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

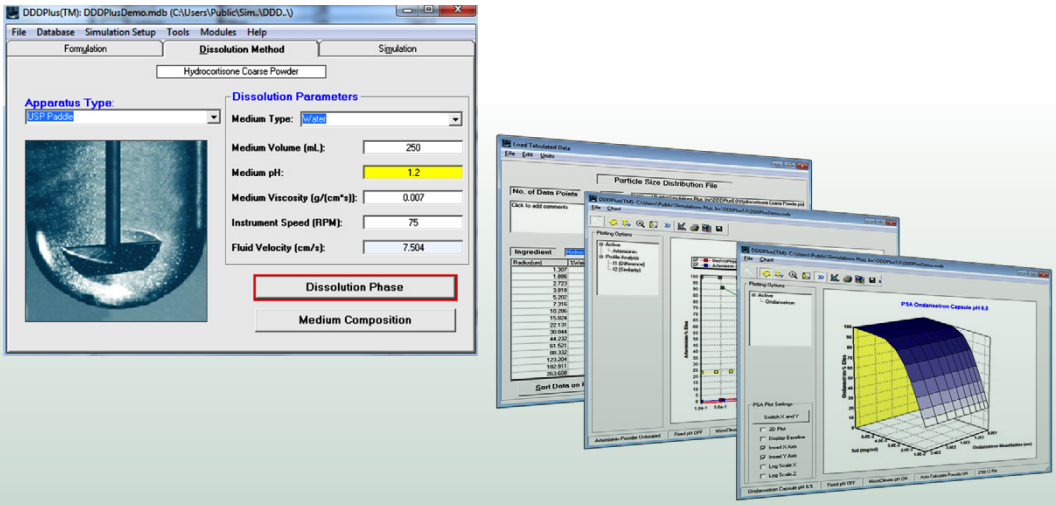
What's new in version 6?

- **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



SimulationsPlus
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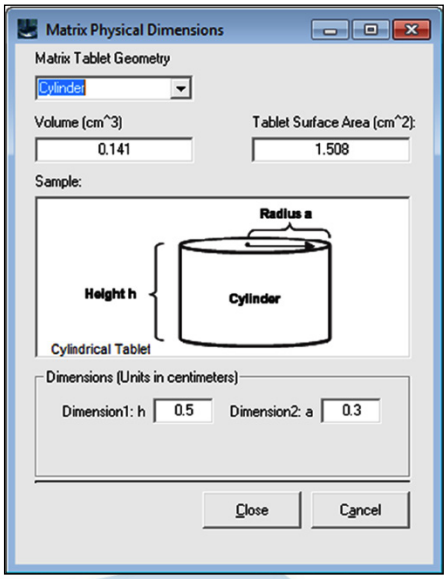
simulations-plus.com/dddplus

What is DDDPlus?

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:

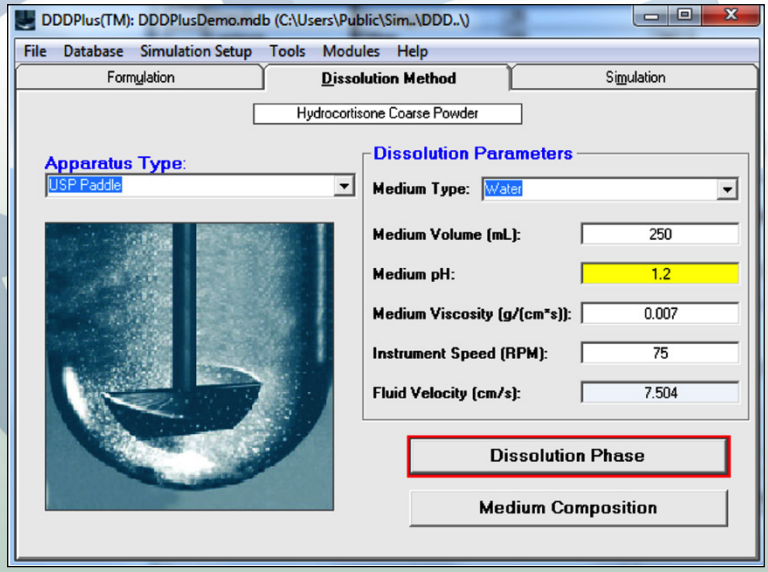
- **NEW** Long Acting Injectable models for PLGA microspheres
- **NEW** IR: Solution Model (precipitation options)
- **NEW** CR: Coated Bead Model
- Powders
- Capsules
- Tablets
- Polymer Matrix (Swellable & Non-Swellable)
- Coated beads
- Bilayer tablets
- Delayed release coated tablets



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

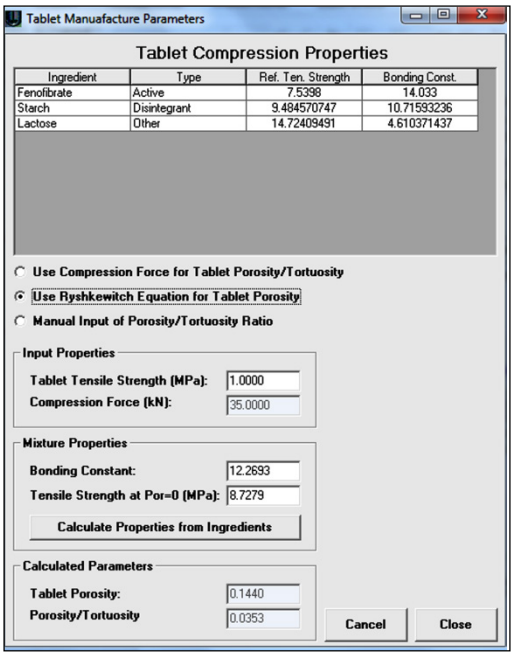
  (closed and open loop options)
- Rotating Disk
- Pion µDISS Profiler™

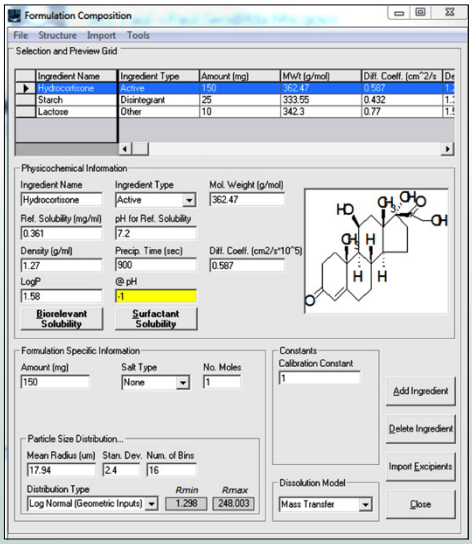


What is DDDPlus?

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)





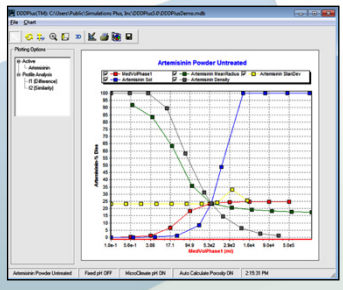
- Physicochemical properties of the formulation ingredients under study: pKa's, aqueous solubility vs. pH, biorelevant solubility, diffusion coefficient, logP, and density
- Particle size distributions for each of the formulation ingredients
- Interactions between the active ingredient and formulation 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!

- 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!

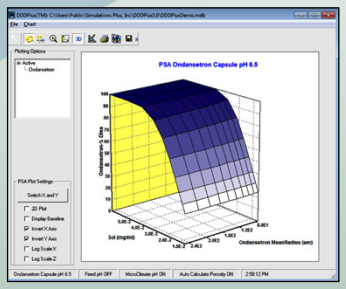
Simulation Modes

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.



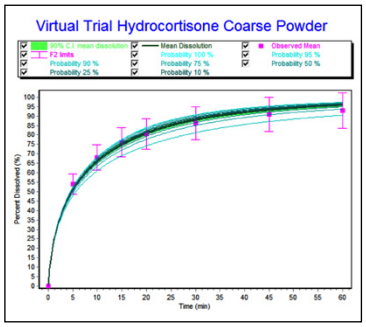
Parameter Sensitivity Analysis (PSA): select any formulation or experimental parameters to assess the impact of changes on the *in vitro* dissolution vs. time profiles

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



Simulation Modes

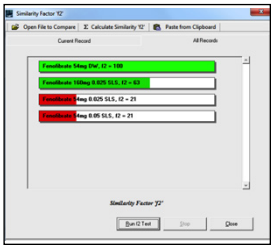
Virtual Trials: run a series of simulations for different dissolution experiments, each of which is described by a random sample of formulation and/or experimental parameters, to imitate the variances expected with actual formulation or experimental setups. This powerful capability allows you to assess 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':

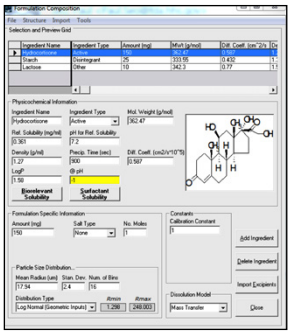
The Difference Factor 'f1' and Similarity Factor 'f2' are recommended for dissolution profile comparisons in the FDA guidance for the industry. Once you run a simulation, you can load a reference profile and use the Difference Factor and Similarity Factor tools in DDDPlus to automatically run simulations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



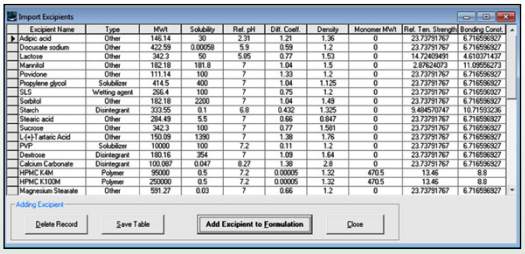
Model Inputs

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.

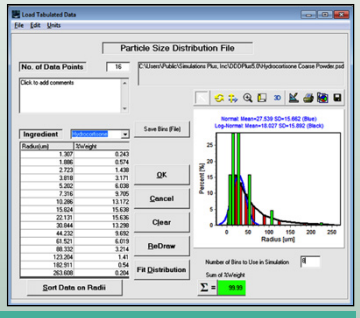


ADMET Predictor Module: using the industry's #1-ranked Quantitative Structure-Activity Relationship (QSAR) models from our ADMET Predictor program, import chemical structures (as SMILES strings or .mol/.sdf formats) to predict the physicochemical properties required for the DDDPlus. This can provide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



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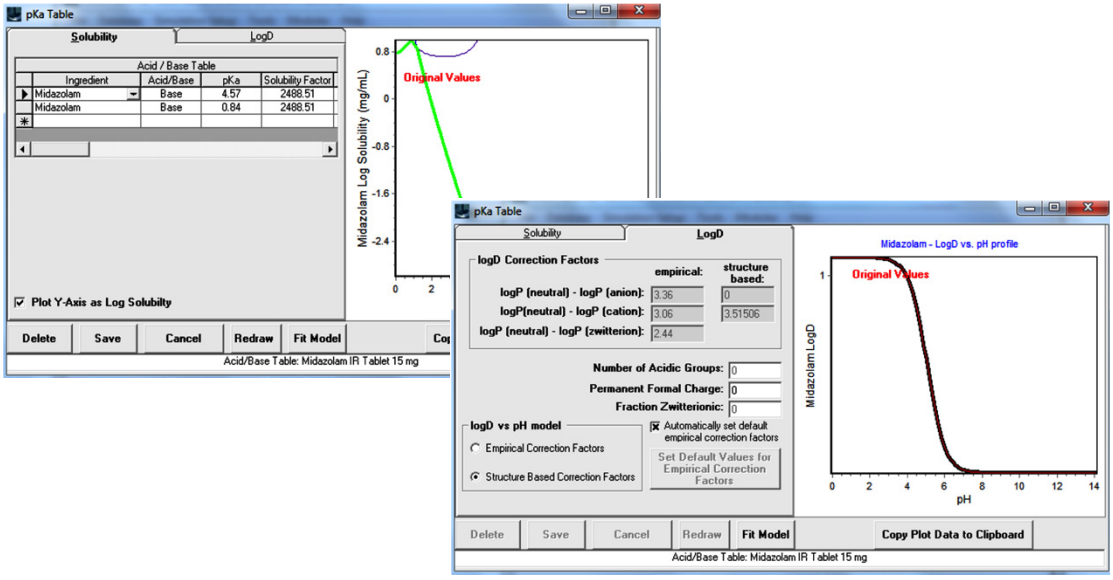
Model Inputs

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

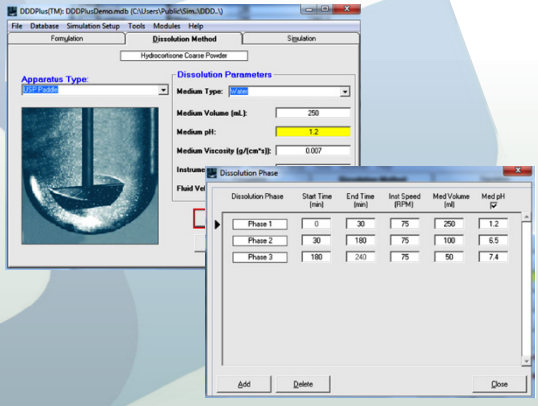
Dissolution Method Conditions and Multi-Phase Experiments

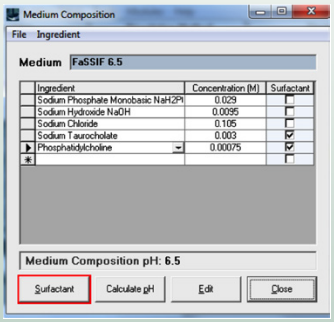
With DDDPlus, you can define your dissolution method conditions like apparatus, instrument speed, medium volume and medium type. DDDPlus calculates the fluid velocity automatically based on the instrument speed and apparatus type and utilizes this information to capture basic hydrodynamic effects on 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 also vary the concentrations of the different ingredients to create custom buffers at various pH.



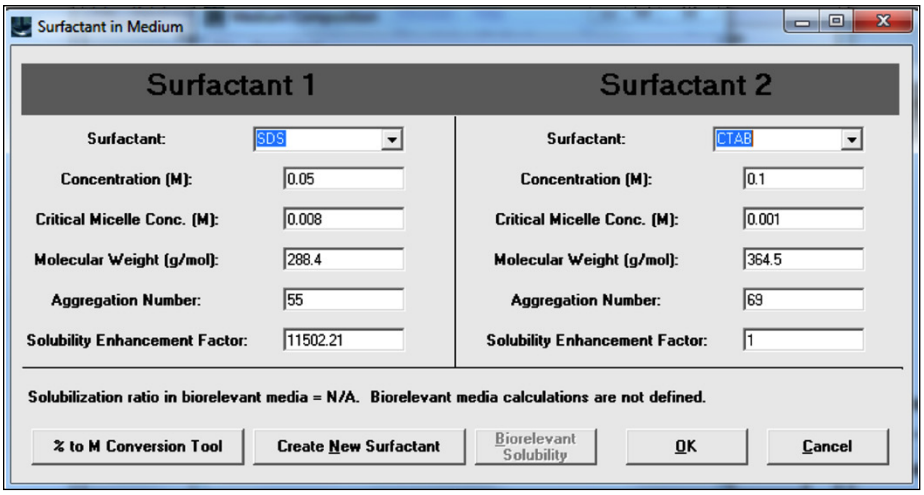


Microclimate pH

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 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.