alcohol after topical application to human skin in vitro and showed that evaporation plays a significant role. They found that two-compartment models were adequate to describe the first-order loss of benzyl alcohol from the vehicle surface.

2.4.5 Shunt Transport

The importance of shunt transport by appendages has been well-recognized. Scheuplein [66] and Wallace and Barnett [36] assumed a parallel pathway with a minimal lag time relative to transepidermal transport for diffusion and compartmental models, respectively. In our attempted modeling of epidermal and shunt diffusion, we assumed that the overall amount penetrating was the sum of the amounts penetrating through independent epidermal and shunt pathways [8]. The amount penetrating through each pathway was assumed to be defined by Equation (2.9) in which K_m and D_m were defined in terms of the corresponding constants for the two pathways.

More recently, the presence of polar and nonpolar pathways through the intercellular region of the SC has been recognized, as described in Equation (2.3). Mathematical models described include those for steady-state conditions [67, 68] and an infinite dosing condition [69]. Yamashita et al. [70] have presented the Laplace solution for a well-stirred, finite donor phase in contact with SC in which solutes can diffuse through both polar and nonpolar routes. The solute can then diffuse through the epidermis into a sink. Numerical inversion of the Laplace transform with FILT was then undertaken to generate real-time profiles. Edwards and Langer [71] have derived expressions for a range of conditions and suggested their theory confirmed the importance of shunt and intercellular transport for small ions and uncharged solutes, respectively.

More recently, a top down pharmacometrics approach [123], a finite element 2D and 3D simulation approach [124], a multicompartment Simcyp MechDermA PBPK approach [125] and a porous pathway feature in an existing skin diffusion model [126] have been used to analyse the closed and open follicle data for the skin absorption of caffeine [127], with quite disparate results. Each o the models describe parallel SC diffusion and appendageal absorption. These various studies emphasise a move away from conventional analytical diffusion equations into complex and more realistic representations of processes associated with percutaneous absorption by *in silico* driven numerical and quantitative structure -permeability relationships. There are now many papers in this area that are beyond the scope of this overview the on mathematics of skin absorption.

2.4.6 Reservoir Effect

It is well recognized that significant amounts of solute can accumulate in the SC and be released into lower tissues on rapid skin hydration, the so-called "reservoir" effect [72, 73]. Modeling of this process, including the effects of desquamation, has been undertaken using both diffusion [74] and compartmental models [75]. In the latter model, the kinetics of reservoir depletion was shown to be dependent on solute diffusivity in the SC solute clearance from the underlying tissue and the rate of epidermal turnover. This topic is not discussed here as it is in in some depth in a later chapter in this volume (see chapter 4).

2.5 SIMPLE IN VIVO MODELS IN PERCUTANEOUS ABSORPTION

2.5.1 Compartmental Pharmacokinetic Models

One of the first evaluations of the pharmacokinetics of skin penetration was reported by Riegelman [35]. Absorption of solutes through the skin was generally assumed to follow first-order kinetics with a rate constant k_a (unit: sec^{-1}). Much of the data analyzed appeared to be characterized by "flip-flop" kinetics, where the absorption half-time is much longer than the elimination half-time, as illustrated later in Figure 2.15. This modeling approach has been used by a number of authors, including the