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PKSolver: An add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel

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ABSTRACT

This study presents PKSolver, a freely available menu-driven add-in program for Microsoft Excel written in Visual Basic for Applications (VBA), for solving basic problems in pharmacokinetic (PK) and pharmacodynamic (PD) data analysis. The program provides a range of modules for PK and PD analysis including noncompartmental analysis (NCA), compartmental analysis (CA), and pharmacodynamic modeling. Two special built-in modules, multiple absorption sites (MAS) and enterohepatic circulation (EHC), were developed for fitting the double-peak concentration–time profile based on the classical one-compartment model. In addition, twenty frequently used pharmacokinetic functions were encoded as a macro and can be directly accessed in an Excel spreadsheet. To evaluate the program, a detailed comparison of modeling PK data using PKSolver and professional PK/PD software package WinNonlin and Scientist was performed. The results showed that the parameters estimated with PKSolver were satisfactory. In conclusion, the PKSolver simplified the PK and PD data analysis process and its output could be generated in Microsoft Word in the form of an integrated report. The program provides pharmacokinetic researchers with a fast and easy-to-use tool for routine and basic PK and PD data analysis with a more user-friendly interface.

1. Introduction

Analysis of drug concentration–time or drug effect-concentration data plays an important role in pharmacokinetic (PK) and pharmacodynamic (PD) research. Tedious mathematical calculations, optimization algorithms, and graph plotting are essential for pharmacokinetic data analysis. To streamline such analyses, various software packages have been developed and marketed. More often than not, many of these commercially available packages, such as WinNonlin and Kinetica, are expensive or have a steep learning curve. Therefore, it is worthwhile exploring the possibility of cost-effective and easy-to-use alternatives for PK/PD analysis.

Microsoft Excel has been widely used by scientists for data collection, calculation, and analysis. While custom designed spreadsheet templates can be easily built, sophisticated and highly customizable macros can also be compiled using Excel Visual Basic for Applications (VBA). Several templates and add-in programs have already been developed for biological and medicinal applications [1–4]. In pharmaceutical science, Excel has been adopted for pharmacokinetic data analysis such as noncompartmental analysis (NCA) calculation [5,6], nonlinear fitting analysis [7], complex pharmacokinetic model

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simulation [8], bioavailability/bioequivalence (BA/BE) simulation [9], in vitro/in vivo correlation (IVIVC) analysis [10,11] and modeling of quantitative structure–pharmacokinetic relationships [12]. However, some of these programs have only a few NCA calculation functions [5,6] or were built as predetermined spreadsheet templates limiting data input in specified ranges as well as the amount of data. These data sets are usually paired concentration–time data and often have limited data sets (for example, "up to 30 plasma samples" [7]); thus, most of these programs lack flexibility. Moreover, according to previous reports [13,14], it is time-consuming to perform a step-by-step nonlinear fitting because only a single set data can be fitted using Excel's SOLVER each time. Additionally, PK models for analyzing double-peak concentration–time data are rarely embedded in popular, commercially available packages. Thus it is highly desirable to have these models coded as an add-in program with user-friendly interface, predefined menus and forms for easy recall.

In this study, a VBA program, PKSolver, was developed for a range of applications for PK/PD data analysis including: (1) noncompartmental analysis for plasma data after extravascular administration, IV bolus injection, and IV infusion; (2) compartmental modeling of concentration–time data; (3) compartmental model analysis for double-peak concentration–time curves; (4) modeling of pharmacodynamic data; and (5) twenty frequently used pharmacokinetic functions that can be invoked within an open spreadsheet. Last, but not least, all the features mentioned above can be programmed to run in batches and can subsequently generate integrated report in MS Word documents with only a few simple operations.

2. Computational methods

Because of journal space restrictions, a detailed description of frequently used PK compartmental models and PD models is beyond the scope of this article. Only certain special computational strategies are listed.

2.1. Noncompartmental analysis

Noncompartmental analysis is a frequently used method in PK analysis because the calculations are simple. The basic theory of statistical moment concepts and details of NCA calculation have been summarized previously [15]. PKSolver provides many flexible options for calculating parameters. Area under the zero and first moment curves from 0 to last time t (AUC_{0-t}, $AUMC_{0-t}$) can be calculated using the linear trapezoidal method, log-linear trapezoidal method or linear up/log down method. Terminal elimination slope, λ_z, can be calculated based on user-specified terminal data points or automatically estimated using the regression with the largest adjusted R^2 where the regressions are performed based on the last three data points, then the last four points, last five, etc., but the points prior to C_{max} or prior to the end of infusion are not used for the regression.

$$\text{Adjusted } R^2 = 1 - \frac{(1-R^2)\cdot(n-1)}{n-2}$$

where n is the number of data points in the regression and R^2 is the square of the correlation coefficient [16]. For IV bolus input data, concentration at time 0 (C_0) can be supplied by the user or estimated by stripping back to time 0 using two points automatically, or set equal to the concentration of the first data point ($C_0 = C_1$). For extravascular input data, users can either specify the time delay of absorption T_{lag} or set $T_{lag} = 0$ using a default setting. Area under the zero and first moment curves from the last sampling time to infinity ($AUC_{t-\infty}$, $AUMC_{t-\infty}$) can be calculated based on the last observed or predicted concentration using

$$AUC_{t-\infty} = \frac{C_{last}}{\lambda_z}$$

$$AUMC_{t-\infty} = \frac{C_{last}\cdot t_{last}}{\lambda_z} + \frac{C_{last}}{\lambda_z^2}$$

Other parameters including $t_{1/2}$, mean residence time (MRT), clearance (Cl), volume of distribution based on the terminal slope (V_z) can be subsequently calculated.

2.2. Model diagnostics

Selecting a suitable PK model for fitting concentration–time data is essential for quantitative evaluation of drug transport processes in the body. To select an appropriate model with good precision of estimated parameters, PKSolver provides several model diagnostics such as correlation coefficient, sum of squares of residuals (SS), standard error of weighted residuals (SE), Akaike's information criterion (AIC) and Schwarz criterion (SC). AIC and SC are the most important ones [17], and are calculated as follows:

$$AIC = N\cdot\ln(WSS) + 2p$$

$$SC = N\cdot\ln(WSS) + p\cdot\ln(N)$$

where N is the number of observations, WSS is the weighted sum of squared residuals, and p is the number of estimated parameters.

2.3. Multiple absorption sites (MAS) model

In the classical pharmacokinetic model, it was impossible to interpret the double-peak phenomenon. Several reports [18–20] have proposed a practical, two-site absorption model to clarify this issue. In brief, as shown in Fig. 1, the drug enters the central compartment with two first-order absorption processes from two sites and is subsequently eliminated from

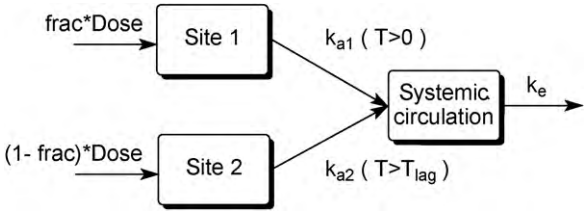

Fig. 1 – Scheme of two-site absorption model illustrates drug kinetics after oral administration.

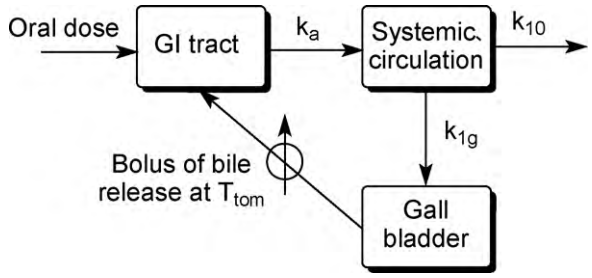

Fig. 2 – Scheme of the EHC model illustrates drug kinetics after oral administration.

the body followed by a classical one-compartment open model with first-order process. The relationship of concentration and time can be described as follows:

$$C = \frac{k_{a1} \cdot frac \cdot X_0}{V(k_{a1} - k_e)}(e^{-k_e \cdot t} - e^{-k_{a1} \cdot t}) \qquad \text{when } 0 < t \le T_{lag}$$

$$C = \frac{k_{a1} \cdot frac \cdot X_0}{V(k_{a1} - k_e)}(e^{-k_e \cdot t} - e^{-k_{a1} \cdot t}) + \frac{k_{a2} \cdot (1 - frac) \cdot X_0}{V(k_{a2} - k_e)}(e^{-k_e \cdot (t - T_{lag})} - e^{-k_{a2} \cdot (t - T_{lag})}) \quad \text{when } t > T_{lag}$$

where k_{a1} and k_{a2} are the absorption rate constants for two absorption sites, *frac* is the fraction of drug absorbed through site 1, V is the volume of distribution, and k_e is the elimination rate constant.

2.4. *Enterohepatic circulation (EHC) model*

The enterohepatic circulation model, sometimes called the enterohepatic recirculation model, is another widely used model to describe the double-peak concentration–time curve [21]. The EHC model is based on the classical one-compartment model. As shown in Fig. 2, k_a is the first-order rate constant for drug absorption from the gastrointestinal (GI) tract, k_{1g} is the first-order rate constant for drug excreted into the bile, and k_{10} is the elimination rate constant of drug from systemic circulation. In contrast to the common pharmacokinetic model, release of bile is assumed to occur as a bolus at the time of expulsion from the gall bladder (T_{tom}) into the GI tract. After a single oral dose, the drug concentration–time profile can be described as follows:

$$C = \frac{k_a \cdot X_0}{V(k_a - (k_{10} + k_{1g}))}(e^{-(k_{10}+k_{1g}) \cdot t} - e^{-k_a \cdot t}) \qquad \text{when } 0 < t \le T_{tom}$$

$$C = \frac{k_a \cdot X_0}{V(k_a - (k_{10} + k_{1g}))}(e^{-(k_{10}+k_{1g}) \cdot t} - e^{-k_a \cdot t}) + \frac{k_a \cdot X_{Bile}}{V(k_a - (k_{10} + k_{1g}))}(e^{-(k_{10}+k_{1g}) \cdot (t - T_{tom})} - e^{-k_a \cdot (t - T_{tom})}) \quad \text{when } t > T_{tom}$$

where X_{Bile} is the amount of drug accumulated in the gall bladder until the time T_{tom} which can be calculated using the following equation:

$$X_{Bile} = k_{1g} k_a X_0 \left(\frac{1}{(k_{10} + k_{1g})k_a} + \frac{e^{-(k_{10}+k_{1g}) \cdot T_{tom}}}{(k_{10} + k_{1g})(k_{10} + k_{1g} - k_a)} - \frac{e^{-k_a \cdot T_{tom}}}{k_a(k_{10} + k_{1g} - k_a)} \right)$$

A set of secondary parameters and diagnostics for both MAS and EHC models were calculated based on corresponding primary parameters and input data information.

2.5. *Automatic nonlinear curve fitting*

Nonlinear curve fitting using Excel's SOLVER with step-by-step operations has been reported previously [1,4,13,14]. The SOLVER add-in must be installed before the nonlinear regression with a series of elective settings can be performed. To automatically recall and run SOLVER and to keep SOLVER Results dialog box from showing up, we encoded all the operations in a single, integrated module that is capable of performing data input and tabulation, equation setting, initial parameter estimating, SOLVER recalling, executing, primary and secondary parameter calculating, model diagnostics evaluating, graph creating, and final report generating in Microsoft Word. Initial parameters can be obtained using the curve stripping technique [22] by the add-in program or, alternatively being specified by user. All the above processes can be executed by a single mouse click, and only take a fraction of a second for a three-compartment IV infusion model.

3. Program description

3.1. *Interface and flowchart*

Once the add-in program has been installed, a pull-down PKSolver menu appears in the menu bar when Excel is launched. As shown in Fig. 3, users may select a module of interest from the menu and input time and concentration data by simply drag-selecting a range of cells in the spreadsheet and then setting calculation options interactively. The PKSolver program provides many customizable options for PK/PD modeling, including optimization algorithms, initial values, fitting weight, and chart and report output. The entire data analysis process of the program is schematically shown in Fig. 4. In addition, a built-in sample data set can be loaded by clicking on the Sample button in each module. This feature is provided as a guide for new users to help them arrange their data into a suitable form for processing by the program.

3.2. *Model library*

As shown in Table 1, three NCA calculation modules and one PK function calculation module have been developed. The NCA modules can be used in interactive forms while the PK functions module can be used as Excel's built-in functions. All the twelve PK modeling modules and eight PD modeling mod-

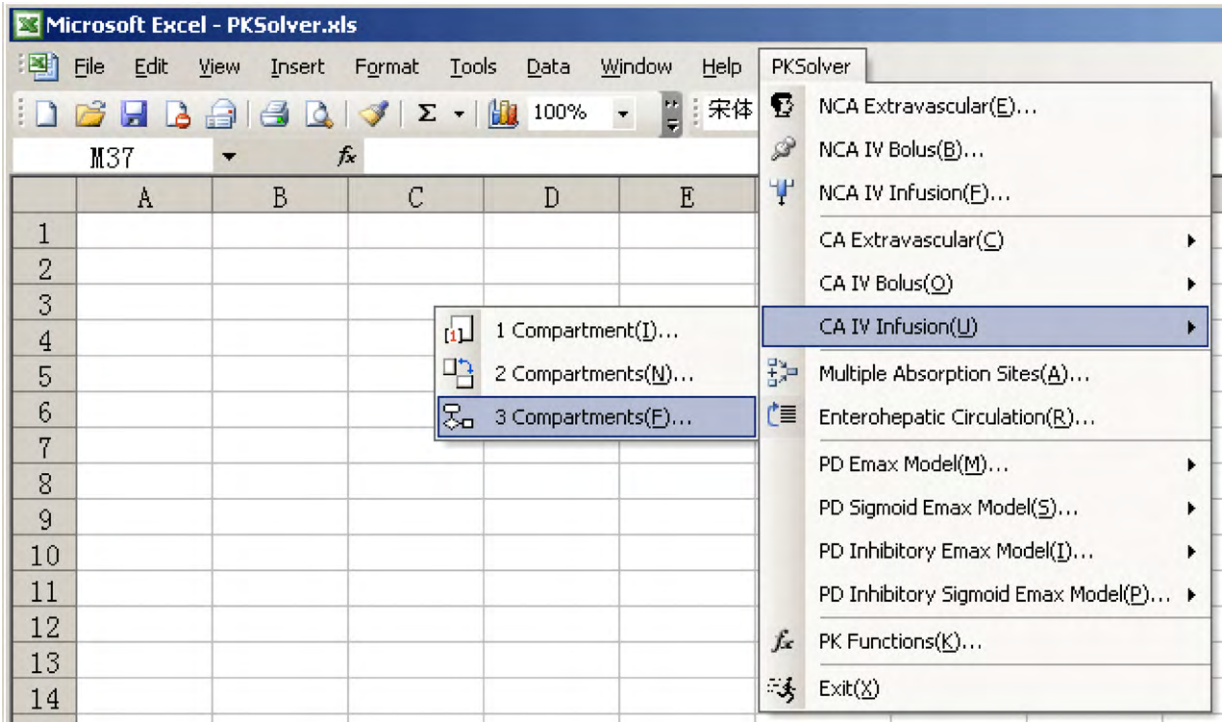

Fig. 3 – PKSolver menu in MS Excel spreadsheet environment.

ules and brief descriptions are also listed in Table 1. When a PK module is used, the add-in program can generate both concentration–time plots with linear and logarithmic scaling of the Y-axis.

Table 1 – The modules available in PKSolver.

Module	Module description
# 101	Noncompartmental analysis, extravascular
# 102	Noncompartmental analysis, IV bolus
# 103	Noncompartmental analysis, IV infusion
# 201	CA, extravascular, 1 compartment
# 202	CA, extravascular, 1 compartment, with T_{lag}
# 203	CA, extravascular, 2 compartments
# 204	CA, extravascular, 2 compartments, with T_{lag}
# 205	CA, IV bolus, 1 compartment
# 206	CA, IV bolus, 2 compartments
# 207	CA, IV bolus, 3 compartments
# 208	CA, IV infusion, 1 compartment
# 209	CA, IV infusion, 2 compartments
# 210	CA, IV infusion, 3 compartments
# 211	Multiple absorption sites model
# 212	Enterohepatic circulation model
# 301	PD, Simple Emax Model
# 302	PD, Simple Emax Model, with E0
# 303	PD, Sigmoid Emax Model
# 304	PD, Sigmoid Emax Model, with E0
# 305	PD, Inhibitory Effect Emax Model
# 306	PD, Inhibitory Effect Emax Model, with E0
# 307	PD, Inhibitory Effect Sigmoid Emax Model
# 308	PD, Inhibitory Effect Sigmoid Emax Model, with E0
# 400	PK functions

3.3. *Specific features*

To satisfy routine PK/PD analysis and to facilitate PK calculation tasks in the spreadsheet, 24 different modules have been developed in PKSolver. MAS and EHC modules have been purposely implemented to fit double-peak profiles that otherwise would not fit well with the classical PK compartmental model. The PKSolver program provides a simple way to solve the problem using predefined built-in models. Moreover, a set of secondary parameters such as T_{max1}, C_{max1}, T_{max2} and C_{max2} can be automatically estimated as opposed to manual calculation based on user-defined models in other software packages. To fit double-peak profiles with MAS or EHC models, users should manually define the initial value of parameters, which can be obtained by a preliminary analysis of concentration–time data based on the mathematical theory described in Sections 2.3 and 2.4.

Another distinctive feature of PKSolver is the implementation of 20 user-defined functions for PK calculation. It is extremely convenient to use these functions in the same way as using SUM() or other built-in function in MS Excel. Fig. 5 shows a sample sheet with applications of all the PK functions. The statistical moment parameters are calculated using the linear trapezoidal method; C_{last}, AUC_i, $AUMC_i$, MRT_i, CL, and Vd can be calculated based on either observed or predicted concentration values at the last observed time point.

The specificity of the add-in program is also evidenced by its capability to perform data analysis and generate integrative Microsoft Word reports in batches, a unique feature that previously reported template-based Excel spreadsheets do not have.

Table 2 – Detailed comparison of PKSolver estimates with those of WinNonlin and Scientist.

Parameter	Unit	One-compartment model			Two-compartment model			Three-compartment model		
Primary parameters		WinNonlin	Scientist	PKSolver	WinNonlin	Scientist	PKSolver	WinNonlin	Scientist	PKSolver
A	μg/L	1.4028	1.4029	1.4029	1.0566	1.0578	1.0578	0.6584	0.6644	0.6649
Alpha	1/min	0.0079	0.0079	0.0079	0.0482	0.0478	0.0478	0.0885	0.0877	0.0876
B	μg/L				0.7868	0.7833	0.7832	0.6311	0.6265	0.6261
Beta	1/min				0.0033	0.0033	0.0033	0.0220	0.0217	0.0217
C	μg/L							0.6411	0.6389	0.6386
Gamma	1/min							0.0025	0.0025	0.0025
Secondary parameters										
k_{10}	1/min	0.0079	0.0079	0.0079	0.0071	0.0071	0.0071	0.0067	0.0067	0.0067
k_{12}	1/min				0.0219	0.0218	0.0218	0.0195	0.0195	0.0195
k_{21}	1/min				0.0225	0.0222	0.0222	0.0631	0.0623	0.0622
k_{13}	1/min							0.0120	0.0119	0.0119
k_{31}	1/min							0.0117	0.0116	0.0116
$t_{1/2}$Alpha	min	87.8260	87.8157	87.8156	14.3702	14.4934	14.4941	7.831	7.9023	7.9087
$t_{1/2}$Beta	min				208.7132	210.2038	210.2141	31.5067	31.8820	31.9240
$t_{1/2}$Gamma	min							272.8234	274.0037	274.1722
C0	μg/mL	1.4028	1.4029	1.4029	1.8434	1.8411	1.8410	1.9307	1.9297	1.9296
V_c	(mg)/(μg/L)	71.2870	71.2809	71.2826	54.2469	54.3168	54.3180	51.7957	51.8218	51.8236
CL	(mg)/(μg/L)/min	0.5626	0.5626	0.5626	0.3864	0.3851	0.3851	0.3466	0.3461	0.3460
$AUC_{0-\infty}$	μg/L·min	177.7411	177.7353	177.7308	258.8288	259.6466	259.6540	288.4816	288.9438	289.0195
AUMC	μg/L·min^2	22520.8950	22517.5171	22516.9137	71794.1736	72495.3634	72500.9726	100715.7803	101247.8891	101328.6596
MRT	min	126.7062	126.6913	126.6911	277.3809	279.2079	279.2215	349.1238	350.4068	350.5945
V_{ss}	mg/(μg/L)	71.2870	71.2809	71.2826	107.1677	107.5338	107.5360	121.0212	121.2716	121.3048
Diagnostics										
$r_{obs\text{-}pre}$		0.9529	0.9529	0.9529	0.9987	0.9987	0.9987	0.9993	0.9993	0.9993
SS		0.2598	0.2598	0.2598	0.0065	0.0065	0.0065	0.0037	0.0037	0.0037
SE		0.1471	0.14713	0.1471	0.0255	0.0255	0.0255	0.0214	0.0214	0.0214
AIC		−14.8711	−14.8709	−14.8711	−62.5241	−62.5333	−62.5334	−66.4705	−66.4712	−66.4712
SC		−13.5930	−13.5928	−13.5930	−59.9679	−59.9771	−59.9771	−62.6361	62.6369	−62.6369

The data were fitted with one-, two- and three-compartment models for IV bolus administration, respectively.

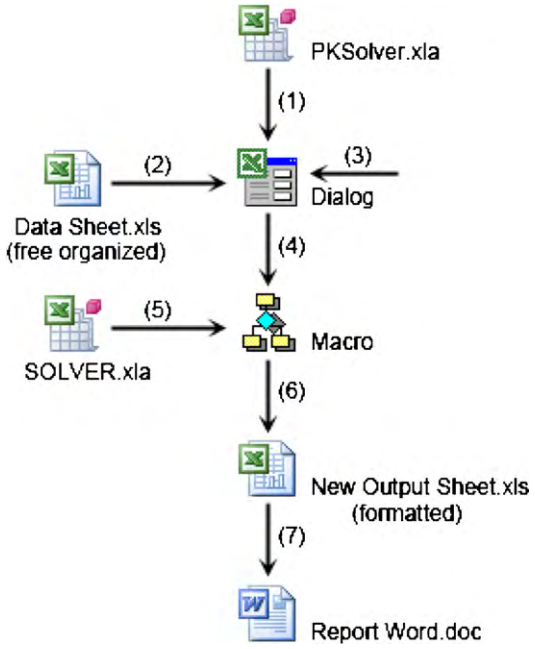

Fig. 4 – Flowchart represents the data analysis process of the program. (1) Start the program from PKSolver menu and select a module for specific analysis. (2) Input data by selecting the data ranges in the spreadsheet, usually two or more sets of cells. (3) Set calculation options and input required model parameters in the dialog box. (4) Execute the macro containing a series of operations including validating input data, validating setting options, and data analysis. (5) Automatically recall SOLVER add-in to perform nonlinear optimization while executing modeling modules. (6) Complete the new output sheet containing parameters and charts. (7) If required, export additional user information, input data, option settings and all the final results into a Microsoft Word document as an integrated report.

4. Sample program runs

Validation of a newly developed program is an important aspect of its acceptability. For this purpose, we compared the results of PKSolver with the professional PK/PD software packages WinNonlin (Pharsight, Mountain View, USA) and Scientist (Micromath, Saint Louis, USA) using two sample data sets from a published book.

4.1. *Compartmental analysis*

Compartmental analysis is a widely used technique to quantitatively evaluate and predict the in vivo fate of a drug by modeling the concentration–time data with a suitable PK compartment model. In contrast with noncompartmental analysis, it is nearly impossible to perform PK modeling by hand because of the involvement of nonlinear optimization and mathematical iteration that cannot be easily solved without the aid of a computer. Compartmental analysis using PKSolver is quick and easy to perform. As shown in Fig. 6, the compartmental analysis can be initiated after completing the following steps. (1) Pull down the PKSolver menu and select the module for data analysis. (2) Input time and concentration data by drag-selecting the data range in the spreadsheet. (3) Specify the parameters' units and input dosing information in the dialog box. (4) If required, set calculation options by clicking the Option button. (5) Click the Run button to perform and complete the analysis.

One data set and its analysis outcome from a published book [23] were used in a comparison to evaluate PKSolver. The concentration–time data following IV bolus administration of 100 mg of a drug which obeys multicompartment kinetic model was fitted with one- two- and three-compartment IV-bolus input models. Table 2 summarizes the results using PKSolver, WinNonlin, and Scientist. It is shown that all the primary and secondary parameters yielded with PKSolver are similar to those calculated with WinNonlin and Scientist. Although there is a big absolute difference in AUMC, the relative difference is acceptable for PK analysis. Moreover, the most important parameters for evaluating the accuracy of model fitting, the objective function SS and the model diagnostic AIC, are nearly identical, which suggests that the results of PKSolver are acceptable. Table 2 shows small numerical differences between the estimates of PKSolver and those of WinNonlin and Scientist. The reason is that tolerance and convergence settings and different optimization strategies were adopted. For data fitting, Excel's Gauss–Newton algorithm was used in PKSolver, while WinNonlin used the Levenberg–Hartley method and Scientist adopted the Simplex method.

4.2. *Multiple absorption sites modeling*

As a specific feature of the add-in program, both predefined MAS and EHC models provide a practical and simple way to deal with the problem of the double-peak phenomenon in PK research. The data for MAS model testing in PKSolver were also selected from a published book [20]. They were obtained from a male subject treated with 2 mg of drug and fitted by a user-defined multiple absorption sites model that was written in differential equations. As shown in Fig. 7, the double-peak profile fits well with the MAS model by PKSolver. A comparison of estimated parameters obtained from PKSolver and those of WinNonlin and Scientist is presented in Table 3. The main parameters, *frac*, T_{lag}, k_{a1}, k_{a2}, k_e, V/F, SS, AIC, and SC are nearly the same as those estimated by WinNonlin and Scientist.

5. Conclusion and specification

In this study, a menu-driven program for PK/PD data analysis in MS Excel was developed. PKSolver was much more flexible than those programs tailored as spreadsheet templates that limit data input in specified ranges, as well as the amount of data. Abundant calculation options were provided in all the modules, an advantage that cannot be provided by a spreadsheet template-style tool. The flexibility of PKSolver was demonstrated by the 20 NCA PK functions embedded in the program and used directly in the spreadsheet. The software reliability was demonstrated by a comparison of

E12 =pk_aumci(A2:A15,B2:B15,B20)

	A	B	C	D	E	F
1	Time	Conc		Parameter	Value	Function
2	0	0		Cmax	24.76	=pk_cmax(A2:A15,B2:B15)
3	0.5	2.72		Tmax	2	=pk_tmax(A2:A15,B2:B15)
4	1	7.98		Clast	0.59	=pk_clast(A2:A15,B2:B15)
5	1.5	18.61		Tlast	24	=pk_tlast(A2:A15,B2:B15)
6	2	24.76		AUCt	98.11	=pk_auct(A2:A15,B2:B15)
7	3	18.37		AUMCt	559.7575	=pk_aumct(A2:A15,B2:B15)
8	4	7.28		MRTt	5.705407196	=pk_mrtt(A2:A15,B2:B15)
9	5	5.47		Lz	0.0909291	=pk_lambdaz(A2:A15,B2:B15,B20)
10	6	4.03		T1/2	7.622941166	=pk_thalf(A2:A15,B2:B15,B20)
11	7	5.17		AUCi	104.5985719	=pk_auci(A2:A15,B2:B15,B20)
12	8	2.61		AUMCi	786.8418088	=pk_aumci(A2:A15,B2:B15,B20)
13	12	1.73		MRTi	7.522490937	=pk_mrti(A2:A15,B2:B15,B20)
14	16	1.46		CL	7.887296981	=pk_cl(A2:A15,B2:B15,B20,B17)
15	24	0.59		Vd	86.74117493	=pk_vd(A2:A15,B2:B15,B20,B17)
16				Clast_pre	0.619530671	=pk_clast_pre(A2:A15,B2:B15,B20)
17	Dose	825		AUCi_pre	104.9233378	=pk_auci_pre(A2:A15,B2:B15,B20)
18				AUMCi_pre	798.2078291	=pk_aumci_pre(A2:A15,B2:B15,B20)
19	Number of			MRTi_pre	7.607533712	=pk_mrti_pre(A2:A15,B2:B15,B20)
20	points for Lz	4		CL_pre	7.862883679	=pk_cl_pre(A2:A15,B2:B15,B20,B17)
21				Vd_pre	86.47268771	=pk_vd_pre(A2:A15,B2:B15,B20,B17)

Fig. 5 – Sample sheet showing the usage of predefined functions. The names of the functions are listed in Column F; Column E shows the calculation results.

the analysis results of PKSolver with those of professional software WinNonlin, the results showed that the parameters estimated with PKSolver were satisfactory, and the program can serve as a useful tool for routine PK/PD data analysis.

The PKSolver add-in program is available in Supplementary material; interested users can download and install it for free. The program was developed in Microsoft Excel 2003 (both English and Simplified Chinese versions) in a Windows XP SP2 environment and was compatible with Microsoft Excel 2007 and 2010 on Windows platform. A quick installation of the program is in the Supplementary document.

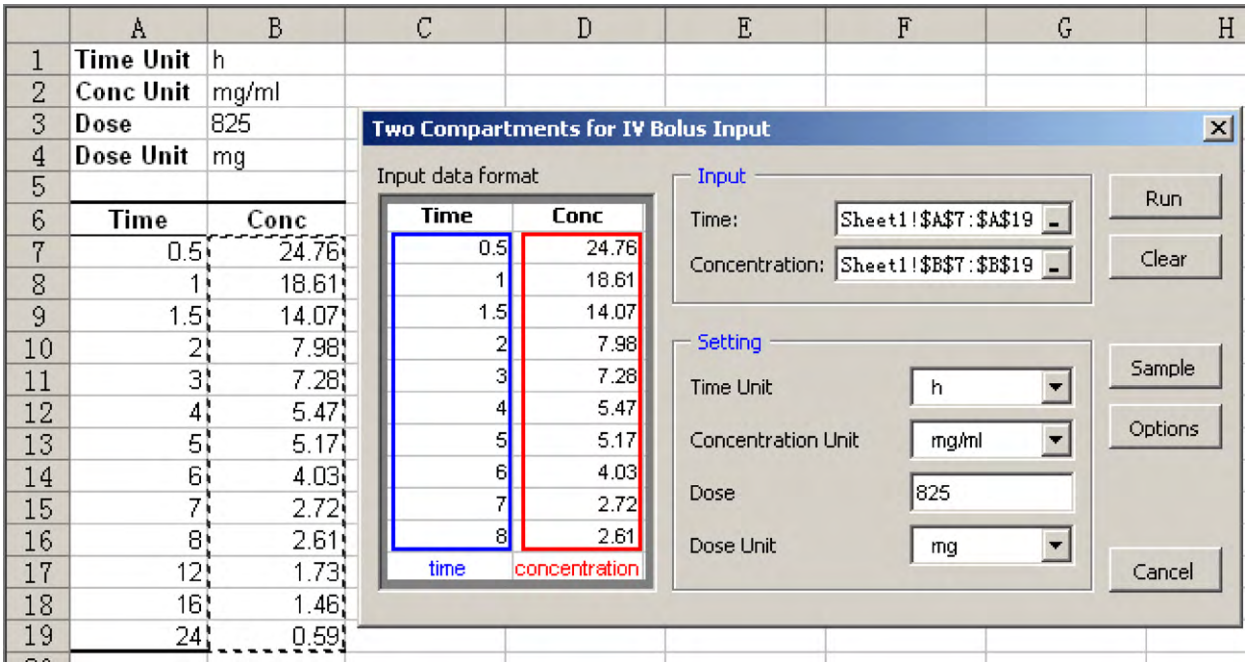

Fig. 6 – Excel worksheet showing data input, parameter setting, and program execution.

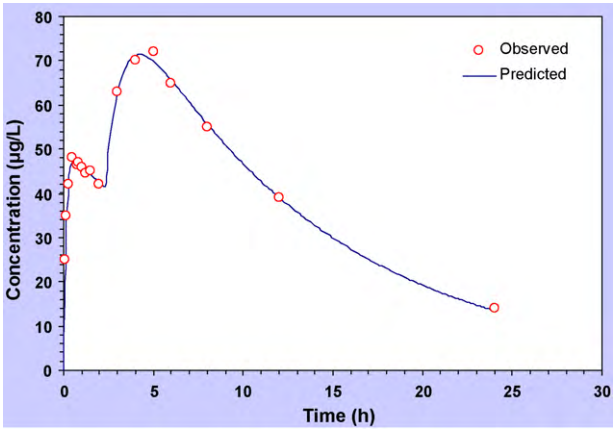

Fig. 7 – Concentration–time profile with double peaks fitted with MAS model by using PKSolver.

Table 3 – Comparison of PKSolver estimates with those of WinNonlin and Scientist.

Parameter	Unit	Software		
		WinNonlin	Scientist	PKSolver
frac		0.5147	0.5147	0.5147
T_{lag}	h	2.2962	2.2862	2.2862
k_{a1}	1/h	7.6249	7.6226	7.6226
k_{a2}	1/h	1.0718	1.0588	1.0587
k_e	1/h	0.0888	0.0888	0.0888
V/F	L	20.6118	20.6150	20.6145
SS		12.6291	12.9650	12.9652
AIC		55.1120	55.5583	55.5585
SC		60.1113	60.5576	60.5578

The data were fitted with MAS model in PKSolver.

Conflicts of interest

The authors claim no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.cmpb.2010.01.007.

REFERENCES

[1] A.M. Brown, A step-by-step guide to non-linear regression analysis of experimental data using a Microsoft Excel spreadsheet, Comput. Methods Programs Biomed. 65 (2001) 191–200.
[2] H.A. Khan, SCEW: a Microsoft Excel add-in for easy creation of survival curves, Comput. Methods Programs Biomed. 83 (2006) 12–17.
[3] G. Gorog, An Excel program for calculating and plotting receiver-operator characteristic (ROC) curves, histograms and descriptive statistics, Comput. Biol. Med. 24 (1994) 167–169.
[4] A.M. Brown, A non-linear regression analysis program for describing electrophysiological data with multiple functions using Microsoft Excel, Comput. Methods Programs Biomed. 82 (2006) 51–57.
[5] C. Dansirikul, M. Choi, S.B. Duffull, Estimation of pharmacokinetic parameters from non-compartmental variables using Microsoft Excel, Comput. Biol. Med. 35 (2005) 389–403.
[6] H. Sato, S. Sato, Y.M. Wang, I. Horikoshi, Add-in macros for rapid and versatile calculation of non-compartmental pharmacokinetic parameters on Microsoft Excel spreadsheets, Comput. Methods Programs Biomed. 50 (1996) 43–52.
[7] H. Delboy, A non-linear fitting program in pharmacokinetics with Microsoft Excel spreadsheet, Int. J. Biomed. Comput. 37 (1994) 1–14.
[8] I. Meineke, J. Brockmoller, Simulation of complex pharmacokinetic models in Microsoft Excel, Comput. Methods Programs Biomed. 88 (2007) 239–245.
[9] H.Y. Abdallah, T.M. Ludden, A spreadsheet program for simulation of bioequivalence and bioavailability studies, Comput. Biol. Med. 25 (1995) 349–354.
[10] F. Langenbucher, Handling of computational in vitro/in vivo correlation problems by Microsoft Excel: V. Predictive absorbability models, Eur. J. Pharm. Biopharm. 67 (2007) 293–299.
[11] F. Langenbucher, Handling of computational in vitro/in vivo correlation problems by Microsoft Excel: IV. Generalized matrix analysis of linear compartment systems, Eur. J. Pharm. Biopharm. 59 (2005) 229–235.
[12] M. Beliveau, K. Krishnan, A spreadsheet program for modeling quantitative structure–pharmacokinetic relationships for inhaled volatile organics in humans, SAR QSAR Environ. Res. 16 (2005) 63–77.
[13] W.P. Bowen, J.C. Jerman, Nonlinear regression using spreadsheets, Trends Pharmacol. Sci. 16 (1995) 413–417.
[14] S. Walsh, D. Diamond, Non-linear curve fitting using Microsoft Excel Solver, Talanta 42 (1995) 561–572.
[15] J. Gabrielsson, D. Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications, 3rd ed., Swedish Pharmaceutical Press, Stockholm, Sweden, 2000, pp.141–150.
[16] Pharsight, Corporation, WinNonlin® User's Guide Version 5.2, Mountain View, 2007.
[17] T.M. Ludden, S.L. Beal, L.B. Sheiner, Comparison of the Akaike Information Criterion, the Schwarz criterion and the F test as guides to model selection, J. Pharmacokinet. Biopharm. 22 (1994) 431–445.
[18] E Shang, B. Xiang, G. Liu, S. Xie, W. Wei, J. Lu, Determination of phenazopyridine in human plasma via LC–MS and subsequent development of a pharmacokinetic model, Anal. Bioanal. Chem. 382 (2005) 216–222.

[19] K. Murata, H. Yamahara, M. Kobayashi, K. Noda, M. Samejima, Pharmacokinetics of an oral sustained-release diltiazem preparation, J. Pharm. Sci. 78 (1989) 960–963.
[20] J. Gabrielsson, D. Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications, 3rd ed., Swedish Pharmaceutical Press, Stockholm, Sweden, 2000, pp. 654–659.
[21] T. Funaki, Enterohepatic circulation model for population pharmacokinetic analysis, J. Pharm. Pharmacol. 51 (1999) 1143–1148.
[22] M. Gibaldi, D. Perrier, Pharmacokinetics, 2nd ed., Marcel Dekker, New York, 1982, pp. 433–444.
[23] J. Gabrielsson, D. Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications, 3rd ed., Swedish Pharmaceutical Press, Stockholm, Sweden, 2000, pp. 409–414.