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Book reviews

Pharmaceutical Process Engineering

Anthony J. Hickey, D. Ganderton. Marcel Dekker Inc., NY, Basel (2001), 288 pages, ISBN: 0-8247-0298-0, Price $135, ($65 on orders of five or more copies, for classroom use only)

In the preface of his book A.J. Hickey states that 'pharmaceutical manufacturing entails the combination of a number of unit processes. The efficiency, quality, and economy of manufacturing depend on an understanding of the individual operations involved in processing.'

The book is structured into two main sections, Fundamentals and Processes. The first part, 'Fundamentals', comprises of chapters on Fluid Flow (35 pages), Heat Transfer (20 pages), Mass Transfer (10 pages), and Powders (12 pages). In the second part, 'Processes', Air Conditioning and Humidification (12 pages), Drying (24 pages), Solid-Liquid Extraction (7 pages), Crystallization (11 pages), Evaporation and Distillation (22 pages), Filtration (24 pages), Size Reduction and Classification (24 pages), Mixing (17 pages), Solid Dosage Forms (13 pages), Sterilization (7 pages), and Bioprocessing (14 pages) are discussed.

A separate chapter on 'Units and Dimensions' is preceding the book. The author differentiates between fundamental and derived dimensions. This aspect is important as at different places in the text these fundamental dimensions are used in dimensional analysis, e.g. of the flow through a tube.

In the chapter on Fluid Flow the author first discusses properties of fluids as e. g. viscosity, compressibility and surface tension in a narrative way. Shear stress is represented by the symbol t instead of τ. Poise is chosen as unit of viscosity instead of Pa·s as recommended internationally. The symbol Q stands for volume flowing in unit time as well as for volumetric flow rate which is not wrong but confusing. Normally rates are characterized by a dot above the corresponding letter indicating that a rate is the time derivative of the corresponding size. In the derivation of Poiseuille's law on pages 16 and 17 the symbols π and t are used for the shear stress. The viscous force acting on the surface of a cylinder of a radius r and length l is then given by $2t\pi l$. On page 17 the following integral can be found:

$$\int_0^u du = -\frac{\Delta \mathrm{Pr}}{2\eta l}\int_R^r r\,dr \qquad \text{instead of}$$

$$\int_0^u du = -\frac{\Delta \mathrm{P}}{2\eta l}\int_r^R r\,dr$$

On page 18 the concept of dimensional analysis is introduced in an extremely short way. Unfortunately there is a printing error, $[L^3\ T-{}^2] = ... = [L^n-{}^1\ T-{}^1]$, in the first equation is used to explain the basic ideas. A novice in dimensional analysis will have difficulties to understand the rationale behind this approach. On page 20 shear stress is represented by the letter R. After an intensive discussion of the fluid flow through pipes and of the pressure drop due to friction at the walls of the pipes or at pipe fittings different types of pumps and their working principles are presented.

The basic equations describing the heat transfer between fluids, through a wall or in pipes and tubes are given in the chapter 'Heat Transfer'. They are then applied to more complex systems as heat exchange between a fluid and a solid boundary. It is shown that by means of dimensional analysis a relation between the three dimensionless numbers, the Nusselt number, the Grashof number and the Prandtl number can be obtained which describes the convective heat transfer. As the Grashof and the Prandtl numbers comprise only system parameters they can be calculated directly. Knowing these two numbers the Nusselt number can be determined experimentally. In further paragraphs boiling under various conditions as well as condensation are treated in a narrative way. The chapter is concluded by a short overview on heat transfer by radiation.

The chapter 'Mass Transfer' describes primarily diffusion in gases and liquids. The letter N is used as a symbol for the rate of diffusion. In principle this is not wrong however it is confusing that a time derivative is labelled in this way. To describe the mass transfer in turbulent and laminar flows the following dimensionless relation is given:

$$\frac{kd}{D} = \text{constant}(\mathrm{Re})^q\left(\frac{\eta}{\rho D}\right)$$

'Re is the Reynolds number, k the mass transfer coefficient, D the diffusivity, and d is a dimension characterizing the geometry of the system'. Unfortunately there is no further definition of d. In consequence the reader will not be able to apply this relation. The interfacial mass transfer is shortly described in a narrative way only.

Powders are the subject of Chapter 4. Compared with gases or liquids they are more difficult to handle and process. This is explained by their fundamentally different flow properties. As the variability in bulk density they are due to the fact that powders 'will resist to stresses less than a limiting value without continuous deformation'. Under the headline 'Properties' the different origin of particles, their structure and their properties are discussed. The discussion of properties is just a stringing together of different items as

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'particle size and distribution, shape, specific area, true density', etc. A few more words are used for the description of polymorphism and its evaluation by thermal techniques. Under the headline 'Particle interactions' the origin of cohesion is discussed. Van der Waals forces and effects of humidity layers are seen as a main contribution to cohesion. The measurement of the angle of repose is recommended as a method to determine the extent of cohesion. Two additional methods to determine the tensile and the shear strength are introduced shortly. It is impossible to apply these methods just on the basis of this description, however literature references are not given. As literature dealing with the method to determine the shear strength is associated with the name of A.W. Jenike it would have been helpful to at least mention his name. The information which is given on six pages under the headlines 'Powder flow', 'Packing of powders', 'Granulation', 'Fluidization', and 'Mixing and Blending', is common place for an experienced pharmacist, but for a beginner it is too short to offer any help especially as almost no literature references are given.

Chapter 5 deals with 'Air Conditioning and Humidification'. A rather short introduction of the terms humidity, percentage humidity and relative humidity is followed by a detailed description of the fundamentals of psychrometry (Eq. 5.7 is wrong). The topic 'Humidification and Dehumidification' which is really important in practice is described in a few lines only. The diagrams used to explain these processes are hard to understand.

'Drying' is the topic of Chapter 6. The 'Theory of Drying' is limited to the discussion of the term 'equilibrium moisture content' as 'theories of drying are limited in application in that drying times are normally experimentally determined'. Under the headline 'Evaporation of water into an airstream' most of the equations derived in section 5.2 are derived once more. Under the headline 'Static beds of non-porous solids' moisture content/time curves are introduced and three different 'falling rate periods' are briefly discussed. Section 6.2 deals with 'the internal mechanism of drying'. It is stated that 'capillary forces offer a coherent explanation for the drying periods of many materials'. Unfortunately in these discussions the letter h is used to describe the height of liquid in a capillary. Two pages above h described the heat transfer coefficient. On the next page, in the same section, h_x or h_i describe the suction potential acting at a depth x. This is rather confusing. The main conclusion of the section 'Static beds of porous solids' is that the different falling periods are shorter. They can even be further shortened by 'Through circulation drying', section 6.5. In the section 6.7, four sentences, it is stated that fluid bed dryers and spray dryers are 'methods involving movement of the solid'. Section 6.8, 'Other Methods of Drying', begins with the statement 'Apart from specialized dryers using infrared or dielectric heating, the chief method of passing heat into a drying solid, other than from a hot airstream, is by conduction from a heated surface'. What follows is a description of the changes of the temperature gradient and of the movement of a fictitious drying line through the cake. Under the headline 'Batch Dryers' the construction as well as the operating principles of hot air ovens, of vacuum tray dryers, of tumbling dryers, of fluidized bed dryers, of agitated batch dryers as well as of freeze-drying are described in a narrative way. Again an experienced pharmacist will not find any new information. A freshman however will not learn more than that these different techniques exist. He will get a rough idea about pros and cons of the different techniques but he would not be able to develop a drying procedure except by trial-and-error. The chapter is concluded by a description of spray and drum dryers. In the case of spray dryers different techniques to produce sprays are presented. But again the descriptions are narrative only.

Chapter 7 is devoted to solid-liquid extraction. Percolation and immersion are described as two techniques used to extract soluble constituents from a solid or semisolid by means of suitable solvents. Whereas percolation is carried to completion immersion only allows incomplete extraction. The extent of extraction depends on the proper choice of solvent. Some examples illustrate what kind of solvents have been used successfully. Among the 'factors affecting the rate of leaching' the 'size and size distribution of the solid particles', 'temperature', 'physical properties of the solvent' as well as the 'relative movement imposed on the solids and the liquid' are discussed in a very general way.

Crystallization in melts or from solutions is the topic of Chapter 8. In both cases, two stages of crystallization can be observed: nucleation and crystal growth. In most cases nucleation and crystal growth are two independent processes in melts whereas in materials crystallizing from solutions nucleation and crystal growth occur simultaneously. Nucleation in melts requires supercooling. With decreasing temperature an increase in nucleation rate is observed until the optimum nucleation temperature is reached. Below this temperature nucleation can become very slow, however the rate of crystal growth increases. To achieve crystallization from solutions the latter ones have to become supersaturated by decreasing the temperature or by removing the solvent. Whereas at low supersaturation nuclei have to be added, spontaneous nucleation is observed with greater supersaturations. The rate of crystal growth can be influenced by stirring the liquid. Initially agitation increases the growth rate until with increased agitation a limit is reached. After a short overview over 'Principles underlying the design and operation of crystallizers' some details are given on the 'Production of very fine crystals' as well as on the 'Production of large crystals'. Unfortunately there are no legends on the axis of the diagram (Fig. 8.5) which should explain the production of large crystals. The chapter is concluded by a short presentation of cooling, evaporative and vacuum crystallizers.

Chapter 9 deals with 'Evaporation and Distillation'. After a definition of 'Evaporation' has been given 'heat transfer to boiling liquids in an evaporator' is discussed in a short and

very general way. Under the headline 'Physical properties of solution and liquids' 'Relations between Boiling temperature and solute concentration', 'of Boiling temperature and external pressure', 'of viscosity to temperature and solute concentration' as well as the 'Effect of temperature on solubility' and the 'Effect of heat on the active constituents of a solution' are listed up. Again I had to ask myself, what is the target group of this book A statement as 'For dilute solutions the expected rise in boiling point can be calculated from Raoult's law' is of no help for beginners. However, this procedure is not applicable to concentrated solutions or to solutions of uncertain composition. For aqueous concentrated solutions, Duhring's rule may be used to obtain the boiling point rise of a solution at any pressure'. For an experienced pharmacist this is common place. The discussion of all other effects listed up above remains very superficially. Each section just comprises of some five to ten phrases. 'Evaporators' is the next topic which is discussed in the same way. 'Natural circulation evaporators', 'Forced circulation evaporators' and 'Film evaporators' are shortly mentioned. In a few additional phrases statements are made on 'Efficiency of evaporators', on 'Vapor Removal and liquid entrainment' and on 'Evaporation without boiling'. 'Distillation' is discussed a little bit deeper. In a first step steam distillation of a binary mixture of immiscible liquids is presented. The next step deals with 'Binary mixtures of miscible liquids'. Formulas to calculate the composition of the vapour phase from the composition of the liquid phase are given. The relation of boiling point and mixture composition is discussed in a narrative way. The same holds for the use of 'Vapor-Liquid Equilibrium Diagrams'. Also the sections 'Simple or Differential Distillation' and 'Rectification or Fractionation' remain just at the surface. Keywords as 'fractionating columns' or 'height equivalent of theoretical or ideal plate (HETP)' are mentioned. However the information is not sufficient to perform a distillation and to calculate the required length of a column.

Filtration is the topic of Chapter 10. A differentiation is made between clarification and cake filtration. Filtration theories describing the fluid flow through porous media and the particle retention in a depth filter are presented. The word 'theory' is misleading in so far as the information given in this chapter would not help to solve problems in a given filtration process nor is it sufficient to develop a filtration process. Under the headline 'Filters' short descriptions of gravity, vacuum and pressure filters as well as of the centrifuge are given. In addition a short overview over the 'mechanism of air filtration' as well as over 'the design, operation, and testing of air filters' is given.

'Size reduction and Classification' is the title of Chapter 11. Increase in particle surface is considered as the most important result of grinding. Under the headline 'Fundamental aspects of crushing and grinding' mechanical properties of solids are discussed. It is mentioned that the effective strength of crystalline materials is smaller than the theoretical one. This is explained by the number of flaws in a crystal. It is said that with a decrease in particle size the number of flaws is reduced. In consequence a further reduction in particle size will become more difficult. This explanation neglects the so-called differential and integral energy requirements which have to be fulfilled for the crack propagation. These energy requirements are also decisive in the selection of the most appropriate grinding equipment. The grinding efficiency is defined by a relation between the energy supplied to a mill and the achieved size reduction. Experiments carried out under free-crushing conditions show that the grinding efficiency of the roll crusher is about 80%, the swing hammer mill is 40%, the ball mill is 10%, and the fluid energy mill is only 1%. Under the headline 'Operation of Mills' the author compares dry and wet grinding. In his opinion wet grinding offers more advantages than dry grinding not only under the aspect of mill capacity, energy consumption and elimination of hazards from dust but also under the aspect of contamination. Under the headline 'Grinding equipment' edge and end runner mills, hammer, pin and ball mills as well as vibratory, fluid energy, colloid and roller mills are discussed. The particles obtained from a grinding process are characterized by a particle size distribution. For many applications particles of a suitable size have to be selected. This is achieved by classification. Sieving as well as elutriation and sedimentation are presented as techniques appropriate to select particles of a suitable size.

Chapter 12 deals with 'Mixing'. 'Mixing is carried out to secure uniformity of composition so that small samples withdrawn from a bulk material represent the overall composition of the mixture.' 'Whether materials are satisfactorily mixed depends on the subsequent operation in which the mixture plays a part.' Based on this statement the author introduces the term 'scale of scrutiny.' This term describes 'the minimum size of the regions of segregation in a mixture which would cause it to be regarded as insufficiently mixed.' In order to fulfil the content uniformity requirement e.g. in the manufacture of tablets the mass of the samples withdrawn from the mixture may not be higher than the mass of the tablet itself. A mixture is considered as perfect when the probability of finding one type of particle at any point in the mixture is equal to the proportion of that type of particle in the mixture. In the case of a binary mixture consisting of particles being alike in particle size, shape and density and only distinguished by some neutral property the variation in the composition of samples drawn from a random mixture is given by the standard deviation of the binomial distribution. To measure the degree of mixing the author introduces an index M of mixing. It is defined as the ratio of the standard deviation of a random mixture to the standard deviation of samples drawn from the mixture under examination. This index approaches unity as mixing is completed. Under the headline 'Mechanisms of mixing' convective mixing, diffusive mixing and shear mixing are shortly described. After a short comment on the mixing rate

a few lines are devoted to mixing machines. The chapter is concluded by some statements on the mixing of liquids. As mixing devices paddle mixers, propeller mixers and turbines are described.

'Solid dosage forms' is the topic of Chapter 13. This is a bit strange as in the preceding chapters in agreement with the title of the book techniques and processes have been described. The author lists up a series of properties which are studied during the preformulation phase and continues with a very short overview (27 lines) on granulation. This is immediately followed by statements on the manufacture of hard gelatin capsules, (they 'are prepared by dipping manganese bronze pins into a bath of molten gelatin.') on the different capsule sizes and eventually on their filling. Another section deals with tablets. In a very condensed form compression of tablets is described. 'One method of evaluating tablet manufacture considers the effect of applied pressure on porosity of the compressed powder. Data may be plotted as the negative natural logarithm of porosity against applied pressure in the form of a Heckel plot. The slope is proportional to the yield value $1/3\Phi$.' The next statement is on the tooling of a tablet press. All issues are addressed in a very superficial way. No more than two statements on tooling, on coating or on chewable tablets are mentioned. Inhalation products as metered dose inhalers (MDI) and dry powder inhalers (DPI) are profoundly handled on 25 lines.

Chapter 14 (four pages) is devoted to 'Sterilization'. The section on thermal sterilization starts with 'The use of heat to sterilize depends on the magnitude (T), duration (t), and amount of moisture present: $t \propto 1/T$.' A few lines later the following general statement is made: 'Spores and vegetative forms of bacteria may be effectively destroyed in an autoclave employing steam under pressure, either 1.03×10^5 N/m^2 at 394 K for 20 min or 1.86×10^5 N/m^2 at 405 K for 3 min.' Obviously individual D numbers or the effectiveness F of a sterilization procedure are unknown to the author. Performing a sterilization process as described above without further precautions as sterile filtration would end in a disaster! It is surprising that at the end of the chapter the use of ethylene oxide as a sterilant is described. At least in the EU the use of ethylene oxide as a sterilant has already been forbidden for years.

The last chapter, Chapter 15, deals with 'Bioprocessing'. The first few sections describe 'Pharmaceutical water systems', this means pretreatment and sources of water, water for injection and methods to produce it, its storage and distribution as well as quality control and validation. After a short section on 'Cell Kinetics' some information is given on bioreactor design. Issues like rheology, mass and heat transfer, mixing, and shear are shortly addressed in the authors own way. The chapter is concluded with some profound remarks on 'Bioprocessing plant design' (14 lines) and on 'Protein purification' (less than one page).

In its preface the author makes the following statement: 'The efficiency, quality, and economy of manufacturing depend on an understanding of the individual operations involved in processing.' This is absolutely correct. For a long time little attention has been paid to process engineering in pharmaceutical development and production. As process engineering has never been a part of pharmaceutical curricula most pharmacists are not familiar with its basic concepts. Insofar there is a need for textbooks on 'Pharmaceutical process engineering'. Unfortunately the book written by A.J. Hickey does not fill this gap. First of all the different topics are described in a too superficial way. Most physical problems are handled in a narrative way only. For a beginner it is too difficult to translate these statements in a formula which would allow him to work with it. On the other hand for most practicians the statements are common place. The use of symbols is rather strange. This holds especially if for a given parameter different symbols are used. In the first part of the book flow rates, heat or mass transfer rates and other rates are abbreviated by upper case letters only. For an experienced reader this is certainly not a serious problem. However a reader not being familiar with process engineering may not recognize that 'rate' stands for a time derivative of a given parameter. In addition only few references are made. If citations are given often the corresponding articles have been published 20, 30 or more years ago. In summary it is difficult to identify a target group which might draw an advantage from reading this book.

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Drug Stability, Principles and Practices, 3rd Edition, revised and expanded

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One might think that there would not be much new in the field of drug stability testing to warrant a 3rd edition of this book. As the editors mention in the preface, there have been no fundamental changes in the equations that govern chemical reaction. Nor has the underlying theory of processes such as oxidation or hydrolysis been revolutionised since the last edition of this work. There have, however, been substantial improvements in our knowledge of the stability and the stability testing of macromolecules. Just think about