active [12, 13]. Recognizing that potency differences may play a role, they also found the highest corticosteroid potency with fluocinolone acetonide and the lowest with hydrocortisone acetate [13].

In an effort to eliminate the complex situation of SC penetration (which would also tease out the seemingly opposing effects of potency and polarity, as seen by McKenzie et al.), Sutton et al. [14] used the intradermal injection route instead of topical application and confirmed that intradermal injection is a feasible and practical method for testing corticosteroid potency via vasoconstrictive activity and that taking SC penetration out of the equation made a difference—as they compared their results to McKenzie's [14]. Questions remain about exactly how polarity affects percutaneous penetration and deeper/systemic absorption.

21.2.1.5 pH

The pH of the environment will determine the proportion of drug or chemical that is ionized versus un-ionized. Skin membrane proteins are basic in nature. It is the un-ionized form of a drug or chemical that passes through membranes. Thus, drugs and chemicals which are primarily in their un-ionized form in a basic pH environment will be optimally absorbed. Basic drugs will have a greater proportion in un-ionized form than acidic drugs; therefore, in a basic environment, basic drugs will be absorbed better than acidic drugs. Less ionization leads to increased lipid solubility and passage through membranes [15].

pH can also affect drug or chemical volatility. Salocks et al. [16] demonstrated the role of pH on methamphetamine: (1) increasing the solvent pH above 4 or so changes methamphetamine from a nonvolatile salt to a volatile base, and the higher the solvent pH, the greater the volatility and the less drug remains i.e., there is an inverse parabolic relationship; and (2) when applied to *in vitro* human skin, the amount of methamphetamine evaporated is significantly higher at a skin pH of 7 than at a skin pH of 4 [16]. Volatility is further discussed in Section 2.15.

21.2.1.6 Acid Dissociation Constant (pK_a)

The acid dissociation constant (pK_a) is a measure of a chemical's acid strength and provides details of the dissociation of an acid in aqueous solution. Since there is a specific pK_a for each substance that relates to pH, knowing the pK_a of a drug becomes a useful predictor of percutaneous drug absorption [15].

21.2.1.7 Partition coefficient (P)

The partition coefficient is the ratio of concentrations of a substance in a mixture of two immiscible phases at equilibrium. This ratio is therefore a measure of the difference in solubility of the substance in these two phases. There are two partition coefficients of relevance to percutaneous absorption: the oil to water partition coefficient (i.e. octanol:water P) and the partition coefficient for cream or ointment to the SC (i.e. formulation:skin P). Hydrophobic drugs or chemicals will have a high octanol:water P and will be mainly distributed to hydrophobic areas such as the lipid bilayers of cell membranes, whereas hydrophilic drugs or chemicals (with low octanol:water Ps) will penetrate SC poorly, and once absorbed systemically, will be mainly distributed to aqueous areas such as serum. The partition coefficient between a cream/ointment and the SC will depend on the product formulation. Thus, knowing the partition coefficients of a drug or chemical, for various immiscible phases, may be a useful predictor of percutaneous drug absorption and/or drug partitioning between biologic systems, which can include solids such as bone (i.e. blood:bone P).

Partitioning can also occur between environmental substances and SC or its components. This is an important consideration for hazardous chemicals found in our environment that may come into contact with human skin. For example, some polycyclic aromatic hydrocarbons (PAH) formed by incomplete combustion of organic materials (such as coal or crude oil processing or forest fires or vehicle exhaust fumes, etc.) may have genotoxic or carcinogenic potential [17]. A study assessing the soil:sebum partition coefficients of high MW PAH, using soil samples collected from former UK gasworks and artificial sebum, found that partitioning varied with the soil type and, not surprisingly, PAH properties (e.g. MW, octanol:carbon P) [17].