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A Brief Review on Dissolution Simulation Software

Mehak Jain[1,*], Kaushiki Patel[1]

Abstract

Pharmaceutical industries frequently use simulation software with real-time responses for a variety of purposes, such as dissolution simulation. In essence, it is a tool that lets the user to simulate an operation and see it happen without actually conducting it. Equipments are frequently designed using simulation software to ensure that the finished output will be as near as to the design specifications as possible without costly process adjustments. Advanced computer programs can simulate power system behavior and complex biological processes. These are employed to simulate physical responses in real time. A set of mathematical formulas are used to simulate real-world phenomena in simulation software. Simulator software is frequently used in equipment design to get the finished product as near to the design parameters as feasible without having to make expensive process adjustments. The purpose of simulation software is to examine the feasibility and reproducibility of developing an in vitro/in vivo interaction using GastroPLUS™, PK-Sim®, Simcyp®, and DDDPlus (IVIVR). These findings emphasize the significance of choosing a suitable experimental strategy to determine the in vitro dissolution rate, which will later be used as a basis to create in vitro- in vivo correlations.

Keywords: Dissolution simulation software, vitro-in vivo relationship (IVIVR), GastroPLUS™, PK-Sim®, Simcyp®, DDDPlus

INTRODUCTION

A computer can simulate any phenomenon that can be reduced to numerical values and equations. Power systems and different biological processes that occur inside the human body can be mimicked by sophisticated computer programmes [1]. Currently, systems for in vitro experiments and simulation are used to forecast the performance of generic drugs. GastroPlus™, PK-Sim®, and SimCyp® are a few examples of computer simulations that have incorporated drug modeling [2]. To assess the reliability of these technologies, a thorough review of publications is necessary given the pervasive use of optimization of computational models to fit observed data (Figure 1).

COMMON STEPS FOR IN VITRO DEVELOPMENT PREDICTIVE DISSOLUTION MODEL

There have been many methods for forecasting oral absorption documented up to this point. Simple dissolving tests, bio relevant dissolution studies, and laboratory simulations of the GI tract using his PBPK model were all used to estimate oral medication absorption depending on the physicochemical characteristics of the drug component.

Although any of these methods can be used to generate qualitative hypotheses about oral absorption, only particular drug and dosage form combinations permit them to be utilized to generate quantitative assumptions about oral

***Author for Correspondence**
Mehak Jain
E-mail: mehakjain287@gmail.com

[1]Reseach Scholar, Department of Pharmaceutics, Indore Professional Studies Academy, College of Pharmacy, Rajendra Nagar, Bijalpur, Indore, Madhya Pradesh, India

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absorption. This PBPK model can currently produce quantitative and qualitative predictions of plasma levels following oral administration for both formulations with an early release and those with a prolonged release by merging the outcomes of biologically relevant dissolving tests with that model [3]. The principles of the standard experimental dissolution method are applied in the development of predictive in vitro dissolution modeling, and the rejection of batches that are not bioequivalent is based on these principles (i.e., dissolution behavior clearly addresses unexpected deviation from expected bio performance.). There are numerous documents used for the development of predictive solution models as well as empirical and principle-based approaches (Figure 2) [4].

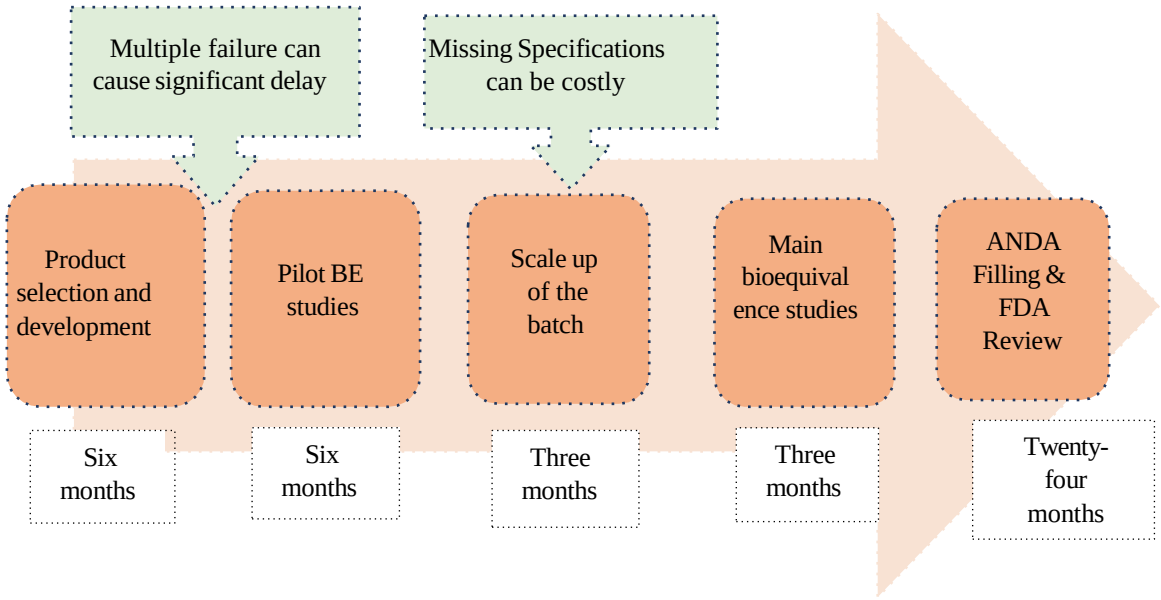

Figure 1. Schematic showing the generic product development process and where delays can be avoided using an in-silico platform.

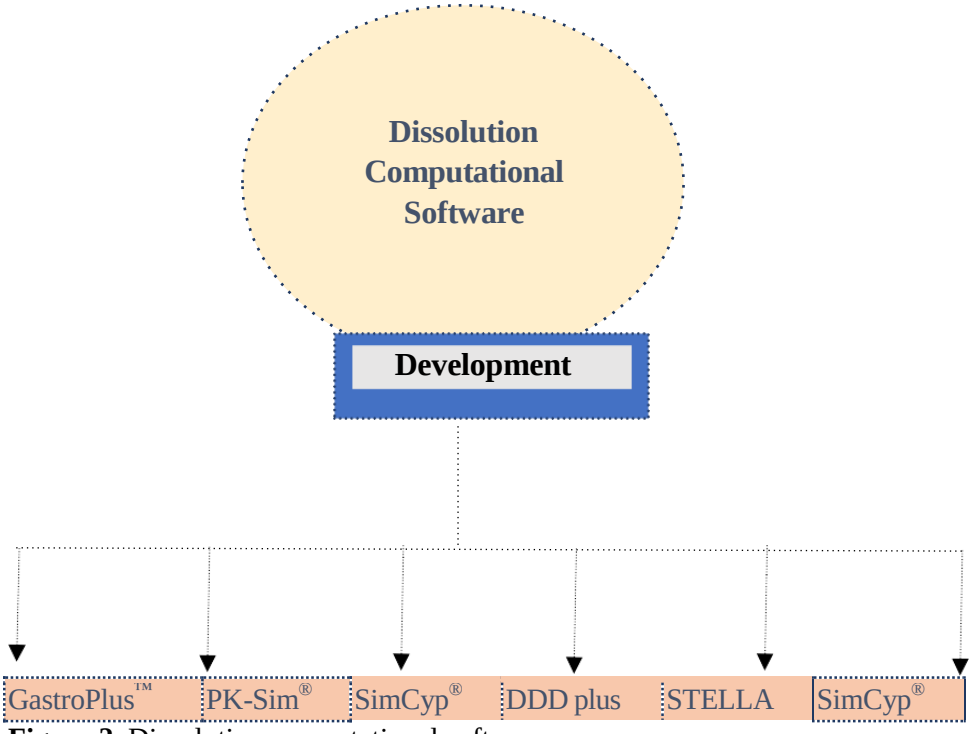

Figure 2. Dissolution computational software.

NEED OF DISSOLUTION SIMULATION SOFTWARE

The primary bodily organ for absorption is the GIT, which consists of the stomach, small intestine, and mouth. To predict in vivo medicinal outcomes, the small intestine is further divided into the duodenum, jejunum, and ileum. Drug compounds that need in vitro testing must show what behavior they will exhibit when exposed to the GIT's changing environment [5]. For quality control, the traditional in vitro pharmacopoeia dissolution test was mostly employed. However, this type of test does not consider dynamically changing upper GIT conditions. These traditional problem-solving methods replicate one or more GIT circumstances.

Most frequently, a dissolution test is used for quality assurance to guarantee batch-to-batch repeatability of pharmaceuticals used in clinical studies and therapies. To evaluate whether the medication can deliver the active pharmaceutical ingredient (API) on schedule manner, this frequently entails employing a simple aqueous buffer media (Figure 3) [6].

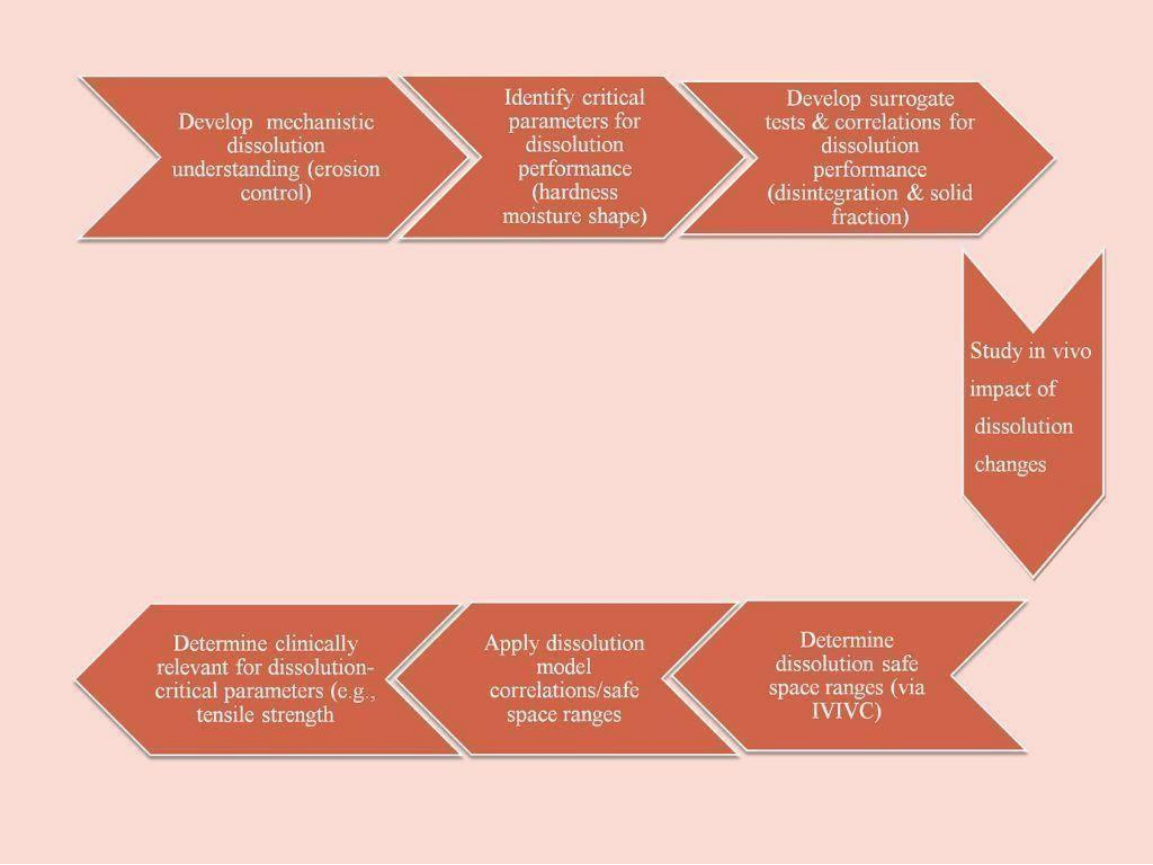

Figure 3. Dissolution model building.

Since the majority of medications in the current pipeline of drug research are poorly soluble, more careful consideration of in vivo settings is needed when developing dissolving algorithms to predict in vivo drug performance [7]. Necessary for ensuring quality. It was recommended to use a variety of media to mimic upper gastrointestinal tract diseases.

BIO RELEVANT MEDIA

It is suggested that some media imitate physiological conditions more accurately than a dose form's in vivo dissolving characteristics. These media configure the media discussed in this section, and they are listed in the tables that follow. Details on how to prepare for and justify specific media appearances are given Tables 1 and 2 [8].

PHARMACOKINETIC MODEL BASED ON PHYSIOLOGY

Segmenting the body into several physiological compartments is a crucial aspect of PBPK modeling. Oral administration to investigate how the elements of the digestive system are arranged in relation to one another. The use of PBPK modeling is becoming more prevalent in fields and industries outside of its traditional usage in assessing the danger of chemicals in the environment. Examples include drug development, evaluating the safety of consumer products, and clinical or medical practice [9]. The advancement of cheminformatics methodologies to estimate the physicochemical and pharmacokinetic (PK) characteristics of substances is helping to support the growing usage of PBPK modeling by filling in the gapsin the in vivo and in vitro data that underlie the simulation model [10].

Table 1. Gastric media composition.

Composition	**SGF**	**FaSSGF**	**FaSSGF V2**	**FeSSGF**
Lecithin (mM)	–	0.02	0.02	–
Sodium taurocholate (mM)	–	0.08	0.08	–
Pepsin (mg/ml)	3.2	0.1	0.1	–
Acetic acid (mM)	–	–	–	17.1
Sodium acetate (mM)	–	–	–	
Sodium chloride (mM)	34.2	34.2	68	237.0
Hydrochloric acid (mM)	71.0	25.1	q.s	–
Milk/buffer	–	–	–	1/1
Characteristic parameter				
pH	1.2	1.6	1.6	5.0
Osmolarity (mOsm/kg)	–	120±2.5	–	400
Buffer capacity (mmol/l/ΔpH)	–	–	–	25

SSG – Simulated gastric Fluid, FASSG – fasted state simulated gastric fluid, FeSSGF – fed state simulated gastric fluid, q.s – quantum sufficit

Table 2. Small intestinal media composition.

Composition	**SIF**	**FaSIF**	**FaSSIF V2**	**FeSSIF**
Lecithin (mM)	–	0.75	0.2	3.75
Sodium taurocholate (mM)	–	3	3	15
Glycerol monooleate (mM)	–	–	–	–
Pancreatin (mg/ml)	10	–	–	–
Acetic acid (mM)	–	–	–	144.0
Maleic acid (mM)	–	–	19.1	–
Monobasic Potassium phosphate (mM)	50.0	28.7	–	–
Sodium Chloride (mM)	–	–	68.6	–
Potassium chloride (MM)	–	103.3	–	203.9
Sodium hydroxide (mM)	15.4	q.s	34.8	q.s
Characteristic Parameter				
pH	6.8	6.5	6.5	5.0
Osmolarity (mOsm/kg)	–	270 ± 10	180 ± 10	635 ± 10
Buffer capacity (mmol/l/ΔpH)	–	–	10	–

SIF – Simulated intestinal fluid, FaSSIF – fasted state simulated intestinal fluid, FeSSIF – fed state simulated intestinal fluid, q.s – quantum sufficit.

The necessity for PBPK modeling has grown as regulatory organizations have pushed for the creation of alternatives to animal models. More accurately in silico prediction tools new software programmes connected to PBPK are developing in response to the growing emphasis on alternatives to animal models. Thus, a broad variety of PBPK modeling systems have been developed, typically to handle problems from the viewpoint of a particular discipline, providing aspiring modelers with a wide range of software choices [11].

GastroPLUS™

In both humans and animals, the pharmacokinetic and absorption processes of oral and intravenous medications are modeled using the GastroPLUS™ simulation software. The physical processes involved in drug transport, dissolution/precipitation, intraluminal degradation, absorption/release, intestinal metabolism, hepatic metabolism, renal clearance, excretion, and other clearance mechanisms are all well-represented in each simulation [12]. About 90 differential equations must be numerically integrated to represent the event. The purpose of this study was to determine whether using the simulation programs GastroPLUS™ in conjunction with in vitro/in vivo relationships (IVIVR) was feasible and reproducible [13]. For a few BCS II connections, a bio waiver was used because of Gastroplus™. Thus, a broad variety of PBPK modeling systems have been developed, typically to handle problems from the viewpoint of a particular discipline, providing aspiring modelers with a wide range of software choices [14].

Model for Advanced Compartmental Absorption and Transit (ACAT model)

The modeling tool GastroPLUS™ serves as the foundation for the ACAT model. The BCS classification concept and prior understanding of GI physiology serve as the foundation for this semi-physiological model. A framework of coupled linear and nonlinear rate equations is used to explain how physiological circumstances affect medication absorption as it passes through various GI compartments [15].

The CAT model, which considers intestinal absorption and first-pass metabolism, served as the foundation for the development of the ACAT model [16]. This model has nine compartments, including the stomach and seven small and large intestine segments, six drug states, including unreleased, undissolved, dissolved, degraded, metabolized, and absorbed, and three excretion stages (unreleased, undissolved, dissolved). Along with non-linear metabolic/transport kinetics, it also has linear transfer dynamics. To predicting oral medication absorption, physiological changes, physicochemical factors (pka, solubility, density, permeability & particle size), physiological factors (gastric emptying, intestinal transit, first-pass metabolism, intestinal transit, luminal transport), and dosage considerations must all be considered (dosage form, dose) (Figure 4) [17].

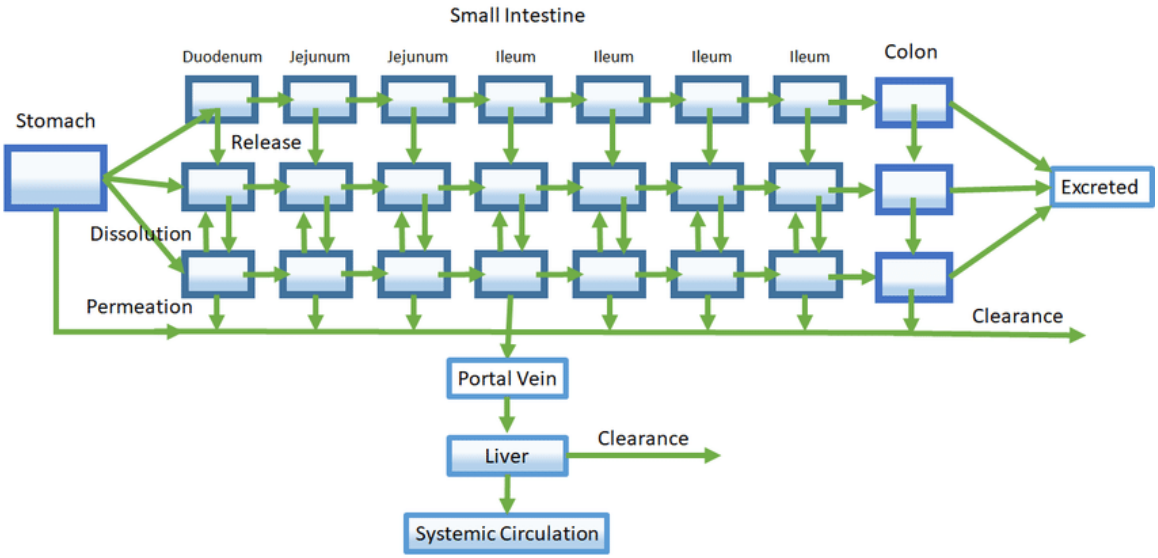

Figure 4. ACAT model.

TNO Gastro-Intestinal Model (TIM1)

TNO Nutrition and Food Research developed and constructed a dynamic multi-compartment system (Zeist, Netherlands). The system includes a model of the TNO digestive system (TIM1) [5]. It has four compartments: the jejunum, ileum, duodenum, and stomach.

Each compartment contains several valves that enable the regulated transfer of contents via impulses from one object to another [18].

Additionally, the level sensors attached to each segment of the small intestine, which appear when you need to pulse to the subsequent segment, control the movement. The water jacket in each compartment contains two parts that alternately contract and maintain a temperature of 37°C to simulate body temperature, simulating peristalsis, pH, established procedures [19]. Each compartment has its own set of predefined procedures and pH profiles, and the model automatically updates these profiles as necessary by secreting acid or base.

Pepsin, lipase, electrolytes, pancreatin, and bile salt are just a few of the physiological secretions that are delivered into different compartments [20, 21].

TIM1 mimics various parameters of upper GIT, i.e.:

i. The peristalsis processes.
ii. PH regulation in each compartment.
iii. Secretion of enzymes and enzymatic activity.
iv. Salt content of bile.
v. The physiological transit time and gastric emptying.
vi. Dissolution and removal of digesting and solubilization products.

Any sort of human subject, including (infant, geriatric, etc.), as well as eating nutritional effect, can alter any of the factors mentioned. This model has been demonstrated to be reliable and reproducible based on in vivo evidence [22].

PK-Sim®

A technology called PK-Sim® is used to analyzes in vivo PBPK in people and based on the experimental laboratory animals such mice, guinea pigs, dogs, rats, and monkeys. For various IR and

ER dosage forms, depending on the dose form, this model encompasses the GI transit, disintegration, and dissolution processes.

Software for full-body pharmacokinetics simulation based on physiology is called PK-SIM®. Permit an explanation of biological foreign matter, particularly medication fate, based on a mammal's body's mathematical expression, physical makeup, and physiological determination elements [23].

Because it incorporates descriptions of oral absorption, systemic distribution, dissolution and metabolism, and excretion, PK-Sim® differs from other available on the market physiology-based models. These other models just address the process of gastrointestinal absorption [24]. While this results in a very complex structural model, it has the advantage of simply describing each activity and producing simulation results that are equivalent to those of genuine pharmacokinetic trials.

A transit behavior, which shows how the substance-containing package moves through the intestine, and a feeding-dependent, gastric release function, which enters the intestine, are characteristics of the passage of an applied dose of substance [25]. At each time point, the amount of substance absorbed into the portal vein is computed.

SimCyp®

The most comprehensive physiological pharmacokinetics (PBPK) platform for determining first-in-human dose is the Simcyp® Simulation, clinical trial design optimization, evaluation of new drug formulations, and dosing validation in untested populations. Create; carry out virtual bioequivalence evaluations, drug forecasts, and drug-drug interactions (DDI) [26]. Simcyp® is appropriate for use with biologics, ADCs, generic medications, and novel therapy medicines. The simulator has a vast library of information on demography, physiological development, and the evolution of drug elimination pathways. This simulator, an amazing scientific collection with 25 subpopulations, over 100 compound files, and 10 advanced mechanical organs, is used by member firms [27]. Absorption distribution, metabolism, and excretion (ADME)and pharmacokinetic/pharmacodynamic (PK/PD) in vitro analysis to in vivo studies will allow clinical situations to be investigated and will help in drug development selections.

Unique Capabilities Specialized Modules

- *Simcyp pediatric:* Simcyp pediatrics is one of the most cutting-edge technologies for simulating medication performance and is frequently utilized in neonates, babies, and kids. This simulator includes sizable libraries on developmental physiology, drug demography, and drug elimination routes' ontogeny.
- *Cardiac safety simulator simcyp (CSS):* The biology-driven modeling and simulation system CSS evaluates the pro-arrhythmic potential of drugs, xenobiotics, and novel chemical entities with the target clinical population as a platform for the early pre-clinical and clinical evaluation of cardiovascular hazard.
- *Simcyp long acting injectables (LAI):* The LAI module of Simcyp is typically used to plan various experiments, identify potential formulation candidates, and decide whether to do animal-based studies or clinical trials.
- *Simcyp lactation:* Simcyp is primarily concerned with the health of women throughout the entire gestation period. Simcyp's lactation module is used to forecast drug exposure in nursing mothers and their infants, providing guidance on the appropriate dosage for vulnerable populations [28].

ADAM Model

The ADAM model was very similar to the ACAT model, which was just recently established based on CAT mode, with its seven-compartment small intestine transport model.

The ADAM model considers elements including gastric emptying time, small intestine transit time, and the small intestine's radius and length as estimated by the CAT model and available data [29].

The ADAM model is comparable to the ACAT model in that it also accounts for the dissolving process, gastrointestinal fluid movement, intestinal wall permeability, drug degradation, intestinal metabolism, and active transport.

The ADAM model also considers the diversity of the gastrointestinal tract, including uneven distribution of enzymes in enterocyte blood flow and the intestinal wall [30]. Dietary impacts include changes in urine, visceral blood flow, and luminal pH, as well as effects on the stomach.

A simulation tool called Simcyp® was utilized to create the model. Simcyp® correctly anticipated the plasma concentration profiles of his three modified-release formulations (rapid, moderate, and slow-acting) [31].

DDD Plus

A sophisticated computer tool called DDD Plus (Dose Disintegration and Dissolution Plus) helps drug formulating researchers model the in vitro dissolution and disintegration of active pharmaceutical ingredients (APIs).

With the new API, one calibration test is adequate under many experimental circumstances. DDD Plus makes predictions on the impact of altering the formulation or experimental conditions [32]. DDD has an impact on dissolution rate. Additionally, you are no longer restricted to finishing synthesis design via the 'cut and try' methodology.

The DDD plus model is commonly used for long-acting injectable models for PLGA microspheres, IR: Solution Model (precipitation choices), NEW CR: Coated Bead Model, Powders, Capsules, Tablets, Polymer Matrix (Swellable & Non-Swellable), Coated beads, Bilayer tablets, Delayed release coated tablet [33].

You can choose from 5 mathematical models in DDD Plus to see how any prescription component is broken down. The implications are [34]:

- Features for manufacturing products (e.g., compressive strength, tensile strength, average disintegration time).
- Physio-chemical characteristics of the formulation's pka, water solubility vs. pH, bio relevant solubility, diffusion coefficients, logP, and density components.
- The distribution of each ingredient's particle size.
- Interactions between formulation excipients and active ingredients (e.g., solubilizers, disintegrants, wetting agents).
- Precipitation solubility and dissolution are pH-dependent in microclimates.
- The fundamental hydrodynamic effects of various fluid velocities and flow patterns on each experimental instrument.
- Micelle dissolution brought on by the introduction of surfactants in the media.

STELLA Simulation

An effective quality control technique for formula evaluation and determination of the estimated in vivo drug release profile is in vitro dissolution assay. A dry powder formulation is tested for its ability

to dissolve using equipment designed for the task in a small volume of stationary medium [35]. A STELLA simulation model was developed to comprehend your system and forecast crucial variables that affect the resolution of respirable particles.

A clear and simple simulation model called STELLA® (Structural Thinking, Experimental Learning Laboratory with Animation, is systems, Lebanon, New Hampshire, USA) was developed to forecast how respirable dry powder particles would dissolve in a small volume of mucus mimetics and how they would diffuse across a membrane in a special dissolution device. Software for modeling that uses icons is called STELLA®. It creates graphic representations of project complexity [36].

STELLA® is successfully employed in the creation of different simulation models for the pharmaceutical industry, including those for gene expression, sustained-release dosage forms, prodrugs, and the pharmacokinetics of drugs taken orally and delivered topically. Using the STELLA simulation model, permeation (dissolution followed by diffusion) was computed [37].

KinetDS

In vitro dissolution testing is the best option because drug quality is the focus of the pharmaceutical industry and regulatory bodies. It is evolving into a common method for describing manufactured goods. Results of dissolution tests, however, must be available and presented in mathematical form. To do this, various models are fitted to the cumulative melting curve. Either mechanical or empirical models are used [38]. Automate the process of customization and the identification of potential drug release mechanisms from dosage forms by using software (like KinetDS). Software is readily available and is FOSS (free open-source software). A programme for fitting curves was created, called KinetDS. Specifically, to use a straightforward equation or combination of equations to explain the cumulative dissolution curve. Most of the equations used to characterize drug dissolution curves used general mechanistic and empirical models [39]. In vitro correlations are frequently developed step-by-step using curve fit using drug release data (IVIVC). The KinetDS program is needed to fit the parameters of the processing model. The GUI, high-level software commercial and commercial automation, and free availability for non-commercial use are its key objectives [40, 41].

CONCLUSION

Drug modeling has been done using computer simulations using applications like GastroPlus, PK-Sim, and SimCyp. To evaluate the dependability of these platforms, a rigorous assessment of publications is necessary due to the extensive use of optimization of in silico predictions to match observed data.

A growing number of companies and fields of study, including medication development, safety of consumer products evaluation, and medical or clinical practices, to fill in the gaps in the in vivo and in vitro data that support the modeling process, cheminformatics methodologies have been developed to predict the physicochemical and pharmacokinetic properties of compounds. This has led to an increase in the application of PBPK modeling. Regulatory organizations have supported the development and use of in silico tools as a substitute for animal models, which has raised the necessity for PBPK modeling. This has led to the development of several various PBPK modeling platforms.

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Conflict of Interest

The authors declared no conflict of interest.

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