S+ SimulationsPlus

SCIENCE + SOFTWARE = SUCCESS

Simulation software for the in vitro dissolution experiment of pharmaceutical dosage forms



www.simulations-plus.com



+1-661-723-7723

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DDDPlus[™]... The industry's only *in vitro* dissolution software for formulation and analytical scientists.

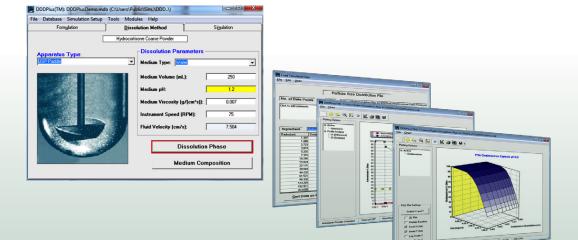
What's new in version 6?

- NEW mechanistic Artificial Stomach-Duodenum model
- NEW in vitro dissolution apparatus models for improved IVIVE of precipitation kinetics with GastroPlus®:
 - Biphasic dissolution
 - Membrane dissolution
- NEW controlled release and Long Acting Injectable dosage form models
- ... and more!

What is DDDPlus?

Utilize modeling and simulation to...

- Integrate with GastroPlus absorption/PBPK models to optimize formulations and generate mechanistic IVIVCs – better extrapolation of dissolution and precipitation inputs for PBPK models
- Assist with dissolution method development
- Assess various formulation strategies to achieve a target in vitro dissolution profile
- Apply virtual 'lot-to-lot' variability effects to help establish dissolution specifications remove the 'guesswork' associated with the identification of dissolution variability and its impact on PK exposure



2

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DDDPlus (Dose Disintegration and Dissolution Plus) is an advanced computer program for formulation scientists to simulate the *in vitro* disintegration and dissolution of active pharmaceutical ingredients (API) and excipients under various experimental conditions. For new API's, a single calibration experiment is all that is needed, after which DDDPlus will predict how changes in formulation or experimental parameters will affect the dissolution rate. With DDDPlus, you no longer have to rely on 'cut and try' methods to finalize a formulation design.

DDDPlus models the following dosage forms:

- NEW Long Acting Injectable models for PLGA microspheres
- NEW IR: Solution Model (precipitation options)
- NEW CR: Coated Bead Model
- Powders
- Capsules
- Tablets
- Polymer Matrix (Swellable & Non-Swellable)
- Coated beads
- Bilayer tablets
- Delayed release coated tablets

Matrix Physical Dimensions	
Matrix Tablet Geometry	
Cylinder 🗨	
Volume (cm^3)	Tablet Surface Area (cm^2):
0.141	1.508
Sample:	
Cylindrical Tablet	rension2: a 0.3
2	Close Cancel

4 USP experimental apparatus are defined, with estimates of fluid velocity and hydrodynamic effects for each:

- NEW Artificial Stomach Duodenum (ASD)
- NEW Membrane Dissolution
- **NEW** Biphasic Dissolution
- USP Paddle
- USP Basket
- USP Flow Thru

(closed and open loop options)

- Rotating Disk
- Pion µDISS Profiler™

DDDPlus(TM): DDDPlusDemo.mdb (C:\Users\Public\Sim\DDD\)			
File Database Simulation Setup Tools Modules Help			
Form <u>u</u> lation <u>D</u> issol	ution Method Simulation		
Hydrocortis	one Coarse Powder		
Apparatus Type: USP Paddle	Medium Type: Water		
	Medium Volume (mL): 250		
	Medium pH: 1.2		
	Medium Viscosity (g/(cm*s)): 0.007		
	Instrument Speed (RPM): 75		
	Fluid Velocity (cm/s): 7.504		
	Dissolution Phase		
	Medium Composition		

DDDPlus allows you to select from one of 5 mathematical models to describe the dissolution of any ingredients included in the formulation. The mathematical models for the *in vitro* dissolution simulation account for the effects of:

• Manufacturing properties for the product (e.g., compression force, tensile strength, mean disintegration times)

	Tablet Co	mpression Proper	ties
Ingredient	Туре	Ref. Ten. Strength	Bonding Const.
enofibrate	Active	7.5398	14.033
Starch	Disintegrant	9.484570747	10.71593236
.actose	Other	14.72409491	4.610371437
Use Compress	sion Force for Tabl	et Porosity/Tortuosity	
Use Ryshkew	itch Equation for T	ablet Porosity	
	(D) /T)	- 'h - D - 1'-	
Manual Input	of Porosity/Tortuo	isity Hatio	
Input Properties			
Tablet Tensile	Strength (MDa)-		
	s Suengui (mi aj.	1.0000	
Compression F		35.0000	
Compression F	Force (kN):		
	Force (kN):		
Compression F	Force (kN):		
Compression F Mixture Properti Bonding Const	Force (kN): ies tant:	35.0000	
Compression F Mixture Properti Bonding Const	Force (kN):	35.0000	
Compression F Mixture Properti Bonding Const Tensile Streng	Force (kN): ies tant: gth at Por=0 (MPa):	35.0000 12.2693 : 8.7279	
Compression F Mixture Properti Bonding Const Tensile Streng	Force (kN): ies tant:	35.0000 12.2693 : 8.7279	
Compression F Mixture Propert Bonding Const Tensile Streng Calculate	Force (kN): ies tant: yth at Por=0 (MPa): Properties from In	35.0000 12.2693 : 8.7279	
Compression F Mixture Properti Bonding Const Tensile Streng	Force (kN): ies tant: yth at Por=0 (MPa): Properties from In	35.0000 [12.2693 [8.7279 gredients	
Compression F Mixture Propert Bonding Const Tensile Streng Calculate	Force (kN): ies tant: th at Por=0 (MPa): Properties from In ameters	35.0000 12.2693 : 8.7279	
Compression F Mixture Properti Bonding Const Tensile Streng Calculate Calculated Para	Force (kN): lies tant: that Por=0 (MPa) Properties from In ameters	35.0000 12.2693 (8.7279 gredients 0.1440 0.0252	ncel Clos

	Ingredient Type	Amount (mg)	MWt (g/mol)	Diff. Coeff. (cm^2/:
Hydrocortisone Starch	Active Disintegrant	150 25	362.47 333.55	0.587
Lactose	Other	10	342.3	0.432
wsicochemical Infor				
gredient Name	Ingredient Type	Mol. Weight (g	/molj	a Ola
ydrocortisone	Active	362.47	— н	o en ero
ef. Solubility (mg/ml)	pH for Ref. Solubility	,		
361	7.2			нн
ensity (g/ml)	Precip. Time (sec)	Diff. Coeff. (cm	2/s*10^5)	ili L
27	900	0.587		ΥY
oP	@ pH			Н Н
58	4	_		\sim
Biorelevant	Surfactant	1	p ·	•
Solubility	Solubility			
Solubility		_		
Solubility	nformation		Constants	
Solubility ormulation Specific In mount (mg)	nformation Salt Type	No. Moles	Calibration Consta	int
Solubility	nformation	No. Moles		
Solubility ormulation Specific In mount (mg)	nformation Salt Type		Calibration Consta	nt
Solubility ormulation Specific In mount (mg)	nformation Salt Type		Calibration Consta	
Solubility mulation Specific In mount (mg) 50	None		Calibration Consta	
Solubility mulation Specific In mount (mg) 50 Particle Size Distribu	None vition	1	Calibration Consta	
Solubility mount (mg) 50 Particle Size Distribu Mean Radius (um)	None	1	Calibration Consta	

- Physicochemical properties of the formulation ingredients under study: pKa's, aqueous solubility vs. pH, biorelevant solubility, diffusion coefficient, logP, and density
- Particle size distributions for each of the formulation ingredients
- Interactions between the active ingredient and formulation excipients (e.g., solubilizers, disintegrants, wetting agents)
- Microclimate pH-dependence of solubility and dissolution/precipitation
- Basic hydrodynamic effects, including different flow patterns and fluid velocities, for each experimental apparatus
- Micelle-facilitated dissolution through the incorporation of surfactants in the media
- ... and more!

4

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- In early stage development, sufficient amounts of compound are not available for repeated conventional testing. What would be the expected dissolution profile for an initial formulation?
- You make your first formulation for a new compound, and dissolution is too slow. What formulation parameters can you change to make it acceptable?
- You're asked to develop a formulation for a low solubility compound. You run one experiment with powder that does not dissolve fast enough. What can be done to produce the desired dissolution rate micronization, solubilizer, wetting agent, or some combination?
- A dissolution experiment produces unexpected results. You suspect human error, but what best explains the data (buffer composition, instrument speed, fluid volume, etc.)?
- You need to develop a dissolution experiment that mimics a deconvoluted *in vivo* release profile. What experimental conditions are needed to generate a meaningful IVIVC/R (instrument type, fluid volume, instrument speed, buffer composition, etc.)?
- As you scale up manufacturing, you identify a certain level of variability in key formulation properties (e.g., dose, excipient content). How much 'lot-to-lot' variability are you allowed before you begin falling outside the established dissolution specifications? And, how would these simulated dissolution profiles be translated to changes with the *in vivo* pharmacokinetics (PK)?

Find answers to these questions and more with DDDPlus!

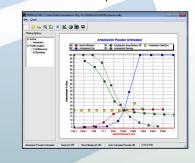
Simulation Modes

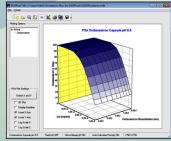
Single Simulation: based on compound properties (whether measured or predicted through the ADMET Predictor[®] Module), formulation information, and *in vitro* dissolution setup, easily run a simulation to predict the

time course changes in amount (or percent) dissolved for any ingredient in the product. Also track changes in microclimate and bulk pH levels vs. time.

Parameter Sensitivity Analysis (PSA): select any formulation or experimental parameters to assess the impact of changes on the *in vitro* dissolution vs. time profiles

3D PSA – now analyze the impact of changes in a 'design space' by simulating all combinations of any two selected parameters. Quickly identify an optimal combination that achieves the desired dissolution result





Virtual Trials: run a series of simulations for different dissolution experiments, each of which is described by a random sample of formulation and/or experimental parameters, to imitate the variances expected with actual formulation or experimental setups. This powerful capability allows you to assess the combined effects of variations in formulation or experimental variables on the *in vitro* dissolution profiles, helping to establish dissolution specifications as you scale up manufacturing. And, when coupled with GastroPlus models, you can begin to translate the dissolution 'variability' to expected changes in pharmacokinetic profiles and assess virtual bioequivalence between formulation lots.

Optimization Module: calibrate your DDDPlus dissolution model using

experimental in vitro dissolution vs. time data. Fit any combination of parameters to build your baseline model once built and validated with existing data, use it to explore changes in formulation, experiment and more.

Difference Factor 'f1' and Similarity Factor 'f2':

The Difference Factor 'f1' and Similarity Factor 'f2' are recommended for dissolution profile comparisons in the FDA quidance for the industry. Once you run a simulation, you can load a reference profile and use the Difference Factor and Similarity Factor tools in DDDPlus to automatically run simulations across all formulation records and calculate the 'f1' and 'f2' values.

Model Inputs

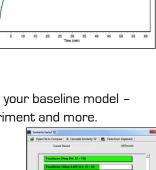
Physicochemical Parameters

With DDDPlus, you can add as many excipients to the formulation as you like. This is done through the Formulation Composition window shown.

ADMET Predictor Module: using the industry's #1-ranked Quantitative Structure-Activity Relationship (QSAR) models from our ADMET Predictor program, import chemical structures (as SMILES strings or .mol/.sdf formats) to predict the physicochemical properties required for the DDDPlus. This can provide a quick, reliable foundation for your modeling activities.

DDDPlus now allows you to enter multiple ingredients of the same type: define multiple excipients in the formulation. Any excipients can be entered, or you can use the database of commonly used excipients, provided with the program, where all necessary physicochemical properties are defined!

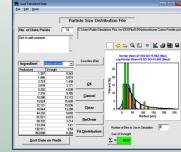
You can either input mean radius and standard deviation for the particle size distribution or load your own sieve distribution data (fractional or cumulative). DDDPlus comes with a tool to easily convert your cumulative particle size distribution data (e.g., D(10), D(50), D(90)) into a full normal or log-normal distribution function.



Virtual Trial Hydrocortisone Coarse Powde







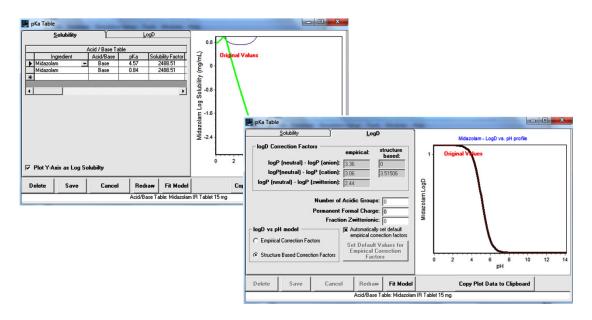


6





With DDDPlus, you can enter multiple pKa ionization constants for each ingredient. This information is used to define the aqueous solubility vs. pH profile and in the calculation of media pH during the simulation. Plus, the theoretical logD vs. pH profile is generated, which can be applied to estimate the bile salt solubilization effect



Experimental Setup

Dissolution Method Conditions and Multi-Phase Experiments

With DDDPlus, you can define your dissolution method conditions like apparatus, instrument speed, medium volume and medium type. DDDPlus calculates the fluid velocity automatically based on the instrument speed and apparatus type and utilizes this information to capture basic hydrodynamic effects on the dissolution rate.

You can add as many experimental phases as you want to better mimic the *in vivo* environment. This can be helpful when trying to design an *in vitro* dissolution method to achieve a meaningful *in vitro-in vivo* correlation (IVIVC).

Dissolution Media and Microclimate pH

DDDPlus has a sophisticated pH engine to calculate the dissolution media pH and solubility of each ingredient at the surface and bulk pHs. You can select from more than 90 built-in buffers, including all USP and biorelevant recipes, or easily design your own. You can

	Ingredient	Concentration (M)	Surfactani
	Sodium Phosphate Monobasic NaH2PI	0.029	
	Sodium Hydroxide NaOH	0.0095	
	Sodium Chloride	0.105	
	Sodium Taurocholate	0.003	
<u>}</u>	Phosphatidylcholine 💌	0.00075	

also vary the concentrations of the different ingredients to create custom buffers at various pH.

DDDPlus(TM): DDDPlusDemo.m File Database Simulation Setup Formulation			inulation	×				
Fomgeson	Hydrocortisone Coarse Pow		guaton					
Appendix Type	Medium Type Medium Volu Medium pH: Medium Visc		250 1.2 0.007 Stat Time [min] 0 30 180	End Time [min] 30 180 240	Inst Speed (RIPM) 75 75 75 75	MedVolume [mi] 250 100 50	MedpH F 1.2 6.5 7.4	
		Add	Delete				glose	

Microclimate pH

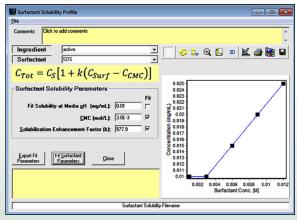
DDDPlus dynamically calculates the microclimate pH (pH at the diffusion layer of the particle) for each ingredient in the formulation. You can select either "microclimate pH" to calculate the solubility of the ingredient at the diffusion layer or "bulk pH" for solubility in the dissolution media. The "bulk pH" is utilized to capture any potential precipitation effects once the dissolved material reaches the bulk environment.

Surfactants

DDDPlus allows you to add up to 2 surfactants per dissolution media. You have the option to choose from a list of common surfactants or create your own.

Surfactant in Medium				
Surfactant 1	Surfactant 2			
Surfactant: SDS 💌	Surfactant: CTAB 💌			
Concentration (M): 0.05	Concentration (M): 0.1			
Critical Micelle Conc. (M): 0.008	Critical Micelle Conc. (M): 0.001			
Molecular Weight (g/mol): 288.4	Molecular Weight (g/mol): 364.5			
Aggregation Number: 55	Aggregation Number: 69			
Solubility Enhancement Factor: 11502.21	Solubility Enhancement Factor: 1			
Solubilization ratio in biorelevant media = N/A. Biorelevant media calculations are not defined.				
% to M Conversion Tool Create <u>New</u> Surfactant	Biorelevant Solubility QK Cancel			

Surfactant solubility tool: easily calculate the CMC and/or surfactant enhancement factor provided you have selected a media with one or two surfactants. This applies to non-biorelevant surfactants like SDS, CTAB, BRIJ, CHAPS, etc.





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