Increasing Efficacy-Decreasing Toxicity Via Controlled Delivery

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NEXT-GENERATION DELIVERY INNOVATIONS

Past and Recent History

For more than 100 years, all derivations in pharmacokinetics were based on differential equations. As a result, all textbooks and all teaching of pharmacokinetics by me and everyone else have assumed that the rate of drug input has no effect on systemic clearance and area under the systemic concentration time-curve (AUC). Yet, it is well recognized that slow drug delivery can lead to the "flip-flop" model where the terminal concentration time-curve can reflect a slow rate of drug absorption.

Over the past 3 years we have published 10 peer reviewed papers culminating in our May 2025 Pharmacological Reviews paper "Application of Kirchhoff's Laws to Pharmacologic and Pharmacokinetic Analyses" and our June 2025 tutorial (Benet, LZ and Sodhi, JK. "Simplifying Pharmacokinetics, Applying it to Drug and Dosage Form Development, and Making Drug Dosage Decisions in Clinical Medicine: The Adaptation of Kirchhoff's Laws from Physics" AAPS J. 27, 116 https://doi.org/10.1208/s12248-025-01099-6) demonstrating an alternative method to derive all pharmacokinetic clearance and rate constant equations.

Recent History

This new methodology based on principles from physics to derive clearance shows that in vivo drug total clearance (*CL*) will always be correctly given by

$$\frac{1}{CL_{total}} = \frac{1}{CL_{entering}} + \frac{1}{CL_{leaving}} \quad (1)$$

where $CL_{leaving}$ is the sum of the rate-defining processes leading to irreversible elimination from the systemic circulation(e.g., hepatic and/or renal clearance) and $CL_{entering}$ is the sum of the rate-defining processes passing into the measured circulation (e.g., clearance from the delivery site, $CL_{delivery\ site,}$ and organ blood flow).

I have no time for a pharmacokinetic (PK) tutorial, but the take home message from this presentation is that contrary to all previous PK teaching if clearance from the delivery site is the slowest step, then in vivo drug clearance will be equal to the clearance from the delivery site, controlled by the dosage form formulator. That is for a hepatic cleared drug (CL_H) with hepatic blood flow (Q_H)

$$\frac{1}{CL_{total}} = \frac{1}{CL_{delivery\ site}} + \frac{1}{Q_H} + \frac{1}{CL_H} \quad (2)$$

How Can In Vivo Total Drug Clearance Equal $CL_{delivery\ site}$?

$$\frac{1}{CL_{total}} = \frac{1}{CL_{delivery\ site}} + \frac{1}{Q_H} + \frac{1}{CL_H} \qquad (2)$$

$CL_{delivery\ site}$ is a new concept that we introduced. For first order absorption from the GI tract it is just the first order absorption rate constant, k_a, multiplied by the volume of distribution of drug in the absorption site ($V_{absorption\ site}$). For a slow- release dosage form to be rate limited in vivo by $CL_{delivery\ site}$, one must have a drug where CL_H is greater than $CL_{delivery\ site}$, as we reported in our recent paper [Benet et al. (2024) The potential for developing high hepatic clearance drugs via controlled release. J. Control. Rel. 373, 564-567]. It is this principle of relative clearances as to why it is possible to see increased dose corrected efficacy corresponding to an increased AUC for an extended release (ER) dosage form vs an immediate release (IR) dosage form.

Table I Inferential Analysis Results for Percent Change in LDL, HDL, Total Cholesterol, and Triglycerides from Baseline to Endpoint in 20 mg Population.
Adapted from Lukacsko et al. (2004) Current Medical Research and Opinion 20:13-18.

Treatment 20 mg (n=149)	Percent Change LS Mean ± SE (95%) CI			
	LDL Cholesterol	HDL Cholesterol	Total Cholesterol	Triglycerides
ER Lovastatin	**–26.4 ± 1.06** (–28.5, –24.3)	4.1 ± 1.04 (2.0, 6.1)	**–19.1 ± 0.83** (-20.7, -17.4)	**–7.4 ± 2.14** **(-11.7, -3.2)**
IR lovastatin	**–23.1 ± 1.06** (–25.2, –21.0)	4.3 ± 1.04 (2.3, 6.4)	**-17.2 ± 0.83** (-18.8, -15.5)	-10.4 ± 2.14 (-14.7, -6.2)
ER vs IR	**-3.3 ± 1.08** **p = 0.0028**	-0.2 ± 1.28 p = 0.8584	**-1.9 ± 0.91** **p = 0.0355**	3.0 ± 2.81 p = 0.2867

All numbers are from a two-way ANOVA for percent change with treatment and center as factors

Plasma concentrations were not measured in this study, but in a second study by the company, 24 h lovastatin AUCs at day 28 averaged 77.6 ng·h/ml for the 20 mg ER formulation versus 44.7 ng·h/ml for the 20 mg IR formulations. No statistics were reported for the AUC measurements.

In our June, 2025 AAPS J tutorial, we present data for a hypothetical, very hydrophilic drug, KL25A, that following iv bolus dosing is eliminated by both renal (CL_R = 15.4 L/h) and hepatic biliary (CL_H = 11.4 L/h) processes with only minor metabolites measured in urine and blood. When this very hydrophilic drug is given orally, urinary measurement of bioavailability is, F_{urine} = 7.7%. However, because clearance from the intestine is so low, 1.89 L/h (See Wakuda et al. (2024) AAPS J. 26:22 for methodology), a marked increase in AUC is observed following oral dosing, with a resulting bioavailability calculated from systemic concentrations of 95.6%.

What are the Relevant Implications to My Presentation?
Why Am I Presenting at the Controlled Release Society?

What are the Relevant Implications to My Presentation?

1. There are marked previously unrecognized assumptions, as our recent work describes, in calculating F from systemic concentrations for non-parenteral routes of administration that are not inherent in measurements of unchanged drug in urine. Yet, since more than 2/3^{rds} of drugs are essentially eliminated by metabolic processes, there is little reliability in any measures of unchanged drug in urine. Probably the reason that regulatory agencies discourage use of urinary measurements. Thus, for most drugs it is not possible to know if $F_{\text{systemic concentrations}}$ is really the bioavailability.

2. Yet, the extent of exposure, as measured by the systemic area under the concentration-time curve (AUC), is the drug characteristic that relates overwhelmingly to measures of drug efficacy. And almost all drug dosing decisions are based on AUC and changes in AUC measurements. Thus, for KL25A, even though the urinary F is very low, one would expect the pharmacodynamic effect from the oral dose to match that of the iv dose.

Why Am I Presenting at the Controlled Release Society?

3. For the first time, I am suggesting that dosage form designers have the ability to characterize the in vivo clearance of a drug, independent of the drug and the patient characteristics. That is, independent of whether a drug exhibits saturable kinetics, independent of pharmacogenomic differences in enzymes and transporters, independent of many disease state characteristics and in many cases even independent of drug-drug interactions

4. However, this requires a paradigm shift in drug development. For point 3 to be relevant, the preferred non-parenteral drugs to develop are high systemic clearance compounds so that clearance from the manufactured dosage form will be lower and thus control systemic concentrations. It may be that subcutaneous vs oral formulations may be preferred so as to avoid intestinal and hepatic first pass loss. However, as seen in the ER vs IR lovastatin data, slow input can benefit the outcome for an orally dosed drug.

But I have yet to address my title: Increasing Efficacy/Decreasing Toxicity

Increasing Efficacy-Decreasing Toxicity Via Controlled Delivery

In our new approach to deriving pharmacokinetic parameters and the KL25A analysis, I have presented for the first time a discontinuity between systemic concentrations and the amount of drug dosed that has never been previously described. The 7.7% of the oral dose of KL25A that reached the systemic circulation yielded a systemic concentration that was equivalent to that observed for 95.6% of a dose corrected KL25A iv dose.

It is generally universally believed that systemic concentrations relate to efficacy, so that drug dosing adjustments are based on changes in systemic concentrations. But is it true that toxicity (except for toxicity from too much efficacy) is related to systemic concentrations? In fact, there is a great deal of speculation that toxicity more often relates to dose. For example, the best toxicologic predicter to avoid DILI (Drug Induced Liver Injury) is keeping the drug dose ≤ 50 mg.

Can controlled drug delivery increase efficacy via systemic concentrations while decreasing the dose required to obtain that systemic concentration?

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Copy of the slides available from Leslie.Benet@UCSF.edu

But KL25A is a Hypothetical Drug

Can I prove the principles presented here that slow input from the delivery site increases *AUC*, which goes against everything that has been taught in pharmacokinetics since its founding? I needed to identify a drug that a) was approved for both iv and oral dosing; b) was measurably eliminated unchanged so that *F* could be calculated both using unchanged drug in urine and systemic concentrations; c) was absorbed very fast following oral dosing so that it was possible to mimic a slow first order absorption process using small doses at intermittent dosing intervals; and d) did not have a slow iv bolus clearance. **The anti-viral nucleoside zidovudine (Retrovir, AZT) meets these criteria: a) iv in Canada and UK, b) only 18% but measureable in humans, c) and d) clearance approaching organ blood flow. We are contracting to run a dog study (t½ = 1 h) with each dog receiving 500 mg iv, 500 mg oral syrup administered at time zero, and a 500 mg oral syrup administered as a first order formulation with a 2 h absorption half-life.**