The Theory and Practice of Industrial Pharmacy

SECOND

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SECOND EDITION

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Preface

Because the first edition of this book was also the first book on the comprehensive treatment of industrial pharmacy, its editors were faced with making decisions on scope, format, and level of presentation of material with no benchmarks to serve as guides other than their own instinctive awareness of the needs of students and workers in the field of industrial pharmacy. Since the book's publication in 1970, comments received from the United States and abroad provided us with many helpful suggestions for improvement of its contents. Because of these valuable suggestions and the many advances that have taken place in pharmaceutical technology and governmental regulations affecting drugs, a revision of this book was necessary.

This second edition, like the first, is written as a teaching text for undergraduate and graduate students in the pharmaceutical sciences, and it is also intended to serve as a comprehensive reference source on modern industrial pharmacy. As such, this book will be useful to practitioners in the pharmaceutical sciences, hospital pharmacists, drug patent attorneys, governmental scientists and regulatory personnel, those in the allied health sciences, and others seeking information on the design, manufacture, and control of dosage forms and government regulations pertaining to drug manufacture.

The second edition required considerable updating of existing chapters, elimination of certain chapters from the first edition, and inclusion of new chapters on Preformulation, Production Management, Packaging Materials, Science, and Drug Regulatory Affairs.

It also provides for an improved flow of the subjects covered. The early chapters are concerned with the theoretical concepts needed to approach dosage form design on a scientific basis. These are followed by chapters that discuss specific dosage forms. The chapters toward the end of the book provide for an understanding of pilot plant operations, production management and operations, packaging materials science and operations, quality control, and drug regulatory affairs.

Through this revision the second edition amplifies the usefulness and uniqueness of the book's comprehensive coverage of industrial pharmacy. All the material is presented in a readily comprehendible form to those of varying scientific backgrounds using the book as a text or as a reference source.

Each contributor was chosen because of expertise in a particular area of industrial pharmacy or the pharmaceutical sciences as well as ability to select material of major importance and present it in a readily comprehensible form. The acceptability and usefulness of the book

should be largely attributed to the efforts of these contributing authors. Each is a nationally or internationally recognized expert.

We editors express our deep appreciation to these authors for their cooperation and extensive labors in working with us to weld their efforts into a comprehensive text with a single common objective. Their forbearance with our demands for revision and modification of their efforts is deeply appreciated. The choices of subject matter and format have been our responsibilities. It is hoped that our judgment and the labors of the contributors have resulted in an improved book on theory and practice of industrial pharmacy.

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Contents

CHAPTER 1

PREFORMULATION

ELIE G. SHAMI, JOHN R. DUDZINSKI, AND RUSSELL J. LANTZ, JR.

Preformulation may be described as the process of optimizing a drug through the determination and/or definition of those physical and chemical properties considered important in the formulation of a stable, effective, and safe dosage form. The possible interactions with the various components intended for use in the final drug product are also considered.

It is an effort that encompasses the study of such parameters as dissolution, polymorphic forms and crystal size and shape, pH profile of stability, and drug-excipient interactions, which may have a profound effect on a drug's physiological availability and physical and chemical stability. The data obtained from the aforementioned studies are integrated with those obtained from preliminary pharmacological and biochemical studies, providing the development pharmacist with information that permits the selection of the best drug form, and the most desirable excipients for use in its development.

Pharmaceutical preformulation work is generally initiated after a compound shows sufficiently impressive results of biological screening. Since the development of analytical procedures, stability indicating methods in particular, may require a considerable amount of time, and because of the importance of stability testing, analytical and preformulation work should begin simultaneously. At the very least, one should have a thin-layer chromatographic procedure capable of determining whether the drug molecule has undergone degradation.

Stability, although important, should not be the only initial concern of the physical pharmacist. The compound, as received, may exhibit biological inactivity as a result of undesirable physical properties, such as too large a particle size resulting in slow rate of dissolution and/or undesirable chemical properties, e.g., the propensity to hydrolyze in gastric fluid. For example, Table 1-1 shows that the 7-esters of lincomycin are more resistant to hydrolysis by intestinal enzymes than are the corresponding 2-esters.[1] Lack of additional investigation of such properties could lead to the discarding of an otherwise promising drug candidate. Biological scientists are becoming increasingly aware of the importance of physicochemical properties of drug substances and their effects on the living organism. However, the physical pharmacist remains primarily responsible for recommending the best drug forms.

Flexibility is the key to a successful preformulation program. Some experimental drugs may need more effort in some areas than in others. These areas become evident

TABLE 1-1. *Hydrolysis of Lincomycin Esters by Homogenates of Rat Intestine*

Derivative	*mcg.* Placed into Flask*	*Intrinsic Activity mcg. in Control Flask†*	*Lincomycin, mcg. after incubation*
2-Butyrate	2,280 ± 28‡	421 ± 2	2,220 ± 48
7-Butyrate	2,050 ± 68	60 ± 6	610 ± 62
2-Propionate	2,640 ± 10	400 ± 18	2,630 ± 45
7-Propionate	2,700 ± 56	< 15	< 15

(From Fletcher, H., et al.: J. Pharm. Sci., 57:2101, 1968.)
* Determined by microbiological assay.
† Contained boiled homogenate.
‡ Mean of six flask ± SE.

as data are accumulated, e.g., a hydrochloride salt of a drug may be hygroscopic and a change to the phosphate salt may solve the problem. This approach isolates early undesirable physicochemical properties before time-consuming and costly toxicological, biological, or clinical trials are undertaken.

PREFORMULATION METHODOLOGY

The starting point for the preformulation of a new drug entity should be to obtain from the medicinal chemist such information as structure, spectral data, and melting point. At the same time, a prudent literature search on compounds with closely related structures may be indicated.

The major direction of the investigation is determined by: (1) the type of compound under investigation, and (2) the intended dosage form(s) to be developed. For example, if a compound has a basic phenothiazine structure, it may be assumed that light catalyzed oxidation will be a prime degradation pathway necessitating possible investigation of antioxidants. A drug with a steroid nucleus might be expected to have a number

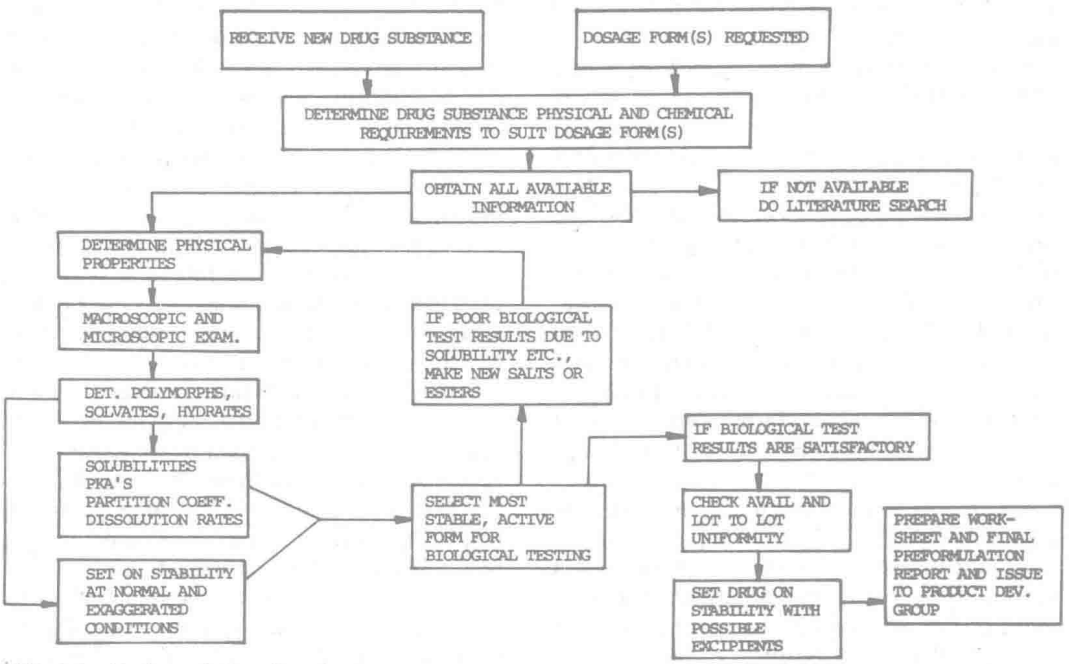

FIG. 1-1. Preformulation flowsheet.

of polymorphic forms, as is common to this type of structure. Investigating the polymorphic properties is important, since polymorphic forms in many cases exhibit differences in biological availability.

A good practice in planning preformulation work is to prepare an outline in the form of a flow diagram (Fig. 1-1). The data generated during preformulation studies is best summarized on a work sheet (Fig. 1-2), which serves as an effective means of information transfer to the development pharmacist. This work sheet form varies from company to company, its format being left to the discretion of the investigator(s).

SOLID STATE PROPERTIES

Macroscopic Observations. The general appearance, color, and odor of a drug substance under investigation should be recorded, along with the bulk density and flow properties. This establishes a basis of comparison for future lots. In some cases, the sense organs can detect subtle differences which, though important, were not detected during analysis. For example, one of two lots of a new drug compound received from a particular source is free-flowing, whereas the second lot is aggregated in large, hard-to-fracture lumps. Recording and comparing the differences in general appearance, odor, and color might indicate to the investigator that the latter of these two lots had possibly picked up moisture, was not free of recrystallizing solvent, or may have fused because of exposure to excessive heat. The difference in the two lots raises a question as to the control or reproducibility of the manufacturing process.

Taste becomes an important factor when the drug is intended for oral use, particularly in pediatric dosage forms or extremely bitter substances. In such cases other possible forms of the drug might be considered, such as insoluble esters (e.g., chloramphenicol palmitate).

Microscopic Observations. In many respects the microscopic examination of solid drug substances in preformulation work is as important as, if not more so than, the macroscopic examination, because it acquaints one with the unit particle of a substance and its properties.

These basic properties may be best identified through the polarizing microscope, which often provides the pharmaceutical scientist with information impossible to obtain by other methods.

When a drug is first received, a sample is mounted on a slide in air and in a liquid refracting medium in which the drug is insoluble. Examination under several different magnifications, usually between 40× and 400×, will reveal the approximate particle size and size range, the particle shape and/or basic crystal habit, and the degree of particle agglomeration or aggregation. (Particle size and shape and their importance will be discussed on page 5.)

All crystalline substances that are transparent or near transparent, when observed through polarizing filters with their vibrational directions oriented at right angles to one another (Fig. 1-3), fall into one of two refractive index classes:

1. *Isotropic class*—materials such as glass and sodium chloride which have a single refractive index; i.e., all light waves travel through the substance at the same velocity and transmit no polarized light (total black field with polarized light).
2. *Anisotropic class*—materials showing two or three refractive indices which show up bright, often times with brilliant colors, against the black polarized background; i.e., different light waves travel through the substance at different velocities interfering with the normal make-up of white light. These materials are divided into two groups: (a) uniaxial material having two principal refractive indices such as quartz and synthetic fibers; and (b) biaxial materials having three principal refractive indices such as sucrose and talc.

Most drug substances are anisotropic and biaxial, and they exhibit a characteristic known as birefringence, which is the numerical difference between the maximum and minimum differences in refractive indices of the substance. By taking advantage of the birefringence characteristics, the physical pharmacist, with the aid of the Michel-Levy interference color chart,[2] may identify sub-

Date _____

Compound _____

Lot No. _____

Investigator _____

1. Color _____ 3. Odor _____

2. Taste _____ 4. Appearance _____

5. Microscopic Examination Comments and Photomicrographs

6. Polymorphism, Solvates and Crystal Habit

7. Particle Size

8. Solubility (mg./ml.)

Water _____ 0.1N HCl _____

Ethanol _____ Buffer pH 7.4 _____

Other _____

9. Melting Point and DSC

10. Density

a) True _____ b) Bulk _____

11. pH _____% in H_2O

12. pKa and Partition Coefficient

13. Dissolution Rate in _____

a) Constant Surface b) Suspension

14. Stability of Bulk Drug

a) 60°C. for 30 days _____

b) 600 foot candles for 30 days _____

c) 80% RH/25°C. for 30 days _____

FIG. 1-2. Work sheet for summarizing data.

stances, and in some cases, estimate the amount of impurity in a substance without having to determine the individual principal refractive indices of the compound. Establishing this type of microscopic test for new drug substances is important, because it may permit the identification of future lots of a substance as well as an estimate of their impurity before costly and time-consuming analytical procedures are developed and/or performed.

A semiquantitative estimate of purity may be obtained by use of a microscope fitted with a hot stage. The hot stage permits heat-

15. Solution Stability

pH	Rate Constant 40°C.	50°C.	60°C.	70°C.
_____	___	___	___	___
_____	___	___	___	___
_____	___	___	___	___
_____	___	___	___	___

Activation Energy _____

16. Relative Humidity — %Wt. Gain or loss at equilibrium

30%	_____
50%	_____
60%	_____
70%	_____
90%	_____
Initial	_____

17. Solid State Study with excipients

Excipient	Physical Observation	TLC Data
Lactose Anhydrous		
Lactose USP		
Starch		
Carboxymethyl Starch		
Microcrystalline Cellulose		
Magnesium Stearate		
Stearic Acid		
Dicalcium PO_4		

Excipient	DSC Data
Lactose Anhydrous	
Lactose USP	
Starch	
Carboxymethyl Starch	
Microcrystalline Cellulose	
Magnesium Stearate	
Stearic Acid	
Dicalcium PO_4	

18. Analytical Data

ing of the sample at a constant slow rate, which allows sharp melting points to be observed with pure materials that are essentially crystalline in nature. Soluble impurities in a compound tend to lower the final melting point, and instead of the characteristic sharp melting point, a melting temperature range is observed.

If the sample is mounted in silicone oil and heated, bubbles may be seen when the hot stage temperature reaches the point at which hydrated or solvated crystals release their lattice-bound solvents. Figure 1-4 shows a compound before and after desolvation on heating.

Particle Size. Drug dissolution rate, absorption rate, content uniformity, taste, texture, color, and stability are dependent, to varying degrees, on particle size and size distribution. In many cases, drug particle

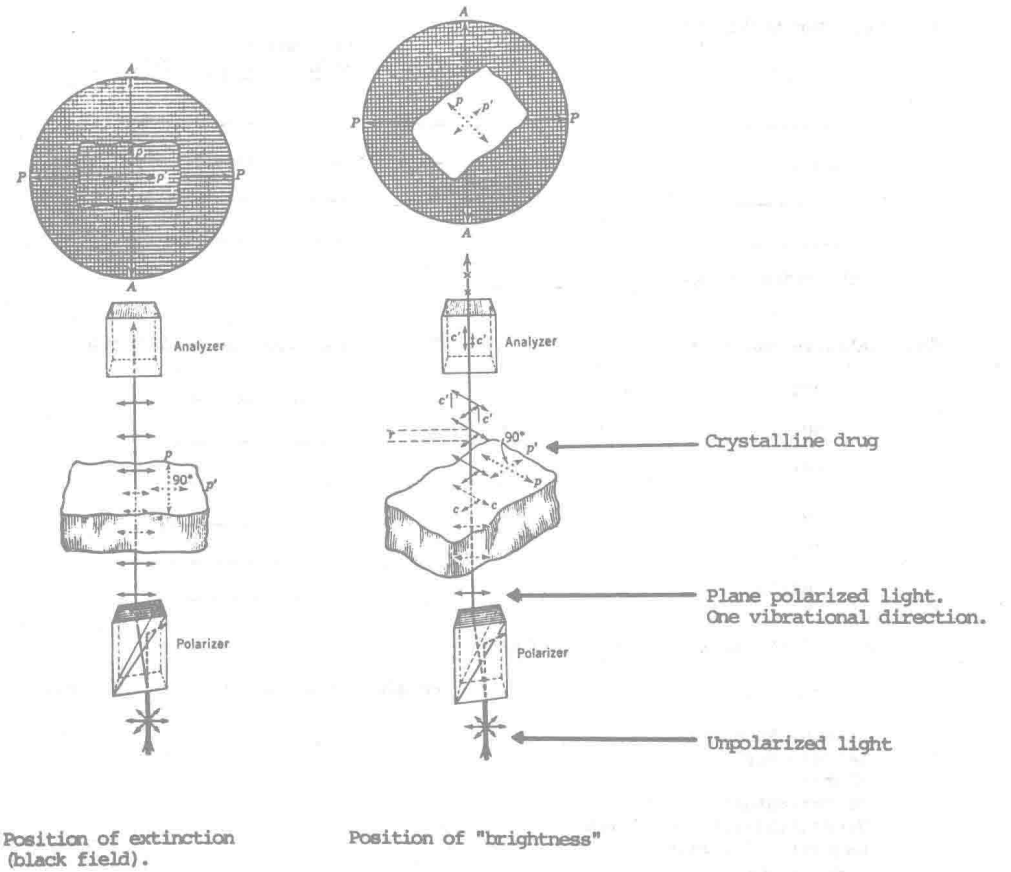

FIG. 1-3. Passage of light through an optically anisotropic substrate between crossed polarizers. (Modified from Chamot, E. M., and Mason, C. W.: Handbook of Chemical Microscopy. John Wiley & Sons, Third Edition, 1958.)

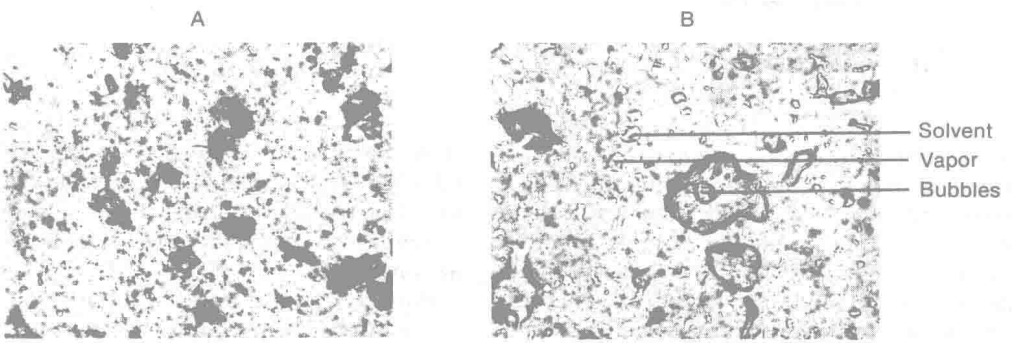

FIG. 1-4. A dihydrate compound heated in silicone oil. *A*, Before dehydration; *B*, after dehydration.