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PK/PD SOFTWARE – CURRENT RESEARCH AND FUTURE PERSPECTIVES

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ABSTRACT

Development of dosage forms requires PK/PD evaluation which helps scientists to elucidate the mechanism of action of drug and for the optimal composite design. Inclusion of PK/PD efficacy studies at early stages during the lead identification and optimization stages of a drug development program can significantly accelerate the selection of the most promising dosage forms. Nowadays the rapid development of computer hardware, software and algorithms, drug screening and PK/PD evaluation have benefited much from various computational methods which greatly reduce the time and cost of drug development. Computational PK/PD modeling helps to increase the translation of *in vitro* compound potency to the *in vivo* setting, reduce the number of *in vivo* animal studies. The purpose of this review is to provide those who are unfamiliar with the *in silico* software, with a fundamental understanding of the underlying theory. In this review, we firstly discussed the importance of *in silico* software in the PK/PD evaluation, secondly the history, applications, developer of the software, latest version and the future prospective of the popular commercial PK/PD software were discussed.

INTRODUCTION

The computational approach is one of the newest and fastest developing techniques in pharmacokinetics, ADME (absorption, distribution, metabolism, excretion) evaluation, drugdiscovery and toxicity prediction.Human pharmacokinetic (PK) predictions play a critical part in assessing the quality of potential clinical candidates where the accurate estimation of clearance, volume of distribution, bioavailability, and the plasma-concentration-time profiles are the desired end points. Although these predictions can be performed using *in vivo* data it can also be conducted successfully using *in vitro* or *in silico* data, by applying modelling and simulation techniques [1][2]. In order to reduce the consumption of time in the tedious drug development and *in vivo* evaluation process various modelling and simulation commercial software packages were developed which shows the results with greater accuracy in fraction of a second [3].The infancy of *in silico* pharmacology has been established in the early 1960s when quantitative relationships between chemical structure and pharmacodynamics (PD) and pharmacokinetic effects in biological systems began to be unveiled by computational means [4][5]. *In silico* software can be categorized into two main classes. They are Comprehensive methods and Specific methods. Comprehensive methods are also known as expert systems which mimic human reasoning and formalize existing knowledge on ADME pathways.Specific methods can be divided into ligand-based and target-based techniques [6]. There are several advantages in the commercial modelling and simulation software over the conventional *in vivo*

techniques in the estimation of PK/PD parameters. The *in silico* software offer very high throughput at a reasonable cost, the end points can be determined with high accuracy, they offer a potential to screen virtual compounds [7].*In silico* models of disease can accord to a better understanding of the pathophysiology of the disease, suggest new treatment strategies, and provide insight into the design of experimental and clinical trials for the investigation of new treatment modalities [8][9].

VARIOUS SOFTWARE USED IN EVALUATION OF PK/PD

1. PK-Sim®

PK-Sim® is a comprehensive software tool for whole body physiologically based pharmacokinetic (PBPK) modeling.This PBPK software tool PK-Sim®, is a part of the Computational Systems Biology Software Suite which was developed by Bayer Technology Services, Leverkusen, Germany [10]. It combines the ease-of-use of a graphical user interface (GUI)- supported PBPK modelling software with a great extent of flexibility. It enables rapid access to all relevant anatomical and physiological parameters for humans and the most common laboratory animals (mouse, rat, minipig, dog, and monkey) that are contained in the integrated database. Relevant generic passive processes, such as distribution through blood flow as well as specific active processes such as metabolization by a certain enzyme are automatically taken into account by PK-Sim® [11]. A fully integrated Parameter Identification (PI) Toolbox provides a straightforward means to adjust key parameters of the PBPK models automatically within user-defined ranges. The Gastrointestinal (GI) model of PK-Sim® is represented using a compartmental model in which the alimentary canal which starts from the stomach to the rectum is divided into 12 compartments, each representing a distinct GI segment which is used for studying the ADME of drugs in GI tract [12].

Applications

a) Optimize multiple simulations, with different dose levels, and multiple observed data sets, simultaneously.
b) Population simulations are conveniently performed.
c) GI simulation can be performed for evaluation of various drugs.
d) Gene specific expression data are directly integrating into PBPK models using the PK-Sim® Express database which is used for the simulation at the cellular and genetic level.

Latest version

The latest version of PK-Sim® has been launched in October, 2021. This latest PK-Sim® Version 10 is comprising of new features such as, new population templates and modeling of protein expressions in PK-Sim® has been redesigned and extended.

2. GastroPlus®

GastroPlus® is a mechanistically based simulation software package that simulates intravenous, oral, oral cavity, ocular, inhalation, dermal, subcutaneous, and intramuscular absorption, biopharmaceutics, pharmacokinetics, and pharmacodynamics in humans and animals [13].GastroPlus® is a product of SimulationsPlus which was incorporated in Lancaster, California in July, 1996. The GastroPlus® Version 1.0 was released by SimulationsPlus in July, 1998. GastroPlus® has been separated into modules to make it easier for companies and academic institutions to license only the features they need in each department. The currently available ten modules are, Drug-Drug Interaction, PBPKPlus™, ADMET Predictor® [14], Additional Dosage Routes, Metabolism and Transporter, Biologics, Optimization, PDPlus™, PKPlus™, IVIVCPlus™. The underlying principle of the GastroPlus®is the ACAT (Advanced Compartmental and Transit) model [15]. The PBPKPlus™ Module extends GastroPlus® to define a PBPK model consisting of various tissues which can easily simulate the distribution and elimination of compound throughout the body and track concentrations in any tissue. The ADMET Predictor® of GastroPlus® can be used to predict over 175 properties, including solubility, logP, pKa, sites of CYP metabolism etc. The other modules of the GastroPlus® can be used to simulate mechanistic absorption and disposition through dermal (topical and subcutaneous),

intraoral (oral cavity), pulmonary (intranasal and respiratory), ocular, and intramuscular routes and to predict mechanistic and static drug-drug interactions (DDIs) [16] among drugs and metabolites [17], and to predict PD effect changes due to changes in dose, dosage form, and dosing regimens estimate PK [18] parameters for noncompartmental analysis (NCA) [19], along with 1-, 2-, and 3-compartment PK models from pharmacokinetic studies (IV and/or oral) without the need to run full simulations.

Applications

a) Simulation can be easily performed to study oral drug absorption and pharmacokinetics.
b) Easily simulate the distribution and elimination of compound throughout the body and track concentrations in any tissue.
c) Parameter Sensitivity Analysis (PSA) feature in the software can predict the effect of inter-individual variation in PK parameters on drug absorption and guide formulation design.
d) IVIVC (*In Vitro-In Vivo* Correlation) developed by GastroPlus® can be used to predict plasma concentration-time profiles for formulations with different *in vitro* release rates or dose strengths to support internal research and regulatory applications.

Latest version

SimulationsPlus releases the latest version of GastroPlus® Version 9.8.2 on October, 2021.

3. Simcyp™ PBPK Simulator

The Simcyp Simulator is one of the pharmaceutical industry's most sophisticated PBPK platform for determining first-in-human dosing, optimizing clinical study design, evaluating new drug formulations, setting the dose in untested populations, performing virtual bioequivalence analyses, and predicting drug-drug interactions (DDIs) [20]. Simcyp founded in the year 1999 by the Certara, Princeton, New Jersey. In the beginning the development of Simulator started with simple static drug-drug interaction calculations. This was expanded to dynamic models and the minimal PBPK model which was subsequently expanded to full PBPK models [21].Simcyp® Pediatric Simulator [20], Simcyp® Cardiac Safety Simulator (CSS), Simcyp® Long Acting Injectable (LAI), Simcyp®Lactation are some of the specialized modules developed by Certara which can be connected to the PBPK Simulator.

Applications

a) Early pharmacokinetic determination of first-in-human dosing can be determined.
b) The Simulator provides valuable information for designing clinical trials, to reduce trial size and complexity and to obtain clinical trial waivers [22].
c) Quantitative evaluation and prediction of drug-drug interactions (DDIs) involving drug-metabolizing enzymes and membrane transporters, to evaluate PK variability as a function of ethnicity, organ impairment, and pharmacogenomics [23].
d) Dosing recommendations for different populations of patients, including paediatrics, geriatrics, ethnicities, and organ impairment can be easily predicted.

Latest version

The latest version of Simcyp™ PBPK Simulator is Version 21 which has the key features of hepatic and renal impaired populations, expansion of genotype library, expansion of compound library and expansion of the human brain model to 5 compartments.

4. NONMEM®

NONMEM® stands for NONlinear Mixed Effects Modelling. The NONMEM computer programme is written and distributed in ANSI (American National Standards Institute) FORTRAN 95 code and therefore can be used with most hardware and operating systems incorporating a FORTRAN 95 compiler adhering to the ANSI standard. The NONMEM software was originally developed by Lewis Sheiner and Stuart Beal and the NONMEM Project Group at the University of California, and has been used for over 30 years for studying population analysis by many pharmaceutical companies and the PK/PD modeling community [24]. Its continued development and improvement by ICON Development

Solutions, Dublin, Ireland assurepharmaceutical companies that they may continue to use the analysis tool with which they are familiar for present day pharmaceutical development.

Applications

a) Population pharmacokinetic data can be analyzed.
b) Mixed effect modeling can be conveniently performed which is especially useful when there are only a few pharmacokinetic measurements from each individual sampled in the population, or when the data collection design varies considerably between these individuals [25].

Latest version

The latest version of NONMEM is NONMEM® 7.5.

5. Phoenix WinNonlin®

WinNonlin is a pharmacokinetic software package which was developed by Certara, Princeton, New Jersey that has grown and evolved over the past 20 years. The most familiar versions of WinNonlin (Version 3 – Version 5) were stand-alone Windows-based software packages used to perform NCA[26] and single subject non-linear model fitting [27]. The Version 6 [28][29] represents a complete redesign of the software and incorporates many new features of modern software. From this version it was renamed as "Phoenix".

Applications

a) It is a NCA, PK/ PD, and toxicokinetic (TK) modeling tool, with integrated tools for data processing, post-analysis processing including statistical tests and bioequivalence analysis, table creation, and graphics [30].
b) Bioequivalence, Linear Mixed Effects, Crossover, Convolution, Deconvolution, Non Parametric Superposition and Semi compartmental Modelling can be performed.

Latest version

The latest version of Phoenix WinNonlin® is Version 8.3.

6. BOOMER

BOOMER is the one of the oldest pharmacokinetic software. It is an improved version of an earlier non-linear regression program, MULTI-FORTE.Models could be defined in terms of integrated or differential equations. It is a desktop computer program for parameter estimation or simulation. Its program is written in FORTRAN 77 and compiled on the Apple Macintosh computer using the Microsoft FORTRAN (Version 2.2) compiler or on the IBM PC XT using the Microsoft FORTRAN (Version 4.01) compiler [31].

Applications

a) Weighted least-squares optimization was performed using a Gauss-Newton, Marquardt, or Simplex method.

7. QikProp

QikProp predicts the widest variety of pharmaceutically relevant properties such as log S (aqueous solubility), log BB (Blood-Brain partition coefficient), overall CNS (Central Nervous System) activity, Caco-2 (Colorectal adenocarcinoma cells) and MDCK (Madin-Darby Canine Kidney cells) cell permeability, log Khsa for human serum albumin binding, and log IC50 [32]. QikProp was developed by Schrödinger, New York.

8. PK Tool

This is a tool to analyse *in vitro* and *in vivo* ADME & PK data. The Bill and Melina Gates Foundation has funded a project to develop a free Pharmacokinetic prediction tool. It is a freeware tool which can be downloaded from Medicines for Malaria Venture (MMV) website. Version 1.0 of PK Tool developed by XenologiQ which is now a part of Certara and the Version 2.0 developed by StevicaCvetkovic.

Applications

a) Human PK and dose can be easily predicted.
b) Gives guidance on the relative confidence that can be attached to any simulation.

Latest version

The latest Version 3.0 has been launched on February 2020 [33].

9. PKSolver

PKSolver is a freely available menu-driven add-in program for Microsoft Excel

which is written in Visual Basic for Applications (VBA), for solving basic problems in pharmacokinetic and pharmacodynamic data analysis [34]. This program provides a range of modules for PK and PD analysis including NCA, compartmental analysis (CA), and PD modeling. Multiple absorption sites (MAS) and enterohepatic circulation (EHC) are the two special built-in modules, were developed for fitting the double-peak concentration–time profile based on the classical one-compartment model [35]. Although PKSolver [36] is an add-in program it gives satisfactory results as that of the commercial PK/PD software packages like WinNonlin.

Applications

a) NCA calculation, nonlinear fitting analysis, complex PK model simulation, BA/BE simulation, IVIVC analysis and modeling of quantitative structure PK relationships can be effortlessly performed.

10. DDSolver

DDSolver is a freely available add-in program [37]. It is capable of performing most existing techniques for comparing drug release data, including exploratory data analysis, univariate ANOVA, ratio test procedures, the difference factor f_1, the similarity factor f_2, the Rescigno indices, the 90% confidence interval (CI) of difference method, the multivariate statistical distance method, the model-dependent method, the bootstrap f_2 method, and Chow and Ki's time series method [38]. It is written in VBA. Since many scientists and students are already familiar with the Excel it is easier to operate this DDSolver [39].

Applications

a) Study the characterization of drug release.
b) Assessment of similarity between drug dissolution data.

a.

b.

c.

d.

e.

f.

Fig 1: Commercially available software:a. PK-Sim®; b. GastroPlus® ; c. Simcyp™ PBPK Simulator; d. NONMEM®; e. Phoenix WinNonlin®; f. QikProp

FUTURE OUT LOOK

In silico drug designing and pharmacokinetic software play an important role in designing innovative proteins or drugs in biotechnology or the pharmaceutical field and to eliminate the tedious *in vivo* study. Future PK/PD prediction using *in silico* tools should be focused on the integration of high quality PK database, bioinformatics, systems biology and toxicology data [40]. Apart from the whole organ simulation the present research is going on in the cellular, protein and gene level simulation which leads to the development of various commercial software [41]. Computational Software Market size is estimated at $700.4 million in 2021, projected to grow at a Compound Annual Growth Rate of 3.5% during the forecast period 2022-2026.

CONCLUSION

This review not only helps in knowing the history of the software but also assist in getting more knowledge about pharmacokinetics and pharmacodynamics simulation. Considerable progress has been made in the last few years in the development of computational approaches for the prediction of ADME which have wide utility in the research and pharmaceutical sector. Different software tools are appropriate for the different stages of drug development, the user must know about the fitness for purpose of the software. In recent days the transparency of the software are enhanced by the producers which assure the researchers and pharmaceutical industries to utilize the software without any fear and thus promising tool for the development of dosage forms.

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