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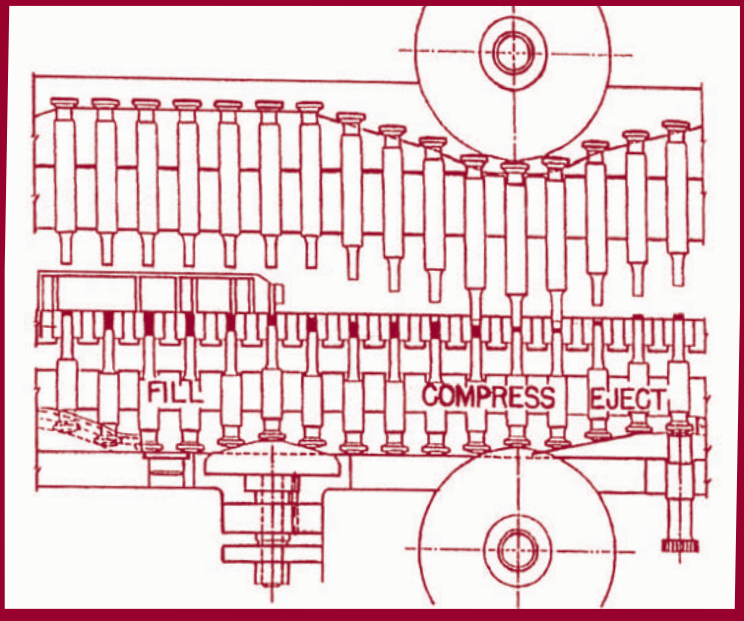
SECOND EDITION

Pharmaceutical Process Engineering



Anthony J. Hickey
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Pharmaceutical Process Engineering

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SECOND EDITION

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Preface

The motivation for expanding and updating *Unit Processes in Pharmacy* (David Ganderton, 1968) into the first edition of a book titled *Pharmaceutical Process Engineering* was a desire to make this valuable introductory volume available to a new generation of pharmaceutical scientists and technologists. The basic principles have not changed in the intervening years, but the environment in which manufacturing is conducted, both from a practical and a regulatory standpoint, has undergone a substantial evolution. The important principles of Quality by Design and the subtopic of Process Analytical Technology are routinely found on the programs of symposia devoted to pharmaceutical engineering and have a clear impact on the future of pharmaceutical manufacturing.

The present volume covers the basic principles with updated examples of the unit operations in pharmacy and their application. As in the first edition, the many unique drug delivery systems that extend beyond classical oral and parenteral dosage forms are not covered extensively as these are specialized topics covered in other volumes in this series.

A new section has been added on quality principles and the underlying mathematical and statistical methods. Adoption of known input variables that define the relevant process space can bring about consistency of product performance. The current capacity to store and manipulate data could not have been envisaged when the original volume on unit operations was published. The evolving tool of computer-aided design is likely to become a standard procedure in the future and, therefore, deserves to be addressed in the revised edition.

This volume remains an introductory text for pharmaceutical scientists and technologists who require an understanding of engineering principles. We hope that academic, industry, and government scientists and students will find this a useful text that serves the purpose of an easily accessible reference.

Anthony J. Hickey
David Ganderton

Acknowledgments

We are grateful for the support and encouragement of Carolyn Honour and Sandy Beberman, of Informa Healthcare, to prepare a second edition of this book. Kathryn Fiscelli assisted in collating materials used in the manuscript.

The first edition would not have been possible without the contribution of Dr Vasu Sethuraman. His endeavors with respect to integration of chapters, production of figures, and copyediting were the foundation on which the text was built. There is no doubt that his activities contributed to the clarity and continuity of the book. In addition, Dr Paul Pluta was generous in sharing his thoughts on solid dosage forms and allowed their use in the relevant sections of the volume.

The majority of the text continues to be based on a portion of David Ganderton's *Unit Processes in Pharmacy*, a book published in 1968 by Heineman Medical Books, Ltd., and now out of print. It is appropriate to acknowledge the contributions of that original volume.

The original text was the commission of Dr D. M. Moulden. We acknowledge the considerable help given by his ideas, plans, and drafts. In addition, we thank Mr Ian Boyd and Dr John Hersey, who read and evaluated manuscripts.

Contents

Units and Dimensions

The pharmaceutical scientist is familiar with the units (dimensions) of centimeter (length), gram (mass), and second (time) or the conventional Système Internationale (SI) units of meter, kilogram, and second. The engineer, in contrast, will express equations and calculations in units that suit quantities he or she is measuring. To reconcile in part this disparity, a brief account of units and dimensions follows.

Mass (M), length (L), time (T), and temperature (°) are four of six fundamental dimensions, the units of which have been fixed arbitrarily and from which all other units are derived. The fundamental units adopted for this book are the kilogram (kg), meter (m), second (sec), and Kelvin (K). The derived units are frequently self-evident. Examples are area (m^2) and velocity (m/sec). Others are derived from established laws of physics. Thus, a unit of force can be obtained from the law that relates force, F, to mass, m, and acceleration, a:

$$F = kma$$

where k is a constant. If we choose our unit of force to be unity when the mass and acceleration are each unity, the units are consistent. On this basis, the unit of force is Newton (N). This is the force that will accelerate a kilogram mass at 1 m/sec.

Similarly, a consistent expression of pressure [i.e., force per unit area is Newtons per square meter (N/m^2 or Pascal, Pa)]. This expression exemplifies the use of multiples or fractions of the fundamental units to give derived units of practical importance. A second example is dynamic viscosity [M/(L·T)] when the consistent unit kg/(m·sec), which is enormous, is replaced by kg/(m·hr) or even by poise. Basic calculations using these quantities must then include conversion factors.

The relationship between weight and mass causes confusion. A body falling freely due to its weight accelerates at kg·m/sec^2 (g varies with height and latitude). Substituting $k = 1$ in the preceding equation gives $W = mg$, where W is the weight of the body (in Newtons). The weight of a body has dimensions of force, and the mass of the body is given by

$$\text{mass(kg)} = \frac{\text{weight (N)}}{g\,(\text{m/sec}^2)}$$

The weight of a body varies with location; the mass does not. Problems arise when, as in many texts, kilogram is a unit of mass and weight of a kilogram is the unit of force. For example, an equation describing pressure drop in a pipe is

$$\Delta P = \frac{32ul\eta}{d^2}$$

when written in consistent units—ΔP as N/m^2, viscosity (η) as kg/(m·sec), velocity (u) as m/sec, distance (l) as m, and tube diameter (d) as m. However, if

the kilogram force is used (i.e., pressure is measured in kg/m^2), the equation must be

$$\Delta P = \frac{32\,ul\eta}{gd^2}$$

where $g = 9.8$ m/sec^2. In tests using this convention, the conversion factor g appears in many equations.

The units of mass, length, and time commonly used in engineering heat transfer are kilogram, meter, and second, respectively. Temperature, which is a fourth fundamental unit, is measured in Kelvin (K). The unit of heat is the Joule (J), which is the quantity of heat required to raise the temperature of 1 g of water by 1 K. Therefore, the rate of heat flow, Q, often referred to as the total heat flux, is measured in J/sec. The units of thermal conductivity are $J/(m^2 \cdot sec \cdot K/m)$. This may also be written as J/(m·sec·K), although this form is less expressive of the meaning of thermal conductivity.

1 Introduction

Process engineering has been a central activity in pharmaceutical product development since its inception. The knowledge that key fundamentals and the processes to which they are applied were in most respects equivalent to those in other industries allowed chemical and mechanical engineering principles to be adopted, which were thoroughly understood (McCabe et al., 1997).

The first chapters of this book describe in some detail the important fundamentals of fluid flow, heat and mass transfer. The intent is not to duplicate the authority of an engineering text of which there are many to which this volume owes tribute. Rather it is hoped that the topics are covered in sufficient depth to allow professionals in the pharmaceutical sciences, without engineering training, to feel comfortable when faced with matters pertaining to these topics. The chapters immediately following the fundamentals introduce processes that either employ the principles described earlier or that relate to important aspects of pharmaceutical development. Hence, these might be considered methods of handling and conveying different states of matter, that is, solids, liquids, or gases. The heterogeneous nature of many pharmaceutical formulations leads to a degree of empiricism in the understanding of processes and their application to achieve the desired goals of uniform and reproducible drug delivery from the designated dosage form or the handling of environmental or other conditions related to their preparation. Consequently, the chapters dealing with solids (including crystallization, powders, size, mixing, and blending), filtration, sterilization, evaporation, drying, and humidity have their basis in theory but often invoke semiempirical interpretation. Figure 1.1 illustrates the relationship between the various unit processes and the underlying fundamental principles.

The value of any text in pharmaceutical process engineering is that the fundamental nature of the topics presented gives it a long shelf life since the science and engineering have not changed significantly in decades. However, the last decade has been characterized by changes in the common practices of conducting experiments to rapidly and efficiently define the process accompanied by a change in the regulatory environment in which manufacturing is conducted.

It may seem premature to introduce this evolving technical and regulatory consideration into an otherwise slowly changing foundational text. However, it appears that the important principles of statistical experimental design, risk assessment, and quality by design, including specific tools to aid with these approaches, are established elements of process engineering.

The final chapters of the book relate to these topics. In the information age, the advent of computer technology allows the collection of vast quantities of data, which can then be manipulated in real time or near real time to promote the quality of the product and to ultimately bring therapies to patients. The challenge of working in this environment is to manipulate this data to fulfill the promise shown in Figure 1.2.

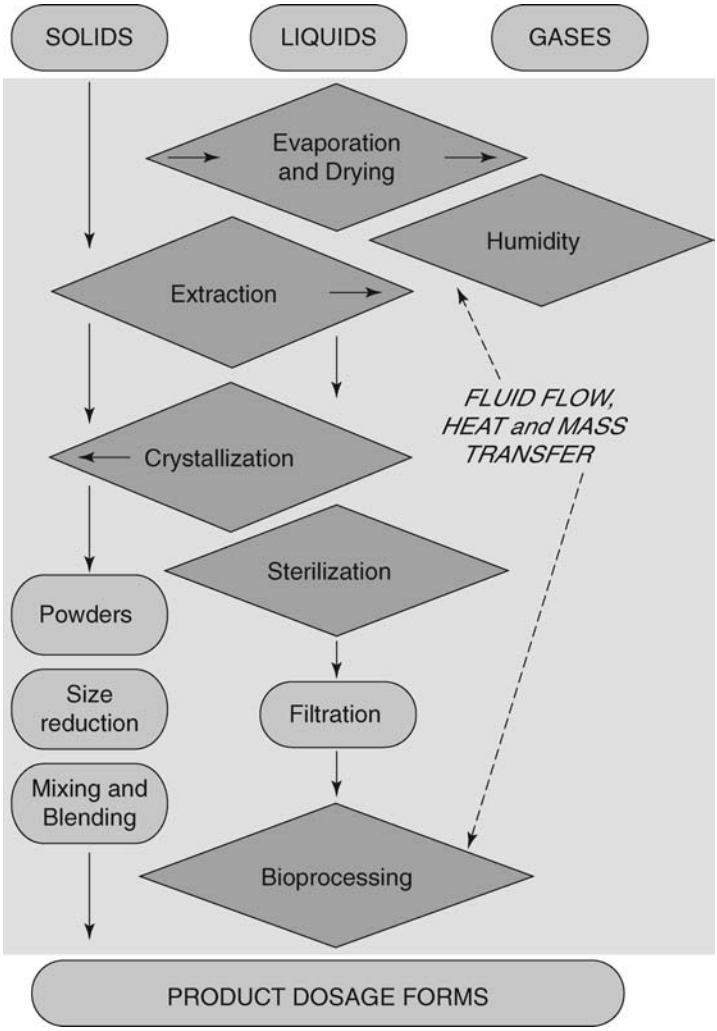

FIGURE 1.1 Relationship of unit processes in the background of fundamental principles.

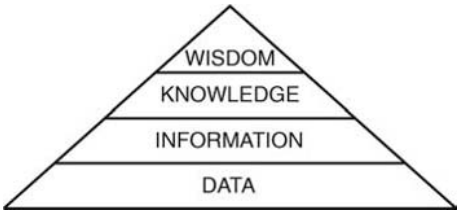

FIGURE 1.2 Schematic of levels of understanding that emanate from a comprehensive base of data.

The intent is to derive from an extensive database crucial information that increases the body of knowledge of the process or product and ultimately allows the wise intervention to bring about a desired objective. This may seem self-evident, but it could be argued that until relatively recently insufficient data could be acquired to adequately elevate our understanding through the upper levels of intelligent management. The practicalities of the experiments and their conduct in a regulated environment may not differ dramatically from previous periods in history, but the consideration of an operating framework and the facility to acquire relevant data has changed substantially. This is undoubtedly an improvement and should be embraced by all to elevate activities to a higher level of control and prediction commensurate with a 21st century industry.

In this context, the final chapters of the book cover in some detail the basis for statistical experimental design, risk assessment, and supporting tools of process analytical technology associated with quality by design. Figure 1.3 illustrates the collation of input variables that is required to predict and control the output for any process.

If successful in this endeavor, the cost and efficiency of processes in the future may be managed by informed decisions that facilitate rapid product development. In broad terms, the following sections, therefore, consider: (*i*) fundamental principles; (*ii*) unit processes; and (*iii*) experimental design, data management, and interpretation. The intent is to begin to address process engineering in a quality systems environment.

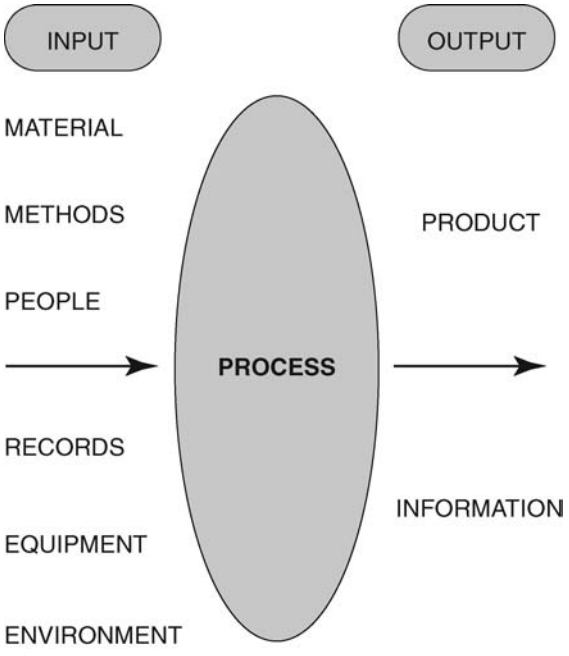

FIGURE 1.3 Process input variables and their contribution to output properties.

2 Fluid Flow

INTRODUCTION

Fluid flow is an essential element of many pharmaceutical processes. The ability to propel fluids through pipes and to direct materials from one location to another is central to the successful manufacture of many products. Fluids (liquids and gases) are a form of matter that cannot achieve equilibrium under an applied shear stress but deform continuously, or flow, as long as the shear stress is applied.

Viscosity

Viscosity is a property that characterizes the flow behavior of a fluid, reflecting the resistance to the development of velocity gradients within the fluid. Its quantitative significance may be explained by reference to Figure 2.1. A fluid is contained between two parallel planes each of area A m^2 and distance h m apart. The upper plane is subjected to a shear force of F N and acquires a velocity of u m/sec relative to the lower plane. The shear stress, t, is F/A N/m^2. The velocity gradient or rate of shear is given by u/h or, more generally, by the differential coefficient du/dy, where y is a distance measured in a direction perpendicular to the direction of shear. Since this term is described by the units velocity divided by a length, it has the dimension T^{-1} or, in this example, reciprocal seconds. For gases, simple liquids, true solutions, and dilute disperse systems, the rate of shear is proportional to the shear stress. These systems are called Newtonian, and we can write

$$\frac{F}{A} = t = \eta \frac{du}{dy} \tag{2.1}$$

The proportionality constant η is the dynamic viscosity of the fluid: the higher its value, the lower the rates of shear induced by a given stress. The dimensions of dynamic viscosity are $M\ L^{-1}\ T^{-1}$. For the SI system of units, viscosity is expressed in $N{\cdot}sec/m^2$. For the centimeter-gram-second (CGS) system, the unit of viscosity is poise (P). One $N{\cdot}sec/m^2$ is equivalent to 10 P. The viscosity of water at room temperature is about 0.01 P or 1 centipoise (cP). Pure glycerin at this temperature has a value of about 14 P. Air has a viscosity of 180×10^{-6} P.

Complex disperse systems fail to show the proportionality described by equation (2.1), the viscosity increasing or, more commonly, decreasing with increase in the rate of shear. Viscosity may also depend on the duration of shear and even on the previous treatment of the fluids. Such fluids are termed non-Newtonian.

Equation (2.1) indicated that wherever a velocity gradient is induced within a fluid, a shear stress will result. When the flow of a fluid parallel to some boundary is considered, it is assumed that no slip occurs between the boundary and the fluid, so the fluid molecules adjacent to the surface are at rest ($u = 0$). As

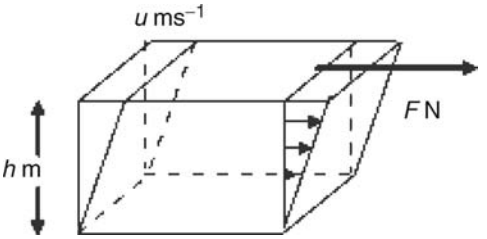

FIGURE 2.1 Schematic of fluid flow depicting the applied force, velocity in the direction of motion, and thickness of the fluid.

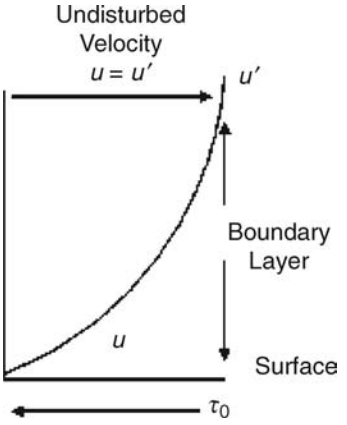

FIGURE 2.2 Distribution of velocities at a boundary layer.

shown in Figure 2.2, the velocity gradient du/dy decreases from a maximum at the boundary ($y = 0$) to zero at some distance from the boundary ($y = y'$) when the velocity becomes equal to the undisturbed velocity of the fluid ($u = u'$). The shear stress must, therefore, increase from zero at this point to a maximum at the boundary. A shear stress, opposing the motion of the fluid and sometimes called fluid friction, is therefore developed at the boundary. The region limited by the dimension y', in which flow of the fluid is perturbed by the boundary, is called the *boundary layer*. The structure of this layer greatly influences the rate at which heat is transferred from the boundary to the fluid under the influence of temperature gradient or the rate at which molecules diffuse from the boundary into the fluid under a concentration gradient. These topics are discussed in chapters 3 and 4.

Compressibility

Deformation is not only a shear-induced phenomenon. If the stress is applied normally and uniformly over all boundaries, then fluids, like solids, decrease in volume. This decrease in volume yields a proportionate increase in density. Liquids can be regarded as incompressible, and changes of density with pressure can be ignored, with consequent simplification of any analysis. This is not possible in the study of gases if significant changes in pressure occur.