Theory of Pharmaceutical Systems

Volume I/General Principles

J. Thurø Carstensen

theory of pharmaceutical systems

J. THURØ CARSTENSEN
University of Wisconsin
Madison, Wisconsin

VOLUME I

General Principles

ACADEMIC PRESS *New York and London* 1972

ACADEMIC PRESS, INC.
111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS, INC. (LONDON) LTD.
24/28 Oval Road, London NW1

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 72-82630

PRINTED IN THE UNITED STATES OF AMERICA

preface

It is the intent of this book to describe phenomena involved with pharmaceutical systems and the methods employed in investigating them. For this purpose, it has been necessary to touch on a variety of fields. First, for the description of experimental design and discussion of quality control (both important aspects of the dosage form), statistics are necessary; a fair amount of this topic as it relates to pharmaceutics is therefore included. Second, pharmaceutical research is, by necessity, tied to physicochemical principles and a chapter dealing with pharmacoenergetics has therefore been deemed essential; in treating this subject, brevity has been emphasized since the book is not intended to be used as text material in thermodynamics. Third, technology and engineering principles are part of the topic and have been included where needed. Hence, the book is by no means homogeneous, but spans a range of disciplines. It is hoped that it will bring to the pharmaceutical reader a better insight into his own problems as well as an insight into the means by which problems are viewed and solved in the pharmaceutical sciences.

Most of the material presented here has been used as lecture material in courses at the School of Pharmacy at the University of Wisconsin, Madison, Wisconsin, particularly courses in physical pharmacy, the theory of dosage forms, pharmaceutical solids theory, and statistical aspects of pharmaceutics, the latter two being graduate level courses. In addition, a great deal of the material has been drawn from lecture notes used for industrial short courses

offered by the University extension program in pharmaceutical product development (courses on solutions, disperse systems, solids, and statistics).

The subject matter can logically be divided into a section dealing with homogeneous systems and one dealing with heterogeneous systems and the material has, therefore, been separated into two volumes. However, each volume can be viewed as a separate entity.

The author is indebted to the following for aid and encouragement in preparing these books: Dr. E. R. Garrett, Dr. S. H. Rubin, Dr. W. Blockstein, Mr. J. J. Vance, Mr. H. Newmark and Mr. J. F. Weidenheimer. The author is indebted to Miss Margaret L. Cotton for some of the typing of Volume II and to Peter Thurø Carstensen, for the drawing of a large portion of the figures in Volume II.

contents

OF VOLUME II

HETEROGENEOUS SYSTEMS

1 DISPERSE SYSTEMS

2 FUNDAMENTAL PROPERTIES OF THE SOLID STATE

3 POWDERS

4 SOLID DOSAGE FORMS

5 STABILITY IN THE SOLID STATE

Author Index—Subject Index

contents

Preface xi
Contents of Volume II xiii

1 STATISTICS IN PHARMACEUTICAL THEORY, EXPERIMENTATION, AND QUALITY CONTROL

List of Symbols 2
1-1 Model Systems and Dosage Forms 3
1-2 Stages in Product Development 4
1-3 Single Determinations 5
1-4 The Gaussian Distribution Curve 6
1-5 Comparison of Averages 10
1-6 Standard Deviation of Sums, Differences, and Ratios 14
1-7 Statistics of the Straight Line 14
1-8 Transformations 19
1-9 Best Fits 21
1-10 Least-Squares Fits of Many Parameters 23
1-11 Least-Squares Nonlinear Fits 24
1-12 Factorials 25
1-13 Formulation–Response Limits 29
1-14 Curvature 31
1-15 Lagrangian Multipliers 33
1-16 Phenomenology 37
1-17 Theoretical Curves 38

1-18 The Monte Carlo Method 40
1-19 The Binomial Distribution 42
1-20 Probability in Sampling 43
1-21 Manufacturer's Cost and Consumer's Risk 44
1-22 Sampling 51
1-23 Shewhart Control Charts 53
General References 55
Specific References 55

2 PHARMACOENERGETICS

List of Symbols 58
2-1 Units 59
2-2 Thermodynamics 61
2-3 The Thermodynamic Functions 61
2-4 Heat 62
2-5 Measurement of Heat 63
2-6 Ideal Gases and the Gas Constant 64
2-7 Chemical Potential and Reactions 65
2-8 Equilibria 67
2-9 Absolute Values of Thermodynamic Functions 68
2-10 The Gibbs Phase Rule 68
2-11 Entropy 69
2-12 Boltzmann's Distribution Law 70

3 HOMOGENEOUS LIQUID SYSTEMS

List of Symbols 74
3-1 Solutions 76
3-2 Ideal Solutions 77
3-3 The Clausius–Clapeyron Equation 81
3-4 Optical Properties of Solutions 83
3-5 Viscosity of Newtonian Substances 87
3-6 Viscosity of Non-Newtonian Liquids 91
3-7 Colligative Properties 101
3-8 Electrolytes 106
3-9 Isotonicity 108
3-10 Strong Electrolytes 109
3-11 Weak Electrolytes 111
3-12 Ionic Effects 116
3-13 Determination of pK_a and pK_b 117
3-14 Buffers 119
3-15 Solubility of Strong Electrolytes 123
3-16 Solubility of Weak Electrolytes 125
3-17 Solubility of Nonelectrolytes 128
3-18 Surface Tension 141
3-19 Heat Capacity of Solutions 144
3-20 Structure of Liquid Water 146
3-21 Parenteral Solutions 148
3-22 Aerosols 161
References 163

4 KINETIC, DIFFUSIONAL, AND PHARMACOKINETIC PROCESSES

List of Symbols 168
4-1 Order of a Reaction 170
4-2 Pseudoorder Reactions 172
4-3 Temperature Dependence 177
4-4 Consecutive Reactions 181
4-5 Equilibria 182
4-6 Nonisothermal Kinetics 183
4-7 Shelf Life at Nonconstant Temperature 184
4-8 Stability Prediction by Fractional Life 185
4-9 Formation Rates of Decomposition Products 190
4-10 Room-Temperature Data 193
4-11 Complexation 194
4-12 Transition-State Theory 196
4-13 Kinetic Salt Effect 197
4-14 Linear Free-Energy Relationships 203
4-15 Solvent Effects 206
4-16 Vitamin Stability 206
4-17 Enzyme Kinetics 218
4-18 Diffusion 219
4-19 Diffusion of Vapors and Gases through Polymers 219
4-20 Dissolution Rates 238
4-21 Biopharmaceutics and Pharmacokinetics 242
4-22 Effectiveness 242
4-23 The One-Compartment Open Model 243
4-24 Availability 246
4-25 The pH-Partition Hypothesis 252
4-26 Multiple Doses 254
4-27 The Two-Compartment Model 256
4-28 Responses 261
4-29 Urinary Excretion 263
4-30 Protein Binding 264
References 265

Author Index 271
Subject Index 277

chapter 1

STATISTICS IN PHARMACEUTICAL THEORY, EXPERIMENTATION, AND QUALITY CONTROL

LIST OF SYMBOLS

- A arbitrary number differing from the mean
- a preexponential factor
- B batch size
- b non-Briggsian exponent
- C concentration
- D standard deviation in control charts
- f function
- g function
- i running index in summations
- j running index in summations
- k rate constant
- m degrees of freedom with $m + n$ data and n parameters
- N number of determinations
- n (a) number of determinations, (b) exponent in binomial expansion
- OC operational characteristic
- p (a) number of determinations in a row in rank testing, (b) probability in binomial expansion
- R range
- r radius
- S^2 sum of squares of distances from actual points to a least-squares-fit curve
- s (a) sample size, (b) standard deviation
- s_b standard deviation in F-test
- $s^2_{x,y}$ sum of squares of distances of actual points to least-squares-fit curve, divided by $n - 2$
- T total
- t time
- x independent variable
- y dependent variable
- $\tilde{y}_0$ y-value when the value x_0 is inserted in the least squares fit equation
- w weight
- α (a) slope, (b) proportionality factor
- β intercept
- Δ difference between a point and the least-squares-fit curve
- γ one-half the length of a confidence interval about an extrapolated value
- λ Poisson exponent
- μ (a) mean, (b) Lagrangian multiplier
- σ^2 variance
- χ^2 parameter for χ^2-test

1-1. MODEL SYSTEMS AND DOSAGE FORMS

The purpose of this book is to explore the theories underlying scientific investigations in the field of pharmaceutics. Such investigations are either carried out through academic motivation or are related to the development of a dosage form. Pharmaceutical compounding today is rarely carried out in the pharmacy, but rather in large scale by the pharmaceutical industry, and therefore product development is compounding in a different framework.

The immediate goals of academic vis-à-vis pharmaceutical development investigations may seem different in the sense that the purpose of the former is to elucidate a mechanism or phenomenon and that of the latter is to solve a problem on a technical scale. Where the former employs model systems with as few variables as possible, the latter is forced to consider multivariable situations. For this reason, investigations of actual pharmaceutical systems frequently result in phenomenological equations; the investigations lead to dosage forms and the phenomenological equations arrived at may allow, at times, conclusions concerning the molecular state of the system to be reached. The academic pursuit arrives at a conclusion regarding the molecular state of affairs, but rarely results in a dosage form.

Common to both forms of development are experimentation and the statistical principles underlying the design of experiments and the interpretation

of the results. This is one reason why the topic of statistics is the vantage point of this text. Another reason is that it and thermodynamics form a base for much of the material to follow.

Statistics is of importance both in model and practical investigations for the determination of best estimates of parameters (slopes and intercepts), to test whether two values are different, and to elucidate which type of curve may fit a set of data best. These concepts will be discussed in the following sections. One concept useful in product development but not frequently employed in model system investigations is that of optimization; some space will be devoted to this topic at this point since it fits in conceptually with statistical principles. On the other hand, the Monte Carlo method is probably of more interest in model system investigations, but is treated here since it fits in under the main topic.

1-2. STAGES IN PRODUCT DEVELOPMENT

Development of a dosage form involves, among other considerations, that a timetable be met. This may have the following appearance:

Phase 0
- (a) Synthesizing and screening.
- (b) Toxicity tests.
- (c) Preformulation trials.
- (d) Analytical techniques development.

Phase I
- (a) Clinical pharmacology.
- (b) Phase I pilot batch.
- (c) Phase I synthesis scale-up.
- (d) Analytical techniques development.

Phase II
- (a) Intermediate-size clinical trials.
- (b) Phase II pharmaceutical scale-up.
- (c) Analytical in-process controls.
- (d) Package testing.

Phase III
- (a) Large clinical trials.
- (b) Production-size pharmaceutical batches.
- (c) Arrival at final package.
- (d) Final quality control procedures.
- (e) Long-term toxicity tests.

Phase IV (new drug application):
- (a) Clinical data.
- (b) Analytical data.

(c) Label and packaging data.
(d) Synthesis data.
(e) Pharmaceutical process data.
(f) Stability and physicochemical data.

The time schedule for such a series of events is complex and in general the PERT system or similar systems are used as a scheduling and decision-making tool. The points directly concerned with pharmaceutics relate to manufacturing, packaging, raw materials, physicochemical properties, and stability. Since it is in order to obtain as soon as feasible a firm or reasonably firm formula and package for the product, experimentation and optimization are necessary. It is apparent that factors such as the ones mentioned here are of no relevance to model system investigations, and hence the material covering optimization in the following section is of interest to industrial pharmacists only.

1-3. SINGLE DETERMINATIONS

In any investigation or determination, measurements $(x_1, x_2, \ldots, x_i, \ldots, x_n)$ are usually made more than once (n times) and the conventional practice is to use the average $(\bar{x} = (1/n) \sum x)$ as a representative figure. The goodness of the average is usually determined by its standard deviation σ, which by definition is

$$\sigma = \left(\frac{\sum (x - \bar{x})^2}{n - 1} \right)^{0.5} \tag{1-1}$$

but a more manageable form from a computational point of view is

$$\sigma = \left(\frac{\sum x^2 - (\sum x)^2/n}{n-1} \right)^{0.5} \tag{1-2}$$

Most calculators carry cumulative registers so that $\sum x$ and $\sum x^2$ can be obtained in one operation. As an example, the figures 1.9, 2.0, and 2.1 would have an average of 2.0 and a standard deviation calculated from Eq. (1-1) of

$$\sigma = \left(\frac{0.1^2 + 0 + 0.1^2}{3 - 1} \right)^{0.5} = 0.1$$

and similarly from Eq. (1-2),

$$\sigma = \left(\frac{3.61 + 4.00 + 4.41 - (36/3)}{3 - 1} \right)^{0.5} = 0.1$$

It frequently happens that several duplicates have been performed; in this case

$$\sigma = [(\sum d_i^2)/2n]^{0.5} \tag{1-3}$$

where n is the number of duplicates ($2n$ total measurements) and d_i is the difference between duplicates. Table 1-1 gives an example. In this case, then, $\sigma^2 = [(25 + 36 + 16) \cdot 10^{-4}/(2 \cdot 3)] = 2.4 \cdot 10^{-2}$.

Table 1-1

Standard Deviation of a Series of Duplicates

Sample no.	Duplicates	Difference
1	1.95 2.00	0.05
2	1.96 2.02	0.06
3	1.97 2.01	0.04

The term $(n - 1)$ in the denominator of Eqs. (1-1) and (1-2) is usually referred to as the degrees of freedom and is actually the number of determinations minus the number of figures calculated.

The standard deviation of a set of data is given by Eq. (1-2) and implies probabilities of finding individual values at certain distances from the mean or average.

The average, of course, is an estimate of a true average and the more determinations n that are employed, the closer one may expect the found average to be to the "true" average, i.e., the larger n is, the smaller is the standard deviation of the average.

The actual expression relating the standard deviation σ from Eq. (1-3) to that of the average σ_{av} is

$$\sigma_{av} = \sigma/\sqrt{n} \tag{1-3a}$$

1-4. THE GAUSSIAN DISTRIBUTION CURVE

Most data encountered in pharmaceutical investigations are normally distributed. The significance of "normally distributed" is that the frequency of the value x is given by

$$f(x) = [1/\sigma(2\pi)^{1/2}] \exp[-(x - \mu)^2/2\sigma^2] \tag{1-4}$$

where σ is the standard deviation and μ the mean. This curve has the shape shown in Fig. 1-1.

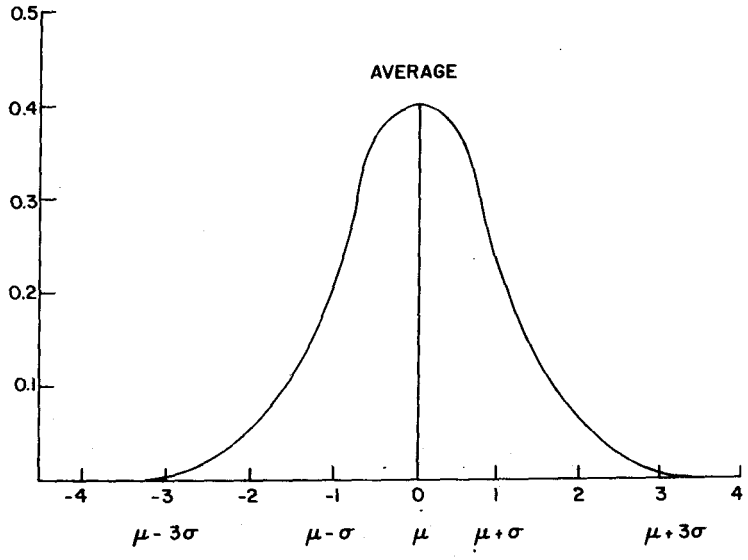

Fig. 1-1. The normal distribution curve, showing the mean at the origin and the abscissa in terms of units of one standard deviation. The curve is normalized so that the area under the curve equals unity.

One of the significant features of the curve is that given a set of values, one may compute the probability of a unit of the sample population being below a certain value. The probability of a sample falling one standard deviation below the mean is given by the cross-hatched area in Fig. 1-2 divided by the total area.

Since the function in Eq. (1-4) is "normalized," the total area under the curve is 1.0, and hence the probability is simply the cross-hatched area. These areas are given as a function of the value of the number of standard deviations in Table 1-2. It is noted that the probability of a unit having values less than a standard deviations below the mean is the same as it being more than a standard deviations above the mean. The table therefore gives the area as shown in Fig. 1-3.

For instance, the probability of a sample having a value (e.g., weight in milligrams) higher than the average plus 2.7 standard deviations is $0.5 - 0.4965 = 0.0035$ or 0.35%. It is noted that $2[0.5 - 0.4773] \simeq 5\%$ lies outside (above and below) the average $\pm$ two standard deviations, and this "2σ-limit" is often referred to as "95% confidence limits."

Given a set of numbers, the sum of the squares about the average of that set is the smallest such sum of squares. Consider a set of n numbers x_1,

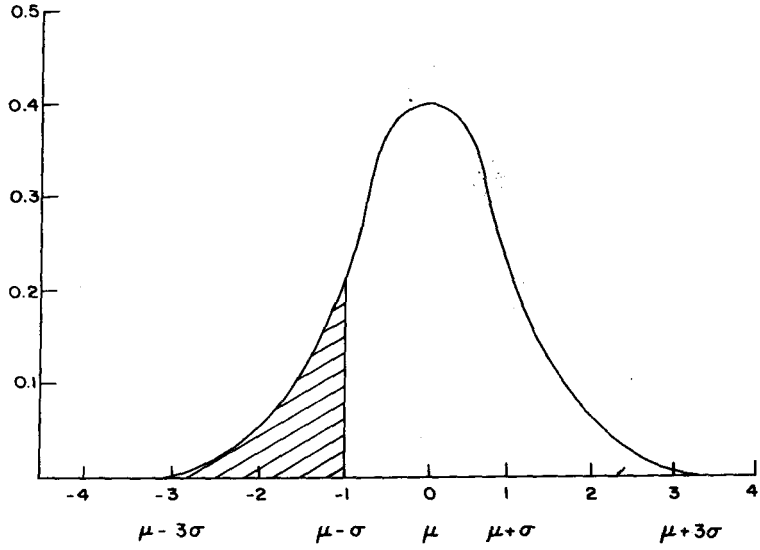

Fig. 1-2. The probability of a sample falling below the mean less one standard deviation. The probability is the darkened area.

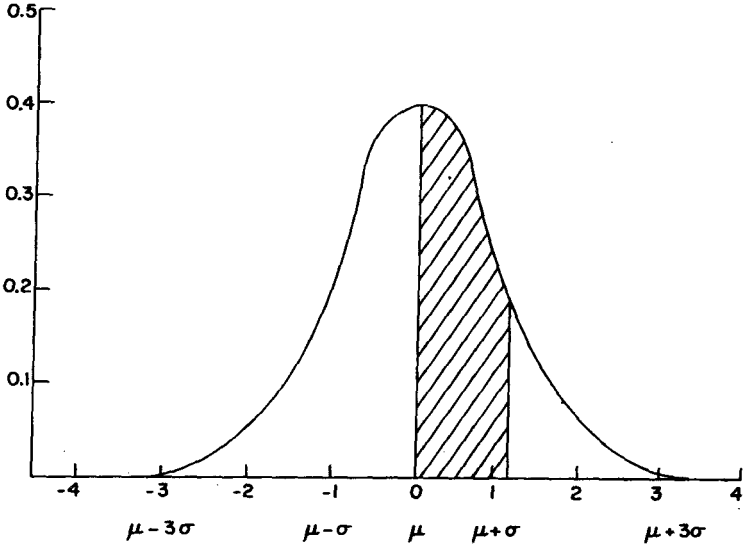

Fig. 1-3. The darkened area is that referred to in Table 1-2.