous writers and philosophers have provided us with over the centuries. For example, Voltaire left us the consideration that “The secret of being a bore... is to tell everything.”

The chance to write a textbook came when Rudolf Voigt, the founder of the original German version of this textbook half a century ago, asked me to continue his life's work, 20 years ago. Over the following German editions, while basically sticking to Voigt's original intentions, I tried to follow the early philosophers as much as scientific restrictions would allow. Obviously, by doing so it was unavoidable to accept compromises, some of which I have specified below.

Teaching the complex subject of pharmaceutical technology is approached differently in different areas of the world. In some countries, pharmacy students are just taught to make an ointment and become acquainted to various extents with other technologies by means of demonstrations or videos. In Europe, on the other hand, pharmaceutical technology is taught to pharmacy students in extensive and comprehensive courses, including several practical courses concluded by highly demanding exams. In Germany, each individual student prepares ALL conceivable formulations in the lab so that he or she is familiar with each relevant detail of each product sold in a pharmacy and also gains a solid background for a career in pharmaceutical industry.

Students do not invariably undergo this learning process with great pleasure and enthusiasm. This makes teachers aware of specific difficulties that students experience in thoroughly understanding the scientific background of the various technologies. At the same time, it will hopefully teach them to effectively and elegantly handle situations arising from the lack of understanding of students. The educational experience, thus gathered over the past decades, has been gradually integrated into this book. Thus, we have tried to visualize the manifold principles of the different technologies and their applications, both by means of text and technical illustrations.

We are aware that for many students, it is a nightmare to discover that understanding pharmaceutical technology is based on a solid background in fields such as chemistry, physics, biology, material science, medicine, and (worst of all!) mathematics (statistics).

The reader will find these topics in the first few chapters, including, for example, statistics. In Germany, statistics is not taught at the required level in the regular pharmacy curriculum. Therefore, the statistics chapter was added with the idea in mind that the combination of any rudimentary exposure to stats with thorough reading of this chapter should enable the reader to build a sufficient level of comprehension to serve as a solid base in statistics for a professional career in pharmacy.

As the reader may have guessed, this is one of the compromises I mentioned above. I do believe it is worthwhile.

The other compromise the reader will encounter is in Chapter 5, in which we deal with all known excipients. A large number of German readers (students and professionals alike) were

in favor of this idea. A potential drawback of this decision is that it may occasionally require the reader to browse through this chapter for detailed information on certain excipients described in the context of pharmaceutical formulations in other chapters (but that is why the index register was created!).

Other features which may be helpful to the reader are the boxes explaining details and text boxes derived from paragraphs of the Ph. Eur., which may serve to give insight in the way scientific observations find their way into regulatory texts. In the English edition, we added in these text boxes the corresponding texts from USP and the Japanese Pharmacopeia in a comparative way. The Annex section was improved similarly. Here the reader can find descriptions of representative pharmaceutical formulations taking into consideration the differences with respect to preparation methods and tests between the three main pharmacopeias for the dosage forms chosen. We trust this will be helpful not only for the pharmacy student to guide her or him on the way to become a pharmacist and beyond, but will be appreciated by the established professional pharmacist as well.

About the English edition: The mission of all of us was to compose a textbook that was both comprehensive and comprehensible. It was meant to offer relatively easy but scientifically sound reading to an audience of students and professionals, much like the latest German edition. When Wiley suggested that publication of an English version of the book might be worth considering, we set out to find someone knowledgeable enough in the field to grasp at least the scientific backgrounds of the immense field involved and at the same time possessing enough passive knowledge of the German language to understand the German texts and active knowledge of English to produce an acceptable first draft of an English text, although not necessarily being a native speaker. Such a person was found, and his initial English texts were edited by us for scientific and terminological correctness. The resulting texts were subsequently edited by five motivated British PhD students of pharmacy. In addition to language editing they also provided useful suggestions for missing content.

Together with the contributors, I monitored all these processes.

Meanwhile—this process alone took over one year—I also consulted a number of highly competent colleagues from industry and academia about novel trends, devices, and processes. It was highly gratifying to observe how generously all these experts were willing to provide me with relevant information. The names of all these individuals can be found below. Thus, this first English edition has become much more than a mere translation of our 12th German edition. I already have started thinking about translating the English edition into our next 13th German edition.

We anticipate that Wiley's decision to produce a multicolored edition will substantially add to its readability and thus to the digestion by the reader. Prof. Dr. Judith Kuntsche, who created the modern graphics in the latest German editions, appropriately transformed those and produced new ones to offer a new dimension in visualisation.

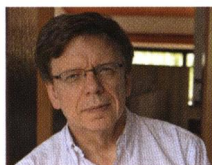
My special thanks go to Rebecca Stubbs and Sarah Keegan at Wiley in the UK for their constant support and unconventional assistance all through the translating part of the project. I thank Cheryl Ferguson in the USA for the very interactive time during her copy editing work and her teaching of good (American) English. The final production process of the book including composing and the almost never-ending story of proofreading and—changing was done on another continent for this international book by Audrey Koh in Singapore and Shalini Sharma in India, two very lenient and patient ladies. Surely there were many other people at Wiley involved whom I want to say “Thank You” for accompanying me on this long journey.

I would also thank my family for their understanding for the last years. This goes especially to my kids Sophie and Fabian, that on many days an unshaved man appeared to finish off his breakfast or dinner in the upper rooms of the house, rapidly disappearing again in his haunts back to his computers and books. *Was this daddy?*—Yes! my loving wife would have answered. Thanks for understanding my interpretation of the word “retired”, dear Sabine!

We all hope that you will appreciate our efforts. We do not have the illusion that this book will be different from other textbooks by being flawless (particularly as being the 1st edition). Therefore, we are soliciting your alertness for typos and—yes, we will be prepared to face it—blatant errors and other mistakes like untranslated German words.

Please email me when you have found one or more of those in this book. I will collect all errors found by the users of the book and every half year I will draw one of the reporters for a prize. For the German edition, I have awarded thus far bottles of wine from my hometown on Lake Constance as a token of our appreciation. For the international book, I might have to think of a less fragile item.

The elimination of any bugs and additional information about new trends in pharmaceuticals and more profound and detailed insights into technologies you might find on my website www.alfred-fahr.com. Please email me (alfred.fahr@uni-jena.de) for any suggestions.



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Finally, I would like to thank Kalpa Nagarsenker and Mukul Ashtikar, for their proofreading and contributions in providing explanations at the proper places to make this book even more readable.

List of Abbreviations

A

AE	anion exchanger
AAS	Atomic absorption spectrometry
ACTH	adrenocorticotrophic hormone
ADME	absorption, distribution, metabolism, elimination
AFM	Atomic Force Microscopy
AIO	all in one
ANM	amylum non mucilaginosum
API	active pharmaceutical ingredient
ASTM	American Society for Testing and Materials
AUC	Area under the curve

B

BA	bioavailability
BBB	blood brain barrier
BE	bioequivalence
BET	bacterial endotoxin test
BET theory	Brunauer-Emmett-Teller theory
BFS	blow fill seal
BHA	butylhydroxyanisole
BHT	butylhydroxytoluene
BODI	Bioadhesive ophthalmic drug inserts
BSE	Bovine Spongiform Encephalopathy

C

CAP	cellulose acetate phthalate
CCS	container closure system
CE	cation exchanger
CEN	Comité Européen de Normalisation (European Committee for Standardization)
CFR	Code of Federal Regulations
CFU	colony forming unit
CMC	critical micelle concentration (the concentration of surfactants above which micelles are spontaneously formed)
CMV	cytomegalovirus
COC	certificat of conformity
COMOD	continuous mono dose
CQAs	critical quality attributes
CTD	common technological document

D

d	day
DAB	Deutsches Arzneibuch (German Pharmacopeia)
DAC	Deutscher Arzneimittel-Codex (German Drug Codex)
DB	double blind
DCJI	disposable-cartridge jet injector
DER	Drug-Extract-Relation
DIN	Deutsche Industrienorm (German Industrial Standard)
DIN	German Institute for Normalization

DLVO theory	named after Boris Derjaguin, Lev Landau, Evert Verwey and Theodor Overbeek
DOE	design of experiments
DPI	Dry powder inhaler
DSC	differential scanning calorimetry
DVS	Dynamic Vapor Sorption
E	
EDTA	ethylenediaminetetraacetate
ELISA	enzyme-linked immunosorbent assay
F	
FDA	Food and Drug Administration (federal agency of the United States Department of Health and Human Services)
FIP	Fédération Internationale Pharmaceutique (International Pharmaceutical Federation)
FTIR	Fourier transform infrared spectroscopy
G	
GACP	Good Agricultural and Collection Practice
GCP	Good Clinical Practice
GIT	gastrointestinal tract
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GRAS	generally recognized as safe
H	
HAB	Homöopathisches Arzneibuch (Homeopathic Pharmacopeia)
HDPE	high density polyethylene
HEC	hydroxyethylcellulose
HEMA	hydroxyethylmethacrylate
HEPA filter	high-efficiency particulate air filter
HES	hydroxyethyl starch
HFA	hydrofluoroalkane
HFC	partially fluorinated hydrocarbon
HIV	human immunodeficiency virus
HLB	hydrophilic-lipophilic balance
HPC	hydroxypropylcellulose
HPMC	hydroxypropylmethylcellulose
HPMCP	hydroxypropylmethylcellulose phthalate
I	
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IUPAC	International Union of Pure and Applied Chemistry
J	
JP	Japanese Pharmacopeia
L	
LADME	liberation, absorption, distribution, metabolism, excretion
LAF	laminar air flow
LAL	Limulus Amebocyte Lysate (test)
LDPE	low density polyethylene (see also PE-LD)
lg	logarithm with base 10
LOD	limit of detection
LVP	large-volume parenterals