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ORIGINAL PAPER

Limited sampling strategy models for estimating the AUC of gliclazide in Chinese healthy volunteers

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Abstract The aim of this work is to reduce the cost of required sampling for the estimation of the area under the gliclazide plasma concentration versus time curve within 60 h (AUC_{0-60t}). The limited sampling strategy (LSS) models were established and validated by the multiple regression model within 4 or fewer gliclazide concentration values. Absolute prediction error (APE), root of mean square error (RMSE) and visual prediction check were used as criterion. The results of Jack-Knife validation showed that 10 (25.0 %) of the 40 LSS based on the regression analysis were not within an APE of 15 % using one concentration–time point. 90.2, 91.5 and 92.4 % of the 40 LSS models were capable of prediction using 2, 3 and 4 points, respectively. Limited sampling strategies were developed and validated for estimating AUC_{0-60t} of gliclazide. This study indicates that the implementation of an 80 mg dosage regimen enabled accurate predictions of AUC_{0-60t} by the LSS model. This study shows that 12, 6, 4, 2 h after administration are the key sampling times. The combination of (12, 2 h), (12, 8, 2 h) or (12, 8, 4, 2 h) can be chosen as sampling hours for predicting AUC_{0-60t} in practical application according to requirement.

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1 Introduction

Gliclazide is a second generation sulphonylurea oral hypoglycaemic agent widely used by patients with type 2 diabetes. The particular interest in this drug is because it has shown certain effects on the blood for which phenomena it is hoped there may be some clinical benefit for diabetic angiopathies. Some studies have demonstrated that it has the effect of reducing platelet adhesiveness and aggregation, whilst possibly enhancing platelet metabolism with a reduction in coagulant factors (Holmes et al. 1984; Davis et al. 2000). In this study, data from a bioequivalence evaluation of formulations of gliclazide were used to develop limited sampling strategy models (LSS) for estimating the area under the concentration–time curve (AUC) of gliclazide. Limited sampling strategies (LSS), a type of statistical method, put forward by Johnston et al. (1990) for therapeutic drug monitoring has been proven sufficiently robust for the accurate estimation of individual pharmacokinetics. This quantitative methodology is very valuable, especially when sampling at "unsociable" hours is better avoided (Monchaud et al. 2003; Zicheng et al. 2006; Bolon-Larger et al. 2007; Dickinson et al. 2007; Jiao et al. 2007). Pharmacokinetic parameters, such as AUC, etc., can be evaluated according to mathematical modeling based on the limited sampling points achieved. Some literature reveals that adjusting the drug administration regimen for patients through AUC monitoring is adopted widely (Frey et al. 2003). However, the calculation of AUC is based on the abundant sampling points, which are intolerable for the patients (Kim et al. 2003). The application of LSS could

ensure the quality of AUC monitoring and reduce the sampling points as only 2–4 points are needed, thus considerably relieving the suffering of the patients whilst also reducing the cost of the sampling and analysis work of the medical staff. This study determines whether these LSS might be useful for AUC prediction of gliclazide with the use of healthy Chinese volunteers.

2 Materials and methods

2.1 Study subjects and methods

All the data used are from randomized, dual crossing bioequivalent trials of gliclazide tablets in healthy Chinese volunteers. Twenty subjects in each group received the reference product and 20 received the test product. All the subjects are healthy males, aged (years) 20.1 ± 1.3 (18–23) [mean ± SD (range), height (cm) 172.0 ± 4.7 (160–182), weight (kg) 62.0 ± 6.7 (52–85)]. All the subjects signed the informed consent form, and the study protocol was approved by the Ethics Committee.

Eligible participants were randomly assigned in a 1:1 ratio to receive one tablet of either the test or the reference formulation, followed by a 2-week washout period and then administration of the alternate formulation. Twenty volunteers received the two formulations in one sequence, and the other 20 received the two formulations in the reverse order. The gliclazide tablets were administered with 200 mL water at 8:00 am after a 10-h overnight fast, one tablet of the test product or reference product administered as a single oral dose under fasting conditions. Blood samples of 3 mL were withdrawn prior to administration as well as 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48 and 60 h after administration of the drug. The whole blood samples were collected in heparinized tubes. The serum was separated within 30 min and stored at −20 °C. Gliclazide concentrations in the serum were analyzed by liquid chromatography tandem mass spectrometry (Cho et al. 2009; Mendes et al. 2007; Najib et al. 2002).

2.2 Extraction and separation of biological samples

20 μL (6 μg/mL) diazepam was added into 0.2 mL serum as an internal standard, then 1 mL dichloromethane was added and mixed for extraction. The mixture was centrifuged at 14,000 rpm for 15 min. Pipet 0.8 mL solution from the lower layer, then concentrated by nitrogen and dissolved in 80 μL mobile phase. Figure 1 shows a typical chromatogram of mixture of diazepam and gliclazide.

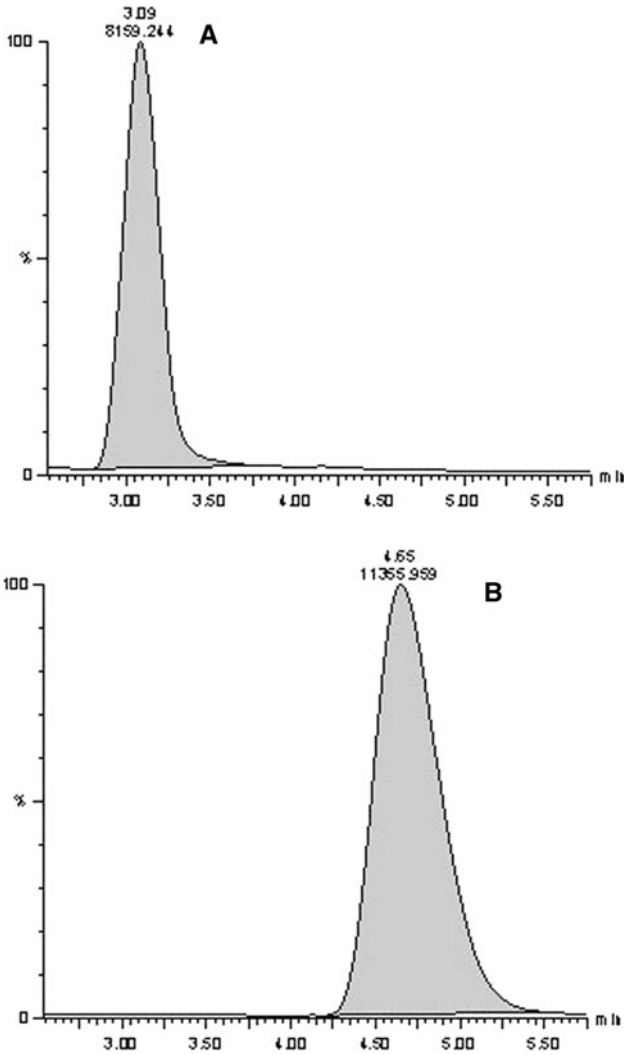

Fig. 1 Typical chromatograms of diazepam and gliclazide, peak identification: **a** diazepam, **b** gliclazide

2.3 Chromatographic conditions

The experiments were conducted with Waters HPLC-MS system. The source was a nebulizer assisted electrospray unit. The analytical column was Agilent Zorbax SB-C18 (3.5 μm, 3.0 mm ×100 mm). The mobile phase consisted of acetonitrile and ammonium acetate buffer (pH = 3.5, 70:30), with a flow rate of 0.25 mL/min. The mass spectrometer parameters were spray voltage, 3.0 kV; cone voltage, 29 V; gas temperature 350 °C; auxiliary gas 450 L/h. The standard curve showed good linearity for gliclazide concentrations which range from 20 to 5,000 ng/mL, and the coefficient of correlation was 0.999. The detection limit was 0.01 mg/L.

2.4 Pharmacokinetic analysis

The AUC_{0-60t} from 0 to 60 h was calculated by trapezoidal summation. The $AUC_{0-\infty}$ from time zero to infinity were the AUC_{0-60t} by adding the value of the plasma drug concentrations at 60 h divided by ke. The peak concentrations of gliclazide in plasma (C_{max}) and the time to reach C_{max} (t_{max}) were determined from the individual plasma drug concentration data. The data were analyzed statistically by both parametric (one-way analysis of variance for natural log-transformed data) and nonparametric methods. The bioequivalence range for the individual percentage ratios of natural log-transformed variables was defined as 80–125 % for AUC_{0-60t} and $AUC_{0-\infty}$ and 70–143 % for C_{max}, respectively.

2.5 Limited sampling strategies (LSS)

Twelve blood sampling times at 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48 and 60 h were taken for estimating AUC_{0-60t}. The formula is

$AUC_{0-60t} = A_0 + A_1 \times C_1 + A_2 \times C_2 + \cdots + A_n \times C_n$, C_n and A_n refer to the nth blood sampling points and coefficients for modeling respectively. The observed value was calculated by the trapezoidal method based on the 12 sampling points as the approximation of AUC_{0-60t}. We select the 1, 2, 3, 4 points respectively as a limited sampling from those 12 points and substitute them into the formula above to estimate the AUC_{0-60t}. All of the possible assembled numbers are $C_{12}^1 + C_{12}^2 + C_{12}^3 + C_{12}^4$, 793 regression equations in total. All of the regression coefficients were computed and ordered according to the determination coefficient r^2 and the number of parameters, where r^2 is an important parameter for assessing the model quality, and the first-order Jack-Knife was adopted to test and confirm the model (Quenouille 1949, 1956). One case is removed from the total 40 cases each time. The remaining 39 cases serve as a Jack-Knife sample that is used to calculate the fitting parameter of the regression equations, then the regression equations are used to estimate the case initially removed. All of the cases are ergodic and obtained 40 results. APE (absolute predict error) and RMSE (root mean square error) were used to evaluate the model:

$$\text{APE}\ (\%) = (|\text{Pred} - \text{Obs}|)/\text{Obs} \times 100\ \% \quad (1)$$

$$\text{RMSE} = \sqrt{(1/N) \times \sum (\text{APE})^2} \times 100\ \% \quad (2)$$

where Pred is the predicted value of the LSS model, and Obs is the trapezoidal summation value.

In addition, a *B–A* figure of the predicted value and Obs value was plotted, with the Obs value ±10 and 15 % as the reference line. The discreet interval of the parameters was estimated by adopting the non-parametric Bootstrap method (Efron 1979). According to the 1, 2, 3 and 4 sampling points, the best model was selected and the median and 95 % CI were bootstrap calculated 2,000 times. The calculations above were achieved through the EXCEL–VBA program.

3 Results

3.1 Pharmacokinetic data and bioequivalence

All the volunteers completed the study protocol and none experienced clinically relevant adverse effects. Figure 2 shows the mean serum concentration–time curves for each gliclazide formulation. The values of C_{max}, AUC_{0-60t}, and $AUC_{0-\infty}$ show no significant differences between the two formulations. Table 1 shows that the 90 % confidence intervals (CIs) for individual percentage ratios of C_{max}, AUC_{0-60t}, and $AUC_{0-\infty}$ for both test and reference are within the bioequivalence range of 70–143 and 80–125 %. This result shows that these two formulations are bioequivalent.

3.2 Multiple regression equation of limited sampling

The concentration in plasma data sets from the 20 volunteers enrolled in this study were used to identify the most informative sampling times using 1–4 samples for estimating the AUC_{0-60t}. Three best linear equations were selected according to the coefficient of determination, 12 in total (see Table 2). The highest determination coefficient of 1 sampling point was 0.863. The best sampling time point was at 12 h. The highest determination coefficient of 2 sampling points was 0.902. The best sampling time points were at (12, 2 h), while the highest determination coefficient of 3 sampling points was 0.915. The best sampling time points were at (12, 8, 2 h), 0.924 for 4 sampling points, and the best sampling time points were at (12, 8, 4, 2 h). Figure 3 shows a scatter plot of the observed area under the concentration time curve (AUC_{0-60t}) versus AUC_{0-60t} derived from the LSS model developed for the 4 best assemblies. Figures 3b–d indicate excellent correlation. Figure 4 also indicate mountain plot analysis testing

Table 1 Pharmacokinetic parameters of gliclazide in healthy Chinese volunteers (mean ± SD, $n = 20$)

	Test	Reference	90 % CI
AUC_{0-t} (μg /mL h)	75.49 ± 22.41	75.72 ± 31.03	94.4–112.0
$AUC_{0-\infty}$ (μg/mL h)	85.59 ± 30.21	84.94 ± 38.61	95.5–113.2
C_{max} (μg/mL)	4.28 ± 1.08	3.80 ± 0.840	98.9–128.8

Table 2 Coefficient of determination of some of the best linear equations for estimation of AUC_{0-60t} in 1–4 sample times strategy

Sampling time (h)	r^2	Linear equation
12	0.863	$3.060 + 36.972 \times C_{12}$
8	0.695	$-6.181 + 31.685 \times C_8$
6	0.647	$-7.730 + 27.067 \times C_6$
12, 2	0.902	$-5.052 + 35.626 \times C_{12} + 3.775 \times C_2$
12, 1.5	0.891	$-4.877 + 36.944 \times C_{12} + 3.732 \times C_{1.5}$
12, 1	0.885	$-4.738 + 37.827 \times C_{12} + 4.530 \times C_1$
12, 8, 2	0.915	$-11.292 + 29.389 \times C_{12} + 7.453 \times C_8 + 3.507 \times C_2$
12, 8, 1	0.915	$-17.079 + 28.326 \times C_{12} + 11.426 \times C_8 + 5.629 \times C_1$
12, 8, 1.5	0.913	$-14.298 + 28.652 \times C_{12} + 9.757 \times C_8 + 3.967 \times C_{1.5}$
12, 8, 4, 2	0.924	$-6.423 + 28.661 \times C_{12} + 11.634 \times C_8 - 4.353 \times C_4 + 3.955 \times C_2$
12, 8, 3, 2	0.923	$-9.410 + 28.087 \times C_{12} + 10.563 \times C_8 - 3.380 \times C_3 + 2.813 \times C_2$
12, 6, 4,2	0.920	$-6.161 + 29.374 \times C_{12} + 10.670 \times C_6 - 5.764 \times C_4 + 4.148 \times C_2$

agreement between the abbreviated AUC derived from C_{12}, $C_{12}C_2$, $C_{12}C_8C_2$, and $C_{12}C_8C_4C_2$. The 4-point approach was better than the 1-, 2- and 3-point approach; however, the 3-point method yields acceptable result.

3.3 Model validation

Determination coefficient of the regression equation could be used as a very important measurement for model quality evaluation, but it cannot reflect the stability of the model. Therefore, the internal confirmation was performed by the Jack-Knife method. As per the description in objects and methods, one sample is removed each time and the results are listed in Table 3. When modeling according to only one parameter, the predicted error of 24 (60.0 %) cases was more than 10 %, while 12 (30.0 %) were more than 15 %, so it can be concluded that the accuracy and stability of the parameter estimation based on one parameter was rather poor, while the accuracy of predicted results based on two parameters were significantly increased. The estimated RMSE based on the 2 sampling points (Davis et al. 2000; Mendes et al. 2007) was smaller, so these 2 points were considered as the best sampling points. When using limited sampling modeling with 3 points (Davis et al. 2000; Jiao et al. 2007; Mendes et al. 2007), in addition to the larger coefficient of determination obtained, RMSE and predicted results error were more than 10 %, of which 15 % were lowered significantly, which were considered to be the best sampling points. The predicted accuracy was further improved when 4 points were selected. There were 1 assembly (12, 8, 3, 2 h) of which the determination coefficient increased to 0.924, and where the predicted errors 3 case was beyond 15 %, and only 9 cases were beyond 10 %, with a smaller increase in the RMSE, so the use of 4 sampling points was significantly better. The best assembles of the 1–4 sampling points were respectively (12 h), (12, 2 h), (12, 8, 2 h), (12, 8, 4, 2 h), i.e. the ordering of

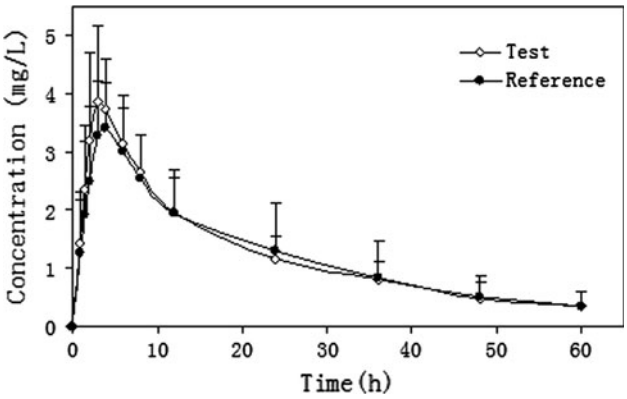

Fig. 2 Gliclazide concentration–time profiles in the serum of healthy volunteers after a single oral dose (80 mg) of the drug in bioequivalence trials. Twenty volunteers were treated with the test product and reference products at two weekly intervals. Data are reported as mean ± SD

importance for the key sampling time points were successively 12, 8, 4 and 2 h.

The Bootstrap method (Efron 1979) is applied for the calculation of the 95 % confidence interval of the model parameter for the four best assemblies, and this method is also applied for the abnormal distribution data. The calculation of the 95 % confidence interval using sampling 2,000 times and taking the quantile of 0.025 and 0.975, see Table 4 for the results. 0 is not included in the 95 % confidence interval of all the parameters.

To intuitively evaluate the accuracy of the prediction we made a *B–A* associated diagram of limited sampling (Dupuis et al. 2008). In Fig. 5a–d are the diagrams of the best assemblies from the possible assembles selected respectively from the sampling points of 1, 2, 3 and 4. The *Y* axis is the percentage error of the observed value minus the predicted value, the central position is the zero error line. The nearer the points are to the line, the better the accuracy is. The dotted line is the 10 % predicted error line, while

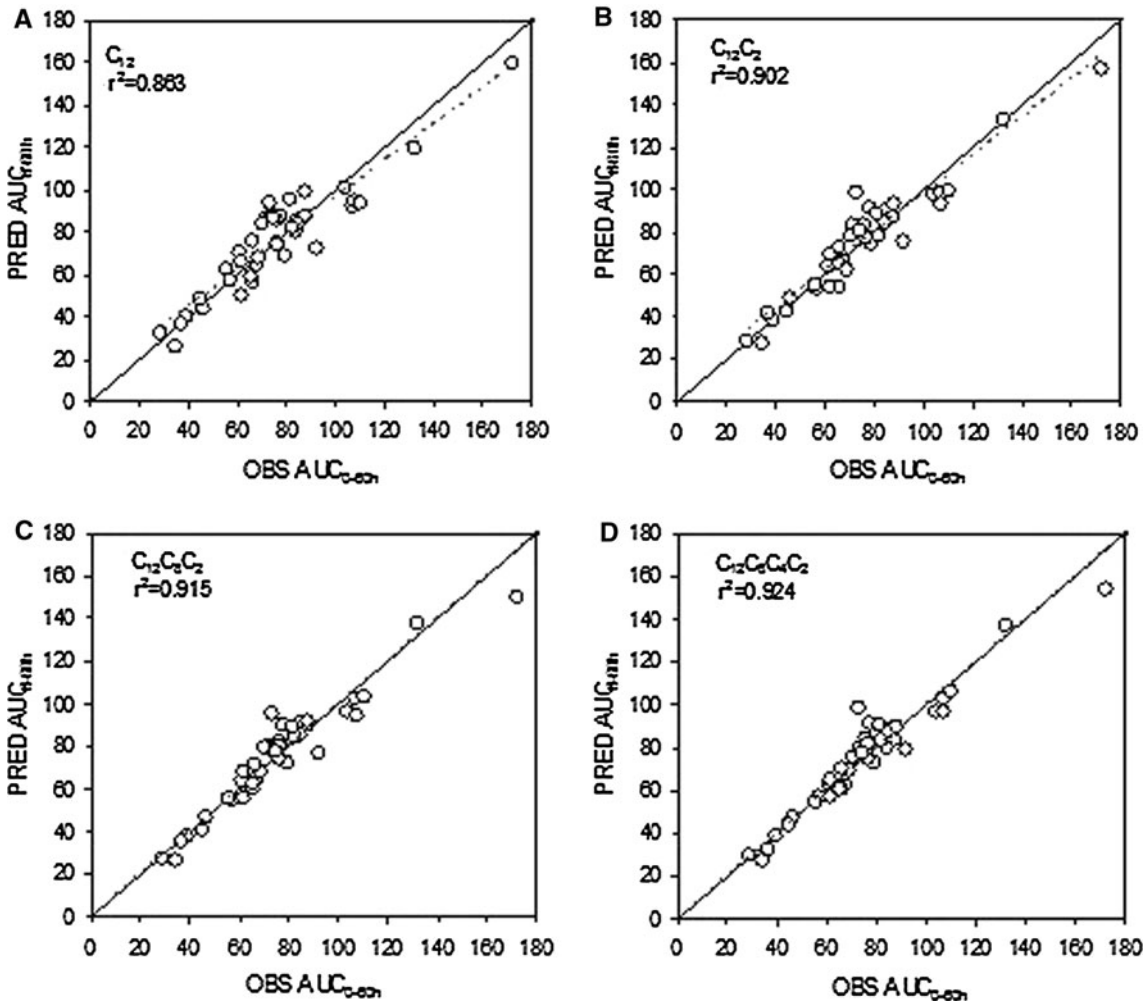

Fig. 3 A scatter plot of the relationship between the observed area under the concentration time curve (AUC_{0-60t}) (μg/mL h) for the gliclazide formulation in 20 healthy subjects and the corresponding AUC_{0-60t} derived from the LSS model developed in this study. The *solid line* represents the accuracy (diagonal)

Table 3 Jack-Knife validation of APE and RMSE in the different sampling strategies for prediction of AUC_{0-60t}

Sample time(s) (h)	r^2	RMSE	L^a_{APE}	U^b_{APE}	>10 % *N* (%)[c]	>15 % *N*(%)[d]
12	0.863	13.431	0.081	29.182	24 (60.0)	12 (30.0)
8	0.695	18.678	0.168	44.608	22 (55.0)	15 (37.5)
6	0.647	19.822	0.474	58.900	25 (62.5)	16 (40.0)
12, 2	0.902	11.705	0.159	37.545	13 (32.5)	6 (15.0)
12, 1.5	0.891	12.888	0.916	37.568	18 (45.0)	7 (17.5)
12, 1	0.885	13.343	0.235	34.397	19 (47.5)	8 (20.0)
12, 8, 2	0.915	10.865	0.121	33.981	12 (30.0)	4 (10.0)
12, 8, 1	0.915	12.327	0.740	37.084	14 (35.0)	6 (15.0)
12, 8, 1.5	0.913	11.413	0.251	33.378	12 (30.0)	5 (12.5)
12, 8, 4, 2	0.924	10.930	0.017	38.865	9 (22.5)	3 (7.5)
12, 8, 3, 2	0.923	11.076	0.006	30.332	15 (37.5)	4 (10.0)
12, 6, 4, 2	0.920	11.154	0.404	38.244	12 (30.0)	6 (15.0)

[a] The lower limited prediction error

[b] The upper limited prediction error

[c] Number and ratio of calculated AUC_{0-60t} with a prediction error beyond 10 %; number and ratio of calculated AUC_{0-60t} with a prediction error beyond 15 %

Table 4 The median (95 % CI) of the intercept and the coefficient (A_i) results of different LSS model calculated by the bootstrap method

Sample time(s) (h)	Intercept	A_1	A_2	A_3	A_4
12	3.264 (−3.716–13.746)	36.877 (30.731–40.437)			
12, 2	−4.872 (−13.353–5.086)	35.594 (29.756–39.171)	3.854 (2.105–5.646)		
12, 8, 2	−10.790 (−20.449 to −3.927)	29.151 (13.837–36.667)	8.339 (2.273–17.116)	3.568 (2.041–5.307)	
12, 8, 4, 2	−6.484 (−13.094 to −0.019)	28.355 (14.280–34.759)	12.391 (7.192–18.7060)	−4.045 (−8.448–0.507)	3.968 (2.283–5.956)

the solid line is the 15 % predicted error line. In Fig. 5a, there are many points outside the 15 % predicted error line, indicating that the accuracy evaluation based on 1 sampling time point is extremely indecisive. The prediction improves significantly when 2 points are selected, see Fig. 5b, with only a few points outside the 15 % predicted error line. The prediction is further improved when taking 3 points, showing a better linearity, The coefficient of determination is close to 1 ($r^2 = 0.915$). The prediction of almost all the points (90.0 %) are inside the 15 % predicted error line (with only 4 prediction errors greater than 15 %, accounting for 10 %), therefore an extremely high accuracy is achieved. Although all of the above could be selected according to the actual need, in Fig. 5d, an excellent fitting is observed (Fig. 5).

4 Discussion

This paper describes the development of LSS for predicting both the plasma AUC_{0-60t} of gliclazide. These strategies were developed using data from a bioequivalence study in which a relatively large number of plasma samples ($n = 480$) were collected from closely monitored and healthy Chinese volunteers. Our LSS analysis and validation procedures indicates that the plasma AUC_{0-60t} of gliclazide following oral administration of a single 80 mg dose can be predicted accurately using only 2–3 plasma samples. The highest determination coefficient of 2 sampling points was 0.902, the best sampling time points were at (12, 2 h), Choosing three or more samples adds little to the accuracy and precision of the estimates (see Table 3). The present study indicates that the implementation of an

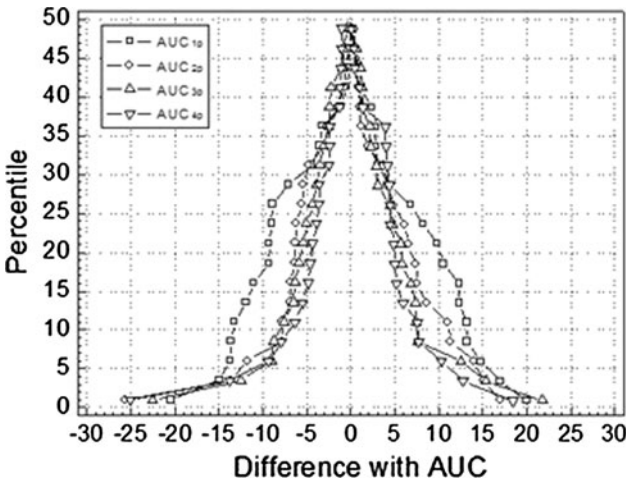

Fig. 4 Mountain plot analysis testing agreement between the abbreviated AUC derived from C_{12}, $C_{12}C_2$, $C_{12}C_8C_2$, and $C_{12}C_8C_4C_2$. The 4-point approach was better than the 1-, 2-, and 3-point approach; however, the 3-point method yields acceptable result

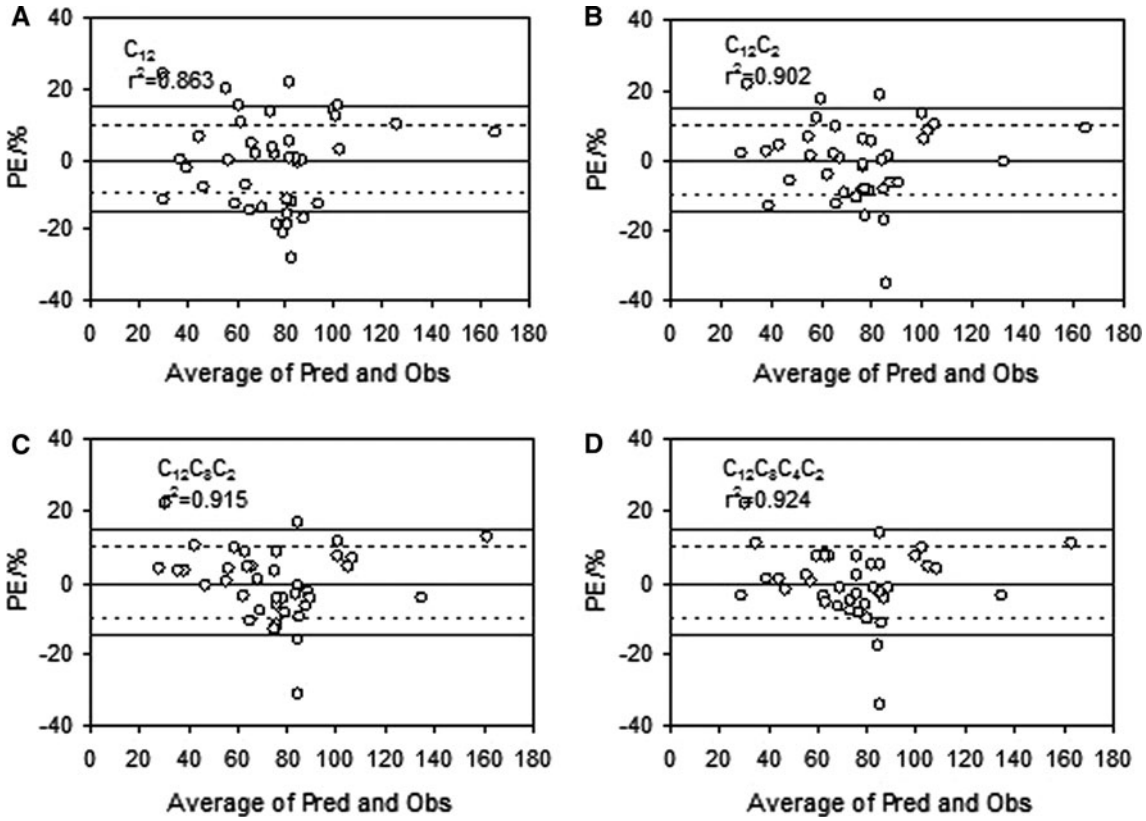

Fig. 5 *B–A* plots of AUC_{0-60t} predicted by each LSS. **a** 1-sample LSS, **b** 2-sample LSS, **c** 3-sample LSS, **d** 4-sample LSS

80 mg dosage regimen enabled accurate predictions of AUC_{0-60t} by the LSS model. This study shows that 12, 8, 4, 2 h after administration are the key sampling times. The combination of (12, 2 h), (12, 8, 2 h) or (12, 8, 4, 2 h) might be chosen as sampling hours for predicting AUC_{0-60t} in practical application according to requirements.

Limited sampling takes the linear relation between sampling points and AUC as the basis of the method, except AUC as the method for the limited sampling. There are other optional parameter, such as C_{max}, T_{max}, etc. It is possible to increase the number of sampling points, so as to increase the accuracy of the prediction of the limited sampling model; however, this raises the cost. In this study, a multiple regression model is applied to obtain the order, based on the determination coefficient with the help of computer programming to calculate all the possible assemblies from 1 to 4 points; this method is more convenient compared with the trapezoidal method. A large amount of sampling data is used in this case and the regression model is very reliable, with considerable reference value for other cases with similar samples.

The modeling of gliclazide in this case is validated internally by the Jack-Knife method, and 95 % CI are calculated according to the Bootstrap method. The high rate of accuracy of the limited sampling model of gliclazide is thus proven, and 2–4 points could be selected for the prediction in accordance with actual needs. With the application of the Bootstrap nonparametric method, the 95 % CI of the limited sampling model parameters is calculated and zero is not included in 95 %. Body weight was once taken into the consideration of whether or not there are influences on the model during the modeling process, and the answer is negative because of the minor influences found that produce no statistical significance. This indicates there is no need to consider body weight in relation to the blood concentration, which is low in the sampling points while having a corresponding low AUC, vice versa, therefore the same formula is applicable for both conditions.

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