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Mechanism-Based Model of the Pharmacokinetics of Enfuvirtide, an HIV Fusion Inhibitor

Utkala Mohanty and Narendra M. Dixit¹

Department of Chemical Engineering, Indian Institute of Science, Bangalore, India 560012

Abstract

We present a model of the pharmacokinetics of enfuvirtide, a potent inhibitor of the fusion of human immunodeficiency virus type 1 (HIV-1) with target cells. We assume that subcutaneously administered enfuvirtide accumulates in the injection region, diffuses locally, and gets absorbed into blood, where it reversibly associates with lipidic cell membranes and is eventually eliminated. We develop mathematical descriptions of each of these processes and predict the time-evolution of the concentration of enfuvirtide in plasma, C_p . We find, interestingly, that diffusion of enfuvirtide in the subcutaneous region is decoupled from absorption, which enables deduction of analytical expressions for C_p following single dose administration and ordinary differential equations following multiple dose administration and renders our model amenable to data analysis. Model predictions provide excellent fits to observed plasma concentration-time profiles of enfuvirtide following the intravenous and subcutaneous administration of a single dose and without any adjustable parameters capture quantitatively concentration-time profiles following the administration of multiple doses. Our model thus presents a robust description of the pharmacokinetics of enfuvirtide and may be applied in conjunction with models of viral dynamics to assess responses of HIV-1 patients to alternative enfuvirtide-based therapies. Further, our model reveals that key pharmacokinetic characteristics of enfuvirtide, viz., steady state values of peak and trough concentrations and area under the concentration-time curve, vary nearly linearly with dosage over a broad range of dosages and for different dosing regimens, which enables a priori estimation of enfuvirtide exposure levels for different treatment protocols and may serve to establish guidelines for therapy optimization.

Keywords

antiretroviral therapy; subcutaneous administration; intravenous administration; multiple dose pharmacokinetics

I. INTRODUCTION

Enfuvirtide, a 36 amino acid synthetic peptide that mimics a portion of the HIV-1 gp41 molecule, effectively blocks the fusion of viral and target cell membranes and prevents new infections of cells by HIV-1 (Kilby et al., 1998). Remarkably, enfuvirtide elicits antiviral responses in highly treatment-experienced patients (Oldfield et al., 2005). In large clinical trials, the addition of enfuvirtide to an optimized background treatment regimen significantly improved virological and immunological responses of HIV-1 patients compared to the

¹Author to whom correspondences should be addressed Correspondence: Department of Chemical Engineering, Indian Institute of Science, Bangalore, India 560012, Email: narendra@chemeng.iisc.ernet.in Phone: +91-80-2293-2768, Fax: +91-80-2360-8121

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responses elicited by the background regimen alone (Lalezari et al., 2003c; Lazzarin et al., 2003). In recent studies with new (ritonavir-boosted) protease inhibitors, a significantly larger percentage of patients achieved undetectable plasma viral loads when background regimens contained enfuvirtide than when background regimens lacked enfuvirtide (Hammer et al., 2006; Katlama et al., 2006; Pozniak et al., 2006). Consequently, enfuvirtide is a key ingredient in current second-line therapies for HIV-1 infection (Hammer et al., 2006). Enfuvirtide, however, is administered subcutaneously - in contrast to other antiretroviral drugs, which are administered orally - and can cause significant injection site reactions (Oldfield et al., 2005). Further, resistance to enfuvirtide may emerge rapidly in patients, but may be reversed upon cessation of enfuvirtide administration (Lu et al., 2006; Poveda et al., 2005). It is of importance, therefore, to identify treatment protocols that maximize enfuvirtide efficacy and/or minimize enfuvirtide-related side-effects. Indeed, a promising once-daily (qd) dosing regimen of enfuvirtide, more convenient than the current standard twice-daily (bid) dosing regimen, is under investigation (Thompson et al., 2006). Therapy optimization hinges on our understanding of the pharmacokinetics of enfuvirtide.

Experimental studies suggest that the pharmacokinetic properties of enfuvirtide are complex. Following intravenous administration, the concentration of enfuvirtide in plasma, C_p , exhibits a biphasic decline (Zhang et al., 2002). Following subcutaneous administration, C_p rises, attains a maximum, C_{max} , and then declines in a single phase (Lalezari et al., 2003a; Zhang et al., 2002). C_{max} is $\sim 4 \mu\text{g/ml}$ following a single subcutaneous dose of 90 mg and increases to $\sim 6 \mu\text{g/ml}$ following multiple doses of 90 mg bid (Thompson et al., 2006). The latter value for the 180 mg qd regimen is $\sim 9.5 \mu\text{g/ml}$. Yet, interestingly, the area under the concentration-time curve, AUC , over a 24 h period is identical for the 90 mg bid and the 180 mg qd regimens ($\sim 115 \text{ h-}\mu\text{g/ml}$) (Thompson et al., 2006). The volume of distribution of enfuvirtide is small, $\sim 5.5 \text{ l}$, and the absolute bioavailability is $\sim 85\%$ (Fuzeon, 2003a; Oldfield et al., 2005; Zhang et al., 2002). Enfuvirtide binds to plasma proteins, primarily albumin, to the extent of $\sim 92\%$ in HIV patients over a plasma concentration range of 2-10 $\mu\text{g/ml}$ (Fuzeon, 2003a). In vitro, enfuvirtide associates non-specifically with the lipidic membranes on blood cells to the extent of 50-80% (Fuzeon, 2003b). The key metabolite of enfuvirtide is Ro 50-6343, formed by the acid hydrolysis of the amide group on the C-terminal phenylalanine residue (van den Broek et al., 2006).

Several mathematical models have been proposed to describe the pharmacokinetic properties of enfuvirtide. Zhang et al. (2002) show that a two-compartment model with an inverse Gaussian input to the first (central) compartment from the subcutaneous injection site along with first order elimination from the central compartment captures the observed plasma concentration-time profiles of enfuvirtide following the administration of a single dose. Mould et al. (2005), on the other hand, suggest that data from two phase 3 studies are best described by a one-compartment model with first order input and elimination and with body weight and gender covariates on clearance. Stocker et al. (2006) investigate several models comprising one, two, and three compartmental structures and find that a two-compartment model with first order absorption and elimination yields best fits to data on serum enfuvirtide levels.

Extant models thus capture experimental plasma concentration-time profiles of enfuvirtide but employ distinct, empirical compartmental structures. Further, the models employ descriptions of underlying pharmacokinetic processes that remain difficult to reconcile. Whereas Zhang et al. (2002) assume that enfuvirtide elimination occurs from the central (first) compartment, Stocker et al. (2006) suggest that the second compartment is responsible for enfuvirtide clearance. Stocker et al. (2006) and Mould et al. (2005) employ first order input processes to describe enfuvirtide absorption in contrast to the semi-empirical inverse Gaussian input function suggested by Zhang et al. (2002). The one-compartment model of Mould et al. (2005) does not capture the biphasic decline of the plasma enfuvirtide concentration following

intravenous administration. A rigorous description of enfuvirtide pharmacokinetics is currently lacking.

In this paper, we develop a model of enfuvirtide pharmacokinetics that employs mechanism-based descriptions of underlying pharmacological processes. We assume that subcutaneously administered enfuvirtide accumulates at the injection site, diffuses locally, gets absorbed into blood, associates reversibly with blood cell membranes, and is eliminated from plasma. Model predictions successfully capture concentration-time profiles of enfuvirtide following intravenous and subcutaneous administration of single and multiple doses. Our model thus enables, in conjunction with models of HIV dynamics, estimation of viral load changes in patients undergoing enfuvirtide-based therapies. Further, model predictions identify the variation of key pharmacokinetic properties, *viz.*, AUC , C_{max} and the minimum plasma concentration, C_{trough} , with dosage over a broad range of dosages and facilitate the establishment of guidelines for therapy optimization.

II. MODEL DEVELOPMENT

A schematic description of our model is shown in Fig. 1. We consider two physiological compartments: the subcutaneous injection region and blood.

Subcutaneous injection region

Upon subcutaneous administration, we assume that enfuvirtide forms a spherical depot of radius r_0 and uniform drug concentration C_0 at the injection site (Wach et al., 1995). We define $C_s(r, t)$ as the concentration of enfuvirtide at a distance r from the center of the subcutaneous depot ($r=0$) at time t after administration. Thus,

$$C_s(r, 0) = \begin{cases} C_0 & r \leq r_0 \\ 0 & r > r_0 \end{cases} \quad (1)$$

C_0 and r_0 are estimated from the dosage, D , and the injection volume, V_{inj} , as

$$r_0 = \left(\frac{3}{4\pi} V_{inj} \right)^{\frac{1}{3}} \quad \text{and} \quad C_0 = D/V_{inj}. \quad (2)$$

Following dose administration, enfuvirtide diffuses in the subcutaneous region and gets absorbed into circulation at a rate proportional to its local concentration. $C_s(r, t)$ therefore satisfies the reaction-diffusion equation (Bird et al., 2002; Crank, 1980)

$$\frac{\partial C_s}{\partial t} = \frac{D_s}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial C_s}{\partial r} \right) - k_a C_s, \quad (3)$$

where D_s is the diffusivity of enfuvirtide in the subcutaneous region, and k_a is the absorption rate constant. We solve Eq. 3 with the initial condition in Eq. 1 and the boundary conditions that the concentration of enfuvirtide in the subcutaneous region is maximum at the center of the depot ($r=0$) and negligible far away from the injection site, *i.e.*,

$$\left. \frac{\partial C_s(r, t)}{\partial r} \right|_{r=0} = 0 \quad \text{and} \quad C_s(\infty, t) = 0, \quad (4)$$

and obtain (Crank, 1980; Wach et al., 1995)

$$C_s(r, t) = \frac{C_0 \exp(-k_a t)}{2} \left[\operatorname{erf} \left(\frac{r+r_0}{2\sqrt{D_s t}} \right) - \operatorname{erf} \left(\frac{r-r_0}{2\sqrt{D_s t}} \right) + \frac{2}{r} \sqrt{\frac{D_s t}{\pi}} \left(\exp \left(-\frac{(r+r_0)^2}{4D_s t} \right) - \exp \left(-\frac{(r-r_0)^2}{4D_s t} \right) \right) \right] \quad (5)$$

$$\text{where} \quad \operatorname{erf}(z) = \frac{2}{\sqrt{\pi}} \int_0^z \exp(-s^2) ds.$$

We consider next an annulus of radius r and infinitesimal thickness dr in the subcutaneous region (Fig. 1), in which the concentration of enfuvirtide is $C_s(r, t)$ (Eq. 5). Enfuvirtide is absorbed from this annular region at the rate $k_a C_s(r, t) 4\pi r^2 dr$, where $4\pi r^2 dr$ is the volume of the annulus. The total rate of absorption of enfuvirtide from the subcutaneous region is therefore

$$\frac{dM_s}{dt} = - \int_0^\infty 4\pi r^2 k_a C_s(r, t) dr, \quad (6)$$

where $M_s(t)$ is the mass of enfuvirtide in the subcutaneous region at time t . Upon substituting $C_s(r, t)$ from Eq. 5 and using the relations in Eq. 2, Eq. 6 simplifies to (Appendix)

$$\frac{dM_s}{dt} = -k_a D \exp(-k_a t), \quad (7)$$

which we solve with the initial condition $M_s(0)=D$ and obtain

$$M_s(t) = D \exp(-k_a t). \quad (8)$$

Equation 8 predicts the time-evolution of the mass of enfuvirtide in the subcutaneous region following the administration of a single subcutaneous dose.

The above analysis indicates, remarkably, that diffusion in the subcutaneous region does not influence enfuvirtide absorption. This decoupling of diffusion and absorption greatly simplifies the description of enfuvirtide pharmacokinetics following the administration of multiple doses.

When multiple doses are administered, a mass D of enfuvirtide is added with each dose to the prevalent mass of enfuvirtide in the subcutaneous region. From Eqs. 6-8, we recognize that enfuvirtide absorption from the subcutaneous region is a first order process in the mass of enfuvirtide. (Eq. 6 implies, as do Eqs. 7 and 8, that $dM_s/dt = -k_a M_s$ because

$M_s(t) = \int_0^\infty 4\pi r^2 C_s(r, t) dr$. Thus, for multiple subcutaneous doses administered at regular intervals I_d , we write (Dixit and Perelson, 2005)

$$\frac{dM_s}{dt} = -k_a M_s + D \sum_{j=1}^{\infty} \delta_D(t - jI_d), \quad (9)$$

where δ_D is the Dirac delta function that satisfies $\delta_D(x \neq 0) = 0$ and $\int_{-\infty}^{\infty} \delta_D(x) dx = 1$. Solving Eq. 9 with the initial condition $M_s(0)=D$ yields (Dixit and Perelson, 2005),

$$M_s(t) = D \exp(-k_a t) \left[\frac{\exp(N_d k_a I_d) - 1}{\exp(k_a I_d) - 1} \right], \quad (10)$$

where $N_d = 1 + \text{int}(t/I_d)$ is the number of doses administered in time t , with $\text{int}(t/I_d)$ the largest integer in t/I_d . Eq. 10 predicts the time-evolution of the mass of enfuvirtide in the subcutaneous region following the administration of multiple doses.

Blood

Whether absorbed enfuvirtide enters blood directly and/or via the lymphatic system (Supersaxo et al., 1990) remains to be established. To account for possible lymphatic transport of enfuvirtide, we allow a lag-time τ for drug absorbed from the subcutaneous region to reach blood. In blood, enfuvirtide may associate non-specifically with lipidic cell membranes (Fuzeon, 2003b). We define C_p as the concentration of enfuvirtide in plasma and C_l as the equivalent concentration of membrane-associated enfuvirtide. The time-evolution of C_p and C_l are then determined by

$$\frac{dC_p}{dt} = \frac{F}{V_d} k_a M_s(t - \tau) - k_b C_p + k_d C_l - k_e C_p, \quad (11)$$

and

$$\frac{dC_l}{dt} = k_b C_p - k_d C_l, \quad (12)$$

where k_b and k_d are the rate constants of enfuvirtide binding to and dissociation from lipidic membranes, k_e is the elimination rate constant of enfuvirtide from plasma including enfuvirtide hydrolysis into metabolites (van den Broek et al., 2006), V_d is the volume of distribution, and F is the bioavailability including any losses in the lymphatic network. We assume here that binding to plasma proteins does not influence the affinity of enfuvirtide for lipidic cell membranes. C_p thus includes both protein-bound and free enfuvirtide in plasma. In addition, we assume that the association of enfuvirtide to lipidic cell membranes does not reach saturation so that k_b and k_d are independent of C_p . $M_s(t)$ is the mass of enfuvirtide in the subcutaneous injection region (Eqs. 8 and 10).

Intravenous administration

Following intravenous administration, enfuvirtide enters plasma directly, so that $M_s(t)=0$. Solving Eqs. 11 and 12 with the initial conditions $C_p(0) = D/V_d$ and $C_l(0) = 0$ then yields the time-evolution of C_p and C_l following the administration of a single intravenous dose:

$$C_p(t) = \frac{D}{V_d} \frac{1}{2\lambda_1} [\lambda_1 (\exp(\lambda_1 t) + 1) - (\lambda_2 - 2k_d) (\exp(\lambda_1 t) - 1)] \exp\left(-\frac{1}{2}(\lambda_1 + \lambda_2)t\right) \quad (13)$$

and

$$C_l(t) = \frac{D}{V_d} \frac{1}{\lambda_1} [k_b (\exp(\lambda_1 t) - 1)] \exp\left(-\frac{1}{2}(\lambda_1 + \lambda_2)t\right), \quad (14)$$

where

$$\lambda_1 = \left[(k_b + k_d + k_e)^2 - 4k_d k_e\right]^{1/2} \quad \text{and} \quad \lambda_2 = k_b + k_d + k_e. \quad (15)$$

We note that in the absence of the binding of enfuvirtide to cell membranes, *i.e.*, when $k_b=0$, Eqs. 13 and 14 reduce to $C_p(t) = (D/V_e)e^{-k_e t}$ and $C_l(t)=0$, respectively, as expected for the single phase decline of C_p due to elimination. The reversible association of enfuvirtide to lipidic cell membranes thus causes the biphasic decline of C_p (see below).

With the administration of multiple intravenous doses, we recognize that a mass D of enfuvirtide is added to plasma at regular intervals, I_d . Following Eq. 9, we therefore modify Eq. 11 to

$$\frac{dC_p}{dt} = -k_b C_p + k_d C_l - k_e C_p + \frac{D}{V_d} \sum_{j=1}^{\infty} \delta_D(t - jI_d) \quad (16)$$

We solve Eqs. 12 and 16 numerically with the initial conditions $C_p(0) = D/V_d$ and $C_l(0) = 0$ to obtain the resulting time-evolution of C_p .

Subcutaneous administration

To predict the time-evolution of C_p following a single subcutaneous dose, we substitute $M_s(t)$ from Eq. 8 into Eq. 11. We then solve Eqs. 11 and 12 with the initial conditions $C_p(0) = 0$ and $C_l(0) = 0$, and obtain

$$C_p(t) = \frac{FD}{V_d} \frac{k_a}{2\lambda_1^2} \frac{\exp\left(-\frac{1}{2}(\lambda_1 + \lambda_2)\varpi\right)}{\lambda_2 k_a - k_a^2 - k_d k_e} \left[\frac{(k_a - k_d)\lambda_1^2 \left(2\exp\left(-\left(k_a - \frac{1}{2}(\lambda_1 + \lambda_2)\right)\varpi\right) - \exp(\lambda_1 \varpi) - 1\right)}{\lambda_1 (\lambda_2 (k_a + k_d) - 2k_d (k_a + k_e)) (\exp(\lambda_1 \varpi) - 1)} \right] \quad (17)$$

and

$$C_l(t) = \frac{FD}{V_d} \frac{k_a k_b}{2\lambda_1} \frac{\exp\left(-\frac{1}{2}(\lambda_1 + \lambda_2)\varpi\right)}{\lambda_2 k_a - k_a^2 - k_d k_e} \left[\lambda_1 \left(\exp(\lambda_1 \varpi) + 1 - 2 \exp\left(-\left(k_a - \frac{1}{2}(\lambda_1 + \lambda_2)\right)\varpi\right) \right) + (\lambda_2 - 2k_a)(\exp(\lambda_1 \varpi) - 1) \right] \quad (18)$$

where $\varpi = t - \tau$, and λ_1 and λ_2 are given by Eq. 15. We observe again that when the binding of enfuvirtide to lipidic membranes is absent ($k_b=0$) and with no lag-time for absorption ($\tau=0$), Eqs. 17 and 18 reduce to $C_p(t) = (FD/V_d)(k_a/(k_e - k_a))(e^{-k_a t} - e^{-k_e t})$ and $C_l(t)=0$, respectively, identical to the standard one-compartment absorption-elimination model (Dixit and Perelson, 2004).

To predict the time-evolution of C_p following the administration of multiple subcutaneous doses, we solve Eqs. 10-12 numerically.

III. MODEL PREDICTIONS AND COMPARISONS WITH EXPERIMENTS

Intravenous administration

We present in Fig. 2 model predictions of the plasma concentration-time profile of enfuvirtide, C_p , and the equivalent concentration of enfuvirtide associated with lipidic cell membranes, C_l , following the administration of a single intravenous dose, D , determined by Eqs. 13-15. We find that C_p exhibits a biphasic decline. In the first phase, the decline is governed by the association of enfuvirtide with lipidic membranes and by elimination. Accordingly, C_p declines rapidly while C_l rises. In the second phase, enfuvirtide association with membranes reaches pseudo-equilibrium. C_p and C_l thus evolve parallel to each other and C_p declines due to elimination.

Zhang et al. (2002) report the time-evolution of C_p in 12 HIV infected patients following the administration of a single intravenous dose of 90 mg. We reproduce the mean concentrations observed by Zhang et al. (2002) in Fig. 2. We fit model predictions of C_p to the mean concentration data using the rate constants k_b , k_d , and k_e and the volume of distribution, V_d , as adjustable parameters. Model predictions provide an excellent fit to the data (Fig. 2). The best-fit parameter estimates and the corresponding 95% confidence intervals are listed in Table 1. We find the best-fit estimates to be $k_b = 0.34 \text{ h}^{-1}$, $k_d = 0.69 \text{ h}^{-1}$, $k_e = 0.37 \text{ h}^{-1}$ and $V_d = 3.85 \text{ l}$.

Using the above parameters, we present in Fig. 3 the time evolution of C_p following the administration of multiple intravenous doses, determined by solving Eqs. 12 and 16. We consider four different values of the dosage, $D = 3, 10, 30$, and 100 mg , administered twice daily, $I_d = 12 \text{ h}$. For all values of D , C_p rises sharply upon dose administration and declines subsequently in a biphasic manner. After 2 to 3 doses, the profile of C_p attains steady state. The maximum concentration, C_{max} , at steady state is slightly higher than the C_{max} after the first dose. Upon increasing D , C_{max} increases gradually. In Fig. 4, we present C_{max} and the trough concentration, C_{trough} , at steady state as functions of D . Power-law fits to our model predictions indicate that $C_{max} \approx 0.27D$ and $C_{trough} \approx 0.01D$ (both with $R^2 \approx 1$), where C is expressed in $\mu\text{g/ml}$ and D in mg . Interestingly, thus, both C_{max} and C_{trough} increase linearly with D . In Fig. 4, we also present the area under the plasma concentration-time curve over one dosing interval, $AUC = \int_{(j-1)I_d}^{jI_d} C_p(t) dt$, where j is chosen to represent a dosing interval after steady state is achieved so that AUC is independent of j . We find that the AUC also increases linearly with D over the range of dosages considered: $AUC \approx 0.69D$ ($R^2 \approx 1$), where AUC is expressed in $\text{h-}\mu\text{g/ml}$ and D in mg .

Kilby et al. (1998) report plasma pharmacokinetic characteristics of T-20 (enfuvirtide) monotherapy following intravenous administration of 3, 10, 30, and 100 mg bid for 14 days.

Each dosage group consisted of 4 patients. As we predict above, Kilby et al. (1998) observe that C_{max} values at steady state are marginally higher than the C_{max} values after the first dose. In Fig. 4, we present the steady state values of C_{max} , C_{trough} , and AUC observed by Kilby et al. (1998) as functions of the dosage D . We find that our model predictions above capture the experimental data well. Model predictions of C_{trough} are in close agreement with the data. Predictions of C_{max} and AUC slightly overestimate the median data. Given the small number of patients in each dosage group, the differences between our predictions and experiments may be within experimental uncertainties. Kilby et al. (1998) estimate the median half-life of T-20 to be ~ 1.83 h, which was stable over time and across all dosage groups. This half-life agrees well with the elimination half-life, $\ln 2/k_e \sim 1.87$ h, we estimate from our comparisons with the data of Zhang et al. (2002) (Fig. 2, Table 1). Thus, using parameter values determined from single dose concentration-time data, our model captures the observed pharmacokinetic properties of enfuvirtide following the administration of multiple intravenous doses over a broad range of dosages.

Subcutaneous administration

We present in Fig. 5 the time-evolution of C_p following the administration of a single subcutaneous dose predicted using Eq. 17. We consider three different dosages, $D = 45, 90$, and 180 mg. For a period τ following dose administration, C_p remains zero, after which C_p rises due to absorption and subsequently declines due to elimination. The first phase of decline observed following intravenous administration (Fig. 2) is masked here by absorption. The maximum concentration, C_{max} , increases with the dosage D ; $C_{max} \sim 2$ $\mu\text{g/ml}$ for $D = 45$ mg and $C_{max} \sim 7$ $\mu\text{g/ml}$ for $D = 180$ mg (Fig. 5). The time at which the concentration reaches the maximum, however, varies only slightly with D (Fig. 5).

We compare our predictions of C_p with the mean experimental plasma concentration-time profiles reported by Zhang et al. (2002) for different values of D . We reproduce the latter experimental data, obtained from 12 patients, in Fig. 5. We expect the cell-membrane association characteristics of enfuvirtide and the volume of distribution to be identical for intravenous and subcutaneous administration. For our present comparisons, we therefore employ the estimates of V_d , k_b and k_d obtained above (Table 1). In addition, we fix the bioavailability of enfuvirtide, F , at 0.85 drawing from earlier studies (Fuzeon, 2003a; Oldfield et al., 2005; Zhang et al., 2002). The remaining parameters, viz., the absorption rate, k_a , the elimination rate, k_e , and the lag-time, τ , are determined uniquely from fits to the data. We find that our best-fit model predictions capture available experimental data for different values of D accurately (Fig. 5). The best-fit parameter estimates and the 95% confidence intervals are listed in Table 1. As expected, we find that the best-fit estimates of k_e are similar (~ 0.35 h^{-1}) for all dosages and to the value estimated from the intravenous data above (0.37 h^{-1}). The absorption rate, k_a , however, decreases slightly and the lag-time, τ , increases upon increasing D ($k_a = 0.18$ h^{-1} and $\tau = 0.46$ h for $D = 45$ mg, whereas $k_a = 0.13$ h^{-1} and $\tau = 0.73$ h for $D = 180$ mg).

Using the parameters determined above (Table 1), we predict C_p following the administration of multiple subcutaneous doses for $D=45$ mg bid, 90 mg bid, and 180 mg qd by solving Eqs. 10-12 (Fig. 6). In each case, we find that enfuvirtide accumulation causes the peak concentration, C_{max} , to increase with the number of doses. A steady-state concentration profile is achieved after 3 doses. For the current standard dosing pattern of 90 mg bid, C_{max} increases from ~ 4 $\mu\text{g/ml}$ after the first dose to ~ 6 $\mu\text{g/ml}$ at steady state (Fig. 6B). The increase in C_{max} is lesser with 45 mg bid (Fig. 6A) and 180 mg once daily (qd) (Fig. 6C). In Fig. 7, we present model predictions of C_{max} , C_{trough} , and AUC at steady state as functions of dosage D

administered bid and qd. AUC is again determined as $AUC = \int_{(j-1)\tau_d}^{j\tau_d} C_p(t) dt$, where j is large enough that a dosing interval after steady state is achieved is considered. Interestingly, we find

that both C_{max} and AUC increase nearly linearly with D in the dosage range considered. From power law fits to our model predictions, we find that $C_{max} \approx 0.07D$ for bid regimens and $C_{max} \approx 0.065D^{0.93}$ for qd regimens, whereas $AUC \approx 0.51D$ for both bid and qd regimens ($R^2 \approx 1$ for all fits), where C is expressed in $\mu\text{g/ml}$, AUC in $\text{h-}\mu\text{g/ml}$ and D in mg . C_{trough} , on the other hand, appears to exhibit a weak power law dependence on D . We find that $C_{trough} \approx 0.02D^{1.18}$ for bid and $C_{trough} \approx 0.00085D^{1.45}$ for qd regimens.

We compare the latter model predictions with available experimental data. Thompson et al. (2006) measure the steady state pharmacokinetic properties of enfuvirtide administered 90 mg bid and 180 mg qd in ~ 20 patients. Lalezari et al. (2003b) report similar data for 45 mg bid from ~ 70 patients. We reproduce the reported mean steady state concentration-time data in Fig. 6. For both the 90 mg bid and the 180 mg qd regimens, our model predictions capture the experimental data remarkably accurately (Figs. 6B and C, respectively). Note that the comparisons here are without any adjustable parameters and represent a successful test of our model. Our model overestimates slightly the data for the 45 mg bid regimen (Fig. 6A). Given the magnitude of the experimental uncertainties (Figs. 6B and C), the difference between our model predictions and the experimental data for the 45 mg bid case (Fig. 6A) may lie within the uncertainties. We also compare our model predictions with reported values of C_{max} , C_{trough} , and AUC for the 45 mg bid (Lalezari et al., 2003b), 90 mg bid, and the 180 mg qd dosing regimens (Thompson et al., 2006) (Fig. 7). Indeed, we find close agreement between our predictions and experimental estimates for all three regimens indicating that our model captures the pharmacokinetics of enfuvirtide accurately.

IV. DISCUSSION

Estimates of model parameters

The best-fit parameter estimates obtained from comparisons of our model predictions with experimental data provide insights into enfuvirtide pharmacokinetics. Our model suggests that the association of enfuvirtide with lipidic blood cell membranes underlies the biphasic decline of the plasma concentration of enfuvirtide following intravenous administration. The lipid binding and dissociation rate constants estimated, $k_b = 0.34 \text{ h}^{-1}$ and $k_d = 0.69 \text{ h}^{-1}$ (Table 1), yield an equilibrium dissociation constant, $K_d = k_d/k_b \approx 2$. Thus, at equilibrium, as in the second phase decline in Fig. 2, $\sim 33\%$ association of enfuvirtide with cells in vivo occurs, lower than the 50-80% association observed in vitro (Fuzeon, 2003b).

The volume of distribution, $V_d = 3.85 \text{ l}$, is in agreement with the estimate obtained by Zhang et al. (2002) ($3.8 \pm 0.8 \text{ l}$) for their central compartment. The concentration-time data following intravenous administration (Zhang et al., 2002) provide a model-independent estimate of V_d as $D/C_p(0) \approx 4.1 \text{ l}$ (using $C_p(0) \approx C_p(0.16 \text{ h})$, the first measurement after dose administration), in agreement with our estimate. Zhang et al. (2002) estimate an additional $1.7 \pm 0.6 \text{ l}$ as the volume of distribution of the peripheral compartment. In our model, the corresponding compartment is represented by enfuvirtide bound to blood cell membranes. We circumvent the need to define a volume of distribution for the latter compartment by considering an equivalent concentration in the compartment (C_l) that is based on V_d . An added advantage of our approach is that fewer parameters need to be determined from available data.

The elimination rate constant $k_e \approx 0.35 \text{ h}^{-1}$ is similar for intravenous and subcutaneous administration for all dosages D . Interestingly, the absorption rate constant, k_a , decreases from 0.18 h^{-1} to 0.13 h^{-1} and the lag-time, τ , increases from 0.46 h to 0.73 h as D increases from 45 mg to 180 mg, implying faster absorption at smaller dosages, as also suggested by Zhang et al. (2002). We speculate that upon increasing dosage a larger fraction of enfuvirtide enters lymphatic circulation and may follow more circuitous routes to blood. τ would thus increase

and k_a decrease upon increasing D . Experiments that determine the absorption and residence time of enfuvirtide in the lymphatic system would test our hypothesis.

Implications for therapy

Remarkably, our model indicates that key pharmacokinetic characteristics, *viz.*, steady state values of AUC , C_{max} , and C_{trough} , vary nearly linearly with the dosage D over a wide range of dosages for both intravenous and subcutaneous administration. For instance, we find that $C_{max} \approx 0.07D$ and $C_{trough} \approx 0.02D^{1.18}$ for bid subcutaneous administration, whereas $C_{max} \approx 0.065D^{0.93}$ and $C_{trough} \approx 0.00085D^{1.45}$ for qd administration, where C is expressed in $\mu\text{g/ml}$ and D in mg. Our model thus allows a priori estimation of C_{max} , C_{trough} , and AUC for different dosages, which serves to establish therapeutic guidelines. For instance, for the steady state C_{trough} to be greater than 1 $\mu\text{g/mL}$ or 2.2 $\mu\text{g/mL}$, both proposed thresholds for virological efficacy (Stocker et al., 2006), the above expressions indicate that the dosage D must be larger than 130 mg or 225.8 mg for a qd regimen and 27.5 mg or 53.7 mg for a bid regimen, respectively. These guidelines are based, however, on comparisons of our model with averaged concentration data from (few) patients. Large inter-patient variations have been observed in data obtained from bigger clinical trials (Mould et al., 2005; Stocker et al., 2006). Accounting systematically for these large inter-patient variations, which is beyond the scope of the present study, would enable the establishment of more accurate and robust therapeutic guidelines.

Our model predicts, interestingly, that $AUC \approx 0.51D$ for both bid and qd subcutaneous dosing regimens, where AUC is in h- $\mu\text{g/ml}$ and D in mg. The linear dependence of AUC on D explains the observation of Thompson et al. (2006) that the steady state (24 h) AUC for 180 mg qd regimen (112 ± 6.2 h- $\mu\text{g/ml}$) is equal to twice the steady state (12 h) AUC for 90 mg bid regimen (115 ± 6.4 h- $\mu\text{g/ml}$). Our analysis has further implications for the relative benefits of the 90 mg bid and the 180 mg qd regimens, currently under evaluation (Thompson et al., 2006). The 24 h AUC , *i.e.*, AUC_{0-24} , are equivalent for the 90 mg bid and the 180 mg qd regimens as observed above. For the bid regimen, because a dose is administered at 0h and at 12h, we may write $AUC_{0-12}^{bid} = AUC_{12-24}^{bid}$. For the qd regimen, however, drug exposure is high during the first 12 h after dose administration and low during the subsequent 12 h. Indeed, our model predicts that $AUC_{0-12}^{qd} \approx (2/3)AUC_{0-24}^{qd}$. The lower drug exposure in the latter 12 h period is also suggested by the lower values of C_{trough} for the 180 mg qd regimen (~ 1.6 $\mu\text{g/ml}$) than for the 90 mg bid regimen (~ 3.8 $\mu\text{g/ml}$) (Thompson et al., 2006). Uniform drug exposure would imply continuous inhibition of viral replication and hence possible greater viral load decline.

To estimate the possible difference in the virological efficacies of the two regimens, we follow Mould et al. (2005) and consider the log viral load change from baseline, E , to be given by $E = E_{max} AUC_{0-12} / ((AUC_{12})_{50} + AUC_{0-12})$, where E_{max} is the maximum viral load change and $(AUC_{12})_{50}$ is that value of the 12 h AUC at which $E = E_{max}/2$. Thus, over a 24 h period, the expected log viral load change for the 90 mg bid regimen is

$$E^{bid} = 2E_{max}AUC_{0-12}^{bid} / ((AUC_{12})_{50} + AUC_{0-12}^{bid}), \text{ whereas the corresponding change for the}$$

180 mg qd regimen is

$$E^{qd} = E_{max}AUC_{0-12}^{qd} / ((AUC_{12})_{50} + AUC_{0-12}^{qd}) + E_{max}AUC_{12-24}^{qd} / ((AUC_{12})_{50} + AUC_{12-24}^{qd}).$$

Recognizing from our analysis above that

$$2AUC_{0-12}^{bid} \approx AUC_{0-24}^{qd} \approx (3/2)AUC_{0-12}^{qd} \approx 3AUC_{12-24}^{qd}, \text{ and assuming that}$$

$$AUC_{0-12}^{bid} \gg (AUC_{12})_{50} \text{ we obtain } E^{qd} \approx 2E_{max}AUC_{0-12}^{bid} / ((9/8)(AUC_{12})_{50} + AUC_{0-12}^{bid}).$$

Thus, the effective $(AUC_{12})_{50}$ for the 180 mg qd regimen is ~ 1.13 times larger than that for the 90 mg bid regimen, suggesting that the latter regimen has slightly greater virological efficacy. Indeed, Thompson et al. (2006) find the short-term (7 days) viral load decline to be greater ($P=0.07$) for the 90 mg bid regimen (1.4 ± 0.2 log) than for the 180 mg qd regimen (1.0

$\pm 0.14 \log$). Conversely, because of the linear relationship between AUC and D , our model predicts that a dosage of $(9/8)180 = 202.5$ mg qd would exert an antiviral effect equivalent to that of the 90 mg bid regimen. Whether the higher dosage of 202.5 mg would be well-tolerated remains to be ascertained.

At the same time, alternating high and low drug exposures may inhibit the emergence of drug resistance and render the qd regimen advantageous compared to the bid regimen. Intermediate drug concentrations are thought to favor the emergence of drug resistance (Dixit and Perelson, 2005; Kepler and Perelson, 1998; Wahl and Nowak, 2000). Integration of our description of enfuvirtide pharmacokinetics with models of viral dynamics (Dixit et al., 2004; Perelson, 2002; Perelson et al., 1996; Wei et al., 1995), which is beyond the scope of the present study, would facilitate more accurate evaluation of the antiviral benefits of the two dosing regimens.

Pharmacokinetics of subcutaneously administered drugs

Models of the pharmacokinetics of subcutaneously administered drugs have been developed previously but are not easily applied to data analysis because they require solutions of complex partial differential equations (Mosekilde et al., 1989; Nucci and Cobelli, 2000). Interestingly, we find that the diffusion of enfuvirtide in the subcutaneous region is decoupled from absorption, which allows prediction of the plasma concentration-time profiles of enfuvirtide using analytical expressions (single dose) or ordinary differential equations (multiple doses) that are readily solved and applied to data analysis. Our model may thus have broader applicability in describing the pharmacokinetics of other subcutaneously administered drugs where absorption and diffusion in the subcutaneous injection region may be decoupled.

V. CONCLUSIONS

We develop a model of the pharmacokinetics of enfuvirtide that employs mechanism-based descriptions of underlying pharmacological processes and predicts plasma concentration-time profiles of enfuvirtide following subcutaneous and intravenous administration of single and multiple doses. Interestingly, we find that diffusion of enfuvirtide does not influence its absorption from the subcutaneous injection region. We exploit this decoupling of absorption and diffusion and derive analytical expressions for the plasma concentration-time profiles of enfuvirtide following single dose administration and ordinary differential equations for multiple dose administration. In contrast to available models of the pharmacokinetics of subcutaneously administered drugs, our model is therefore readily applied to data analysis. Model predictions capture experimental plasma concentration-time profiles quantitatively. Further, model predictions identify nearly linear relationships between the dosage employed and the resulting steady state values of AUC , C_{max} , and C_{trough} over a broad range of dosages and for different dosing regimens, allowing a priori estimation of enfuvirtide exposure levels for different dosing protocols. Our model thus presents a robust description of the pharmacokinetics of enfuvirtide and may be combined with models of HIV dynamics to predict outcomes of enfuvirtide-based therapies and establish guidelines for therapy optimization.

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APPENDIX

We present details of the derivation of Eq. (7). Following Gradshteyn and Ryzhik (1994), we rewrite Eq. (6) as

$$\frac{dM_s}{dt} = -\lim_{h \rightarrow \infty} \int_0^h 4\pi r^2 k_a C_s(r, t) dr. \quad (A1)$$

Substituting $C_s(r, t)$ from Eq. 5 into Eq. A1, performing the integration (Gradshteyn and Ryzhik (1994) or Mathematica®), and rearranging the resulting expressions, we obtain

$$\begin{aligned} \frac{dM_s}{dt} = & 2\pi k_a C_0 \exp(-k_a t) \lim_{h \rightarrow \infty} \left[\frac{2\sqrt{D_s t}}{3\sqrt{\pi}} \left\{ (2D_s t - r_0^2 + r_0 h - h^2) \exp\left(-\frac{(r_0+h)^2}{4D_s t}\right) \right\} \right. \\ & - \frac{2\sqrt{D_s t}}{3\sqrt{\pi}} \left\{ (2D_s t - r_0^2 - r_0 h - h^2) \exp\left(-\frac{(r_0-h)^2}{4D_s t}\right) \right\} \\ & - \frac{1}{3} \left\{ h^3 \left(\operatorname{erf}\left(\frac{h-r_0}{2\sqrt{D_s t}}\right) - \operatorname{erf}\left(\frac{h+r_0}{2\sqrt{D_s t}}\right) \right) \right\} \\ & \left. - \frac{1}{3} \left\{ r_0^3 \left(\operatorname{erf}\left(\frac{h-r_0}{2\sqrt{D_s t}}\right) + \operatorname{erf}\left(\frac{h+r_0}{2\sqrt{D_s t}}\right) \right) \right\} \right]. \end{aligned} \quad (\text{A2})$$

Upon evaluating the limits, we find that the first three terms on the right hand side in Eq. A2 vanish. (Note that $\lim_{x \rightarrow \infty} \operatorname{Limerf}(x) = 1$.) The last term yields

$$\frac{dM_s}{dt} = -2\pi k_a C_0 \exp(-k_a t) \left[\frac{2}{3} r_0^3 \right], \quad (\text{A3})$$

which upon recognizing from Eq. 2 that $D = 4\pi r_0^3 C_0 / 3$ reduces to Eq. 7.

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Figure 1.

Schematic diagram of the model of enfuvirtide pharmacokinetics. Enfuvirtide accumulates in the subcutaneous region, diffuses (darker regions represent higher concentrations) and gets absorbed into blood, where it associates reversibly with lipidic cell membranes and is eliminated from plasma. The rate constants for the various processes are listed in Table 1.

Figure 2.

Model predictions of the time-evolution of the concentration of enfuvirtide in plasma, C_p , (solid line) (Eq. 13) and the equivalent concentration of cell membrane-associated enfuvirtide, C_l , (dashed line) (Eq. 14) following a single intravenous dose of 90 mg. Corresponding experimental plasma concentration data from (Zhang et al., 2002) is reproduced (symbols). Parameter values employed in our calculations are listed in Table 1.

Figure 3.

Model predictions of the time-evolution of the concentration of enfuvirtide in plasma, C_p , with the twice-daily intravenous administration of 3 mg (dotted line), 10 mg (dashed line), 30 mg (dot-dashed line), and 100 mg (solid line) doses, obtained by solving Eq. 16 using parameter values listed in Table 1.

Figure 4.

Comparison of model predictions (lines) and experimental observations (symbols) (Kilby et al., 1998) of the steady state maximum plasma concentration, C_{max} (long dashed line, squares), the trough concentration, C_{trough} (dashed line, circles), and the area under the concentration-time curve, AUC (solid line, diamonds), of enfuvirtide as a function of dosage, D , following twice-daily intravenous administration.

Figure 5. Model predictions of the time-evolution of the concentration of enfuvirtide in plasma, C_p , (lines) (Eq. 17) compared with experimental data (Zhang et al., 2002) following the administration of a single subcutaneous dose of 45 mg (circles), 90 mg (squares) and 180 mg (triangles). The parameter values employed are listed in Table 1.

Figure 6.

Model predictions of the time-evolution of the concentration of enfuvirtide in plasma, C_p , (lines) obtained by solving Eqs. 10-12 compared with experimental data (symbols) following the administration of multiple subcutaneous doses of (A) 45 mg bid (Lalezari et al., 2003b) (B) 90 mg bid (Thompson et al., 2006) and (C) 180 mg qd (Thompson et al., 2006). The parameter values employed are listed in Table 1. The experimental data is shifted in time to coincide with a dosing interval after a steady state concentration profile is achieved.

Figure 7.

Comparison of model predictions (lines) and experimental observations (symbols) (Lalezari et al., 2003b; Thompson et al., 2006) of the steady state maximum plasma concentration, C_{max} (long dashed line, squares), the trough concentration, C_{trough} (dashed line, circles), and the area under the concentration-time curve, AUC (solid line, diamonds), of enfuvirtide as a function of dosage, D , following (A) twice-daily and (B) once-daily subcutaneous administration.

TABLE 1

Estimates of model parameters

D (mg)	Intravenous	Subcutaneous		
	90	45	90	180
$k_b(h^{-1})$	0.34 (0.19, 0.49)	0.34	0.34	0.34
$k_d(h^{-1})$	0.69 (0.53, 0.85)	0.69	0.69	0.69
$k_e(h^{-1})$	0.37 (0.34, 0.40)	0.36 (0.32, 0.40)	0.34 (0.30, 0.37)	0.34 (0.30, 0.37)
$k_a(h^{-1})$	-	0.18 (0.16, 0.21)	0.16 (0.14, 0.18)	0.13 (0.11, 0.15)
$V_d(L)$	3.85 (3.52, 4.18)	3.85	3.85	3.85
$\tau(h)$	-	0.46 (0.23, 0.68)	0.65 (0.44, 0.86)	0.73 (0.51, 0.95)

95% confidence intervals are shown in brackets below the parameter values estimated from model fits to experimental data (Figs. 2 and 5) using MATLAB. D: dosage; k_b : rate of binding of enfuvirtide to lipidic blood cell membranes; k_d : rate of dissociation of enfuvirtide from lipidic blood cell membranes; k_e : rate of elimination of enfuvirtide from plasma; k_a : rate of absorption of enfuvirtide from the subcutaneous injection region; V_d : volume of distribution; τ : lag-time for the absorption of enfuvirtide into blood.