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Letter to the Editor

Maximum flux versus transdermal delivery: Comment on Farahmand and Maibach (2009)

Farahmand and Maibach (2009b) compare estimates of dermal permeation obtained using the maximum flux approach and skin permeability coefficients derived from in vitro experimentation with results obtained from in vivo tests of drug delivery patches and find that in vitro-based predictions deviate dramatically from in vivo observations. At the extremes, Farahmand and Maibach claim that in vitro approaches lead to 1000 to 10,000-fold underestimation of flux for nicotine and nitroglycerin and 1000-fold overestimation for oxybutynin. Agreement, or lack thereof, between results of in vitro and in vivo experiments has been a source of much discussion in the dermal permeation literature. However, such discrepancies have seldom, if ever, been described in terms of three or more orders of magnitude. In a brief review of targeting transdermal systems, Hadgraft and Wolff (1998) concluded that "In vitro experiments, provided they are designed correctly, can be very good predictors of in vivo absorption." If results of well-designed in vitro experiments mimic in vivo outcomes, then it stands to reason that models based on those results, if correctly specified and implemented, should also agree with models based on in vivo experiments.

Given widespread utilization of in vitro measurements in various aspects of dermal permeation science, Farahmand and Maibach's findings are very important if they can withstand scrutiny. We note that Farahmand and Maibach present no new data, but base their arguments on review of prior work. Readers are therefore left to conclude that either (1) the dermal science community, including persons who generated the data Farahmand and Maibach use, or have modeled it previously, has heretofore failed to recognize three to four order of magnitude differences in fluxes through skin in vitro and in vivo, or (2) there is something wrong with Farahmand and Maibach's arguments.

Since flux estimates Farahmand and Maibach attribute to in vitro models are ultimately obtained by multiplying in vitro-based estimates of permeability by aqueous solubility, solubility is very important here. In their Table 2, Farahmand and Maibach (2009b) present aqueous solubilities that they report as having been obtained from the Merck Index (Merck & Co., 1989). Of the 10 compounds listed in Table 2, that edition of the Merck Index provides quantitative estimates of solubility for only scopolamine and nitroglycerin, and in neither case does the value match the one found in Table 2. Nicotine is listed as being fully miscible with water (i.e., it has no solubility limit in water) at temperatures below 60 ° C and only qualitative descriptors of solubility are provided (i.e., insoluble, practically insoluble) for estradiol, methylphenidate and testosterone. For the remaining four compounds listed in Table 2, the Merck Index either does not list the compound or provides no information on solubility in water at all. Since nitroglycerin is one of the compounds for which Farahmand and Maibach find in vitro- based modeling to be particularly poor at predicting in vivo results, an incorrect solubility limit might provide an explanation. However, for nitrogylcerin gross underestimation of flux is evident only for Models 11 and 12 (see Farahmand and Maibach's Table 3) rather than systematic. In those two cases, the results reported for nitroglycerin are inexplicably identical to those for nicotine and are located directly below them in the table. Since many of the models vary only slightly and should produce similar results for a given compound, the largest nitroglycerin flux deviations are likely attributable to tabulation error.

Apparent underestimation of flux for nicotine is more widespread. This is likely to be due to poor specification of solubility. The solubilities of estradiol and nicotine are both reported as 3600 ng/ml even though the former is described in Merck as insoluble and the latter as miscible, and even though Farahmand and Maibach report a roughly three orders of magnitude difference in the respective log octanol–water partition coefficients. Perhaps not coincidentally, nicotine appears directly below estradiol in Table 2. In the case of oxybutynin, Farahmand and Maibach report a solubility of 3.09×10^6 ng/ml. Miyamoto et al. (1994) report the solubility of the non-ionized form to be 1.2×10^4 ng/ml. Substitution of that value invalidates the argument for unreasonable overestimation of oxybutynin flux.

Further examination of the paper reveals that a pattern of carelessness carries over to other results including some insufficiently dramatic to otherwise attract attention. We recalculated results for Model 7 for all 10 compounds using Farahmand and Maibach's stated assumptions. In only 3 of 10 cases are Farahmand and Maibach's results reproducible and one of those cases is nicotine, for which aqueous solubility is erroneously specified.

Even if no computational errors were present, direct comparison of estimated maximum flux values and observed fluxes from drug delivery systems is questionable. Patch systems may or may not be at saturation, sometimes contain penetration enhancers, may have integral rate-limiting membranes, and induce skin temperatures that are higher than both those for which the water solubility values are specified and those at which the in vitro permeability coefficient estimates were made. In the absence of specification of/adjustment for these characteristics for each drug delivery system, comparisons of the type shown in Farahmand and Maibach's Table 3 are potentially misleading. Consideration should also be given to the fact that wide confidence bounds would be expected about estimates obtained using the maximum flux approach due to uncertainties in physico-chemical parameters, and about flux estimates derived from drug trials using single compartment pharmacokinetic models and limited or unsteady blood level measurements.

Additional problems are evident in a preceding paper (Farahmand and Maibach, 2009a), which provides the basis for the in vivo model described in Farahmand and Maibach (2009b). In that paper, the authors develop an equation for predicting the maximum in vivo blood concentration (C_{max}) that arises after appli-

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cation of transdermal delivery systems for various drugs. They use the same symbol for both observed C_{max} and dose-normalized C_{max}, which is poor form, and report both to have units of ng/ml, which cannot be correct. The latter issue is particularly confusing because the process of normalization is not explicitly shown. In some cases Farahmand and Maibach seem to have divided by daily dose (ng/day), while in others they have used total dose (ng) over multiple days and in at least one case (nicotine alza) there seems to be a one order of magnitude error in the normalized dose. In the case of estradiol, where observed C_{max} is reported in the pg/ml range and intended doses are in micrograms rather than milligrams, normalized C_{max} values appear to be three orders of magnitude too small. These inconsistencies and errors may have cancelled out when Farahmand and Maibach reconverted using the same normalizing factors in their flux calculations, but incorrect values were probably used to fit their regression, which is on normalized C_{max}, not flux. Values of coefficients in the in vivo model are therefore likely to be incorrect. Furthermore, and perhaps more importantly, it seems improbable that maximum in vivo blood concentration, which depends heavily on metabolic clearance rates, can be broadly predicted from molecular properties alone using a regression that is calibrated to a very limited number of pharmaceuticals.

In summary we find that Farahmand and Maibach's (2009a,b) conclusions regarding the correspondence of in vitro dermal penetration experiments to in vivo flux observations are not supported by the evidence they present. The two papers discussed here contain a remarkably large number of overt calculation errors and/or results that are irreproducible using stated assumptions, and multiple instances of erroneous parameter specification and/or attribution. Publication of these papers in Int J Pharm provides an archetypical example of the fallibility of peer review.

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