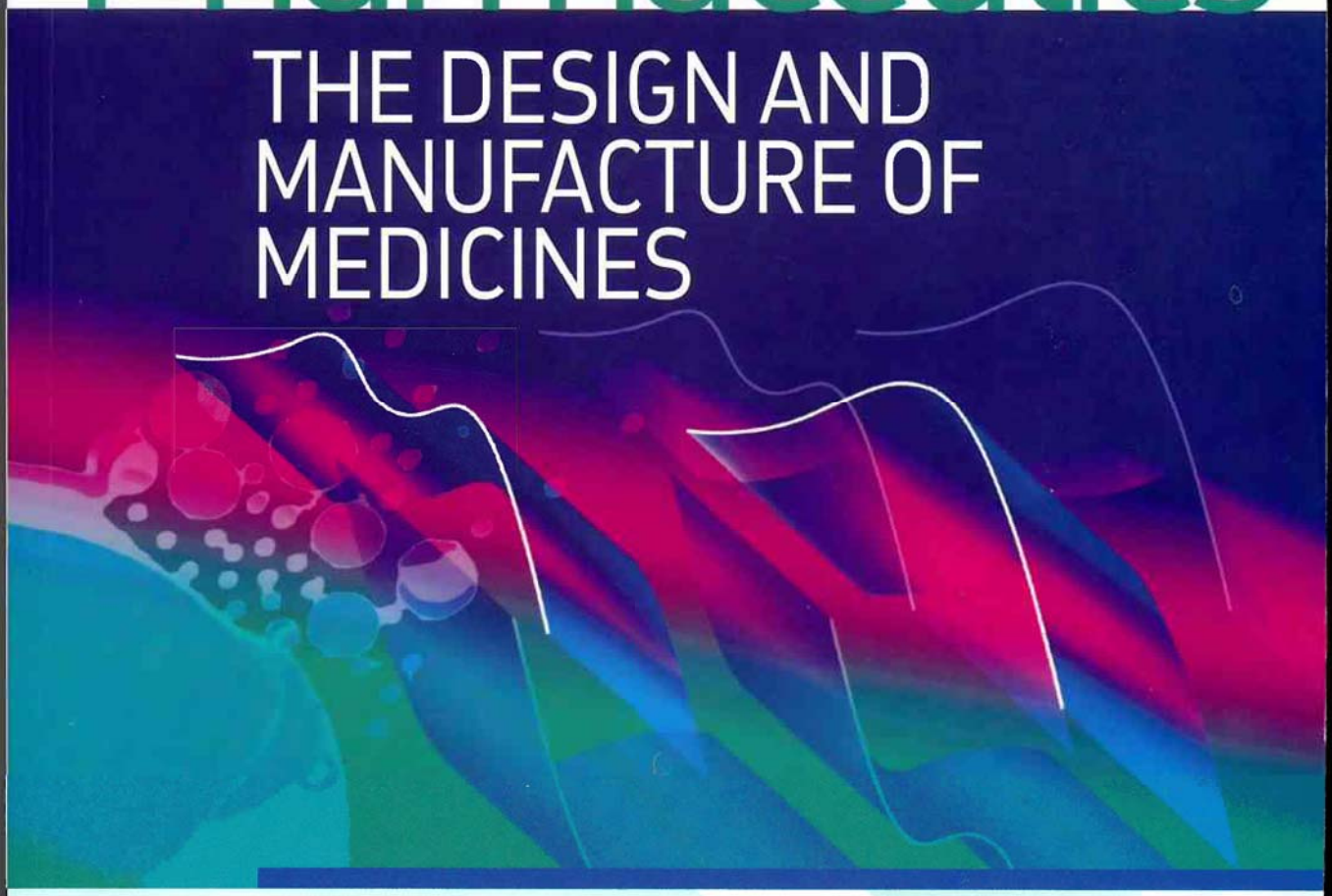
THIRD EDITION

Aulton's Pharmaceutics

THE DESIGN AND MANUFACTURE OF MEDICINES



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Transdermal drug delivery

B. W. Barry

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Delivering the medicament to the diseased site is a problem with appendage treatment. For example, it is difficult to achieve a high antibiotic concentration in a sebaceous gland when, as in acne, a horny plug blocks the follicle. When delivered through the skin, the drug may not be sufficiently hydrophobic to partition from the water-rich viable epidermis and dermis into the sebum-filled gland.

Viable epidermis and dermis treatment

We can treat many diseases provided that the preparation efficiently delivers drug to the receptor. However, many potentially valuable drugs cannot be used topically as they do not readily cross the stratum corneum. Hence, investigators may use stratagems such as adding chemical penetration enhancers to diminish this layer's barrier function (discussed later in this chapter). Another approach develops prodrugs, which reach the biological receptor and release the pharmacologically active fragment. The efficacy of many topical steroids depends partly on molecular groups which promote percutaneous absorption but which may not enhance drug-receptor binding.

Drug examples include topical steroidal and non-steroidal antiinflammatory agents; corticosteroids may also be used in psoriasis. Antibiotics include those listed above. Anaesthetic drugs such as benzocaine, amethocaine and lidocaine reduce pain, and antipruritics and antihistamines alleviate itch, but they may cause sensitization. Topical 5-fluorouracil and methotrexate eradicate premalignant and some malignant skin tumours, and treat psoriasis. The psoralens (particularly in conjunction with ultraviolet light – PUVA therapy) mitigate psoriasis, and 5-aminolaevulinic acid (with visible light irradiation – photodynamic therapy) treats skin cancer.

Transcutaneous immunization

The skin has a highly effective immunological surveillance and effector system. A new therapy involves developing transcutaneous immunization via topical application of vaccine antigens. The process uses an adjuvant such as cholera toxin added to a vaccine antigen (e.g. diphtheria toxoid) to induce antibodies to the diphtheria toxoid. The adjuvant and antigen target Langerhans cells, potent antigen-presenting cells in the epidermis. Simple application of the vaccine formulation to the skin of experimental animals and human volunteers has produced positive responses.

Systemic treatment via transdermal absorption

Generally, in the past we have not used healthy skin as a drug route during systemic attacks on disease, with the noteworthy exceptions of nitroglycerin and antileprotics. The body absorbs drugs slowly and incompletely through the stratum corneum and much of the preparation is lost by washing, by adherence to clothes and by shedding with stratum corneum scales. Other problems include marked variations in skin permeability with regard to subject, site, age and condition, which make control difficult. However, in recent years considerable scientific work has led to the route being used to treat several conditions by means of transdermal patches (discussed later in this chapter).

Figure 38.2 illustrates drug penetration routes and examples of treatments appropriate to various skin strata.

DRUG TRANSPORT THROUGH SKIN

Basic principles of diffusion through membranes

A useful way to study percutaneous absorption is to consider, first, how molecules penetrate inert (artificial) membranes and then move on to the special situation of skin transport. An understanding of the basic principles of permeation through membranes is also valuable in all other areas of biopharmaceutics – oral, buccal, rectal, nasal, lung, vaginal, uterine, injection or eye. The underlying mathematics are also relevant to dosage form design, particularly sustained- or controlled-release formulations and drug targeting.

Diffusion process

In passive diffusion, matter moves from one region of a system to another following random molecular motion. The basic hypothesis underlying the mathematical theory for isotropic materials (which have identical structural and diffusional properties in all directions) is that the rate of transfer of diffusing substance per unit area of a section is proportional to the concentration gradient measured normal to the section. This is expressed as Fick's First Law of Diffusion, Eqn 38.1:

$$J = -D\frac{\partial C}{\partial x} \qquad (38.1)$$

where J is the rate of transfer per unit area of surface (the flux), C is the concentration of diffusing substance, x is the space coordinate measured normal to the section, and D is the diffusion coefficient. The negative sign indicates that the flux is in the direction of decreasing concentration, i.e. down the concentration gradient. In many situations D is constant but in more complex materials, D depends markedly on concentration; its dimensions are $(\text{length})^2(\text{time})^{-1}$, often specified as $\text{cm}^2\ \text{s}^{-1}$.

Fick's First Law contains three variables, J, C and x, of which J is additionally a multiple variable, dm/dt, where m is amount and t is time. We therefore usually employ Fick's Second Law, which reduces the number of variables by one. For the common experimental situation in

which diffusion is unidirectional, i.e. the concentration gradient is only along the x-axis, Eqn 38.2 expresses Fick's Second Law as:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \qquad (38.2)$$

Many experimental designs employ a membrane separating two compartments, with a concentration gradient operating during a run and 'sink' conditions (essentially zero concentration) prevailing in the receptor compartment. If we measure the cumulative mass of diffusant, m, which passes per unit area through the membrane as a function of time, we obtain the plot shown in Figure 38.3. At long times the plot approaches a straight line and from its slope we obtain the steady flux, dm/dt (Eqn 38.3):

$$\frac{dm}{dt} = \frac{DC_0K}{h} \qquad (38.3)$$

Here C_0 is the constant concentration of drug in the donor solution, K is the partition coefficient of the solute between the membrane and the bathing solution, and h is the thickness of the membrane.

If a steady-state plot is extrapolated to the time axis, the intercept so obtained at $m = 0$ is the lag time, L:

$$L = \frac{h^2}{6D} \qquad (38.4)$$

From Eqn 38.4, D is estimated provided that the membrane thickness, h, is available. Knowing these parameters and C_0, and measuring dm/dt, Eqn 38.3 provides one way of assessing K. Eqn 38.3 shows why this permeation procedure may be referred to as a zero-order process. By analogy with chemical kinetic operations, Eqn 38.3 represents a zero-order process with a rate constant of DK/h.

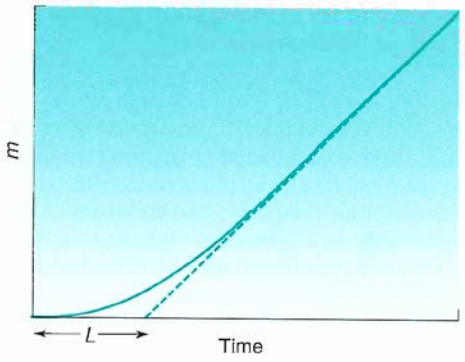

Fig. 38.3 The time course for absorption for the simple zero-order flux case obtained by plotting m, the cumulative amount of diffusant crossing unit area of membrane, as a function of time. Steady state is achieved when the plot becomes linear; extrapolation of the linear portion to the time axis yields the lag time L.

Sometimes with biological membranes (such as skin) we cannot separate the value of D from that of K. We then often employ a composite parameter, the permeability coefficient, P, where $P = KD$ or $P = KD/h$. The latter definition is used when h is uncertain, e.g. diffusion through skin.

Complex diffusional barriers

Barriers in series The treatment above deals only with the simple situation in which diffusion occurs in a single isotropic medium. However, skin is a heterogeneous multilayer tissue and in percutaneous absorption the concentration gradient develops over several strata. We can treat skin in terms of a laminate, each layer of which contributes a diffusional resistance, R, which is directly proportional to the layer thickness, h, and is indirectly proportional to the product of the layer diffusivity D, and the partition coefficient, K, with respect to the external phase. The total diffusional resistance of all the layers in a three-ply membrane such as skin (stratum corneum, viable epidermis and dermis) is given by the expression:

$$R_T = \frac{1}{P_T} = \frac{h_1}{D_1K_1} + \frac{h_2}{D_2K_2} + \frac{h_3}{D_3K_3} \qquad (38.5$$

Here R_T is the total resistance to permeation, P_T is the thickness-weighted permeability coefficient, and the numerals refer to the separate skin layers.

If one segment has a much greater resistance than the other layers (e.g. the stratum corneum compared with the viable epidermis or dermis) then the single high-resistance phase determines the composite barrier properties. Then $P_T = K_1 D_1/h_1$, where the subscript 1 refers to the resistant phase.

Barriers in parallel Shunts and pores, such as hair follicles and sweat glands, pierce human skin (see Fig. 38.1). Investigators often idealize this complex structure and consider the simple situation in which the diffusional medium consists of two or more diffusional pathways linked in parallel. Then the total diffusional flux per unit area of composite, J_T, is the sum of the individual fluxes through the separate routes. Thus:

$$J_T = f_1J_1 + f_2J_2 \ldots \qquad (38.6$$

where f_1, f_2, etc., denote the fractional areas for each diffusional route and J_1, J_2, etc., are the fluxes per unit area of each separate route. In general, for independent linear parallel pathways during steady state diffusion:

$$J_T = C_0(f_1P_1 + f_2P_2 + \ldots) \qquad (38.7$$

where $P_1, P_2, \ldots$ represent the thickness-weighted permeability coefficients.

If only one route allows diffusant to pass, i.e. the other routes are impervious, then the solution reduces to the

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