Received: 24 May 2022 | Revised: 9 August 2022 | Accepted: 12 September 2022

DOI: 10.1002/psp4.12865

PERSPECTIVE

A perspective on the current use of the phase distribution model for predicting milk-to-plasma drug concentration ratio

Mian Zhang | **Caroline Sychterz** | **Ming Chang** | **Lu Huang** | **Brian J. Schmidt** | **Lu Gaohua**

QSP and PBPK, Clinical Pharmacology & Pharmacometrics, Bristol Myers Squibb, Lawrenceville, New Jersey, USA

Correspondence
Mian Zhang, QSP and PBPK, Clinical Pharmacology & Pharmacometrics, Bristol Myers Squibb, Lawrenceville, NJ 08648, USA.
Email: mian.zhang@bms.com

Abstract

The phase distribution model, proposed by Atkinson and Begg in 1990, has been widely used for predicting breastmilk-to-plasma drug concentration ratio. However, misrepresentations of the equations have been noted in recent publications. In this perspective, we revisit the derivation of the equations and provide an R/Shiny interface for the model with a view to helping scientists in this field acquire in-depth understanding of the theoretical background and implementation of the model.

INTRODUCTION

A theoretical model for predicting milk-to-plasma drug concentration ratio (M/P ratio) was first derived by Fleishaker et al. in 1987.[1] The model described the distribution of drug into milk at steady-state with the key assumption that only unbound, unionized species of the drug in the aqueous phase can cross mammary membranes through passive diffusion with no involvement of active transporters. The phase distribution model, developed upon the same theoretical basis as Fleishaker's model, was coupled with additional equations to allow M/P ratio predictions using unbound drug fraction in plasma, pKa, and Log *P* or Log *D* of the drug.[2] Although the phase distribution model has been widely cited, the derivation of the equations has not been explicitly presented, and misrepresentations of the equations have been noted in recent publications.[3–5] Considering the increasing public health concerns around drug safety in lactation and renewed interest in the phase distribution model, we provide the theoretical background linking these important previous works within the context of recent applications and areas for caution that we have observed.

To assist readers in understanding and reproducing the model equations, we have summarized the definitions of the symbols used throughout this work in Table S1 and provided an R script/Shiny app in the Supplementary Information.

REVISITING THE M/P RATIO EQUATION DERIVED BY FLEISHAKER ET AL.

As is shown in Figure 1, unbound drug in the aqueous phase of whole milk can bind to milk protein and distribute into the lipid phase of whole milk. To characterize the parameters governing partitioning into different phases, milk samples from lactating women are often centrifuged to create skim milk, whole milk from which milk fat has been removed. Under these conditions, the aqueous phase of whole milk is assumed to be equivalent to skim milk, therefore, the terms that denote total drug

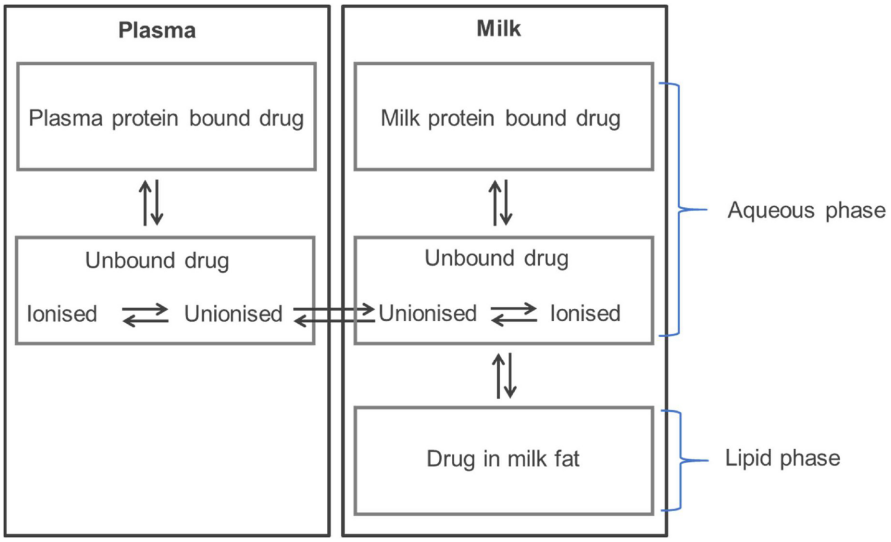

FIGURE 1 Schematic description of drug distribution between maternal plasma and milk according to the phase distribution model.

concentration (C), unbound fraction of total drug (fu) and unionized fraction of unbound drug (f^{un}) are interchangeable between skim milk (denoted by subscript skim) and the aqueous phase of whole milk (denoted by subscript aq, milk). Hence, the unbound, unionized concentration of drug in the aqueous phase of whole milk ($Cu^{un}_{aq,milk}$) is equivalent to that in skim milk (Cu^{un}_{skim}) which can be expressed as follows:

$$Cu^{un}_{skim} = C_{skim} \cdot fu_{skim} \cdot f^{un}_{skim} \quad (1)$$

where C_{skim} denotes the total drug concentration in skim milk, fu_{skim} and f^{un}_{skim} refer to the unbound fraction of drug and unionized fraction of unbound drug in skim milk. The Henderson-Hasselbalch equation can be used to calculate f^{un}_{skim}. As an example, the equation for a monoprotic base is:

$$f^{un}_{skim} = \frac{1}{1 + 10^{pKa - pH_{milk}}} \quad (2)$$

where pKa is the negative base-10 logarithm of the acid dissociation constant (Ka), pH_{milk} is the pH of (skim) milk.

Similarly, the unbound, unionized concentration of drug in maternal plasma can be calculated as follows:

$$Cu^{un}_{plasma} = C_{plasma} \cdot fu_{plasma} \cdot f^{un}_{plasma} \quad (3)$$

Then, the skim milk-to-plasma drug concentration ratio can be calculated as follows:

$$\frac{C_{skim}}{C_{plasma}} = \frac{Cu^{un}_{skim} / \left(fu_{skim} \cdot f^{un}_{skim}\right)}{Cu^{un}_{plasma} / \left(fu_{plasma} \cdot f^{un}_{plasma}\right)} \quad (4)$$

Based on the pH partitioning theory, Cu^{un}_{skim} (equivalent to $Cu^{un}_{aq,milk}$) equals Cu^{un}_{plasma} at steady state, therefore Equation 4 becomes:

$$\frac{C_{skim}}{C_{plasma}} = \frac{fu_{plasma} \cdot f^{un}_{plasma}}{fu_{skim} \cdot f^{un}_{skim}} \quad (5)$$

If we define skim-to-whole milk drug concentration ratio $\left(\frac{C_{skim}}{C_{milk}}\right)$ as $\frac{S}{M}$, Equation 5 becomes:

$$\frac{C_{milk}}{C_{plasma}} = \frac{fu_{plasma} \cdot f^{un}_{plasma}}{fu_{skim} \cdot f^{un}_{skim} \cdot \frac{S}{M}} \quad (6)$$

Here, we have arrived at the equation first presented by Fleishaker et al.[1] This equation was implemented in a commercial physiologically-based pharmacokinetic (PBPK) software used in a recent publication, but unbound fraction in whole milk (fu_{milk}) was mistakenly used in the place of unbound fraction in skim milk (fu_{skim}).[4] This mistake was corrected by the authors in a later publication and a later version of the PBPK software.[6]

DERIVATION OF ATKINSON AND BEGG'S PHASE DISTRIBUTION MODEL

Because total drug amount in whole milk consists of drug amount in aqueous and lipid phases, the total drug concentration in whole milk (C_{milk}) can be expressed as follows:

$$C_{milk} = \frac{V_{aq,milk} \cdot C_{aq,milk} + V_{fat,milk} \cdot C_{fat,milk}}{V_{milk}} \quad (7)$$

where $V_{aq,milk}$ and $V_{fat,milk}$ represent the volume of aqueous phase and lipid phase of the whole milk, C is total drug concentration in the respective phase, and V_{milk} is the total volume of whole milk.

If we define $f_{aq,milk}$ and $f_{fat,milk}$ as $V_{aq,milk}/V_{milk}$ and $V_{fat,milk}/V_{milk}$, respectively, Equation 7 then becomes:

$$C_{milk} = f_{aq,milk} \cdot C_{aq,milk} + f_{fat,milk} \cdot C_{fat,milk} \quad (8)$$

Then $\frac{S}{M}$ ratio is calculated as follows:

$$\frac{S}{M} = \frac{C_{skim}}{f_{aq,milk} \cdot C_{aq,milk} + f_{fat,milk} \cdot C_{fat,milk}} \quad (9)$$

Substituting $C_{aq,milk}$ for C_{skim} and rearranging Equation 9 yields:

$$\frac{S}{M} = \frac{1}{f_{aq,milk} + f_{fat,milk} \cdot \frac{C_{fat,milk}}{C_{skim}}} \quad (10)$$

Because milk lipid-to-ultrafiltrate distribution coefficient D_{milk} represents the ratio of $C_{fat,milk}$ to unbound drug concentration in the aqueous phase of whole milk ($Cu_{aq,milk}$) at milk pH, $C_{fat,milk}$ can be expressed using Equation 11:

$$C_{fat,milk} = D_{milk} \cdot Cu_{aq,milk} \quad (11)$$

Substituting Equation 11 into Equation 10 gives:

$$\frac{S}{M} = \frac{1}{f_{aq,milk} + f_{fat,milk} \cdot \frac{D_{milk} \cdot Cu_{aq,milk}}{C_{skim}}} \quad (12)$$

The total drug concentration in skim milk (C_{skim}) can be expressed as follows:

$$C_{skim} = \frac{Cu_{skim}}{fu_{skim}} \quad (13)$$

Then substituting Equations 13 into 12 and substituting Cu_{skim} for $Cu_{aq,milk}$ in Equation 12 gives:

$$\frac{S}{M} = \frac{1}{f_{aq,milk} + f_{fat,milk} \cdot D_{milk} \cdot fu_{skim}} \quad (14)$$

In contrast, a previous publication calculated the $\frac{S}{M}$ ratio using the following equation[4]:

$$\frac{S}{M} = \frac{1}{1 + Crt \cdot (fu_{milk} \cdot Log\, P_{o:w} - 1)} \quad (15)$$

where Crt denotes creamatocrit and is equivalent to $f_{fat,milk}$, fu_{milk} denotes unbound fraction of drug in whole milk, and $Log\, P_{o:w}$ is the logarithm of octanol-to-water partition coefficient. Given that $f_{fat,milk} + f_{aq,milk} = 1$, Equation 15 can be rearranged as follows:

$$\frac{S}{M} = \frac{1}{f_{aq,milk} + f_{fat,milk} \cdot Log\, P_{o:w} \cdot fu_{milk}} \quad (16)$$

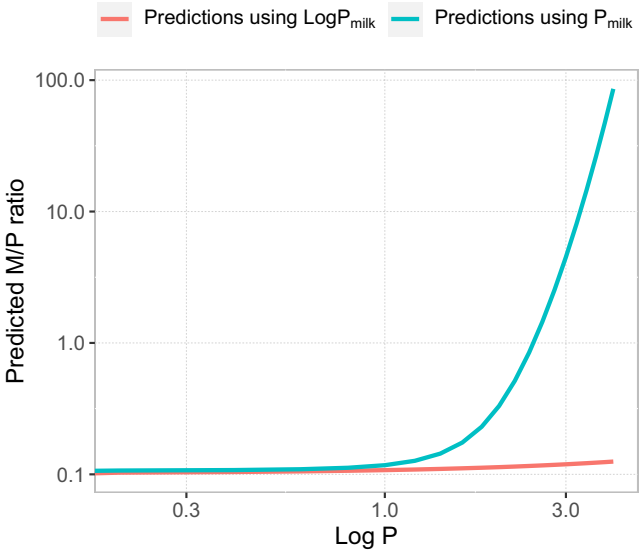

FIGURE 2 The impact of incorrectly using Log D_{milk} instead of D_{milk} in the phase distribution model equation (Equation 17) on the predicted milk-to-plasma drug concentration ratio (M/P ratio) for neutral compound with an fu_{plasma} of 0.1. The predicted M/P ratio using Log D_{milk} substantially deviates from that using D_{milk} for high Log P compounds.

Comparing Equation 16 with the correct equation (Equation 14) shows that Equation 16 from this previous publication mistakenly used fu_{milk} in the place of fu_{skim}. Furthermore, Equation 16 mistakenly used Log $P_{o:w}$ in the place of milk lipid-to-ultrafiltrate distribution coefficient D_{milk} (or $P_{o:w}$ as a surrogate of D_{milk}), and this can lead to substantially underestimated M/P ratio as compared to the correct equation (Equation 14), especially for highly lipophilic drugs (Figure 2). This error has also been identified in the associated PBPK software and is expected to be resolved in the next version.

To derive the final form of the phase distribution model, substituting Equation 14 into Equation 6 gives:

$$\frac{C_{milk}}{C_{plasma}} = fu_{plasma} \cdot \frac{f^{un}_{plasma}}{f^{un}_{skim}} \cdot \left(\frac{f_{aq,milk}}{fu_{skim}} + f_{fat,milk} \cdot D_{milk} \right) \quad (17)$$

As another area for caution, in two recent papers,[3,5] the term $\frac{f_{aq,milk}}{fu_{skim}} + f_{fat,milk} \cdot D_{milk}$ was misrepresented as $Log\left(\frac{f_{aq,milk}}{fu_{skim}}\right) + f_{fat,milk} \cdot D_{milk}$ and $\left(\frac{f_{aq,milk}}{fu_{skim}}\right) + f_{fat,milk} \cdot Log\, D_{milk}$, respectively, with slight differences in notations. Note that the latter mistake is identical with that in Equation 16, where Log D_{milk} or Log $P_{o:w}$ was mistakenly used in the place of D_{milk} or $P_{o:w}$. As an essential input of the model, fu_{skim} can either be measured using techniques, such as equilibrium dialysis,[1] or predicted as a function of fu_{plasma}[7]:

$$fu_{skim} = \frac{fu_{plasma}^{0.448}}{\left(6.94\times10^{-4}\right)^{0.448} + fu_{plasma}^{0.448}} \quad (18)$$

This function reasonably described the relationship between plasma and skim milk unbound fractions for several drugs with diverse physicochemical and binding properties and enables prediction of fu_{skim} from fu_{plasma} in lieu of measured fu_{skim}.[7,8] Note that this equation has been misrepresented in a recent publication where the exponent (0.448) of the constant term 6.94×10^{-4} has been omitted.[3]

Another essential input of the model, D_{milk}, can be predicted using the following equation in lieu of experimental data[9]:

$$\text{Log}\, D_{milk,pH\ 7.2} = -0.88 + 1.29 \cdot \text{Log}\, D_{o:w,pH\ 7.2} \quad (19)$$

It should be noted that above relationship was established at pH 7.2. Therefore, if $\text{Log}\, D_{o:w}$ is not measured at pH 7.2, it should be converted to $\text{Log}\, D_{o:w}$ at pH 7.2 to satisfy the relationship. Similarly, the predicted $\text{Log}\, D_{milk,pH\ 7.2}$ should be converted to $\text{Log}\, D_{milk}$ at the milk pH if the milk pH of interest deviates from 7.2. Such conversions can be done using the rearranged Henderson-Hasselbalch equation. As an example, the equation to convert the distribution coefficient for a monoprotic base at a given pH (D_{pH_b}) to that at another pH (D_{pH_a}) is:

$$D_{pH_a} = D_{pH_b} \cdot \frac{1 + 10^{pKa - pH_b}}{1 + 10^{pKa - pH_a}} \quad (20)$$

ISSUE WITH THE UNBOUND DRUG FRACTION IN WHOLE MILK

Although unbound drug fraction in whole milk (fu_{milk}) is not essential in the derivation of the model equations, this term is reported in recent publications.[4,8] To derive the fu_{milk} equation reported in these publications, one needs to begin by defining fu_{milk} as the ratio of unbound drug concentration in the aqueous phase of whole milk to total drug concentration in whole milk as follows:

$$fu_{milk} = \frac{Cu_{aq,milk}}{\left(V_{aq,milk} \cdot C_{aq,milk} + V_{fat,milk} \cdot C_{fat,milk}\right)/V_{milk}} \quad (21)$$

Substituting $f_{aq,milk}$, $f_{fat,milk}$ and Equations 11 into 21 gives:

$$fu_{milk} = \frac{Cu_{aq,milk}}{f_{aq,milk} \cdot C_{aq,milk} + f_{fat,milk} \cdot D_{milk} \cdot Cu_{aq,milk}} \quad (22)$$

Substituting $\frac{Cu_{aq,milk}}{fu_{aq,milk}}$ for $C_{aq,milk}$ and rearranging Equation 22 gives:

$$fu_{milk} = \frac{1}{f_{aq,milk} \cdot \frac{1}{fu_{aq,milk}} + f_{fat,milk} \cdot D_{milk}} \quad (23)$$

Substituting fu_{skim} for $fu_{aq,milk}$ gives:

$$fu_{milk} = \frac{1}{f_{aq,milk} \cdot \frac{1}{fu_{skim}} + f_{fat,milk} \cdot D_{milk}} \quad (24)$$

Here, we have arrived at the same equation as reported previously.[4,8] However, the issue with the proposed fu_{milk} definition is that, while the amount of unbound drug is the same for whole milk and the aqueous phase of whole milk as unbound drug only exists in the aqueous phase, $Cu_{aq,milk}$ does not equal unbound drug concentration in whole milk due to the volume difference between whole milk and the aqueous phase of whole milk. In many practical cases, it may be sufficient to approximate fu_{milk} as proposed given that the fat content of milk is often less than 5%.[10] However, for drugs with low D_{milk} and high fu_{skim}, ignoring the volume difference may lead to an fu_{milk} greater than one as reported previously,[8] and it is important to be aware of the assumption behind Equation 24 when interpreting such data.

CONCLUDING REMARKS

Since the phase distribution model was first proposed in the 1990s, it has demonstrated reasonable predictive performance for non-transporter substrates and is still considered to be theoretically valid. In recent years, adapting the phase distribution model to PBPK frameworks has emerged as a useful approach to predict drug concentrations in breast milk, and the model can be further refined to account for additional mechanisms such as active transport. However, the misrepresented equations may confound the outcomes of these efforts. This perspective illustrates the derivation of the model equations by linking together the multiple original works, and, alongside the R/Shiny interface included herein, can serve as a useful source for scientists in this field to acquire in-depth understanding of the theory and implementation of the model.

FUNDING INFORMATION

No funding was received for this work.

CONFLICT OF INTEREST

All authors were employees of Bristol Myers Squibb Company at the time the work was conducted and may hold shares in Bristol Myers Squibb Company.

ORCID

Caroline Sychterz https://orcid.org/0000-0002-7255-8500

REFERENCES

1. Fleishaker JC, Desai N, McNamara PJ. Factors affecting the milk-to-plasma drug concentration ratio in lactating women: physical interactions with protein and fat. *J Pharm Sci*. 1987;76:189-193.
2. Atkinson U, Begg EJ. Prediction of drug distribution into human milk from physicochemical characteristics. *Clin Pharmacokinet*. 1990;18:151-167.
3. Job KM, Dallmann A, Parry S, et al. Development of a generic physiologically based pharmacokinetic model for lactation and prediction of maternal and infant exposure to ondansetron via breast Milk. *Clinical Pharmacology & Therapeutics*. 2022;111:111-1120.
4. Abduljalil K, Pansari A, Ning J, Jamei M. Prediction of drug concentrations in milk during breastfeeding, integrating predictive algorithms within a physiologically-based pharmacokinetic model. *CPT Pharmacometrics Syst Pharmacol*. 2021;10:878-889.
5. Yang H, Xue I, Gu Q, et al. Developing an in vitro to in vivo extrapolation (IVIVE) model to predict human Milk-to-plasma drug concentration ratios. *Mol Pharm*. 2022;19:2506-2517.
6. Abduljalil K, Gardner I, Jamei M. Application of a physiologically based pharmacokinetic approach to predict theophylline pharmacokinetics using virtual non-pregnant, pregnant, fetal, breast-feeding, and neonatal populations. *Front Pediatr*. 2022;10:840710.
7. Atkinson H, Begg E. Prediction of drug concentrations in human skim milk from plasma protein binding and acid-base characteristics. *Br J Clin Pharmacol*. 1988;25:495-503.
8. Koshimichi H, Ito K, Hisaka A, Honma M, Suzuki H. Analysis and prediction of drug transfer into human milk taking into consideration secretion and reuptake clearances across the mammary epithelia. *Drug Metab Dispos*. 2011;39:2370-2380.
9. Atkinson HC, Begg EJ. Relationship between human milk lipid-ultrafiltrate and octanol-water partition coefficients. *J Pharm Sci*. 1988;77:796-798.
10. Jensen R, Clark R, Ferris A. Composition of the lipids in human milk: a review. *Lipids*. 1980;15:345-355.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Zhang M, Sychterz C, Chang M, Huang L, Schmidt BJ, Gaohua L. A perspective on the current use of the phase distribution model for predicting milk-to-plasma drug concentration ratio. *CPT Pharmacometrics Syst Pharmacol*. 2022;11:1547-1551. doi:10.1002/psp4.12865