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Invitro-invivo Simulation Studies on Capecitabine Loaded Niosomes Intended for Brain Targeting

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Abstract

Insilico modelling are renowned for their potential to extend the *invitro* data logically into *invivo* data. In the current study pk- sim simulation software by open systems pharmacology (osp) was utilized to extract *invivo* data of in-house developed capecitabine (cptb) niosomes formulation intended for brain targeting. The selected software allowed to consider brain as a compartment and thus estimated the correlation between simulated values and theoretical values of cptb. Various pharmacokinetic parameters of cptb namely molecular weight, solubility in water, p_{ka}, log p, intestinal permeability, unbound plasma fraction were provided as input parameters. Essential pharmacokinetic parameters namely c_{max}, t_{max} auc and plasma half life ($t_{1/2}$) were derived from the pk-sim software. Comparative plasma concentration time profile of experimental values vs simulated values ear-marked that there exists point to point correlation between invitro parameters and invivo parameters. It was also proved that the simulated values obtained were inline with the standard bibliographic pharmacokinetic parameter values of capecitabine indicating the scope for utilization of the pk sim software various other drug molecules and formulations.

Keywords: simulation studies, brain targeting, *insilico,* pk-sim software

Introduction

In-silico model tools are accomplished to recognize the critical parameters that comprise drug physicochemical properties, dosage form related factors that affect the drug *invivo* performance thus predicting the drug absorption built on the selected data set of input factors. The benefits of insilico simulation tools required less investment in resources and time compared to invivo studies and also to suggest potential to screen virtual compounds. Insilico model similarly reduced the number of experiments, simultaneous cost, and time mandatory for compound selection and development. In silico simulations have been recommended to decrease time and effort in developing generic drug products. (1) Physiologically based pharmacokinetic and pharmacodynamic (pbpk/pd) modeling has developed a extensively implemented tool in the industry to get a quantitative description of concentration–time profiles in dissimilar organ and tissues across human populations. A current survey exhibited that nearby 70% of medical company's use pre-clinical pbpk/pd modeling in all therapeutic areas (2).

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Various commercial pbpk modeling simulation software comprising of gastroplus™, pk-sim, simcyp, adme works ddi simulator, chloepk etc. These software packages offer considerably flexibility to the pbpk model developer, nevertheless more innovative modeling and programming skills and experience are essential; thus, they are less appropriate for beginners. These packages are expert pbpk modeling software packages, offer less flexibility in model development, but they also involve less mathematical and modeling experience. (3) Pk-sim® is a comprehensive software tool for whole body simulation by using pbpk modeling. It permits rapid access to all significant anatomical and physiological parameters for humans andthe supreme collective laboratory animals such as a mouse, rats, minipig, dog, monkey, beagle, and rabbit that are confined in the integrated database. Pbpk modeling has been used for decades in the field of toxicological risk assessment and has in current years been extended toward the application in the drug research and development area. Software tools frequently focus on isolated characteristics of drug action, such as pharmacokinetics at the organism scale or pharmacodynamic interaction on the molecular level. Pk-sim offers altered model structures for significant alterations between small and large molecules. (4) Pk-sim is a freeware which is widely available for utilization and easily understandable, compared to other software's used for pk parameter estimation.

In the current study capecitabine loaded niosomes intended for brain targeting through intranasal route was taken as input formulation in pk-sim software. Capecitabine is a chemotherapeutic agent with antineoplastic action consumed orally for the treatment of colorectal & metastatic breast cancer. It has a clinically proven efficacy against brain metastases. However, the role of capecitabine in treating cns disorders is unexplored. Hence, an attempt was made to develop a niosomal formulation which can target brain effectively when administered through intranasal route. (5)

Pk-sim software is used as an alternate and animal less approach for determination of pharmacokinetic parameters of capecitabine. The formulation tested was intended to target the brain. Pk-sim software allows to consider brain as a compartment and thus estimate the correlation between simulated values and theoretical values of capecitabine.

Materials and Methods

Insilico software

Open systems pharmacology (osp) is an open science community converging on systems pharmacology with a robust prominence on the pbpk modeling. Osp makes previously profitablesoftware implements pk-sim and mobi freely presented as osp suite under the gplv2 license where all source code and all content are public. The osp suite comprises different software tools and has a modular design to permit efficient multiscale modeling and simulation. (6)

Method

Simulation studies were carried out by using pk sim® version 9. Generally, this software consists of 2 type's blocks i.E. Building blocks & simulation.

Building blocks

A building block of the current study consist of the following elements:

Selection of individual

European male species was selected for study with their age limit of 30 years, 75 kg body weight, height 176 cm, bmi of 23.57 Kg/m^2.

Population

about 100 population consisting of both male & female can be selected. Currently we are studying the simulation parameters at an individual level (each individual considered as one group).

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Generating compound template

Existing compound template, was regenerated as capecitabine basic template. Various physicochemical properties were given as inputs i.E. Log p value of 0.83nlog units was given as input, albumin was selected as binding site for capecitabine & the amount of unbound fraction was given as 65% in human & effective molecular weight of 359.35 G/mol was loaded as input using theoretical reference data (7 & 8). Further, pka value of capecitabine i.E., 8.30 & Solubility of capecitabine in water i.E., 26 Mg/ml was given as input based on theoretical reference data (9).

Adme parameters like permeability of drug was given as 0.15cm/sec. Metabolizing enzymes like cyp1a2 and cyp 3a4 were mentioned as input, since those enzymes play a major role in drug metabolism as per the literature. (10) Renal clearance of gfr fraction was given as 0.21 According to literature. (11) After loading necessary input values in accordance with the established literature, advanced parameters are auto-generated by the software.

Generation of formulation template

Formulation templates are generated by selecting the options which corresponds to the type of selected drug release kinetics. Capecitabine niosomes formulation followed first order kinetics which is affirmed using the *in-vitro* drug release studies. Hence, the input was selected as first order. Further, as per the input requirements of software capecitabine half-life i.E., 45 Min was given as input to the generated formulation template. (12)

Administration protocol generation

Administration protocol was generated with the following basic elements. Among the available elements for administration type (intravenous bolus, intravenous infusion, oral or user defined), user defined template was selected since our test formulation (capecitabine niosomes) was formulated as intranasal drug delivery system. Various input parameters in the user defined template namely, dose of capecitabine was given as 150 mg, dosing intervals as single dose, targeted organ like brain, targeting compartment as a plasma were given to the software.

Addition of some events

Some events like meal energy content of selected individuals (100 k. Cal), meal volume of 0.591, Meal fraction solid of 0.60, Gall bladder emptying lag time of 30 minutes were auto generated as inputs by the software.

Attachment of observed experimental data

Excel sheet was generated by exporting the data from the graph obtained in the earlier step i.E., Formulation template generation. Alternatively, dissolution data for the selected drug can be given as input if table option was selected in the formulation template generation step.

Excel sheet containing time and fraction dose released was attached for performing simulation in the further step.

Simulation studies

After completion of the above-mentioned building block steps then the stimulation step can be performed using a simple protocol for the simulation of small molecules or advanced protocol for the simulation of proteins or large molecules. In the current study we have followed a protocol for small molecules. In this process, the building block previously generated was added to the simulation icon for human individuals for a small molecule to facilitate simulation. Simulation was initiated by clicking on the define setting & run option to get simulated *invivo* data generated by the software in the form of time profile graph containing both simulated & observed curves. Further simulation can be performed to obtain the parameter identification and sensitivity analysis.

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Results and Discussion

Simulation studies

Simulation studies were performed using pk sim® with the construction of physiological based pharmacokinetic models of both population & human individuals as well as large animal species. In the current study, building blocks were generated using standard european humans as a selected individual. Input in terms of physicochemical properties i.E. Molecular weight of 359.35 G/mole, the solubility of water 26 mg/ml, fraction unbound to albumin of 65%, pka value of 8.3, Log p value of 0.83 Present in the literature for capecitabine were given to simulation software. The same values were represented in table no:1 further, generation of formulation & administration protocol for simple molecule into simulation study of individual humans yielded a comparative profile of simulated & experimental data as illustrated in figure no:1 the results conclude that the simulated pk parameter values were in correlation with bibliographic values as tabulated in table no:2.(13) The obtained pk parameter values which were within the acceptable bibliographic ranges indicate that the simulation model was significant.

Table no: 1 capecitabine parameters included in the software as input

Input parameters	Values
Molecular weight	359.35 g/mole
Solubility (water)	26 mg/ml
Pka (acid)	8.3
Log p	0.83 Log
Intestinal permeability	3.44 × 10−7 cm/min
Unbound plasma fraction (fup)	0.0065

Table no: 2 pharmacokinetic parameters with simulated data in comparison with bibliographic values.

Pharmacokinetic Parameters	PBPK simulation model	Bibliographic values
AUC	0.58 mg*h/l	0.461 – 0.698 mg*h/l
Cmax	5.98 µ mol/1	0.64 - 15.4 µ mol/l
Tmax	1.15 h	1 - 3 h
t1/2	0.75 h	0.55 to 0.89 h

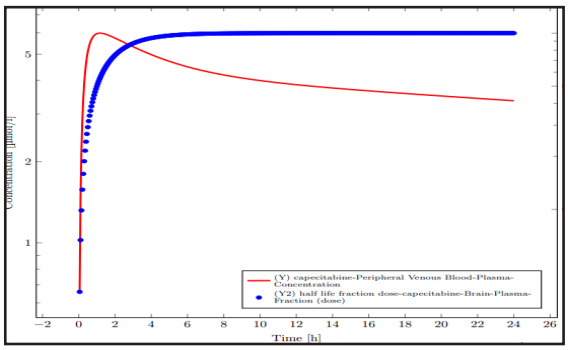

Figure no: 1 comparative plasma concentration time profile of experimental and simulateddata.

Conclusion

Pk-sim® is a novel whole-body pbpk in silico model that can be used throughout all stages of the drug r&d process. It was developed, tested and evaluated in real-life projects within the pharmaceutical industry. Comparison of simulation results with experimental data provides a valuable method of interpreting rather than simply describing pk results. This particularly helps the researcher to identify specific effects (e.G. The relevance of active transport processes) very early on and, thus, can guide the experimental efforts, saving time and money.(14)

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Simulation studies performed using pbpk modeling of pk sim software aided in extrapolating the *invitro* drug release data to *invivo* healthy human volunteer data and the obtained pk parameters were in simulation with the bibliographic values. Hence, the study finds the scope of the optimized formulation in delivering the drug incorporated at the brain region when incorporated intranasally. The study also portrays the scope of exploring the potential of optimized formulation in treating various cns disorders.

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