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A Correlative Model to Predict In Vivo AUC for Nanosystem Drug Delivery with Release Rate-Limited Absorption

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ABSTRACT - Purpose. Drug release from nanosystems at the sites of either absorption or effect biophase is a major determinant of its biological action. Thus, in vitro drug release is of paramount importance in gaining insight for the systems performance in vivo. Methods. A novel in vitro-in vivo correlation, IVIVC, model denoted as double reciprocal area method was presented and applied to 19 drugs from 55 nano formulations with total 336 data, gathered from literature. Results. The proposed model correlated the in vitro with in vivo parameters with overall error of 12.4 ± 3.9%. Also the trained version of the model predicted the test formulations with overall error of 15.8 ± 3.7% indicating the suitability of the approach. A theoretical justification was provided for the model considering the unified classical release laws. Conclusion. The model does not necessitate bolus intravenous drug data and seems to be suitable for IVIVC of drugs with release rate-limited absorption.

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INTRODUCTION

Immense attention has been paid to nanotechnology in various branches of science including medical and pharmaceutical sciences. Numerous research papers in the field of pharmaceutical nanotechnology have been appeared in literature citation. Our focus, however, is on some recently published review articles that deal with drug delivery systems administered via different routes (1-4). The drug release from pharmaceutical nanosystems is a major determinant in its biological effect. For this reason the release rate of drug from nano delivery system is often measured in vitro to gain insight to its performance in vivo. In the case of various drug delivery systems including immediate and sustained release ones, the correlation between in vitro and in vivo parameters is of paramount importance. The United States Pharmacopeia discusses the importance as well as different levels of the correlation (5). Also the details and advantages of such correlations were reviewed in a recent article (6). One of the important advantages of establishing in vitro-in vivo correlation, IVIVC, is the calculation of in vivo parameter from the correlation equation after carrying out only in vitro test without performing in vivo experiment on the drug product under consideration (5, 6). Despite extensive investigations on drug nanosystems from in vitro and in vivo points of view, to the best of our knowledge no comprehensive IVIVC study was reported in literature. In the present work the available in vitro release as well as in vivo data of drug nanosystems gathered from various sources was subjected to a

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previously empirical novel IVIVC approach named double reciprocal area, DRA, method (7, 8). The area under drug plasma concentration or biological response vs. time curve, AUC; and the area under drug release curve vs. time were employed as in vivo and in vitro parameters for correlation purpose. The method predicted in vivo parameter from corresponding in vitro data with good accuracy and precision. Unlike the previously established IVIVC methods, the proposed model is less invasive because it does not involve bolus intravenous data of drug. A theoretical justification was also provided for the empirical method.

METHODS

Data

The in vitro and in vivo data of 17 drugs from 55 nanosystems with total number of 336 data points were collected from literature. The name of drugs and the relevant references are given in Table 1 (9-27). As seen in the table the data includes several kind of nanosystems intended for administration via different routes. The coordinates of each point in the in vitro and in vivo profiles of drug nanosystems in the original papers were measured carefully and the data was employed in the subsequent IVIVC analysis.

Table 1. Details of drugs, nanosystems, statistical parameters and constants of double reciprocal area IVIVC model.

<table>
<thead>
<tr>
<th>No.</th>
<th>Drug</th>
<th>NF</th>
<th>N</th>
<th>TNS</th>
<th>R</th>
<th>EC</th>
<th>RA</th>
<th>m</th>
<th>b</th>
<th>j</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5-Fluorouracil*</td>
<td>3</td>
<td>21</td>
<td>NS</td>
<td>0.725</td>
<td>19.2</td>
<td>p.o</td>
<td>28.419</td>
<td>0.980</td>
<td>0.901</td>
<td>(9)</td>
</tr>
<tr>
<td>2</td>
<td>Carbazole</td>
<td>2</td>
<td>10</td>
<td>CL-NP</td>
<td>0.983</td>
<td>7.5</td>
<td>p.o</td>
<td>4.048</td>
<td>0.954</td>
<td>0.021</td>
<td>(10)</td>
</tr>
<tr>
<td>3</td>
<td>Celecoxib</td>
<td>3</td>
<td>24</td>
<td>SLH</td>
<td>0.980</td>
<td>7.2</td>
<td>p.o</td>
<td>3.038</td>
<td>1.271</td>
<td>1.151</td>
<td>(11)</td>
</tr>
<tr>
<td>4</td>
<td>Danazol</td>
<td>3</td>
<td>18</td>
<td>NS</td>
<td>0.889</td>
<td>16.6</td>
<td>p.o</td>
<td>0.114</td>
<td>0.637</td>
<td>0.002</td>
<td>(12)</td>
</tr>
<tr>
<td>5</td>
<td>Docetaxel</td>
<td>4</td>
<td>24</td>
<td>NM</td>
<td>0.956</td>
<td>13.8</td>
<td>p.o</td>
<td>0.005</td>
<td>0.796</td>
<td>0.000</td>
<td>(13)</td>
</tr>
<tr>
<td>6</td>
<td>Estradiol**</td>
<td>2</td>
<td>12</td>
<td>NM</td>
<td>0.970</td>
<td>13.2</td>
<td>p.o</td>
<td>0.755</td>
<td>0.602</td>
<td>0.000</td>
<td>(14)</td>
</tr>
<tr>
<td>7</td>
<td>Estradiol**</td>
<td>3</td>
<td>18</td>
<td>NM</td>
<td>0.929</td>
<td>12.4</td>
<td>p.o</td>
<td>0.455</td>
<td>0.900</td>
<td>0.02</td>
<td>(15)</td>
</tr>
<tr>
<td>8</td>
<td>Estradiol**</td>
<td>4</td>
<td>24</td>
<td>NM</td>
<td>0.804</td>
<td>8.1</td>
<td>p.o</td>
<td>0.505</td>
<td>1.185</td>
<td>0.058</td>
<td>(16)</td>
</tr>
<tr>
<td>9</td>
<td>Flurbiprofen</td>
<td>2</td>
<td>12</td>
<td>LN</td>
<td>0.999</td>
<td>16.7</td>
<td>p.o</td>
<td>0.687</td>
<td>1.196</td>
<td>0.015</td>
<td>(17)</td>
</tr>
<tr>
<td>10</td>
<td>Heparin***</td>
<td>3</td>
<td>18</td>
<td>NS</td>
<td>0.936</td>
<td>9.7</td>
<td>p.o</td>
<td>0.567</td>
<td>1.182</td>
<td>0.050</td>
<td>(18)</td>
</tr>
<tr>
<td>11</td>
<td>Insulin</td>
<td>4</td>
<td>24</td>
<td>NMA</td>
<td>0.905</td>
<td>11.8</td>
<td>n.s</td>
<td>0.444</td>
<td>1.185</td>
<td>0.016</td>
<td>(19)</td>
</tr>
<tr>
<td>12</td>
<td>Methotrexate</td>
<td>4</td>
<td>24</td>
<td>SLN</td>
<td>0.958</td>
<td>10.5</td>
<td>p.o</td>
<td>3.057</td>
<td>1.312</td>
<td>0.333</td>
<td>(20)</td>
</tr>
<tr>
<td>13</td>
<td>Mifepristone</td>
<td>2</td>
<td>16</td>
<td>NS</td>
<td>0.756</td>
<td>15.9</td>
<td>p.o</td>
<td>0.043</td>
<td>1.18</td>
<td>0.004</td>
<td>(21)</td>
</tr>
<tr>
<td>14</td>
<td>Nifedipine</td>
<td>3</td>
<td>18</td>
<td>NM</td>
<td>0.967</td>
<td>8.6</td>
<td>p.o</td>
<td>0.028</td>
<td>0.806</td>
<td>0.001</td>
<td>(22)</td>
</tr>
<tr>
<td>15</td>
<td>Nitrendipine</td>
<td>3</td>
<td>18</td>
<td>SLN</td>
<td>0.826</td>
<td>8.2</td>
<td>i.d</td>
<td>0.008</td>
<td>1.019</td>
<td>0.006</td>
<td>(23)</td>
</tr>
<tr>
<td>16</td>
<td>Rhodamine (Model dye)</td>
<td>2</td>
<td>10</td>
<td>NM</td>
<td>0.758</td>
<td>18.2</td>
<td>p.o</td>
<td>0.458</td>
<td>0.907</td>
<td>0.442</td>
<td>(24)</td>
</tr>
<tr>
<td>17</td>
<td>Tobramycin</td>
<td>3</td>
<td>18</td>
<td>SLN</td>
<td>0.831</td>
<td>16.53</td>
<td>i.d</td>
<td>0.052</td>
<td>0.721</td>
<td>0.032</td>
<td>(25)</td>
</tr>
<tr>
<td>18</td>
<td>Ucb (Anti asthma)</td>
<td>2</td>
<td>12</td>
<td>NC</td>
<td>0.957</td>
<td>13.1</td>
<td>p.o</td>
<td>0.137</td>
<td>0.701</td>
<td>0.001</td>
<td>(26)</td>
</tr>
<tr>
<td>19</td>
<td>Vinpocetine</td>
<td>3</td>
<td>15</td>
<td>SLN</td>
<td>0.923</td>
<td>8.5</td>
<td>p.o</td>
<td>3.208</td>
<td>0.783</td>
<td>0.311</td>
<td>(27)</td>
</tr>
</tbody>
</table>

NF, number of formulations for a given drug; N, number of data for each drug; TNS, type of nanosystems; R, correlation coefficient; EC, error of correlation in percentage; RA, route of administration; m, b and j, model constants; NS, nanosphere; CL-NP, cross-linked nanoparticle; SLH, silica-lipid hybrid particle; NM, nanomatrix; LN, lipid nanoparticle; NMA, nano mucoadhesives; SLN, solid lipid nanoparticle; NC, nano crystal; p.o, per oral; n.s, nasal; i.d, intraduodenal. *One of the formulations of 5-Fluorouracil was the pure drug itself the inclusion of which improved the accuracy of the model. ** The difference in the molecular weight of polymer and solvents involved in the formulations as well as the particle size of the nanosystems affected the model parameters of the same drug estradiol. ***In the case of heparin the biological response was used. The overall mean error, OEC, for 19 drugs calculated by equation 3 is 12.4 ± 3.9%.
Double reciprocal area IVIVC method
The double reciprocal area, DRA, model applied successfully for IVIVC (7, 8) has been advocated to establish a quantitative correlation between in vitro and in vivo parameters of all drug nanosystems given in Table 1. In addition to the total AUC, the partial AUC is also used in bioavailability studies (5, 8). The following nonlinear relationship represents the model:

\[
\frac{1}{(AUC_{i})_{0}^{tn}} = m \left( \frac{1}{[(AUC_{r})_{0}^{tn}]^{b}} \right) + j
\]  

(1)

Where \((AUC_{i})_{0}^{tn}\) is the area under the drug plasma concentration or biological responses vs normalized time \(t_n\) curve between 0 and \(t_n\); \((AUC_{r})_{0}^{tn}\) is area under percent drug released vs \(t_n\) curve between 0 and \(t_n\). These areas are observed ones. The symbols m, b and j are model constants. Several factors are involved in drug release from the complex nanosystems. These include nature of drug, method of preparation and excipients of formulation, technique of release study and mechanisms of processes affecting the overall release. Some of the processes in the release from nanosystems are wettability, dispersability and penetration of water molecules into the nanosystem; hydration and swelling of the polymer in the system as well as drug dissolution and diffusion. These factors which complicate the overall drug release process reflect in the mentioned parameters. Thus, the exact nature of the parameters cannot be clarified. The reason for the use of AUC_i in the correlation is based on well-known pharmacokinetic principles according which in vivo AUC of drug is directly related to its extent of bioavailability and the latter is related to clinical response.

The normalized time is the ratio of any in vivo and in vitro sampling time with respect to the corresponding arbitrary last sampling time. The normalization of time is necessary to bring in vivo and in vitro times to the same scale. The percent released corresponding to each in vivo value of \(t_n\) was obtained by interpolation of the normalized release curve. The values of \((AUC_{i})_{0}^{tn}\) and \((AUC_{r})_{0}^{tn}\) were calculated via trapezoidal rule. The left side of equation 1 was regressed nonlinearly against \(\frac{1}{[(AUC_{r})_{0}^{tn}]^{b}}\) to obtain numerical values of m, b and j of the model. The correlation error, EC, for nanosystems of individual drug was calculated by:

\[
EC = \frac{100}{N} \times \sum_{i} \left( \frac{|(AUC_{i})_{0}^{tn}|_{cat} - [(AUC_{i})_{0}^{tn}]_{obs}}{[(AUC_{i})_{0}^{tn}]_{obs}} \right)  
\]  

(2)

\(N\) \([(AUC_{i})_{0}^{tn}]_{cat}\) and \([(AUC_{i})_{0}^{tn}]_{obs}\) are number of data which belongs to any drug, calculated \((AUC_{i})_{0}^{tn}\) by the model and observed \((AUC_{i})_{0}^{tn}\), respectively. The calculated AUC_i is obtained after insertion of observed AUC, numerical values of m, b and j into the correlation equation 1. The overall mean error of correlation, OEC, for 19 drugs in table 1 was also calculated using equation 3:

\[
OEC = \frac{\sum_{i}^{19} EC}{19}  
\]  

(3)

Development of the IVIVC model
The rate of drug release from nanosystems and solid dispersions in terms of amounts released, w, and unreleased \(M\), was described by an equation obtained from unification of the Noyes-Whitney law of dissolution and Flick’s first law in diffusion with introduction of a time dependent variable X (28,29):

\[
\frac{dw}{dt} = \frac{dM}{dt} = \frac{D}{h} SC X
\]  

(4)

In which \(w\) is amount of drug released up to time \(t\). \(dw/dt\) is the rate of release in term of \(w\). The symbols \(D\), \(S\), \(C\), and \(h\) are drug
molecule diffusion coefficient, effective surface area of drug, drug solubility in the medium and the length of diffusion path, respectively (28, 29). In context of drug nanosystems the release medium can be *in vitro* simulation of either the absorption site or the action biophase e.g. inside of cells after endocytosis. The value of $X$ represents all time-dependent variables affecting drug release in the simulated medium. For a complex system such as nanoparticles, the classical equations of the drug release mentioned above do not include factors influencing the drug release rate among which penetration rate of liquid into the system; hydration, swelling, relaxation, erosion and dissolution of polymer can be mentioned. The extents of liquid penetration and the polymer contributed properties are directly proportional to $t^{1/2}$ and powered of $t$, respectively all of which are embedded in variable $X$ (28, 29). Therefore, assuming all parameters with the exception of $C_s$ in the right-hand site of equation 4 are time-dependent, its integration between times 0 and $t$ gives:

$$ w = C_s \int_0^t \left( \frac{DSX}{h} \right) dt \quad (5) $$

$$ M = M_0 - C_s \int_0^t \left( \frac{DSX}{h} \right) dt \quad (6) $$

$M_0$ is the amount of drug in nanosystem at time 0. Since the value of $w$ increases with time the integral term in equations 5 and 6 should increase with time as well. Also, $M$ deceases with time. The closest measurable substitute supported by experimental evidence for the integral term in equations 5 and 6 is $\int_0^t w \cdot dt$, area under the release curve between times 0 and $t$. $AUC_t$ (7, 8). The latter parameter represents better the cumulative changes of time-dependent variables embedded in the equations at absorption and the biophase sites. Thus, $w$ can be expressed in term of the latter area as power equation 7:

$$ w = C_s \beta [(AUC_t)_0]^\alpha \quad (7) $$

The symbols $\alpha$ and $\beta$ are constants. The negative sign preceding the integral term of the equation 6 indicates an inverse relationship between $M$ and the integral term. The difference between constant $M_0$ and the integral term can be approximated by an inverse powered integral term in the form of:

$$ M = \beta [(AUC_t)_0]^{-\alpha'} \quad (8) $$

The values of $\alpha'$ and $\beta'$ are constants. The positive $\alpha$ and negative $\alpha'$ indicate that $w$ increases and $M$ decreases with time. Thus, equation 8 reflects explicitly the inverse relation between $w$ and $M$. Similar power relationships for $w$ and $M$ were given in previous papers (28, 29). Fraction of drug released, $F$, up to any time is given by:

$$ F = \frac{w}{w+M} = \frac{C_s \beta [(AUC_t)_0]^\alpha}{C_s \beta [(AUC_t)_0]^{\alpha + \beta} [(AUC_t)_0]^{-\alpha}} = \frac{C_s \beta [(AUC_t)_0]^\alpha + \beta'}{C_s \beta [(AUC_t)_0]^{\alpha + \alpha'} + \beta'} = \frac{[(AUC_t)_0]^b}{[(AUC_t)_0]^{\beta' + \mu}} \quad (9) $$

Where $b = \alpha' + \alpha$, and $\mu = \beta' / \beta C_s$. For establishing a meaningful correlation between *in vitro* and *in vivo* parameters it is logical to use area under the curve of biological response and/or plasma drug level, $AUC_t$, as an *in vivo* parameter (7, 8). It is worth to
mention that the partial area under the *in vivo* curve, \((AUC_i)^t_0\), has been recommended by USP as a measure of extent of drug bioavailability. It is obvious in drug release rate- limited biological response and/ or bioavailability there must be a quantitative correlation between \((AUC_i)^t_0\) and \(F\). It would be reasonable to assume a direct relation between the latter parameters via introducing a proportionality constant \(k\):

\[
(AUC_i)^t_0 = kF = \frac{k[(AUC_i)^b_0]}{[(AUC_i)^b_0] + \mu} \tag{10}
\]

Reciprocating equation 10 and subsequent substitution of corresponding normalized areas and rearrangement yields the double reciprocal area method of IVIVC, equation 1, in which \(m=\mu/k\) and \(j=1/k\).

**Training DRA model for prediction**

The aim of obtaining trained model was to determine model parameters for each drug and use the parameters for estimating AUC\(_i\) of an excluded formulation of the same drug from training procedure. To this end, 13 out of 19 drugs (Table 2) with 3 and 4 formulations altogether 264 data were used to assess prediction ability of the model. The drugs with two formulations were omitted from the prediction analysis because of statistical limitation. In the case of drug with 3 formulations, 3 possible combinations consisted of *in vitro* and *in vivo* data of formulations 1, 2; 1, 3 and 2, 3 were employed for training of the model to obtain the numerical values of the model constants. It is obvious that in the training process formulations 3, 2 and 1 were excluded from the combinations, respectively. Then, after inserting the *in vitro* parameter of the excluded formulation into the trained model, it’s *in vivo* parameter was predicted. The same procedure was followed for drugs with 4 formulations. That is 4 possible combinations each consisted of 3 formulations for prediction of the *in vivo* parameters of the excluded ones. The prediction error, \(PE\), for excluded formulation of each drug is given by:

\[
PE = \frac{100}{q} \sum_1^q \left( \frac{[(AUC_i)^t_{0\,\text{pred}}] - [(AUC_i)^t_{0\,\text{obs}}]}{[(AUC_i)^t_{0\,\text{obs}}]} \right) \tag{11}
\]

In which \(q\) is the number of *in vivo* data for excluded formulation of individual drug and \([(AUC_i)^t_{0\,\text{pred}}]\) is its predicted area under the curve by means of the trained model. The accuracy of the trained models for each drug was evaluated by calculating mean prediction error, \(MPE\):

\[
MPE = \frac{1}{N} \sum_1^N PE \tag{12}
\]

\(N\) is 3 and 4 for drugs with 3 and 4 formulations respectively. Also the overall prediction error, \(OMPE\), was assessed taking the average of \(MPEs\) for 13 drugs in Table 2.

**RESULTS**

Table 1 shows the results of *in vitro- in vivo* correlation by DRA model. All the correlation errors were below 20\%, 68.4\% of ECs were below 15\% and 36.8\% were less than 10\%. The overall error of correlation, OEC, was 12.4 ± 3.9\%. The minimum and maximum ECs were 7.2\% and 19.2\%, respectively. The values of \(R\) indicated that the correlations were highly significant (p levels between 0.001 and 0.0005). The model parameters \(m\), \(b\) and \(j\) were also highly significant at the mentioned levels. The model parameters \(m\), \(b\) and \(j\) were also highly significant. The level of significance for the parameters was generally at p values less than 0.001. The correlation between \([(AUC_i)^t_{0\,\text{obs}}]\) and \([(AUC_i)^t_{0\,\text{cat}}]\) for 336 data is depicted in Fig. 1.
When the trained models were applied to the
excluded formulations the minimum mean
prediction error, MPE, was 10% and the
maximum was 22.7%. Overall mean
prediction error, OMPE, was 15.8 ± 3.7%.

The errors of 11 out of 13 drugs were below
20% (Table 2). In Fig. 2 the plot of
\[ [(AUC_{\text{t}}\text{n})_{\text{obs}}] \text{ vs } [(AUC_{\text{t}}\text{n})_{\text{pred}}] \] is seen for
264 data.

Table 2. Drugs with 3 and 4 nanosystem formulations for training, assessing
prediction ability of DRA model and its mean prediction error, MPE together with
overall mean prediction error, OMPE.

<table>
<thead>
<tr>
<th>No.</th>
<th>Drug</th>
<th>MPE</th>
<th>No.</th>
<th>Drug</th>
<th>MPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5-Fluorouracil</td>
<td>22.7</td>
<td>8</td>
<td>Insulin</td>
<td>17.6</td>
</tr>
<tr>
<td>2</td>
<td>Celecoxib</td>
<td>12.4</td>
<td>9</td>
<td>Methotrexate</td>
<td>10.0</td>
</tr>
<tr>
<td>3</td>
<td>Danazol</td>
<td>15.2</td>
<td>10</td>
<td>Nifedipine</td>
<td>14.7</td>
</tr>
<tr>
<td>4</td>
<td>Docetaxel</td>
<td>16.1</td>
<td>11</td>
<td>Nitrendipine</td>
<td>13.9</td>
</tr>
<tr>
<td>5</td>
<td>Estradiol</td>
<td>14.1</td>
<td>12</td>
<td>Tobramycin</td>
<td>22.5</td>
</tr>
<tr>
<td>6</td>
<td>Estradiol</td>
<td>12.7</td>
<td>13</td>
<td>Vinpocetine</td>
<td>16.1</td>
</tr>
<tr>
<td>7</td>
<td>Heparin*</td>
<td>17.4</td>
<td></td>
<td>OMPE</td>
<td>15.8 ± 3.7</td>
</tr>
</tbody>
</table>

*In the case of heparin the biological response was used.

Figure 1. Observed area under the drug plasma concentration or biological response curve, \( [(AUC_{\text{t}}\text{n})_{\text{obs}}] \), against
the calculated area, \( [(AUC_{\text{t}}\text{n})_{\text{calc}}] \), based on the proposed novel IVIVC model. The upper and lower 95% prediction
interval is represented by the broken lines. For the sake of clarity in construction of the regression line, all drug plasma
concentrations were expressed in µg/ml.

\[ [(AUC_{\text{t}}\text{n})_{\text{obs}}] = 0.00 + 1.05 [(AUC_{\text{t}}\text{n})_{\text{calc}}] \]

N=336, R=0.982, p<0.001
DISCUSSION

It is evident from the tables and figures that the proposed model can correlate not only very well the *in vitro* with *in vivo* data but also the prediction capability and reproducibility of its trained versions is quite acceptable. In the correlation procedure 96.7% of 336 data are in 95% prediction interval (Fig. 1). Also 95.8% of the 264 predicted values from the trained models are in the same prediction interval (Fig. 2). These findings indicate the suitability of the proposed model.

This approach of IVIVC can be considered as a novel point by point method (similar to level A correlation in USP). Similar to level A correlation in USP the novel proposed model is a point by point deconvolution method. Unlike most other deconvolution approaches, the model requires no intravenous data. In the USP level A approach, the relationship between the fraction of drug absorbed up to any time and percent drug released *in vitro* up to the same time is linear (8). However, since the present novel DRA model employs the partial area in place of the fraction absorbed, it correlates with the fraction absorbed in a nonlinear fashion (equation 1). The partial area is dependent not only on the drug release rate but also is affected by drug clearance from the body. Therefore, for drugs exhibiting release rate limited absorption from nanosystems, the area should depend highly on the release rate at the absorption site (8).

Due to profound effect of release and/or fraction absorbed it is expected that $AUC_i$ relates to release, but because of the interference of the opposing effect of clearance the IVIVC profile is nonlinear. The OEC and OMPE of the novel DRA model and its trained versions are $12.4 \pm 3.9\%$ and $15.8 \pm 3.7\%$, respectively which are quite acceptable considering the inherent error associated with integration process employing the trapezoidal rule.

Figure 2. Observed area under the drug plasma concentration or biological response curve, $\left[(AUC_i)^{tn}_{0}\right]_{obs}$, against the predicted area, $\left[(AUC_i)^{tn}_{0}\right]_{pred}$ based on the trained proposed novel IVIVC model. The upper and lower 95% prediction interval is represented by the broken lines. For the sake of clarity, in the construction of the regression line, all drug plasma concentrations were expressed in $\mu g/ml$.  

\[
\frac{[\left[(AUC_i)^{tn}_{0}\right]_{obs} = 0.00 + 1.11(\left[(AUC_i)^{tn}_{0}\right]_{pred}}
\]

$N=264, \ R = 0.978, \ p < 0.001$
CONCLUSION

A kind of novel point by point nonlinear IVIVC model was presented and applied to 17 drugs in 55 nanosystems successfully with overall error of correlation 12.4%. A theoretical justification for the model was also provided. When the trained versions of the model were used for prediction of in vivo parameter of untested formulations, the overall error was satisfactory (15.8%). Thus the model could be employed as a suitable IVIVC approach for drug nanosystems. The model may be suitable for IVIVC of drugs with release rate-limited absorption. It may have also advantage over the conventional methods in that it does not require drug data from bolus intravenous drug injection.

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REFERENCES