# Drug Disposition Viewed in Terms of the Fractal Volume of Distribution

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***Purpose.*** (i) Evaluate the predictive performance of the fractal volume of drug distribution, $v_f$, (Pharm. Res.18, 1056, 2001), (ii) develop the concept of the fractal clearance, $CL_f$, which is the clearance analogue of $v_f$, (iii) examine the utility of $CL_f$ in allometric studies, (iv) develop allometric relationships for the elimination half-life, $t_{1/2}$, and (v) evaluate the use of $v_f$ and $CL_f$ in predicting the volume of drug distribution, $V_{ap}$, clearance, $CL$, and elimination half-life, $t_{1/2}$.

***Methods.*** Estimates for $v_f$ of various drugs were obtained and correlated with body mass using data only from animal species. A comparison was made between the predicted and actual $v_f$ values for humans. For a variety of animal species $CL_f$ values were estimated from the equation:

$$CL_f = \frac{v_f}{V_{ap}} CL$$

The allometric equations developed using $CL_f$ were compared with other allometric approaches. Allometric equations were also developed for $t_{1/2}$ utilizing the allometric relationships of $v_f$ and $CL_f$.

***Results.*** The predicted estimates of $v_f$ were very close to the actual values and the correlation exhibited favorable statistical properties. The values of the allometric exponents for $CL_f$ were found to be close to 0.75. The predictive performance for CL using the allometric equations for $CL_f$ in conjunction with the rule of exponents was found to be better than the currently considered most accurate allometric approaches. The values of the allometric exponents for $t_{1/2}$ were found to be close to 0.25

***Conclusion.*** The predictive ability of $v_f$ is high; predictions for $V_{ap}$ based on $v_f$ values are better than the current approaches. $CL_f$ expressed a good behavior both in prospective and retrospective analysis. The allometric exponents, 0.75, 0.25 for $CL_f$ and $t_{1/2}$, respectively, agree with the theoretical expected values.

**KEY WORDS**: allometry; clearance; volume of distribution; elimination half-life; fractal.

## INTRODUCTION

The concept of clearance originates from the physiological function of the eliminating organs (1). In this respect, organ clearance is highly associated with the organ blood flow, is expressed in units of flow rate while the specific organ blood flow comprises a physiological maximum for the measured clearance, e.g., hepatic clearance ≤1350 mL/min (1). Based on the additive properties of clearance, the concept of body clearance, $CL$, which expresses globally the ability of the eliminating organs of the body to remove drug is being used extensively in pharmacokinetics (1). Estimates for $CL$ can be derived from Eq. (1), which indicates that $CL$ is a proportionality constant between the dose reaching the general circulation and the measured area under the plasma drug concentration-time curve, $(AUC)$:

$$Dose = CL(AUC) \tag{1}$$

While $CL$ can be used to characterize drug elimination, the distribution of drug in the body can be characterized by the volume of drug distribution, $V_{ap}$. The values of the two primary pharmacokinetic parameters, $CL$ and $V_{ap}$, determine the values of the secondary pharmacokinetic parameters, elimination rate constant, $k$, and elimination half-life, $t_{1/2}$:

$$k = \frac{\ln 2}{t_{1/2}} = \frac{CL}{V_{ap}} \tag{2}$$

Equation (2) indicates that $k$ and $t_{1/2}$ reflect the values of $CL$ and $V_{ap}$ but not *vice versa* (2). According to Eq. (2), $CL$ refers to the portion of $V_{ap}$ that is cleared per unit of time.

Recently, we developed the physiologically sound concept of fractal volume of drug distribution, $v_f$ (3). This novel parameter takes values smaller or equal to the body mass (expressed in volume units) of the species and corresponds to the part of the total volume of the species body in which the drug is distributed at equilibrium. Using allometric principles, it was found that $v_f$ scales proportionally to body mass (3).

In this study, we first investigate the use of $v_f$ in prospective studies. Further, we examine the properties of the clearance analogue of $v_f$, called for reasons of uniformity fractal clearance, $CL_f$ ; the latter refers to the portion of $v_f$ cleared per unit of time. This quest is justified by the fact that the concepts of volume of distribution and clearance are always linked via the secondary pharmacokinetic parameter $t_{1/2}$ or $k$ [Eq. (2)]. To this end, we calculated the values of $CL_f$ for various drugs utilizing the reported $v_f$ values (3) keeping unaltered the reported elimination rate constant or half-life. Moreover, we applied allometric analysis to the calculated $CL_f$ values of various drugs in different species and compared our results with the allometric studies for clearance reported in the literature. Also, allometric equations for $t_{1/2}$ were derived from allometric relationships of $CL_f$ and $v_f$. Finally, the use of $v_f$ and $CL_f$ in predicting $V_{ap}$, $CL$, and $t_{1/2}$ was evaluated.

## METHODS

Values of $V_{ap}$ for several drugs were transformed to their $v_f$ analogs, using Eq. (3) reported previously (3):

$$v_f = V_{pl} + (v - V_{pl}) \frac{V_{ap} - V_{pl}}{V_{ap}} \tag{3}$$

where $v$ is the total volume of the species (equivalent to its total mass assuming a uniform density 1g/mL), $V_{pl}$ is the plasma volume of the species and $V_{ap}$ is the conventional volume of drug distribution. Allometric equations were generated, utilizing the $v_f$ estimates for various drugs in different species. To evaluate the usefulness of $v_f$ in prospective studies, i.e., in studies where prediction of the human $v_f$ value from animal data is attempted, human data were not included in the allometric analysis.

Also, predictions for $V_{ap}$ using $v_f$ were based on Eq. (4) which is derived from Eq. (3):

$$V_{ap} = V_{pl} \frac{(v - V_{pl})}{(v - v_f)} \tag{4}$$

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Based on the conceptual meaning of $CL_f$ and $v_f$ i.e., $CL_f$ denotes the portion of $v_f$ which is cleared per unit of time, one can write:

$$k = \frac{\ln 2}{t_{1/2}} = \frac{CL_f}{v_f} \quad (5)$$

Equations (2) and (5) ensure that the value of the observable parameter $k$ or $t_{1/2}$ remains unaltered whether classical ($CL$, $V_{ap}$) or fractal ($CL_f$, $v_f$) disposition is considered. Eq. (6) is obtained by dividing Eqs.(2) and (5):

$$CL_f = \frac{v_f}{V_{ap}} CL \quad (6)$$

The available in literature $CL$ values for various drugs were transformed to the corresponding $CL_f$ values using Eq. (6). The estimates for $CL_f$ were subjected to allometric analysis. For comparative purposes, allometric analysis of the same data was also performed using the conventional clearance, $CL$, and the composite parameters $CL{\cdot}MLP$ (4) and $CL{\cdot}BW$ (5), where $MLP$ and $BW$ refer to maximum lifespan potential and brain weight, respectively. Also, predictions for $CL$ were derived from Eq. (6) using $V_{ap}$ values obtained from Eq. (4).

In all cases success was assessed by the geometric mean of the logarithmic ratio of predicted and actual values (6) of N drugs:

$$Average\text{-}Fold\ Relative\ Error = 10^{\frac{\left|\sum \log \frac{\Pr edicted}{Actual}\right|}{N}} \quad (7)$$

The ideal value of average-fold relative error, AFRE, is 1, which means that the method predicts all actual values perfectly. The prediction becomes less precise as the deviation of AFRE from unity becomes larger. Besides, the average relative error (%ARE), which corresponds to *100(predicted-actual)/actual*, was used to evaluate the predictions (6).

## RESULTS

Although in our previous study (3) we found very good linear correlations between the logarithms of $v_f$ and the body mass of the species, in this work we further wanted to investigate whether the successive correlation implies also an accurate precision for $v_f$ (7,8). For each one of the species (except man) the value of $v_f$ was derived from Eq. (3) using the reported in literature $V_{ap}$ values. The calculated $v_f$ values were further used to develop allometric equations. Then, the human mass value reported in the relevant article was used to derive from these equations the predicted estimates for human $v_f$. The expected values of $v_f$ were obtained from Eq. (3) using the apparent volume of drug distribution for humans reported in the reference article. Fig. 1 shows the relationship between the predicted and the expected $v_f$ values. Visual inspection of Fig. 1, illustrates not only a good linear relationship between the predicted and observed values of $v_f$ but also the almost ideal concordance (slope = 0.96). Moreover, evaluation of the predictive performance of $v_f$ with the geometric mean of the ratio of predicted and actual values utilizing Eq. (7) gave AFRE and %ARE values equal to 1.04 and 4.04%, respectively. It is interesting to note that the allometric equations for the conventional $V_{ap}$ using the same data gave AFRE and %ARE values 1.72, 146.8%, respectively. In addition, the literature values for AFRE, utilizing various scaling approaches for the prediction of the apparent volume of drug distribution, have been found (6) much higher, e.g., 1.56, 1.56, 1.83, 2.78; also, the AFRE value for the scaling of the volume of distribution of the central compartment was found 1.3 (9). This means that one can derive an accurate estimate for $v_f$ in humans using data only from animal species.

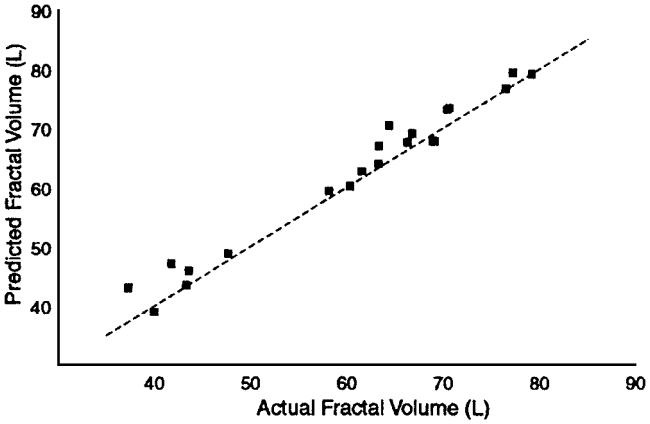


**Fig. 1.** Plot of predicted from allometric scaling human values of $v_f$ (ordinate) vs. actual human $v_f$ values (abscissa). Actual $v_f$ values were derived from Eq. (3) using the human $V_{ap}$ values quoted in the literature (13-28). The dashed line indicates complete concordance.

Because $V_{ap}$ can be used to determine the initial concentration of drug after an i.v. administration for the selection of the first time dose in humans (10), we calculated $V_{ap}$ values using $v_f$. For each one of the species (except human) the value of $V_{ap}$ was derived from Eq. (4) using the corresponding $v_f$ values. The $V_{ap}$ values were used to develop allometric equations which were further used to predict human $V_{ap}$ estimates. The AFRE and %ARE for the predicted $V_{ap}$ values were 1.51 and 99.2%, respectively. These indexes are much better than the aforementioned values 1.72 and 146.8% for $V_{ap}$ derived conventionally. This means that one can derive a more reliable estimate for $V_{ap}$ using $v_f$ than the current approaches and since the administrated dose is known it can be used to calculate plasma concentration at time zero.

The results of the allometric analysis for clearance using four approaches are listed in Table I. The four approaches compared are based on the values of $CL_f$, $CL$, $CL{\cdot}MLP$ and $CL{\cdot}BW$. Although the use of $MLP$ and $BW$ may not have any physiological meaning, it has been suggested that both parameters help in improving the predictive performance in scaling (10). Estimates for $MLP$ and $BW$ were taken either from the relevant article or were calculated using the body and brain weights (11) of the species as described in the literature (12). For comparative purposes, all data were expressed to identical units; thus, the kilogram was used as the measure of mass and L/h as the unit of clearance. The symbols $CL_{tot}$, $CL_{ren}$ and $CL_{hep}$ characterize the type of clearance, i.e., total, renal and hepatic clearance, respectively. The values of $CL_{ren}$ and $CL_{hep}$ were either quoted in literature or calculated from the reported data (13–28). Visual inspection of Table I reveals that the allometric equations of $CL_f$ exhibit coefficient of determination values ($R^2$) higher than $CL$ and comparable with the best values of $CL{\cdot}MLP$ and $CL{\cdot}BW$. Moreover, the allometric exponents of $CL_f$ never exceeded

**Table I.** Allometric Equations Describing the Relationship between the Various Types of Clearance and Body Mass across Species

| Drug[a] | $CL_f$ | $R^2$ | CL | $R^2$ | CL · MLP | $R^2$ | CL · BW | $R^2$ |
|---|---|---|---|---|---|---|---|---|
| Actisomide ($V_d$) | $(CL_{tot})_f = 0.526\ M^{0.948}$ | 0.995 | $CL_{total} = 0.641\ M^{0.951}$ | 0.973 | $CL_{tot} \cdot MLP = 0.0503\ 10^6\ M^{1.485}$ | 0.979 | $CL_{tot} \cdot BW = 0.0053\ M^{2.158}$ | 0.987 |
| | $(CL_{ren})_f = 0.201\ M^{0.898}$ | 0.998 | $CL_{renal} = 0.2445\ M^{0.901}$ | 0.991 | $CL_{ren} \cdot MLP = 0.0192\ 10^6\ M^{1.435}$ | 0.992 | $CL_{ren} \cdot BW = 0.0020\ M^{2.108}$ | 0.994 |
| | $(CL_{hep}) = 0.157\ M^{0.986}$ | 0.893 | $CL_{hep} = 0.191\ M^{0.990}$ | 0.936 | $CL_{hep} \cdot MLP = 0.0150\ 10^5\ M^{1.523}$ | 0.983 | $CL_{hep} \cdot BW = 0.00158\ M^{2.196}$ | 0.993 |
| Amphotericin ($V_1$) | $CL_f = 0.052\ M^{0.886}$ | 0.950 | $CL = 0.0559\ M^{0.827}$ | 0.946 | $CL \cdot MLP = 5.703\ 10^3\ M^{1.242}$ | 0.988 | $CL \cdot BW = 0.000719\ M^{1.827}$ | 0.996 |
| Amphotericin ($V_{ap}$) | $CL_f = 0.020\ M^{0.867}$ | 0.974 | $CL = 0.0559\ M^{0.827}$ | 0.940 | $CL \cdot MLP = 5.703\ 10^3\ M^{1.242}$ | 0.988 | $CL \cdot BW = 0.000719\ M^{1.827}$ | 0.996 |
| Amphotericin ($V_{ss}$) | $CL_f = 0.0195\ M^{0.849}$ | 0.965 | $CL = 0.0559\ M^{0.827}$ | 0.940 | $CL \cdot MLP = 5.703\ 10^3\ M^{1.242}$ | 0.988 | $CL \cdot BW = 0.000719\ M^{1.827}$ | 0.996 |
| Amsacrine ($V_{ss}$) | $CL_f = 0.670\ M^{0.646}$ | 0.987 | $CL = 2.29\ M^{0.460}$ | 0.906 | $CL \cdot MLP = 1.91\ 10^5\ M^{0.856}$ | 0.921 | $CL \cdot BW = 0.020\ M^{1.433}$ | 0.947 |
| BSH ($V_{ap}$) | $CL_f = 0.08\ M^{0.807}$ | 0.964 | $CL = 0.128\ M^{0.676}$ | 0.946 | $CL \cdot MLP = 1.16\ 10^4\ M^{1.133}$ | 0.997 | $CL \cdot BW = 0.00136\ M^{1.772}$ | 0.999 |
| Cefazolin ($V_{ss}$) | $(CL_{tot}) = 1.146\ M^{0.714}$ | 0.992 | $CL_{tot} = 0.271\ M^{0.680}$ | 0.975 | $CL_{tot} \cdot MLP = 0.0236\ 10^6\ M^{1.126}$ | 0.996 | $CL_{tot} \cdot BW = 0.00257\ M^{1.752}$ | 0.997 |
| | $(CL_{ren})_f = 0.873\ M^{0.781}$ | 0.981 | $CL_{ren} = 0.206\ M^{0.746}$ | 0.965 | $CL_{ren} \cdot MLP = 0.0179\ 10^6\ M^{1.192}$ | 0.997 | $CL_{ren} \cdot BW = 0.00196\ M^{1.819}$ | 0.998 |
| Cefmetazole ($V_{ss}$) | $(CL_{tot})_f = 2.25\ M^{0.711}$ | 0.972 | $CL_{tot} = 0.736\ M^{0.594}$ | 0.917 | $CL \cdot MLP = 0.1148\ 10^6\ M^{0.771}$ | 0.947 | $CL_{tot} \cdot BW = 0.0123\ M^{1.396}$ | 0.970 |
| | $(CL_{ren})_f = 1.268\ M^{0.784}$ | 0.965 | $CL_{ren} = 0.415\ M^{0.668}$ | 0.959 | $CL \cdot MLP = 0.036\ 10^6\ M^{1.108}$ | 0.990 | $CL_{ren} \cdot BW = 0.00389\ M^{1.733}$ | 0.991 |
| Cefoperazone ($V_{ss}$) | $(CL_{tot})_f = 1.403\ M^{0.634}$ | 0.908 | $CL_{tot} = 0.402\ M^{0.571}$ | 0.823 | $CL_{tot} \cdot MLP = 0.0377\ 10^6\ M^{0.988}$ | 0.959 | $CL_{tot} \cdot BW = 0.0045\ M^{1.580}$ | 0.983 |
| | $(CL_{ren})_f = 0.465\ M^{0.699}$ | 0.838 | $CL_{ren} = 0.133\ M^{0.635}$ | 0.704 | $CL_{ren} \cdot MLP = 0.01023\ 10^5\ M^{1.144}$ | 0.944 | $CL_{ren} \cdot BW = 0.00112\ M^{1.784}$ | 0.985 |
| Cefotetan ($V_{ss}$) | $(CL_{tot})_f = 1.396\ M^{0.576}$ | 0.917 | $CL_{tot} = 0.379\ M^{0.533}$ | 0.849 | $CL_{tot} \cdot MLP = 0.0337\ 10^6\ M^{0.972}$ | 0.990 | $CL_{tot} \cdot BW = 0.00367\ M^{1.596}$ | 0.999 |
| | $(CL_{ren})_f = 0.872\ M^{0.589}$ | 0.923 | $CL_{ren} = 0.237\ M^{0.547}$ | 0.865 | $CL_{ren} \cdot MLP = 0.021\ 10^6\ M^{0.986}$ | 0.989 | $CL_{ren} \cdot BW = 0.0023\ N^{1.609}$ | 0.997 |
| Cefpiramide ($V_{ss}$) | $(CL_{tot})_f = 0.769\ M^{0.542}$ | 0.890 | $CL_{tot} = 0.245\ M^{0.404}$ | 0.589 | $CL_{tot} \cdot MLP = 0.022\ 10^6\ M^{0.842}$ | 0.875 | $CL_{tot} \cdot BW = 0.0025\ M^{1.461}$ | 0.953 |
| | $(CL_{ren})_f = 0.328\ M^{0.567}$ | 0.791 | $CL_{ren} = 0.105\ M^{0.429}$ | 0.522 | $CL \cdot MLP = 0.093\ 10^5\ M^{0.867}$ | 0.860 | $CL_{ren} \cdot BW = 0.00105\ M^{1.486}$ | 0.954 |
| CI-921 ($V_{ss}$) | $CL_f = 0.707\ M^{0.815}$ | 0.943 | $CL = 0.914\ M^{0.507}$ | 0.830 | $CL \cdot MLP = 7.32\ 10^4\ M^{0.913}$ | 0.910 | $CL \cdot BW = 0.007\ M^{1.503}$ | 0.944 |
| Diazepam ($V_1$) | $CL_f = 2.78\ M^{0.459}$ | 0.605 | $CL = 7.29\ M^{0.103}$ | 0.037 | $CL \cdot MLP = 0.436\ 10^6\ M^{0.604}$ | 0.721 | $CL \cdot BW = 0.0367\ M^{1.234}$ | 0.902 |
| Diazepam ($V_\beta$) | $CL_f = 0.885\ M^{0.353}$ | 0.879 | $CL = 7.29\ M^{0.103}$ | 0.037 | $CL \cdot MLP = 0.436\ 10^6\ M^{0.604}$ | 0.721 | $CL \cdot BW = 0.0367\ M^{1.234}$ | 0.902 |
| Diazepam ($V_{ss}$) | $CL_f = 1.451\ M^{0.315}$ | 0.628 | $CL = 7.29\ M^{0.103}$ | 0.037 | $CL \cdot MLP = 0.436\ 10^6\ M^{0.604}$ | 0.721 | $CL \cdot BW = 0.0367\ M^{1.234}$ | 0.902 |
| Erythromycin ($V_{ss}$) | $CL_f = 0.591\ M^{0.886}$ | 0.985 | $CL = 2.32\ M^{0.713}$ | 0.963 | $CL \cdot MLP = 0.201\ 10^6\ M^{1.119}$ | 0.999 | $CL \cdot BW = 0.0228\ M^{1.705}$ | 0.998 |
| Interferon-a ($V_{ss}$) | $CL_f = 0.872\ N^{0.750}$ | 0.961 | $CL = 0.221\ M^{0.710}$ | 0.980 | $CL \cdot MLP = 0.0185\ 10^6\ M^{1.094}$ | 0.969 | $CL \cdot BW = 0.002\ M^{1.685}$ | 0.975 |
| Lamifiban ($V_{ss}$) | $CL_f = 1.085\ M^{0.632}$ | 0.919 | $CL = 0.368\ M^{0.884}$ | 0.887 | $CL \cdot MLP = 0.03167\ 10^6\ M^{1.311}$ | 0.997 | $CL \cdot BW = 0.00367\ M^{1.891}$ | 0.995 |
| Moxalactame ($V_{ss}$) | $(CL_{tot})_f = 1.118\ M^{0.718}$ | 0.996 | $CL_{tot} = 0.302\ M^{0.662}$ | 0.992 | $CL_{tot} \cdot MLP = 0.0262\ 10^6\ M^{1.107}$ | 0.993 | $CL_{tot} \cdot BW = 0.0029\ M^{1.732}$ | 0.993 |
| | $(CL_{ren})_f = 0.889\ M^{0.769}$ | 0.990 | $CL_{ren} = 0.240\ M^{0.713}$ | 0.981 | $CL_{ren} \cdot MLP = 0.0209\ 10^6\ M^{1.159}$ | 0.995 | $CL_{ren} \cdot BW = 0.0023\ M^{1.783}$ | 0.994 |
| Oleandomycin ($V_{ss}$) | $CL_f = 0.656\ M^{0.934}$ | 0.990 | $CL = 1.828\ M^{0.691}$ | 0.995 | $CL \cdot MLP = 0.0178\ 10^7\ M^{1.108}$ | 0.991 | $CL \cdot BW = 0.0218\ M^{1.700}$ | 0.992 |
| Phencyclidine ($V_\beta$) | $CL_f = 0.314\ M^{0.675}$ | 0.953 | $CL = 3.617M^{0.616}$ | 0.907 | $CL \cdot MLP = 0.032\ 10^7\ M^{1.035}$ | 0.991 | $CL \cdot BW = 0.03967\ M^{1.624}$ | 0.995 |
| Procaterol ($V_\beta$) | $(CL_{tot})_f = 0.61\ M^{0.768}$ | 0.992 | $CL_{tot} = 1.74\ M^{0.827}$ | 0.991 | $CL_{tot} \cdot MLP = 1.22\ 10^5\ M^{1.192}$ | 1.000 | $CL_{tot} \cdot BW = 0.013\ M^{1.712}$ | 0.998 |
| | $(CL_{ren})_f = 0.14\ M^{0.897}$ | 0.993 | $CL_{ren} = 0.4\ M^{0.956}$ | 0.994 | $CL_{ren} \cdot MLP = 2.81\ 10^4\ M^{1.321}$ | 1.000 | $CL_{ren} \cdot BW = 0.003\ M^{1.841}$ | 0.998 |
| | $(CL_{hep})_f = 0.46\ M^{0.727}$ | 0.992 | $CL_{hep} = 1.32\ M^{0.786}$ | 0.989 | $CL_{hep} \cdot MLP = 9.3\ 10^4\ M^{1.151}$ | 1.000 | $CL_{hep} \cdot BW = 0.0097\ M^{1.671}$ | 0.998 |
| Procaterol ($V_c$) | $(CL_{tot})_f = 2.88\ M^{0.863}$ | 0.999 | $CL_{tot} = 1.74\ M^{0.827}$ | 0.991 | $CL_{tot} \cdot MLP = 1.22\ 10^5 M^{1.192}$ | 1.000 | $CL_{tot} \cdot BW = 0.013\ M^{1.712}$ | 0.998 |
| | $CL_{ren})_f = 0.66\ M^{0.991}$ | 0.999 | $CL_{ren} = 0.4\ M^{0.956}$ | 0.994 | $CL_{ren} \cdot MLP = 2.81\ 10^4\ M^{1.321}$ | 1.000 | $CL_{ren} \cdot BW = 0.003\ M^{1.841}$ | 0.998 |
| | $(CL_{hep})_f = 2.19\ M^{0.822}$ | 0.999 | $CL_{hep} = 1.32\ M^{0.786}$ | 0.989 | $CL_{hep} \cdot MLP = 9.3\ 10^4\ M^{1.151}$ | 1.000 | $CL_{hep} \cdot BW = 0.0097\ M^{1.671}$ | 0.998 |
| Remoxipride ($V_{ss}$) | $(CL_{tot})_f = 0.925\ M^{0.525}$ | 0.978 | $CL_{tot} = 2.1\ M^{0.335}$ | 0.854 | $CL_{tot} \cdot MLP = 0.0188\ 10^7\ M^{0.745}$ | 0.976 | $CL_{tot} \cdot BW = 0.0203\ M^{1.328}$ | 0.987 |
| | $(CL_{ren})_f = 0.130\ M^{0.631}$ | 0.964 | $CL_{ren} = 0.298\ M^{0.441}$ | 0.926 | $CL_{ren} \cdot MLP = 0.0265\ 10^6\ M^{0.851}$ | 0.969 | $CL_{ren} \cdot BW = 0.00283\ M^{1.434}$ | 0.980 |
| Tamsulosin ($V_d$) | $CL_f = 1.422\ M^{0.677}$ | 0.999 | $CL_{tot} = 3.67\ M^{0.594}$ | 0.993 | $CL_{tot} \cdot MLP = 0.0242\ 10^7 TM^{0.878}$ | 0.994 | $CL \cdot BW = 0.0275\ M^{1.383}$ | 0.993 |
| Theophylline ($V_{ss}$) | $(CL_{hep})_f = 0.275\ M^{0.729}$ | 0.999 | $CL_{hep} = 0.161\ M^{0.784}$ | 0.965 | $CL_{hep} \cdot MLP = 0.098\ 10^5\ M^{1.325}$ | 0.998 | $CL_{hep} \cdot BW = 0.00105\ M^{1.992}$ | 0.999 |
| | $(CL_{intr})_f = 0.602\ M^{0.660}$ | 0.998 | $CL_{intr} = 0.353\ M^{0.715}$ | 0.975 | $CL_{intr} \cdot MLP = 0.0215\ 10^6\ M^{1.256}$ | 1.000 | $CL_{intr} \cdot BW = 0.0023\ M^{1.923}$ | 0.998 |
| Troglitazone ($V_\beta$) | $CL_f = 0.38\ M^{0.723}$ | 0.994 | $CL = 0.742\ M^{0.808}$ | 0.988 | $CL \cdot MLP = 0.0648\ 10^6\ M^{1.198}$ | 0.994 | $CL \cdot BW = 0.007\ M^{1.781}$ | 0.996 |
| Troglitazone ($V_c$) | $CL_f = 2.02\ M^{0.808}$ | 0.991 | $CL = 0.742\ M^{0.808}$ | 0.988 | $CL \cdot MLP = 0.0648\ 10^6\ M^{1.198}$ | 0.994 | $CL \cdot BW = 0.007\ M^{1.781}$ | 0.996 |
| Troglitazone ($V_{ss}$) | $CL_f = 0.820\ M^{0.826}$ | 0.996 | $CL = 0.742\ M^{0.808}$ | 0.988 | $CL \cdot MLP = 0.0648\ 10^6\ M^{1.198}$ | 0.994 | $CL \cdot BW = 0.007\ M^{1.781}$ | 0.996 |

[a] The volume term in parenthesis was used for the calculation of $v_f$ from Eq. 3.

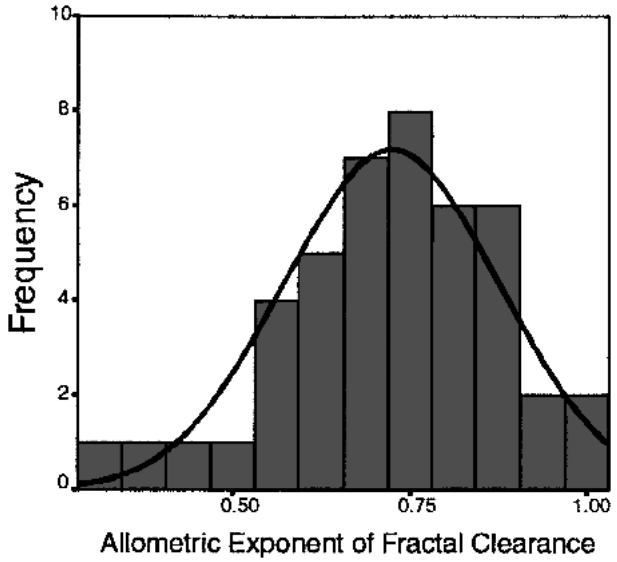


**Fig. 2.** Histogram for the allometric mass exponent of $CL_f$ listed in Table I.

unity, which is frequently the case for the allometric equations of *CL·MLP* and *CL·BW*. In some cases, the equations for *CL·BW* had exponents very close to 2. The smaller than unity values found for the allometric exponents of $CL_f$ are in accord with the theoretical expectations, which suggest that smaller organisms have a greater opportunity to dispose drug molecules. Figure 2 shows the distribution of the numerical values of the allometric exponents for $CL_f$. The graph of Fig. 2 reveals that the values of the exponents are normally distributed around the mean value 0.72 (median 0.73, and CV ~3.2%), which is very close to the expected value 0.75. A characteristic example is interferon-α which exhibits ideal behavior (Table I, allometric exponent 0.750). According to Lavé *et al.* (21), who found 0.71 for the allometric exponent of interferon-α clearance, the scaling works best for interferon-α since it is mainly eliminated by physical transport processes. Their conclusions for interferon-α are verified in our study using $CL_f$ as clearance parameter. Overall, the homogeneous normal distribution of the allometric exponents for $CL_f$ indicates that $CL_f$ scales as a ¾ power of mass i.e., $CL_f \propto M^{3/4}$. This finding is in accord with the general scaling law for clearance, the origin of which was recently found to be associated

**Table II.** Predicted and Observed Human Values of Fractal Clearance and Conventional Clearance

| | Fractal clearance (L/h) | | | Clearance (L/h) | | | |
|---|---|---|---|---|---|---|---|
| | Predicted | | | Predicted from | | | |
| **Drug** | $CL_f$ | $(CL_f)_e$ | Observed[a] | $CL_f$[b] | $(CL_f)_e$[b] | $CL_e$ | Observed |
| Actisomide ($CL_{tot}$) | 32.75 | 22.60 | 23.72 | 34.51 | 23.82 | 35.34 | 25.44 |
| Actisomide ($CL_{ren}$) | 9.1 | 7.34 | 7.83 | 9.59 | 7.74 | 11.48 | 8.4 |
| Actisomide ($CL_{met}$) | 19.44 | 13.42 | 13.52 | 20.48 | 14.14 | 20.98 | 14.5 |
| Amphotericin ($CL_{tot}$) | 1.23 | 0.72 | 1.54 | 1.14 | 0.67 | 1.15 | 1.8 |
| Amsacrine ($CL_{tot}$) | 9.73 | 9.73 | 13.19 | 15.71 | 15.71 | 13.74 | 21.14 |
| BSH ($CL_{tot}$) | 11.22 | 2.59 | 1.62 | 13.32 | 3.08 | 3.22 | 1.51 |
| Cefazolin ($CL_{tot}$) | 24.62 | 12.68 | 18.32 | 5.03 | 2.59 | 3 | 3.18 |
| Cefazolin ($CL_{ren}$) | 27.85 | 14.34 | 16.67 | 5.69 | 2.93 | 3.24 | 2.89 |
| Cefmetazole ($CL_{tot}$) | 50.67 | 24.89 | 33.42 | 10.26 | 5.04 | 10.35 | 6.7 |
| Cefmetazole ($CL_{ren}$) | 35.32 | 17.35 | 28.07 | 7.15 | 3.51 | 7.21 | 5.63 |
| Cefoperazone ($CL_{tot}$) | 19.39 | 19.39 | 21.07 | 4.08 | 4.08 | 4.6 | 4.24 |
| Cefoperazone ($CL_{ren}$) | 19.87 | 12.72 | 5.27 | 4.18 | 2.68 | 3.18 | 1.06 |
| Cefotetan ($CL_{tot}$) | 22.16 | 22.16 | 9.42 | 5.32 | 5.32 | 5.87 | 1.81 |
| Cefotetan ($CL_{ren}$) | 12.78 | 12.78 | 7.25 | 3.07 | 3.07 | 3.38 | 1.4 |
| Cefpiramide ($CL_{tot}$) | 8.71 | 8.71 | 5.98 | 1.51 | 1.51 | 1.61 | 1.05 |
| Cefpiramide ($CL_{ren}$) | 7.32 | 3.80 | 1.49 | 1.27 | 0.66 | 1.36 | 0.26 |
| CI-921 ($CL_{tot}$) | 16.27 | 5.24 | 30.73 | 6.84 | 2.20 | 5.33 | 11.28 |
| Diazepam ($CL_{tot}$) | 33.32 | 16.62 | 4.55 | 70.74 | 54.79 | 84.91 | 2.84 |
| Erythromycin ($CL_{tot}$) | 21.47 | 7.80 | 31.79 | 70.75 | 25.70 | 31.19 | 29.52 |
| Moxalactame ($CL_{tot}$) | 18.89 | 18.89 | 25.19 | 4.03 | 4.03 | 4.37 | 4.95 |
| Moxalactame ($CL_{ren}$) | 19.35 | 10.07 | 23.68 | 4.13 | 2.15 | 2.32 | 4.65 |
| Oleandomycin ($CL_{tot}$) | 22.6 | 9.86 | 46.91 | 28.4 | 12.38 | 28.85 | 38.22 |
| Phencyclidine ($CL_{tot}$) | 9.71 | 5.57 | 3.63 | 105.24 | 60.34 | 72.26 | 22.64 |
| Remoxipride ($CL_{tot}$) | 6.93 | 6.93 | 11.25 | 9.29 | 9.29 | 10.86 | 8.36 |
| Remoxipride ($CL_{ren}$) | 1.02 | 1.03 | 3.31 | 1.37 | 1.37 | 1.6 | 2.46 |
| Theophylline ($CL_{intr}$) | 8.01 | 8.01 | 9.95 | 6.35 | 6.35 | 4.84 | 5.78 |
| Theophylline ($CL_{met}$) | 5.62 | 2.79 | 5.63 | 4.46 | 2.21 | 3.4 | 3.27 |
| **Statistical indexes** | | | | | | | |
| AFRE | 1.31 | 1.21 | | 1.65 | 1.06 | 1.42 | |
| %ARE | 82.8 | 8.43 | | 181.3 | 84.66 | 157.8 | |

[a] Calulated from Eq. 6 using the reported values for $V_{ap}$ and $CL$; $v_f$ was obtained from Eq. 3.

[b] The predicted values for clearance were derived from Eq. 6 which was solved in terms of $CL$; $V_{ap}$ estimates were obtained from Eq. 4 using predicted human $v_f$ values.

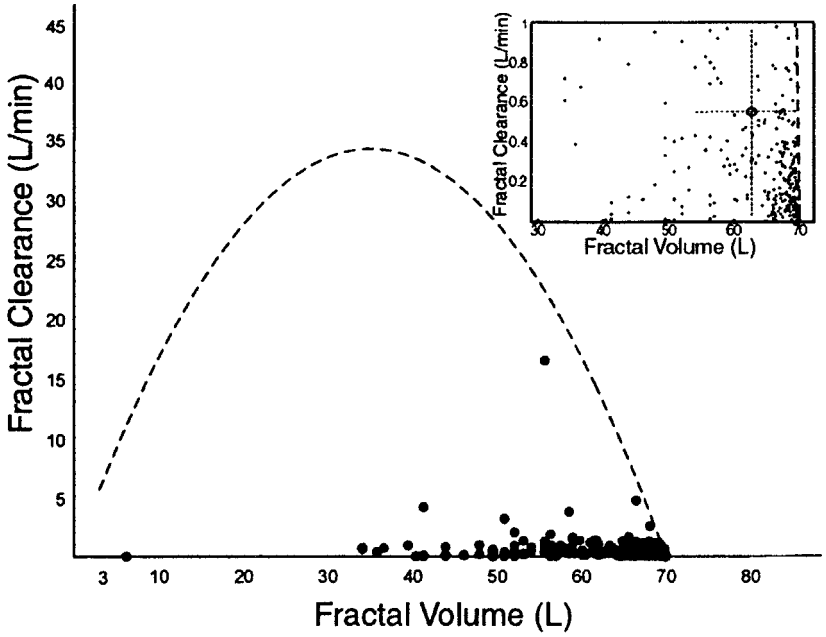


**Fig. 3.** Plot of $CL_f$ vs. $v_f$ using Eq. (8) for humans assigning $V_{pl}=3$L, $v=70$L, and $CL=5.6$ L/min (cardiac output). The values of $v_f$, $CL_f$ of the data points plotted were calculated from Eqs. (3) and (6), respectively, utilizing $V_{ap}$ and $CL$ values taken from the literature (32). A total of 309 drugs are plotted. The inset magnifies the region 0–1 L/min of the ordinate. The symbol (é) indicates the cutoff point 63 L, 0.56 L/min.

with the fractal like architecture of the interior networks that distribute resources within organisms (29,30).

Because a good correlation does not surely imply a good prediction (7,8), the usefulness of $CL_f$ in prospective studies was also explored. To this end, data from various animal species, except human, were used to calculate the allometric equations based on the $CL_f$ values. For comparative reasons the same calculations were used for the estimation of the allometric equations with conventional clearance, $CL$, and its composites with $MLP$ and $BW$ applying the "rule of exponents" (31). The rule of exponents is empirically based on the exponent values of the simple allometry and it was proposed (31) to specify under what conditions the allometric equation, involving either $CL$, $CL{\cdot}MLP$, or $CL{\cdot}BW$ can be used for more accurate prediction of clearance. Table II shows the predicted clearance values with various approaches; the term $CL_e$ quoted in Table II denotes classical clearance derived from the rule of exponents. Comparing the results for $CL_f$, and those derived from the approaches that are currently proposed to be most accurate, it can be concluded that $CL_f$ exhibits better predictive performance than $CL_e$ since the values of AFRE and %ARE are 1.31, 82.8% and 1.42, 157.8%, respectively (Table II). Furthermore, when $CL_f$ is used in conjunction with the rule of exponents (the so derived fractal clearance is denoted with $(CL_f)_e$ ) the statistical indexes exhibit even better performance i.e., 1.21 and 8.43%.

For practical purposes, the conventional clearance, $CL$, was calculated from Eq. (6) using $CL_f$ values. Besides, the same calculations were performed for $CL$ using $(CL_f)_e$ values. The results demonstrate that the best predictive performance (AFRE: 1.06, %ARE: 84.66%) is obtained when $CL$ is derived from $(CL_f)_e$. Overall, the predictive performance of the various clearance expressions for the conventional $CL$ follows the ranking: $(CL_f)_e > CL_e > CL_f$, Table II. One should note however that clearance, $CL$, derived from $CL_f$ requires only one transformation applicable to all cases and it does not rely on any empirical assumption (7,8). On the contrary, the approaches utilizing the rule of exponents are more complicated, use empirical correction parameters ($BW$, $MLP$), while the selection of the exponent is empirical too.

Drug clearance values are better understood when considered in the light of the upper limit values imposed by the physiology. Such a consideration for $CL_f$ can be based on Eq. (8) derived from Eqs. (4) and (6):

$$CL_f = \frac{v_f(v - v_f)}{V_{pl}(v - V_{pl})}\, CL \tag{8}$$

Equation (8) reveals that $CL_f$ can be higher or lower than $CL$ depending on the value of $v_f$, i.e., $CL_f > CL$ when $3L < v_f < 67L$ and $CL_f < CL$ when $70L > v_f > 67L$. The two terms, $CL$, and $CL_f$ become identical when the drug is confined to plasma, i.e., $v_f = V_{pl} = 3L$. Besides, Eq. (8) allows us to calculate the range of the physiologically permitted $CL_f$ values in various species. The results obtained for humans by assigning $v = 70$ L, $V_{pl} = 3$ L and $CL = 5.6$ L/min which is the physiological maximum for the cardiac output (11), are presented in Fig. 3. The physiologically acceptable values for the pairs $v_f$, $CL_f$ lie in the area under the curve of Fig. 3. Accordingly, a large number of drugs taken from the literature (32) were found to lie in this area exclusively. The boundaries imposed by the physiology for $CL_f$ and $v_f$ (3) in conjunction with their functional relationship [Eq. (8)] can be used to develop a pharmacokinetic drug classification scheme (PCS), Fig. 3. The PCS attempts to bring the space-time considerations in pharmacokinetics (33) in a real physiological context. This can be achieved by selecting a cutoff point for both pharmacokinetic parameters ["volume of distribution" for space and "clear-

**Table III.** Drug Examples Classified into Four Categories of PCS Using the Cutoff Point 63 L, 0.56 L/min in the $v_f$, $CL_f$ Plane

| | |
|---|---|
| Class I (HH)[a] $v_f > 63$ L, $CL_f > 0.56$ L/min | Erythromycin, Zidovudine, Haloperidol, Ketamine, Minoxidil |
| Class II (LH)[a] $v_f \leq 63$ L, $CL_f > 0.56$ L/min | Acetylsalicyclic acid, Cefaclor, Chlorothiazide, Cloxacillin, Dicloxacillin |
| Class III (LL)[a] $v_f \leq 63$ L, $CL_f \leq 0.56$ L/min | Glipizide, Ibuprofen, Indomethacin, Ketoprofen, Phenobarbital |
| Class IV (HL)[a] $v_f > 63$ L, $CL_f \leq 0.56$ L/min | Diazepam, Fentanyl, Amiodarone, Caffeine, Chloramphenicol |

[a] H denotes high; L denotes low.

ance" for time, (33)] on the basis of physiological considerations. However, the way we conceive the distribution of drug in the body (space, fractal volume) is of primary importance and crucial for the temporal element (fractal clearance) as the concept of clearance refers to the volume cleared per time unit and therefore is by definition dependent on the notion of volume. Consequently, the value of 63 L was assigned first for the cutoff point of $v_f$ since it corresponds to the 90% of the physiological maximum (70 L) and is very close to the mean value (63.6 L) of $v_f$ for the 309 data analyzed (32). The most plausible physiological maximum for the corresponding temporal component of our classification is the total cardiac output 5.6 L/min. This value when combined with the physiological maximum for volume (70 L), results in a half-life of $\ln 2 \bullet 70/5.6 \approx 9$ min. Thus, the 10% of the total cardiac output, 0.56L/min, was considered as a reasonable cutoff value for drug classification in terms of $CL_f$ since the half-lives of the highly cleared drugs range from 3.7 to 86.6 min for the physiological range of $v_f$ values from 3 to 70 L, respectively; low cleared drugs ($CL_f < 0.56$ L/min) exhibit half-lives >86.6 min irrespective of their $v_f$ values. Accordingly, the cutoff points 63 L, 0.56 L/min in the $v_f$, $CL_f$ plane is suggested for the classification of drugs into four categories, Fig. 3. Some drug examples classified according to PCS are presented in Table III. The PCS can be used complementary to the biopharmaceutics classification scheme (34) to formulate a global biopharmaceutical-pharmacokinetic profile of drugs. This approach will certainly facilitate the pharmaceutical scientist to get an insight into bioavailability-disposition characteristics of a drug candidate in the early phases of development. However, further analysis will be required to elucidate the importance of the underlying physicochemical properties e.g., lipophilicity, solubility, plasma binding for the four drug categories of PCS.

Interspecies pharmacokinetic scaling primarily deals with clearance and volume of distribution; however, the combination of these approaches can be used for $t_{1/2}$ scaling (10). In the present study the allometric equations obtained for $v_f$ and $CL_f$ were used in conjunction with Eq. (5) to develop the corresponding allometric relationships for $t_{1/2}$. Figure 4 shows the frequency distribution of the exponent of the allometric equations (not reported) for $t_{1/2}$. The mean value of exponents was found 0.264, the median 0.258, while the ±2SD interval lies between 0.219 and 0.308. Figure 4, demonstrates that the values of the exponent are normally distributed with a mean value very close to the theoretically expected value 0.25. Thus, the deviations of exponents of the allometric

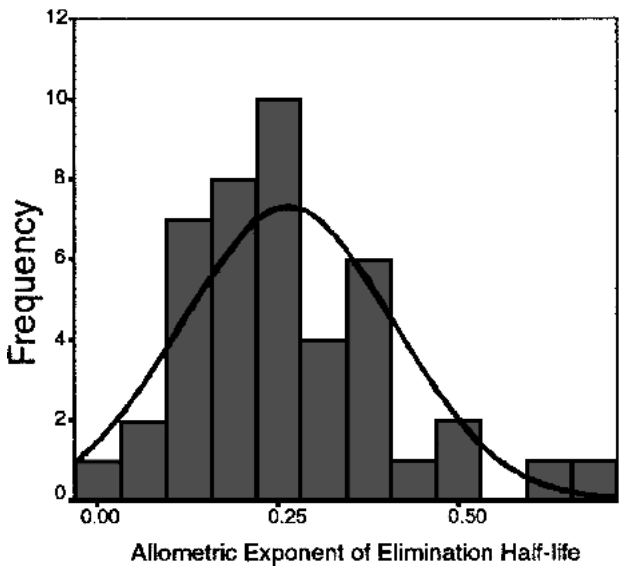


**Fig. 4.** Histogram for the allometric mass exponents of the elimination half-life, $t_{1/2}$.

**Table IV.** Predicted and Observed Human Values of $t_{1/2}$

| Drug | Predicted $t_{1/2}$ (h) Eq. 5[b] | Eq. 2[c] | Observed $t_{1/2}$[a] (h) |
|---|---|---|---|
| Actisomide | 1.28 | 1.87 | 1.76 |
| Amphotericin | 38.23 | 65.64 | 68.67 |
| Amsacrine | 5.64 | 5.64 | 4.15 |
| BSH | 3.95 | 12.56 | 27.00 |
| Cefazolin | 1.23 | 2.38 | 1.41 |
| Cefmetazole | 0.59 | 0.60 | 0.89 |
| Cefoperazone | 1.75 | 1.75 | 1.57 |
| Cefotetan | 1.48 | 1.48 | 3.07 |
| Cefpiramide | 3.11 | 3.10 | 4.63 |
| CI-921 | 2.67 | 2.67 | 1.38 |
| Diazepam | 3.99 | 3.97 | 12.97 |
| Erythromycin | 2.23 | 6.73 | 1.46 |
| Moxalactame | 1.68 | 1.69 | 1.20 |
| Oleandomycin | 2.07 | 2.15 | 0.98 |
| Phencyclidine | 5.47 | 9.54 | 14.61 |
| Remoxipride | 7.94 | 7.94 | 4.75 |
| Theophylline | 5.15 | 10.39 | 4.05 |
| **Statistical indexes** | | | |
| AFRE | 1.22 | 1.11 | |
| %ARE | 1.13 | 40.1 | |

[a] Calculated from Eq. 2 using the reported $V_{ap}$ and $CL$ values.
[b] Calculated from Eq. 5 using the predicted $v_f$ and $CL_f$ values.
[c] Calculated from Eq. 2 using the predicted $V_{ap}$ and $CL_e$ values.

equations of $t_{1/2}$ from 0.25 are most likely associated with the experimental errors encountered in the estimation of clearance and volume of distribution estimates across species.

Although the prediction of half-life from animals to humans is relatively difficult, many indirect methods have been suggested (10). In this study, the predicted values for $v_f$ and $CL_f$ were used to calculate the corresponding value of $t_{1/2}$ using Eq. (5). The results are presented in Table IV along with the predicted values for $t_{1/2}$ derived from Eq. (2) using $CL_e$ and $V_{ap}$. The results of Table IV are controversial judging from the AFRE and %ARE values of the two approaches. However, the absolute values for the indexes AFRE and %ARE estimates were found 1.78 and 73.0% for $t_{1/2}$ calculated from Eq. (2) and 1.80 and 50.5% when $t_{1/2}$ was calculated from Eq. (5). This comparison indicates that predictions based on $t_{1/2}$ calculated from Eq. (5) seem to be more reliable.

## CONCLUSIONS

The allometric relationships for $v_f$, $CL_f$ rely exclusively on the physiologically sound, fractal consideration of drug distribution (3). The use of $v_f$ values from animal species allows a reliable prediction of $v_f$ in humans. Predictions for $V_{ap}$ values based on $v_f$ estimates are better than the current approaches. The mean values of the allometric exponents for $CL_f$ and $t_{1/2}$ were found close to the theoretically expected values 0.75 and 0.25, respectively. Moreover, the values of these exponents for the data analyzed were homogeneously distributed around their means. Because the results for $CL_f$ and $t_{1/2}$ are strongly linked to the estimates for $v_f$, it seems likely that the physiologically relevant $v_f$ lends similar properties to $CL_f$ and $t_{1/2}$. Thus, the predictive performance of $CL_f$ was found better than other approaches which rely on various empirical assumptions, e.g., *BW*, *MLP*, rule of exponents. The predictive performance of the various clearance expressions for the conventional *CL* follows the ranking $(CL_f)_e > CL_e > CL_f$. The results for the prediction of $t_{1/2}$ seem to be more reliable when predictions are based on $CL_f$ and $v_f$. Finally, a pharmacokinetic classification scheme was developed in the present study to be used as the basis for considering drug disposition phenomena.

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