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RKinetDS: A Flexible Open-Source Software for Modeling Dissolution Profiles

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ABSTRACT

Introduction: Analysis of the dissolution process is becoming more prevalent, including fitting mathematical models to describe dissolution profiles. This paper presents the development of RKinetDS, an open-source software for fitting drug dissolution curves to mathematical models. **Methods:** The software was written in R (version 4.2.3), and the graphical user interface was developed using the Shiny R package. RKinetDS currently includes 36 dissolution models. The software uses various measures to evaluate the goodness of fit including RMSE, R^2, $R^2_{adjusted}$, and Akaike Information Criterion (AIC). To evaluate the reliability and practical applicability of the RKinetDS, its performance was assessed using real-world dissolution datasets sourced from published studies to reflect different experimental conditions and formulation types. RKinetDS was used to replicate the model fits. **Results:** RKinetDS produced results that were similar to those reported in published studies for tablets, oral suspension, and microspheres. For tablets, the best fit was the Weibull model (Castro et al.: β = 0.6238, R^2 = 0.9998; RKinetDS: β = 0.8146, R^2 = 0.9999). For oral suspension, Weibull model was the best fit as well (de Silva et al: β = 0.2900, R^2 = 0.9513; RKinetDS: β = 0.2101, R^2 = 0.9958). For microspheres, the Korsmeyer–Peppas model was most suitable (Murtaza et al.: K = 18.191, n = 0.487, R^2 = 0.9891; RKinetDS: K = 15.228, n = 0.5439, R^2 = 0.9841). **Conclusion:** RKinetDS is distinguished by advanced optimizers that enhance its ability to fit the most suitable models, a modern interface that simplifies navigation within the software, and extensive reporting options. RKinetDS supports the dosage form development process in academia and industry. RKinetDS is freely available on GitHub (github.com/AleksanderMendyk/RKinetDS_deploy) and the shinnyapps.io platform (jszlek.shinyapps.io/RKinetDS).

KEYWORDS: Drug dissolution, dissolution modeling, R software, Mathematical modeling

INTRODUCTION

Dissolution tests are an integral part of the pharmaceutical industry. They are essential in dosage form development and quality assurance to ensure appropriate release of the active pharmaceutical ingredient (API). Additionally, dissolution testing is used in developing in vitro-in vivo correlation models (IVIVC), and in certain instances, these tests may also be used directly to prove bioequivalence with a reference product (*1*, *2*). The significance of dissolution testing is supported by their inclusion in the regulatory requirements of the U.S. Food and Drug Administration and European Medicines Agency (*3*, *4*). In vitro dissolution testing provides valuable insight into the in vivo dissolution process, which is fundamental for the development of solid and semisolid dosage formulations. The dissolution profile is used to characterize and evaluate the release of API over time from drug products like tablets, capsules, gels, and novel drug delivery systems, including the most common oral route (e.g. tablets, suspensions) as well as parenteral (e.g., suspensions, implants), rectal (e.g., suppositories), topical (e.g., transdermal patches), sublingual, and buccal (*5*, *6*). Furthermore, dissolution tests are developed for locally acting products, including the vaginal (e.g., vaginal films), topical (e.g., ointments), and ophthalmic routes (*3*, *4*, *6*–*8*). Dissolution testing allows for quantitative evaluation and comparison of different formulations or batches, which can be performed using both model-dependent and model-independent methods (*9*).

Model-independent methods rely on statistical parameters used to quantitatively assess the rate and extent of drug release from a dosage form, such as

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area under the curve (AUC), dissolution efficiency (DE), and mean dissolution time (MDT). Model-dependent approaches involve fitting the dissolution data to predefined mathematical models to describe the kinetics and mechanisms of drug release, offering insights into the formulation's behavior under specific conditions (*9, 10*).

Several dissolution models have been developed over the last few decades. Some are grounded on theoretical principles (e.g., Korsmeyer–Peppas model), and others are derived from experimental data (e.g., Weibull model) (*9, 11*). Among them, linear and nonlinear equations can be found. Linear equations are relatively easy to interpret, as each factor has a straightforward impact on the dissolution rate and contributes to the overall dissolution process; however, linear equations might lack flexibility to accurately describe the drug dissolution process. Nonlinear equations have greater flexibility and potential to represent the dissolution behavior more accurately than linear equations; however, nonlinear models might introduce numerical difficulties during the curve fitting process (*9*).

Fitting mathematical models to drug dissolution curves has become a common part of pharmaceutical research as a way to analyze and describe the relationship between experimental results and theoretical expectations. By applying curve fitting techniques, it is possible to gain insights into the dissolution mechanisms and compare the performance of various formulations. Such analysis can contribute to the optimization of drug formulations and support efforts to achieve more consistent and predictable drug dissolution (*12*). As a result, it enhances the reliability and predictability of dissolution models for regulatory and quality control purposes. Therefore, the significance of easy-to-use, time-efficient, and reliable tools for performing dissolution curve fitting is increasing.

So far, such opportunities remain relatively limited. It is possible to use spreadsheets (e.g., Microsoft Excel, LibreOffice Calc) and statistical software (e.g., Statistica) or packages (e.g., Systat) to fit dissolution data with the appropriate model equations (*13, 14*). Beyond requiring specific skills and specific input data from the user, these approaches are also time-consuming and prone to human errors. Hence, there is a demand for software to perform this type of calculation, though only a few are available. A commonly used and well-established tool is DDSolver, which was introduced in 2010 (*15*) as an add-in program for Excel with an extensive model library and the functionality of comparing drug dissolution profiles. Though it is widely used, its reliance on macros makes it sensitive to changes between different versions of Excel.

Another tool is KinetDS, a free open-source software published in 2010 for dissolution curve fitting written in Object Pascal with the graphical user interface (GUI) developed in the Lazarus (*16*). Although the software is fully functional, its development is hindered by the fact that Object Pascal is rarely used nowadays. Additionally, it is important to highlight that complex commercial tools exist to simulate dissolution studies (e.g., DDDPlus) or comprehensively analyze in vitro studies, including dissolution tests (e.g., Simcyp In Vitro Data Analysis) (*17, 18*).

The objective of this paper is to present the development of RKinetDS, an R-based flexible software for fitting mathematical models to dissolution data. The primary motivation for developing the software is to create a reliable tool that performs consistently across various systems, is easily configurable, and provides a user-friendly interface. RKinetDS, which is a descendant of KinetDS, was deliberately given a similar name by its authors to reflect this relationship.

METHODS

Computer Environment Specifications

RKinetDS was developed using a personal computer with the Microsoft Windows 10 (64-bit operating system). It was written in the R programming and statistical language (version 4.2.3), operating within an RStudio integrated development environment (version 2023.03.1+446) (*19, 20*). This enabled the use of statistical resources available in R, including powerful and state-of-the-art optimization methods, which are described further in this paper. The choice of R was dictated by its stability and reliability as well as the invariable importance of this statistical programming language.

Dissolution Models

Over the years, numerous models have been proposed to quantitatively describe dissolution behavior, such as the Polli dissolution equation (*21*). Therefore, efforts were undertaken to develop a solution that facilitates the straightforward implementation of new models. RKinetDS currently incorporates 36 models that were selected from the available literature with a focus on the most frequently used ones. Lag time was added as an option in every model. Importantly, the software is not restricted to this predefined set of models. Its open architecture, facilitated by the use of configuration files and the GNU license, allows for the addition of other models or modifications to existing ones, if needed.

Configuration Files

The configuration files define settings and parameters

that control the software's behavior. They allow users to customize and save preferred settings without modifying its core code, thereby reducing the risk of errors (*22*). In RKinetDS, the configuration file is divided into five sections: 1) model equations; 2) selected models; 3) optimization methods; 4) optimization parameters; and 5) data file format. The parameters specified in sections 2–5 are adjusted via the GUI depending on the user's individual preferences, which are linked to the type of data entered, preferred models, and available computational capabilities. The model equations can also be adjusted within the software; however, these changes must be made by directly editing the configuration file, as the modifications cannot be performed through the GUI.

Model-Fitting Algorithms

Model fitting algorithms are used to estimate the parameters of the dissolution models. In RKinetDS, several optimization methods are used including Broyden-Fletcher-Goldfarb-Shanno (BFGS), Nelder-Mead, simulated annealing (SANN), and genetic algorithms (Table 1).

Table 1. Optimization Methods Implemented in RKinetDS

Method	Algorithm	Function in R
BFGS	BFGS	optim( )
Nelder-Mead	Nelder-Mead	optim( )
SANN	SANN	optim( )
genSA	Generalized SANN	genSA( )
rgenoud	Genetic + BFGS	rgenoud( )
nloptr	Genetic (CRS2)	nloptr( )

BFGS: Broyden-Fletcher-Goldfarb-Shanno method; SANN, simulated annealing; CRS2: controlled random search v 2.0.

These optimization methods are either built-in with the R basic package called optim or require the installation of additional packages, namely genSA, rgenoud, and nloptr (*23–26*). When implemented in RKinetDS, the optimizers operate in a cascade manner. BFGS is always launched during optimization, while the remaining optimizers are optional. The optimization process starts with the execution of optional algorithms, then the BFGS algorithm is applied to achieve the final optimization result.

Optimization parameters are customized by the user, including tracing of optimization function evaluations, the value of the stop criterion, and the maximum number of iterations. As with most optimization tools, the necessity for careful consideration of the optimization settings should be kept in mind to ensure reliable results.

The strengths and weaknesses of each method should be carefully considered when selecting the most suitable approach. SANN is well-known for being effective in identifying optimal solutions; however, it has a slow convergence rate and may be computationally expensive (*27*). A more suitable option may be an expanded version of the simulated annealing algorithm presented by genSA for complex non-linear objective functions (*24*). The method implemented in the nloptr package relies on genetic search algorithms to efficiently explore a wide search space with no restrictions on the objective function's form. The rgenoud package implements a mix of evolutionary and derivative-based (BFGS) optimization methods, combining the ability to find the global minimum with efficient solution refinement (*25*).

Model Selection Criteria

RKinetDS provides various parameters to compare prediction results with observed data and evaluate curve fitting with mathematical models. These parameters include 1) root-mean-square error (RMSE); 2) coefficient of determination (R^2); 3) adjusted coefficient of determination ($R^2_{adjusted}$); and 4) Akaike Information Criterion (AIC) (*28*, *29*). The exact equations are available as supplementary material. RKinetDS generates a ranking of models based on their errors in an ascending or descending manner, making it easier to differentiate between models. Selection of the most suitable dissolution model should take into account not only the performance of the model itself, but also the dissolution data provided, the characteristics of the drug product, and obtained model parameters.

Graphical User Interface

During the development of RKinetDS, emphasis was placed on providing a user-friendly GUI (Fig. 1), which was built using the Shiny R package. The choice of Shiny was based on its integration with R's practical features, which allowed utilization of R's computational and statistical capabilities, including optimization techniques for modeling dissolution profiles, and facilitated the creation of a visually appealing GUI for integration into web-based applications. This not only improves user engagement but also simplifies the interaction with the software, making it more accessible to a broader audience.

RKinetDS supports reactive programming, ensuring that the GUI is automatically and instantly updated in response to data changes, thus increasing application interactivity with relatively little code, which would be more complex in environments like C#. The GUI provides intuitive and

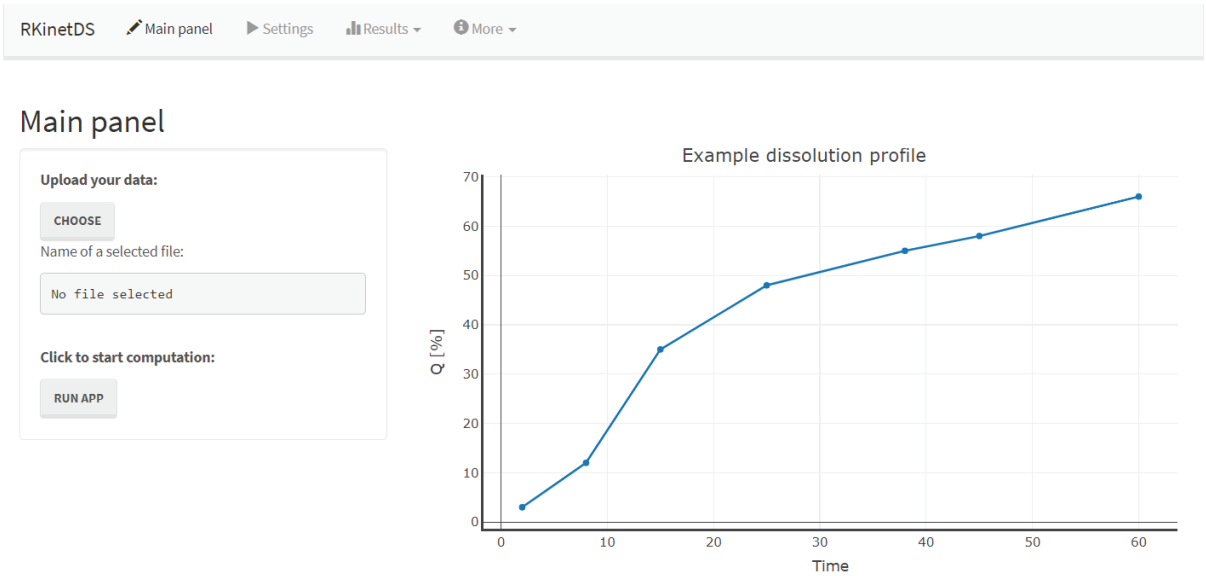

Figure 1. Screenshot of the graphical user interface of RKinetDS (main panel).

customizable data visualization options, allowing for tailored graphical representations of data (*30*). These interactive visualizations enhance the clarity of data insights and facilitate more effective data exploration. This is essential, as the initial assessment of model fitting is typically conducted visually and subsequently validated through measures of the model's fit with the data. Additionally, the software provides extensive reports including system information (operating system, installed packages with versions), settings, and seed values, enabling users to replicate results.

RKinetDS can be run locally with only R and the necessary packages installed, which are freely available for all major operating systems. Alternatively, the application can be deployed to a server and accessed through a web browser, with no additional software required on the client side, making it easy to share applications with users across different platforms and locations. This ease of use is especially beneficial for users without a deep knowledge of the R programming language, with the option of serving solutions as SaaS (Software as a Service). To demonstrate this solution, RKinetDS was deployed on the cloud-based application shinyapps.io to provide wide and easy access to the software for users (*31*).

Software Testing

To evaluate the reliability and practical applicability of the RKinetDS, its performance was assessed using real-world dissolution datasets sourced from published studies to reflect different experimental conditions and formulation types. RKinetDS was used to replicate the model fits and compare with the published results (i.e., obtained with DDSolver, which uses Nelder-Mead optimization algorithms) for each dosage form. Because some publications lacked tabulated dissolution data (i.e., only presented as graphs), WebPlotDigitizer was used to extract the numerical dissolution data (*32*). Thus, small differences in values for coefficients and model selection criteria may result.

In addition, the software was tested on Windows and Linux to ensure its independence from the type of operating system used.

RESULTS

The outcome of this work is a functional software capable of fitting various mathematical models to the provided dissolution data. Results of testing demonstrate the software's capability to analyze the dissolution processes of traditional dosage forms, such as tablets, and more complex systems, such as microspheres.

Tablets

Castro et al. evaluated four different albendazole tablets available in the Mexican market using DDSolver (*33*). The in vitro dissolution data were fitted to the first-order and Weibull models based on R^2 and AIC values to select the optimal model. For product A (reference) and C, the best-fitting model was Weibull (R^2 = 0.9998 and 0.9986, respectively).

The extracted data were used to run RKinetDS with Nelder-Mead and nloptr set as optimizers using default factory

parameters. DDSolver has several different versions of the Weibull equation. In RKinetDS, the analogous equation to the one being tested is called "Weibull with lag time." Satisfactory similarity was demonstrated between the results reported by Castro et al. and those calculated by RKinetDS (Table 2) (*33*). In RKinetDS, the Weibull equation also emerged as the most suitable model for product A and C (R^2 = 0.9999 and 0.9945, respectively) (Table 3). After running all available models in RKinetDS, the best fit was provided by the "double Weibull with lag time" model (not available in DDSolver) for both products (R^2 = 0.9999 and 0.9988, respectively).

Table 2. Amount of Dissolved Drug from Tablets: Castro et al. vs RKinetDS

Time (min)	Dissolved amount (%)	
	Castro et al. (*33*) – Reference[a]	RKinetDS (model: Weibull)
0	0	0
10	77.6057	77.9128
15	88.2992	87.7699
20	93.1652	92.9787
30	96.9130	97.5175
45	98.9131	99.4157
60	99.9686	99.8497
90	100.9758	99.9882

[a]*Product A*

Table 3. Dissolution Modeling Results for Tablets: Castro et al. vs RKinetDS

Model	Castro et al. (*33*) - Reference	RKinetDS
Reference (Product A)		
First order	K_1 = 0.143	K_1 = 0.144
	R^2 = 0.9991	R^2 = 0.9990
	AIC = 17.465	AIC = 2.073
Weibull	α = 2.1505	α = 4.3215
	β = 0.6238	β = 0.8146
	T_i = 3.6676	T_i = 0.0000
	R^2 = 0.9998	R^2 = 0.9999
	AIC = 7.9686	AIC = –5.0236
Test (Product C)		
First order	K_1 = 0.085	K_1 = 0.079
	R^2 = 0.9738	R^2 = 0.9661
	AIC = 23.914	AIC = 28.882
Weibull	α = 1.3421	α = 3.6672
	β = 0.3161	β = 0.5606
	T_i = 7.8703	T_i = 0.0000
	R^2 = 0.9986	R^2 = 0.9945
	AIC = 43.518	AIC = 18.295

AIC: Akaike information criterion.

Bilayer Tablets

Crisan et al. evaluated the dissolution profiles of various formulations of diclofenac sodium bilayer tablets with immediate and sustained dose (*34*). They applied dissolution models to better understand the mechanisms of the behavior of these tablets by evaluating the fit with the zero-order, first-order, Korsmeyer–Peppas, Hixon–Crowell, Baker Lonsdale, and Higuchi models (software used was not specified). The best fit was the Korsmeyer–Peppas model, with suggested Fickian diffusion mechanism, as the n value was below 0.45. For the formulation composed of 19% (w/w) Kollidon SR, Crisan et al reported K = 37.41, n = 0.134, and AIC = 50.5 (*34*). RKinetDS results were similar, with K = 38.50, n = 0.124, and AIC = 41.85.

Oral Suspension

For oral suspension, data from da Silva et al. were used to evaluate RKinetDS (*35*). The Weibull model was considered appropriate for describing the drug's kinetic profile with β < 1, indicating parabolic curves with initial inflection. For product A, de Silva reported β = 0.2900, and R^2 = 0.9513. RKinetDS confirmed these results, obtaining β = 0.2101, and R^2 = 0.9958.

Microspheres

Murtaza et al. evaluated the dissolution process of different formulation cefixime-loaded chitosan microspheres for prolonged drug release (*36*). They performed model analysis of dissolution data using DDSolver, and tested three models: zero order with Q_0, Higuchi, and Korsmeyer–Peppas. For formulation 3, Murtaza et al found that the most suitable one was Korsmeyer–Peppas, with K = 27.328, n = 0.412, and R_2 = 0.9708, suggesting a Fickian diffusion mechanism (*36*). Similar results were obtained using RKinetDS (K = 21.364, n = 0.4556, R^2 = 0.9642). For formulation 5, the appropriate model was also Korsmeyer–Peppas, with K = 18.191, n = 0.487, and R^2 = 0.9891, suggesting anomalous diffusion of drug (*36*). RKinetDS results were similar, with K = 15.228, n = 0.5439, and R^2 = 0.9841.

DISCUSSION

In drug dissolution studies, it is becoming increasingly common to apply suitable mathematical models to the data to better understand the mechanisms underlying the process and to compare dissolution profiles. Model-fitting techniques can be particularly beneficial in drug discovery and development by predicting bioavailability, optimizing formulations, supporting regulatory submissions with robust data about the dissolution mechanism, and comparing dissolution curves. These techniques allow

for better understanding of drug dissolution profiles, which can lead to faster and more efficient formulation development.

RKinetDS was designed to modernize the available free-to-use solutions for model-fitting that have been in use for the past 15 years. In this publication, details of its development, functionality, and effectiveness were presented. The software is fully functional and provides reliable results similar to those obtained by other methods. It is distinguished by its simplicity of use with a modern GUI, which eases navigation and simplifies analysis, and by providing extensive reports of the fitting procedure. RKinetDS features an open architecture, meaning that its source code is freely available for use, allowing for modification and expansion. Users can customize software features based on their specific needs and preferences (e.g., model equations, optimization parameters). In this way, RKinetDS differs from other tools available for free for fitting dissolution models to specific data, such as DDSolver or KinetDS.

RKinetDS is an ongoing project, with plans for future releases that include more advanced analyses using model-independent measures, such as dissolution efficiency (DE), mean dissolution such as dissolution efficiency (DE) and mean dissolution time (MDT). Additionally, future updates will include comparing dissolution profiles using various methods (e.g., similarity factor analysis).

RKinetDS is freely available on GitHub (github.com/AleksanderMendyk/RKinetDS_deploy) and the shinnyapps.io platform (jszlek.shinyapps.io/RKinetDS).

CONCLUSIONS

RKinetDS is designed to fit drug dissolution profiles to various models. This open-source software is fully functional and comprises a wide range of dissolution models, in which the best-fitting parameters are found using up-to-date optimization techniques available in R environment. RKinetDS is freely available under the GNU General Public License v3 license.

SUPPLEMENTAL MATERIAL

Supplementary materials are available upon request by contacting the corresponding author.

DISCLOSURES

The authors of the publication are the developers of RKinetDS software. They received no financial support for this work.

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