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A Physiologically-Based Pharmacokinetic Model of Drug Detoxification by Nanoparticles

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Abstract

Nanoparticles (NPs) may be capable of reversing the toxic effects of drug overdoses in humans by adsorbing/absorbing drug molecules. This paper develops a model to include the kinetic effects of treating drug overdoses by NPs. Depending on the size and the nature of the NPs, they may either pass through the capillary walls and enter the tissue space or remain only inside the capillaries and other blood vessels; models are developed for each case. Furthermore, the time scale for equilibration between the NP and the blood will vary with the specific type of NP. The NPs may sequester drug from within the capillaries depending on whether this time scale is larger or smaller than the residence time of blood within the capillary. Models are developed for each scenario. The results suggest that NPs are more effective at detoxification if they are confined to the blood vessels and do not enter the tissues. The results also show that the detoxification process is faster if drug uptake occurs within the capillaries. The trends shown by the model predictions can serve as useful guides in the design of the optimal NP for detoxification.

Keywords

absorption; adsorption; drug detoxification; drug overdose; microemulsion; nanoparticle; pharmacokinetic model

INTRODUCTION

Drug overdose is a major health care problem in the United States. A number of widely used drugs can cause life-threatening toxicities and are without antidotes. Nanoparticulate systems that can sequester drugs may offer a solution to this problem. Intravenous injections of such systems can potentially treat overdoses by adsorbing/absorbing drug molecules, thereby, reducing the free drug concentration in blood and tissues (1,2). Nanoparticles (NPs) such as microemulsions, core-shell NPs, microgels, liposomes, and nanotubes may be used for detoxification. It is relatively straightforward to quantify the effectiveness of these nanoparticulate systems at sequestering drugs by conducting *in vitro* experiments; however, the uptake of the drug by the NPs is only one of the variables that determine the efficacy of these systems in treating overdoses. Inside the body, the dynamic changes in drug concentration will also depend on a number of physiological factors such as the blood flowrates and the partition coefficients of the drug in various tissues. Thus, in order to

determine the effectiveness of NPs at treating overdoses, one needs to perform animal and human testing. It is not possible to conduct testing on humans until the safety and efficacy of these nanoparticulate systems is firmly established. An alternate means to gauge the effectiveness of NPs is to develop a physiologically based pharmacokinetic (PBPK) model to predict the dynamic drug concentration in various tissues of an overdosed patient after an injection of NPs. In this paper we propose such a model. While numerous others have developed PBPK models (3-10), this report is the first to extend these models to include drug detoxification from the body's blood and tissues following an intravenous injection of NPs.

The main objective of this paper is to illustrate how the addition of NPs to the body may be included into a PBPK model. As an illustration of our model, we show dynamic drug concentration profiles using partition coefficient values for amitriptyline, an antidepressant drug for which there is a need for drug overdose treatment.

Modeling

We use an eight compartment PBPK model that includes blood, liver, gut, heart, brain, kidneys, muscle, and fat compartments. In general every organ that is expected to have a finite drug uptake should be included in the PBPK model, but since this paper only intends to illustrate how to include NPs into a PBPK model, we restrict the model to only eight compartments. The PBPK model for this eight compartment system is available in literature (11, p. 364). Below, we develop mass balance equations for the inclusion of NPs into this model. The clearance of the drug by the body is neglected in the PBPK model because for many drugs (such as amitriptyline) it does not play a significant role in the short time scales of about 15–30 min which are relevant in drug overdose treatment.

In order to develop a model for drug detoxification by any type of NP, it is important to know whether the NPs will cross the capillary wall and enter the tissue space or remain only in the blood. The capillary wall consists of a single layer of endothelial cells and a basement membrane. Between adjacent endothelial cells there are intercellular clefts which are approximately 6–7 nm in size (12-14). Any solute that moves between the vascular and tissue spaces must pass through this capillary wall, either by convection through the intercellular clefts, diffusion through the endothelial cells, or pinocytosis (14). Most NPs will be too large to pass through the intercellular clefts; however, lipid soluble NPs may diffuse directly through the endothelial cells (12). Additionally, some NPs may cross the capillary wall via pinocytosis. This leads to the possibility that some types of NPs will traverse the capillary wall and enter the interstitial space of the tissue. Because some types of NPs will cross the capillary wall and others will not, we develop separate models to simulate the drug detoxification by NP in each case.

In developing a drug detoxification PBPK model, there are two important time scales that must be compared. The first time scale, τ_1 , is the time scale for equilibrium to be established between the blood and the NP. This time scale is essentially the inverse of the rate constant for drug transport from the blood to the NP. For an effective drug overdose treatment system, τ_1 needs to be on the order of seconds. The second time scale, τ_2 , is the time scale for equilibrium to be established between the blood and the tissue. This is essentially the inverse of the resistance offered by the capillary walls to drug transport. Since most PBPK models assume that the tissue and blood compartments are in equilibrium (11,15), τ_2 is of the same order as the time required for blood to flow through the capillaries, which is about 1–3 s (12). It follows that if $\tau_1 \ll \tau_2$, then the NP requires more time to equilibrate with the blood than the time the blood (and thus, the NP) is actually inside the capillary space. In this case, we can neglect the uptake of drug by NP inside the capillary blood. Alternatively, if τ_1 is comparable to τ_2 , there is fast equilibration between the NP and blood, and we must

include the drug uptake by NP in the capillary. Since different NP systems may have different τ_2 values (larger or smaller than τ_1), models are developed for each of these two cases.

Based on the above discussion, the addition of the NPs may fall in four different categories depending on whether they enter the tissue space and whether they sequester drug from within the capillaries. To take into account these possible scenarios, three models are developed in this paper. Models 1 and 2 represent the case in which the NP does not cross the capillary walls and, consequently, does not enter the tissue space. Amongst these, Model 1 reflects the case of slow drug equilibration between the NP and the blood ($\tau_1 \gg \tau_2$), and Model 2 reflects the case of rapid equilibration ($\tau_1 \sim \tau_2$). In Model 3, the NP is assumed to diffuse through the capillary walls into the interstitium, and rapid drug equilibration between the blood and the NP ($\tau_1 \sim \tau_2$) is also assumed. For this model, we neglect any barriers offered by the capillary walls to NP transport. As a result, the NP's drug concentration in the interstitial space is assumed to be the same as that in the capillary blood. Though not shown in this paper, a model in which the NPs enter the tissue space and $\tau_1 \gg \tau_2$ can easily be developed by combining Models 1 and 3. Below we present mass balance equations for each of the three models discussed above.

Model 1: Impermeable Capillary Walls, $\tau_1 \gg \tau_2$

In Model 1, the NP sequesters drug only from within the non-capillary blood vessels. While there is rapid equilibration of the NP with the blood, it is assumed in this model that this equilibration time scale (τ_1) is large when compared to the even more rapid τ_2 . In this model, the NP does not enter the interstitial space and does not sequester drug while in the capillaries. Thus, the NP effectively stays confined to the blood compartment. In this situation, the drug concentration in the tissues and the NP's drug concentration individually equilibrate with drug concentration in the blood, C_b .

The NP may sequester drug through either an adsorption or absorption mechanism. In the case of an adsorption mechanism, we denote the surface drug concentration on the NP as λ . In the case of an absorption mechanism, we denote the drug concentration absorbed in the NP as C_{NP} . In all the models, we assume the NP's drug concentration is in equilibrium with C_b , such that for an adsorption mechanism $\lambda = R_{NP}C_b$ and for an absorption mechanism $C_{NP} = R_{NP}C_b$ where R_{NP} is the partition coefficient between the NP and the blood. For an adsorption mechanism, the total amount of drug present in the blood compartment is

$$V_b C_b + S\Gamma = V_b C_b X, \quad (1)$$

where V_b is the volume of the blood, S is the total surface area of the NPs, and X is a parameter that characterizes the effectiveness of the NP at binding a particular drug, defined for an adsorption mechanism as $1 + (S/V_b)R_{NP}$ where (S/V_b) is the ratio of the surface area of NP to blood volume. For an absorption mechanism, the total amount of drug present in the blood compartment is

$$V_b C_b + \Phi V_b C_{NP} = V_b C_b X, \quad (2)$$

where Φ is the volume fraction of NP in the blood, and X is defined as $1 + \Phi R_{NP}$.

The mass balance for the blood compartment is as follows:

$$X V_b \frac{dC_b}{dt} = \sum_{i=L,H,B,K,M,F} Q_i \frac{C_i}{R_i} - Q_b C_b. \quad (3)$$

In the above equation, the accumulation term, i.e., the term involving the time derivative, includes both the drug in the blood and also the drug sequestered by the NP. Since in Model 1, the NP does not sequester drug inside the tissue compartments, the mass balances for the tissue compartments are rather straight forward (the same as in a normal PBPK model) and are as follows.

For the gut, heart, brain, kidneys, muscle, and fat compartments ($i = G, H, B, K, M,$ and F , respectively)

$$V_i \frac{dC_i}{dt} = Q_i \left(C_b - \frac{C_i}{R_i} \right) \quad (4)$$

for the liver compartment

$$V_L \frac{dC_L}{dt} = (Q_L - Q_G) C_b + Q_G \frac{C_G}{R_G} - Q_L \frac{C_L}{R_L} \quad (5)$$

In the above equations, the subscripts L, G, H, B, K, M, F, and b represent the liver, gut, heart, brain, kidney, muscle, fat, and blood respectively. For a specific tissue i , C_i is the drug concentration in that tissue, R_i is the tissue's drug partition coefficient, V_i is the volume of tissue, and Q_i is the blood flow rate to the tissue. It is important to note that although the NP does not sequester drug inside the capillary spaces of the tissues, the drug concentrations of each tissue are affected by the addition of NP since the blood compartment is directly linked to all the tissue compartments.

Since we assume that the NP and the blood are always in equilibrium inside the blood compartment, C_b instantaneously drops to a lower value after the injection. In all three models, if C_b prior to NP injection is $C_{b,0}$, then the drug concentration in the blood immediately following NP injection, $C_{b,I}$, is such that

$$C_{b,I} = \frac{C_{b,0}}{X} \quad (6)$$

Model 2: Impermeable Capillary Walls, $\tau_1 \sim \tau_2$

In Model 2, the NP is dispersed within the blood and also sequesters drug inside the capillary. Thus, the blood with the NP can be treated as a single phase with an overall drug concentration, C_b^* , that includes the free drug in the blood, C_b , and the drug concentration adsorbed to/absorbed in the NP. This overall concentration is given by $C_b^* = C_b X$. Prior to NP injection $C_b^* = C_b$, and while C_b changes instantaneously once NP is injected, there is no discontinuity in the profiles of C_b^* with time.

Even after the NP injection, the drug concentration in the tissue, C_i for tissue i , equilibrates with C_b , so that

$$C_i = R_i C_b = \frac{R_i}{X} C_b^* \quad (7)$$

We define a new effective partition coefficient for each tissue i , R_i^* , as the ratio between the drug concentration of tissue i , C_i , and the total drug concentration in the blood, C_b^* .

$$R_i^* = \frac{R_i}{X}. \quad (8)$$

The mass balance equations for Model 2 are the same as that of the PBPK model in the absence of NP addition, but R_i and C_b are now replaced by R_i^* and C_b^* , respectively. The Model 2 equations are as follows.

For the blood compartment

$$V_b \frac{dC_b^*}{dt} = \sum_{i=L,H,B,K,M,F} Q_i \frac{C_i}{R_i^*} - Q_b C_b^*. \quad (9)$$

For the gut, heart, brain, kidneys, muscle, and fat compartments ($i = G, H, B, K, M$, and F , respectively)

$$V_i \frac{dC_i}{dt} = Q_i \left(C_b^* - \frac{C_i}{R_i^*} \right). \quad (10)$$

For the liver compartment

$$V_L \frac{dC_L}{dt} = (Q_L - Q_G) C_b^* + Q_G \frac{C_G}{R_G^*} - Q_L \frac{C_L}{R_L^*}. \quad (11)$$

Model 3: Permeable Capillary Walls, $\tau_1 \sim \tau_2$

Model 3 reflects the situation where the NP sequesters drug in all the blood vessels, including the capillaries, and permeates the capillary wall so that it also sequesters drug from within the interstitial space of the tissue. Since NP is continuously entering and leaving the blood and tissue compartments, the concentration of NP is constantly changing. Consequently, in addition to the drug mass balance, we also need a NP mass balance in each of the eight compartments. We assume equilibrium between the blood leaving the tissue and the NP inside the tissue, so that each tissue i is characterized by a partition coefficient, K_i . For an adsorption mechanism, K_i is defined as the ratio of S/V of NP in tissue i (given by $(S/V)_i$) to S/V of NP in the blood leaving the tissue i . For an absorption mechanism, K_i is defined as the ratio between the volume fraction of NP in tissue i (given by Φ_i) to the volume fraction of NP leaving tissue i . As K_i approaches zero, less NP accumulates inside tissue i . We additionally assume the concentration of drug sequestered by the NP inside the tissue is equal to the NP's equilibrium drug concentration in the blood leaving tissue i , i.e., $R_{NP} C_i / R_i$.

As an illustration of our model, the Model 3 mass balance equations are shown below for the case in which the NP sequesters drug through an adsorption mechanism. In the case of an absorption mechanism, replaced $(S/V)_i$ should be by Φ_i in the equations below.

For the gut, heart, brain, kidneys, muscle, and fat compartments ($i = G, H, B, K, M$, and F , respectively):

$$V_i \frac{d(S/V)_i}{dt} = Q_i \left((S/V)_b - \frac{1}{K_i} (S/V)_i \right), \quad (12)$$

$$V_i \left(\frac{dC_i}{dt} + R_{NP} \frac{d}{dt} \left((S/V)_i \frac{C_i}{R_i} \right) \right) = Q_i \left(C_b - \frac{C_i}{R_i} + (S/V)_b R_{NP} C_b - (S/V)_i \frac{R_{NP}}{K_i} \frac{C_i}{R_i} \right). \quad (13)$$

For the liver compartment:

$$V_L \frac{d(S/V)_L}{dt} = \frac{Q_G}{K_G} (S/V)_G + (Q_L - Q_G) (S/V)_b - \frac{Q_L}{K_L} (S/V)_L, \quad (14)$$

$$V_L \left(\frac{dC_L}{dt} + R_{NP} \frac{d}{dt} \left((S/V)_L \frac{C_L}{R_L} \right) \right) = \frac{Q_G C_G}{R_G} \left(1 + (S/V)_G \frac{R_{NP}}{K_G} \right) + (Q_L - Q_G) C_b \left(1 + (S/V)_b R_{NP} \right) - \frac{Q_L C_L}{R_L} \left(1 + (S/V)_L \frac{R_{NP}}{K_L} \right). \quad (15)$$

For the blood compartment:

$$V_b \frac{d(S/V)_b}{dt} = \sum_{i=L,H,B,K,M,F} \left(\frac{Q_i}{K_i} (S/V)_i - Q_b (S/V)_b \right) \quad (16)$$

$$V_b \left(\frac{dC_b}{dt} + R_{ME} \frac{d}{dt} \left((S/V)_b C_b \right) \right) = \sum_{i=L,H,B,K,M,F} \left(Q_i \frac{C_i}{R_i} + \frac{Q_i}{K_i} (S/V)_i R_{ME} \frac{C_i}{R_i} \right) - Q_b C_b \left(1 + (S/V)_b R_{ME} \right). \quad (17)$$

We wish to use X as a parameter rather than specify R_{NP} and an initial $(S/V)_b$ separately. We therefore multiply Eqs. (12), (14), and (16) by R_{NP} and treat $R_{NP}(S/V)_i$ and C_i as the unknown variables. On substituting X for $1 + (S/V)_b R_{NP}$, $R_{NP}(S/V)_b$ simply becomes $X - 1$. Knowing the initial conditions for all 16 variables, we can solve these equations simultaneously to determine the drug and NP concentrations in various tissues as a function of time.

RESULTS AND DISCUSSION

We now discuss the model predictions for the dynamic concentration profiles in the tissues after a NP injection. Assuming the toxic drugs do not significantly deplete organ function, the values used for the volumes and flow rates of each tissue are independent of the type of drug and are given in Table I. In this paper, we use amitriptyline, an antidepressant drug, to illustrate our model. R_i values for amitriptyline are not explicitly known, so we have calculated them by scaling up thiopental R_i values by a constant factor, which is obtained by matching amitriptyline's calculated volume of distribution with the literature value. These calculated R_i values for amitriptyline are given in Table I. In the remainder of this section, we discuss two cases of drug overdose treatment. In the first case, the NP is injected a long time after the overdose has occurred, such that the drug concentrations in the tissues have already reached steady-state. While this is not a very realistic scenario, it helps to identify the key differences between the three models. In the second case, a more realistic scenario is presented, in which the NP is injected a short time after the overdose.

NP Injected a Long Time After Overdose

In the simulations presented below, the PBPK model in the absence of NP was used to determine the steady-state drug concentrations for each tissue following a bolus drug dosage

which caused C_{b0} to be $100 \mu\text{M}$. Subsequently, a bolus of the NP was introduced. The amount of NP introduced in the bolus is reflected in the parameter X . The equations presented above were solved for each model to determine C_i as a function of time. Three of these plots are shown in Fig. 1. The zero time on these plots corresponds to the time at which the NP is added. Please note that the drug concentration shown in these plots does not include the drug sequestered by the NP. For comparison, two values of K_i are shown ($K_i = 1$ and $K_i = 100$) for Model 3. All three models are expected to yield the same steady-state because in all three models, C_i for each tissue is in equilibrium with C_b , and C_{b0} as well as the dosage of NP are the same for each of the model. At the time of NP addition, it is assumed that the drug in the blood immediately equilibrates with the drug on the NP, and thus, C_b drops to a lower value (equal to C_b/X) for all three models, as is shown in Fig. 1(a). C_b then begins to rise as the tissues start losing drug to establish equilibrium with the blood. As is seen in Fig. 1(a), Model 2 shows the quickest concentration response; its predicted C_b increases faster than in either of the other two models. The concentration predicted by Model 2 reaches the steady-state value the fastest, while the Model 1 profiles take the longest to equilibrate. This is reasonable because the NP in Model 1 is not equilibrating with the blood inside the capillaries, and thus it takes a longer time for the blood, tissues, and NP to equilibrate with each other. The fact that Model 3 always has a slower response than Model 2 may be counterintuitive because one may expect that if the NP is also taking up the drug from inside the tissue then the concentration responses will be faster; however, this is not the case. A distinction is not made between the tissue space and the capillary space in the models; thus in both Models 2 and 3, the NP in the tissue compartment equilibrates with the blood. In Model 2, after the NP sequesters drug in the capillaries, it leaves the tissue compartment and enters the blood compartment. Once inside the blood compartment, it releases some of the drug that was sequestered in the tissue to the blood, which has a drug concentration lower than the equilibrium value. Thus, the NP transfers the drug from the tissue to the blood compartment. After releasing drug in the blood compartment, the NP can then circulate through the body, enter another tissue compartment, and transfer more drug to the blood compartment. Consequently, the NP in Model 2 acts as a “transfer agent”, which speeds up the transfer of drug from the tissue to the blood. In Model 3, some of the NP enters the interstitial space of the tissue, causing less NP to leave the tissue compartment and enter the blood. It follows that in Model 3 the NP is not as effective a transfer agent, and the time to reach steady-state is longer. As the K_i values in Model 3 increase, the amount of NP that enters the interstitial space of the tissues increases, and a longer amount of time is needed to attain steady state. As the K_i values approach zero, the plots for Model 3 approach that of Model 2.

The dynamic drug concentration in the heart tissue, starting from its equilibrium value (Fig. 1(b)), follows trends similar to those seen in the other tissues, with the exception of the fat tissue (Fig. 1(c)). The drug concentration in the heart tissue, C_H , decreases immediately following NP administration, reaches a minimum value, and then starts to increase. All other tissues except the fat follow this trend. The drug concentration in the fat tissue, C_F , decreases extremely slowly until the steady-state value is reached. The long equilibration time of the fat tissue (about 500 min for Model 1 and 4000 min for Models 2 and 3) can be attributed to the large value of $R_F V_F / Q_F$. At the time C_H has reached its minimum values, C_F is about the same as its initial value. Thus, the minimum C_H value represents the equilibrium value of the drug concentration in the heart in the absence of the fat tissue. Beyond this time the fat tissue continues to release drug to the blood. A fraction of the drug that is released by the fat to the blood compartment is taken up by the other tissues to re-establish equilibrium with the blood. Beyond the time at which the minimum occurs in the concentration profiles, the tissues (except fat), the blood, and the NP are essentially in equilibrium. This dynamic behavior is a pseudo-steady-state driven by the slowest time scale of the fat tissue.

NP Injected a Short Time After Overdose

In the simulations shown below, at time zero all C_i values are zero and C_{b0} is $10\ \mu\text{M}$ to reflect a bolus overdose. The NP is then introduced at a finite time. The K_i values in Model 3 will vary with the type of NP, but as an illustration of our model, unless otherwise specified, we have taken the K_i values to be equal to the R_i values shown in Table I. In the simulations shown in Figs. 2-4, the profiles from all the models show a decrease in drug concentration at long time scales and reach the same steady-state concentration. Additionally, the Model 2 profiles reach steady-state the fastest. We are primarily concerned with the trends in the drug concentrations in the blood and in the heart, as C_b directly affects all the tissue concentrations, and the heart is the primary organ that determines whether or not an overdose of amitriptyline is lethal.

Figure 2 shows the dynamic C_b for NP addition at 5 min for all the three models and for two different values of X ($X = 2.2$ and $X = 10$). An X value of 2.2 was used because we have calculated this value for one of the microemulsions developed in our laboratory. As is shown in Fig. 2, C_b immediately drops to a lower value at the time of the NP addition due to drug sequestration. The concentration drop is the same for all the three models, but larger for larger values of X . This sudden drop reduces C_b to below the value of the equilibrium drug concentration for most tissues. Accordingly, the tissues begin to release drug into the blood, and C_b begins to increase. The loss of drug from the tissues stops and a maximum value of C_b is reached. At this point, all the tissues (with the exception of the tissues with a very large equilibration time, such as the fat) are in equilibrium with the blood. Beyond this time, the blood and all the other tissues lose some drug to the fat, causing the drug concentrations to decrease slowly. These trends are the same for all the models and for both values of X . As expected, the Model 2 profiles reach the maximum and final steady-state values faster than the Models 1 and 3 profiles.

The C_H profiles are shown in Fig. 3(a) and (b). The only difference between the two graphs is the time at which the NP is added. In the absence of the NP addition, C_H initially increases after the overdose and then begins to decrease as the slowly equilibrating organs begin to absorb the drug. The profiles in Fig. 3(a) correspond to NP addition at 1 min when C_H is still increasing, and the simulations shown in Fig. 3(b) correspond to the case when NP addition occurs at 5 min, at which time C_H has already started to decrease. These plots show the importance of both the values of X and the time at which the NP is added. At 1 min, the heart tissue is still taking up drug from the blood (Fig. 3(a)). When NP is added at this point in time and if the X value is small, such as 2.2, C_H increases after NP addition, though at a slower rate than in the absence of NP. C_H reaches a maximum value and then decreases as the heart loses drug to the blood. With an X value of 2.2, there is not a significant decrease in C_H for Models 1 and 3, while Model 2 shows about a $1\ \mu\text{M}$ reduction at the end of 30 min. This happens because concentrations in Model 2 equilibrate quicker than those in Models 1 and 3. Even though C_H is still increasing at the time of NP addition (1 min), if the X value is large enough, such as a value of 10, then the drug concentration begins to decrease immediately following NP administration. All models show a decrease in C_H immediately following NP addition for $X = 10$, with Model 2 showing the fastest reduction. Thus, the concentration reduction is quicker for higher X values. In the absence of NP, C_H has already started to decrease at 5 min. When NP is added at this point (Fig. 3(b)), the concentration reduction is faster after NP addition than in Fig. 3(a) for all values of X . Larger values of X lead to larger concentration reductions. It is important to note that for each X value, all three models will reach the same steady state in each tissue; however, only the short time responses are important in drug overdose patients. Even though Models 1 and 3 will eventually lead to considerable decreases in drug concentrations for an X value of 2.2, the response time is longer than 30 min. Consequently, a significant decrease in drug concentration is not shown in Fig. 3 for Models 1 and 3 at $X = 2.2$. A comparison of Figs.

3(a) and (b) shows that, despite these opposing trends between NP addition at 1 and 5 min for X values of 2.2, the resulting concentration values at 30 min are relatively the same.

Depending on when the NP is added, an interesting behavior sometimes occurs in the liver, muscle, and fat tissues for Models 2 and 3; the addition of NP sometimes causes an increase in C_i beyond the value of the C_i value in the absence of NP. This trend occurs for Model 2 and for low values of K in Model 3. An example of this trend is illustrated in Fig. 4, which shows the amitriptyline concentration inside the liver tissue, C_L , for NP addition at 5 min. C_L for Model 2 exceeds that of the case with no NP. It is important to note that while the drug concentrations in Models 2 and 3 are sometimes larger than the case in which the NP is not administered, the steady-state drug concentrations are always lower. Moreover, the increased concentration value as a result of NP addition never exceeds the maximum value of concentration for the case when the NP is not added.

In order to explain the reasons behind this drug concentration increase after NP addition, the tissue mass balance for the case where no NP is present (Eq. (18)) must be compared with the tissue mass balance for Model Z (Eq. (19)). For simplicity, we will refer to C_i as the drug concentration inside tissue i for the case where no NP is present and $\widehat{C}_i$ as the drug concentration in tissue i when a Model 2 NP is present. These equations are

$$V_i \frac{dC_i}{dt} = Q_i \left(C_b - \frac{C_i}{R_i} \right) \quad (18)$$

and

$$V_i \frac{d\widehat{C}_i}{dt} = Q_i \left(C_b^* - \frac{\widehat{C}_i X}{R_i} \right) \quad (19)$$

In Eq. (19), C_b^* is the effective drug concentration in the blood, equal to $\widehat{C}_b X$, i.e., the sum of the free and the NP-sequestered drug in the blood. As discussed previously, the drug concentration in the blood changes from $C_{b,0}$ to $C_{b,0}/X$, i.e., $C_{b,f}$ at the time of NP injection. If the X value is large enough, $C_{b,f}$ will be lower than the equilibrium concentration for certain tissues, i.e., $C_{b,f} < C_i/R_i$. This is true for tissues that take up drug quickly, i.e., where $R_i V_i/Q_i$ is small. As a result, the blood will start to sequester drug from these tissues. These tissues may lose so much drug to the blood that C_b^* becomes larger than C_b . The tissues with small drug concentrations, i.e., those with large $R_i V_i/Q_i$ values, will then take up more drug than what they would have taken in the absence of the NP, causing $\widehat{C}_i$ to become larger than C_i (Fig. 4). Mathematically, this behavior may be explained by a comparison of Eqs. (18) and (19). If C_b^* becomes larger than C_b , there will be a tendency for the concentration inside

the tissue to increase at a faster rate. This is compensated by the fact that $\frac{\widehat{C}_i X}{R_i}$ is larger than C_i/R_i since X is a positive value larger than 1. In tissues with large $R_i V_i/Q_i$ values (such as

the fat, liver, and muscle), C_i is approximately zero at the time of NP addition, meaning $\frac{\widehat{C}_i X}{R_i}$ and C_i/R_i are both about zero. Thus, $\widehat{C}_i$ is larger than C_i for a short time span following the NP administration. This same trend occurs for small values of K in Model 3. It can be seen in Fig. 4 that at the end of 25 min, $\widehat{C}_i$ for the $X = 10$ NP was about $2.8 \mu\text{M}$ below C_i however, $\widehat{C}_i$ for the $X = 2.2$ NP was slightly above C_i . At the end of 60 min, both values of X result in a decreased $\widehat{C}_i$ inside the liver.

We now discuss the effects of variations in the K_i values on the predictions of Model 3. To evaluate the effect of the magnitude of the K_i values, simulations are performed in which all the tissues have the same K_i value. These simulations were repeated for different values of K_i (10, 100, and 1000) and show that as K_i get smaller, C_i changes faster. This is demonstrated in Fig. 5, which shows the amitriptyline concentration in the liver tissue, C_L , for NP addition at 5 min for an X value of 10. It is important to note that, for a constant X value, all the Model 3 concentration profiles reach the same steady-state inside each tissue, regardless of the values of K_i , with the smaller K_i values reaching steady-state quicker.

CONCLUSIONS

The goal of this paper is to develop a PBPK model that can be used to predict the kinetic aspects of drug-overdose treatment by NPs. Depending on the properties of the NPs, such as the size and the surface characteristics, the NPs may enter the tissue space. Furthermore, depending on the time scales of the drug-uptake by the NPs, they may be assumed to be confined to the blood compartment. Corresponding to the two properties listed above, four different scenarios are envisaged and models are developed for three of these cases. Since comparison with animal experiments has not yet been done, the models should only be used as guidelines for determining the efficacy of NPs on detoxification. This paper illustrates the methodology of inclusion of NPs in a PBPK model, and the dynamic concentration profiles presented here help us to understand the effect of various parameters on detoxification.

The simulations show that the detoxification process is quicker if the NP does not enter the interstitial space of the tissue and the NP equilibrates with blood in the capillaries, i.e., τ_1 is comparable to τ_2 . Thus, it may be preferable to design NPs that do not cross the capillary wall. It is important to note that we have not included the kinetics of drug transport across the capillary wall in our models. If the mass transfer across the capillary wall slows down the drug transport between the tissue and blood spaces, quicker detoxification may occur using a NP that easily traverses the capillary wall and directly sequesters drug from the interstitium.

We have also determined that the effectiveness of the NP at detoxification can be characterized by the parameter X , and larger X values lead to a more effective and rapid detoxification processes. For each drug, the X value depends on the dosage of the NP administered and the drug's partition coefficient between the NP and the blood. The maximum allowable dosage of NP will be a fixed quantity, but developing NPs that have a larger affinity for the drug may increase the effectiveness of the NP at treating drug overdoses. The model predicts that for amitriptyline, a NP with an X value of at least 10 is required to treat an overdose.

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NOMENCLATURE

Γ	concentration of drug adsorbed on the surface of the NP
Γ_i	surface drug concentration of the NP in tissue i

τ_1	time scale for the drug sequestered by the NP to equilibrate with the drug in the blood
τ_2	time scale for the drug in the blood to equilibrate with the drug concentration in the tissue
Φ	volume fraction of the NP in the blood
Φ_i	volume fraction of the NP in tissue i
C_b	drug concentration in the blood
$C_{b,0}$	drug concentration in the blood prior to NP injection
C_b^*	overall drug concentration in the blood which includes the free drug in the blood and the concentration of drug sequestered by the NP
$C_{b,I}$	drug concentration in the blood immediately following NP injection
C_i	drug concentration in tissue i
$\widehat{C}_i$	drug concentration in tissue i when a Model 2 NP is present
C_{NP}	drug concentration absorbed in the NP
K_i	ratio of the equilibrium concentration of NP in tissue i to the equilibrium concentration of NP in the blood
Q_b	volumetric flowrate of the blood leaving the blood compartment
Q_i	volumetric flowrate of the blood leaving tissue compartment i
R_i	drug-tissue partition coefficient of tissue i
R_i^*	effective drug-tissue partition coefficient of tissue i used in Model 2
R_{NP}	drug partition coefficient between the NP and the blood
S	total surface area of the NPs
$(S/V)_b$	surface area of NP per unit volume in the blood
$(S/V)_i$	surface area of NP per unit volume in tissue i
V_b	volume of blood
V_i	volume of tissue i
X	drug-dependent property of the NP describing effectiveness at drug uptake

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Fig. 1. Amitriptyline concentration in (a) the blood, (b) the heart tissue, and (c) the fat tissue for an injection of NP ($X = 10$) after all tissues have reached their respective equilibrium values.

Fig. 2.
Amitriptyline concentration in the blood for NP addition at 5 min.

Fig. 3. Amitriptyline concentration in the heart tissue for NP addition at (a) 1 min and (b) 5 min.

Fig. 4.
Amitriptyline concentration in the liver for NP addition at 5 min.

Fig. 5.
Effect of K_f -values on amitriptyline concentration in the liver tissue for NP ($X=10$) addition at 5 min.

Table I

Parameters for Various Human Tissues

Organ	Organ volume ^a , V(l)	Blood flow rate ^a , Q (l/min)	Drug-tissue partition coefficient for amitriptyline ^b , R
Blood	5.4	5.14	-
Liver	1.5	1.5	23.58
Gut	2.4	1.2	13.33
Heart	0.3	0.24	11.28
Brain	1.5	0.75	7.18
Kidneys	0.3	1.25	31.79
Muscle	30	1.2	5.13
Fat	10	0.2	79.98

^aValues reflect that of a standard man, 30–39 years of age, weighing 70 kg (11).

^bCalculated from the Thiopental coefficients of a Wistar rat (5), assuming a 70 kg man.