Intracutaneous diffusion and percutaneous absorption become problematic at higher MWs. This was shown in an animal study (male Wistar rats) [7]. Six water-soluble substances with a range of MW from 160 to 39,200 (sodium salicylate [SA, MW 160], sodium calcein [CAL, MW 580], fluorescein isothiocyanate–labeled dextran [FD-4, MW 2,820; FD-10, MW 10,095; FD-20, MW 19,800; FD-40, MW 39,200]) were injected intracutaneously (*in vitro* [excised rat abdominal skin] and *in vivo* [rat abdomen]) versus intravenously (rat jugular vein) to determine apparent diffusion coefficients and bioavailability [7]. Recognizing that rat skin differs from human skin, the *in vitro* study showed SA diffusing most rapidly, and progressively slower diffusion rates were seen as MW increases. Diffusion coefficients ranged from 10^{-4} (SA) to 10^{-5} (FD-40) cm^2/min. *In vivo* studies showed the most rapid elimination rate from the skin for SA and CAL (10% dose remaining after about 60 minutes), followed by FD-4 (10% dose remaining after 180 minutes). For FD-10, FD-20, and FD-40, elimination rates were slow (80% dose of FD-40 still remaining after 8 hours) and bioavailability as per plasma concentrations and area under the curve (AUC) was minimal to nonexistent [7]. Thus, there are *in vivo* animal data corroborating the effect of particle size/MW on percutaneous absorption.

21.2.1.2 Lipophilicity

The outer skin layer (stratum corneum [SC]) are overlapping corneocytes with cell membranes consisting of lipids, with proteins and water. Lipophilic drugs (and lipophilic chemicals) will be more readily absorbed than hydrophilic substances [4, 8]. However, highly lipophilic substances may be less well absorbed than moderately lipophilic compounds.

21.2.1.3 Solubility in Water

It follows from Section 2.1.2 that highly water-soluble drugs and chemicals would penetrate poorly through the SC, sometimes requiring the presence of porin channels for transport through the epithelium. An example is glyphosate, a broad-spectrum herbicide potentially hazardous to humans but is highly water soluble (for both the base and its mono isopropylamine salt used commercially). An *in vivo* study in the rhesus monkey found only 1.5% glyphosate being systemically absorbed over a 12-hour abdomen skin application period and that residual amounts left on the skin could be easily washed off with soap and water or water only [9].

Note that a prewetted i.e. better hydrated SC may affect penetration of substances with high water solubility [4]. This is discussed in Section 2.7.

21.2.1.4 Polarity

Polarity is defined by the distribution of electrical charge over the atoms of a molecule joined by chemical bonding. Although constant, the effect that a drug or chemical's polarity has on percutaneous absorption is potentially altered by many factors. These include type of solution (ethanolic differs from aqueous differs from PEG, etc.), pH of the formulation/environment, and even skin factors. Drugs or chemicals preferentially penetrate in a dissoluted and electrically neutral state; thus formulation plays a big role.

Although one expects the opposite effect to lipophilicity with respect to percutaneous absorption: i.e. the greater the polarity, the less readily the drug or chemical will diffuse through the phospholipid bilayers of the SC, the converse has also been documented [10, 11]. For example, *in vitro* percutaneous penetration of five corticosteroids, using a consistent dose of 25 uL of a 0.1% drug in ethanolic solution, showed *decreasing* penetration correlated with *decreasing* polarity: hydrocortisone (the most polar) > hydrocortisone-17-butyrate = triamcinolone acetonide > clobetasol-17-propionate > clobetasone butyrate (the least polar) [11].

However, in an *in vivo* study of percutaneous application of different corticosteroids in humans and using vasoconstrictor activity as a measure that drug has penetrated through the SC, McKenzie et al. found *increasing* vasoconstrictor activity with *decreasing* polarity, with hydrocortisone acetate (the most polar) being least active and fluocinolone acetonide (much less polar) being the most