F-CAD: Formulation Computer-Aided Design

In silico design with possibilities of design space exploration according to ICH Q8 R(2) immediate or controlled-release tablet formulations, including laboratory validation, for clinical phase I with market-ready tablet formulation of different strengths.

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F-CAD is an ultimate set of modeling and computational tools to assist in formulation design of pharmaceutical solid dosage forms with the goal to save money by replacing lab work with “in-silico” experiments.

Simulations vs. Expert Systems

- Expert System
  - Human Expert knowledge stored in computer-available format
  - Usually a black-box at individual nodes
  - Decision-making is traceable
  - Solution is immediately available
  - Substitutes a human expert
  - For example: Medical Diagnosis
- Simulation
  - Process or physical-chemical effect stored in commuter-available format
  - Mechanistic (or First) Principles-based (ideally)
  - Solution needs to be calculated
  - Requires human expert
  - For example: Astrophysical simulations

Simulations and Computations

- Simulation needs computing power
- Complex simulations needs High Performance Computation (HPC)
- Realistic complex simulations needs Parallel High Performance Computation

Nature works parallel too… ☺

How and why should we apply simulation-based dosage form design?

F-CAD: Current stage and aims

- Solid dosage forms

- Analysis of potential formulation issues at earlier development stages and workaround strategies

- Minimization of lab experiments (in ideal case only calibration experiments needed with minimum of substance)

- Shorter time-to-market

F-CAD Selected Features

- Formulation design with F-CAD starts with final-product desired properties, such as shape, dissolution rate, etc.
- F-CAD is tablet shape sensitive.
  - F-CAD can be used to find out differences in dissolution profiles for different shapes of tablets with identical composition.
- Different particles size distributions of components will result into different dissolution profiles
- Effect of compact porosity is taken into account along with hydrophilicity/hydrophobicity, including solubility and swelling of components.
- Run-time visualization of tablet undergoing in-silico dissolution test.

What is needed to successfully apply F-CAD?

- Physico-chemical data of API:
  - Solubility of API
  - Particle size distributions of API
  - True density
  - Intrinsic dissolution data (not just rate)
- Physico-chemical data of excipients:
  - List of excipients, chemically compatible with API
  - Particle size distributions of an excipient
  - In case of "common" excipients in general no additional physico-chemical data are needed
- **Unit operations involved and/or desired**
  - Wet granulation
  - Direct compaction
- **Desired dosage form shape**
- Required release specifications
  - Immediate release
  - Controlled release

General Workflow

TABLET DESIGNER

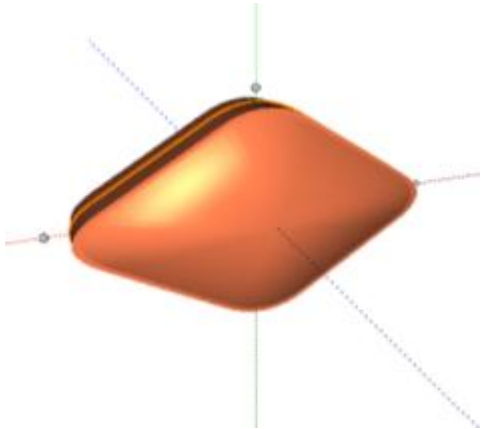
- Shape design
- Shape To Matrix Conversion

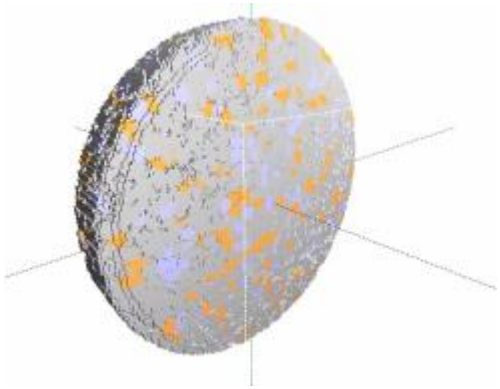
Particle Arrangement and Compaction (PAC)

- Fill matrix with content

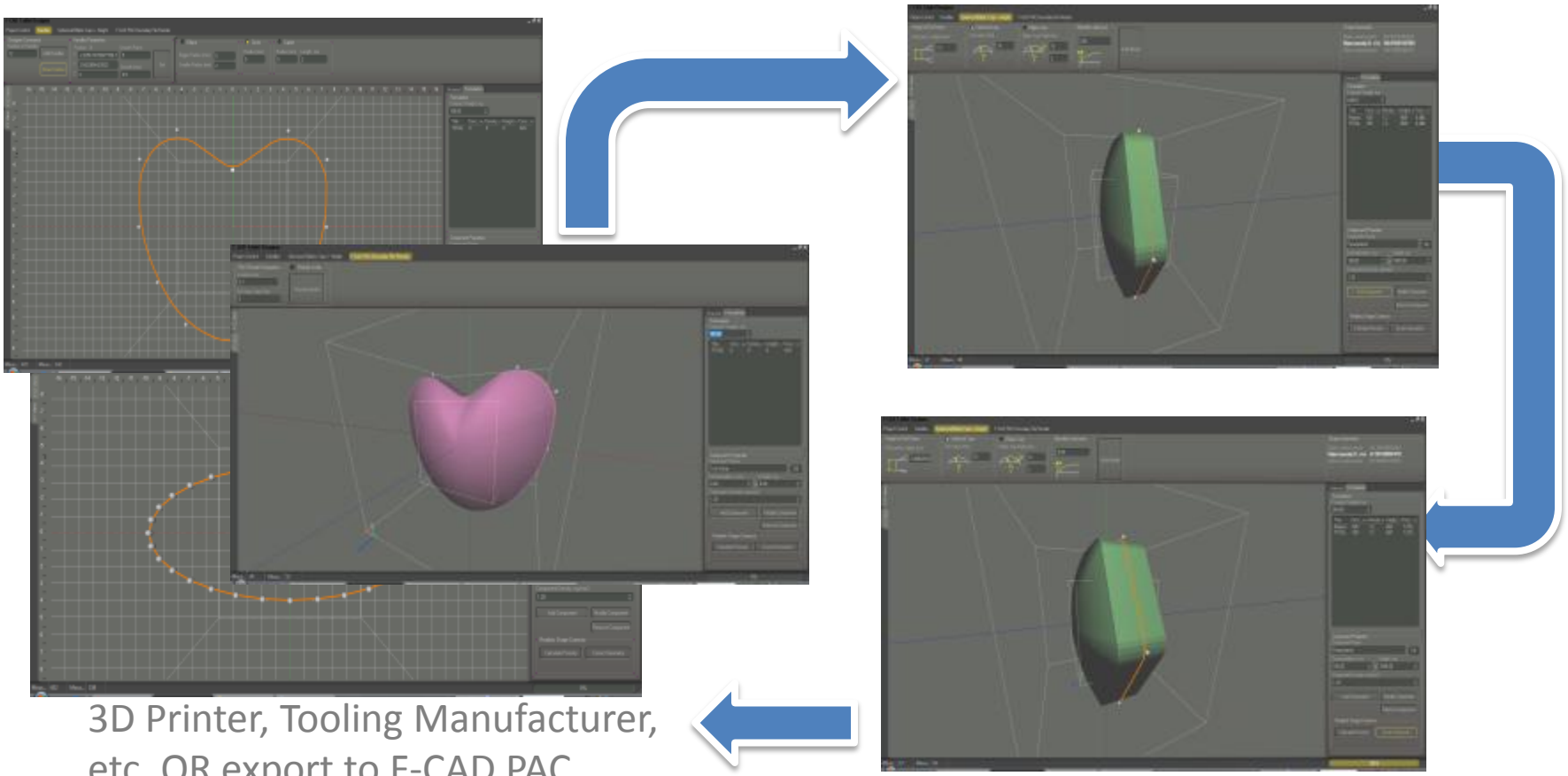
Dissolution Profile Calculation

- Calculate the profile points per unit of time (e.g. sec, min)



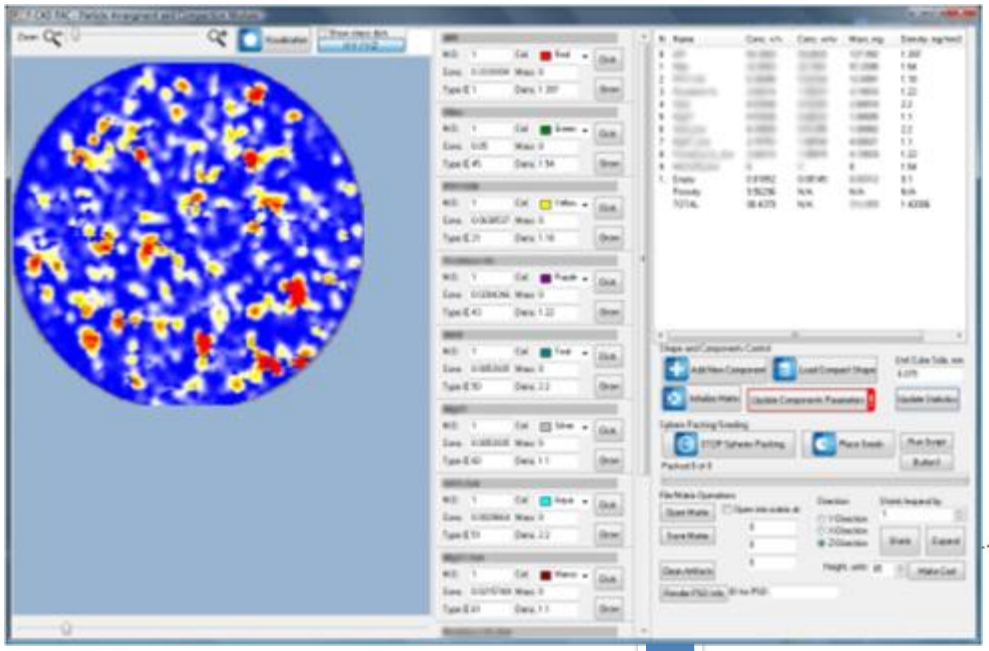


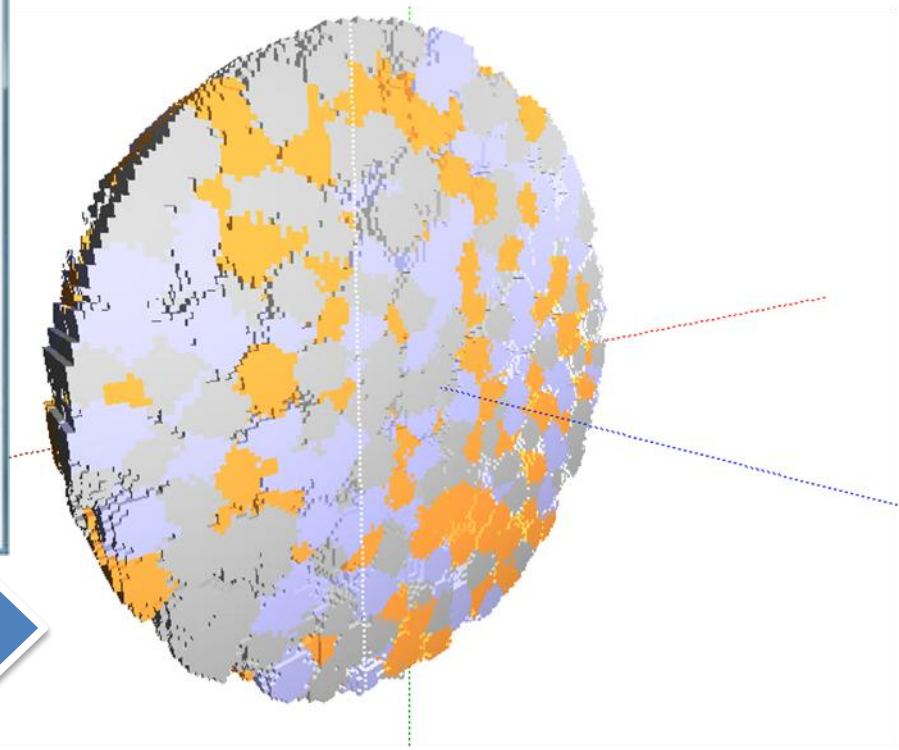
F-CAD Tablet Designer



3D Printer, Tooling Manufacturer, etc. OR export to F-CAD PAC

F-CAD PAC – Particle Arrangement and Compaction





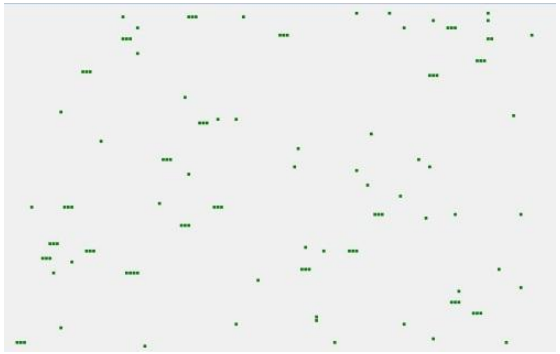


Figure A[1]: MCC seeds in a lateral view on a simulated tablet

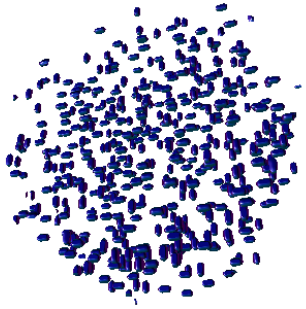


Figure A[2]: 3D visualization of MCC seeds

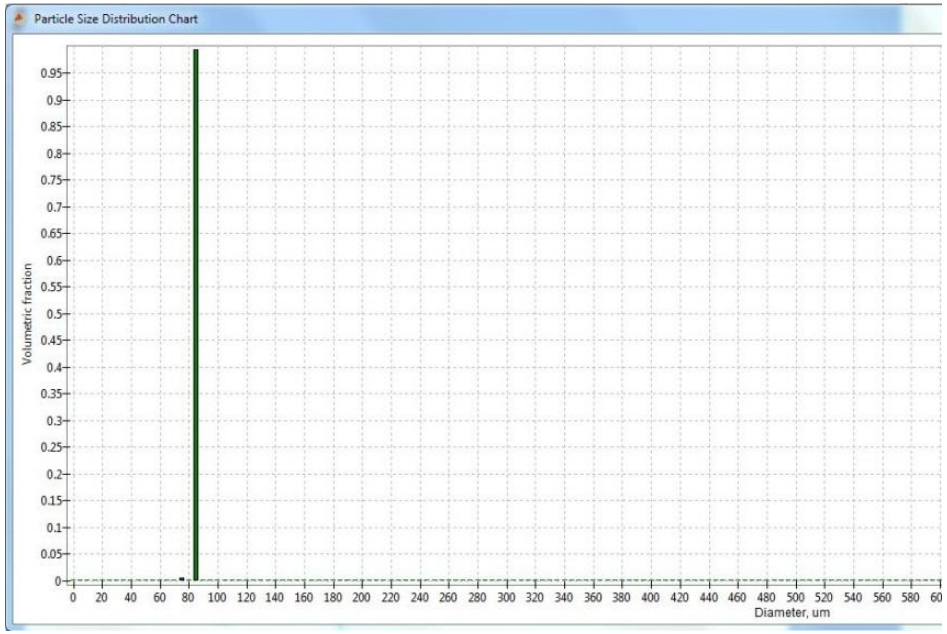


Figure a: Particle size distribution of MCC seeds

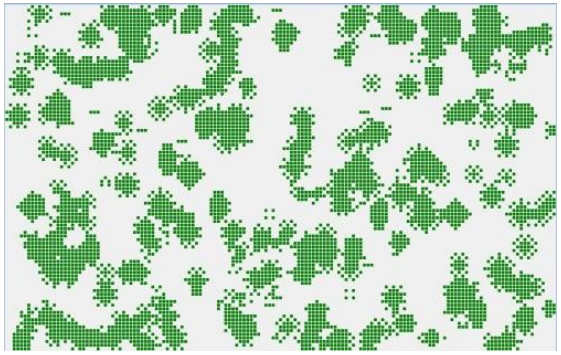


Figure B[1]: MCC particles growing step 4 in a lateral view on a simulated tablet

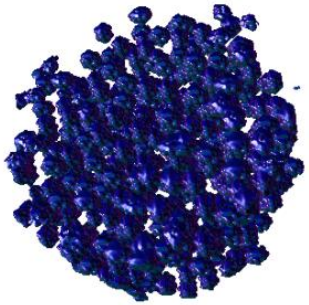


Figure B[2]: 3D visualization of MCC particles

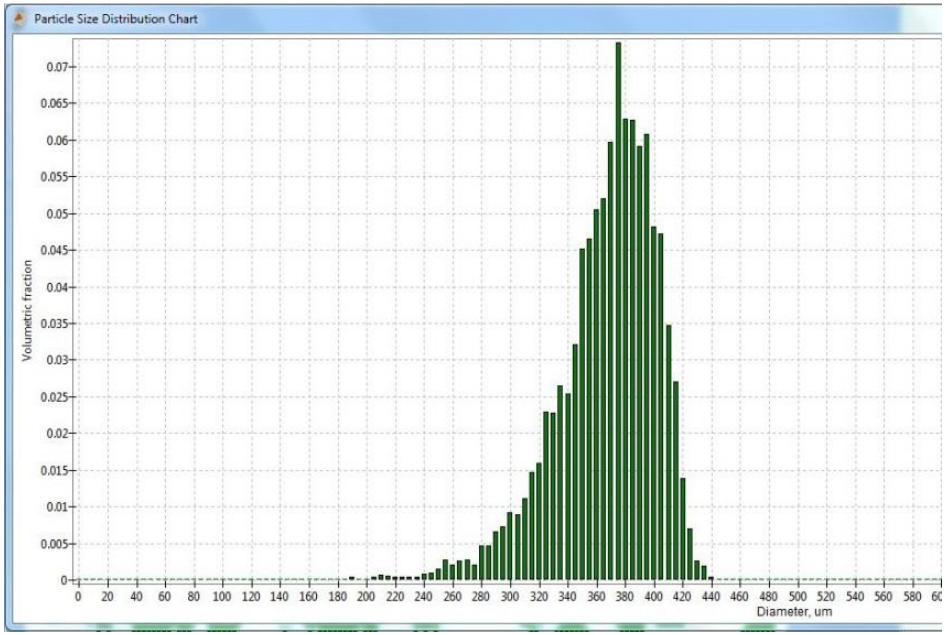


Figure b: Particle size distribution of MCC particles after growing step 4

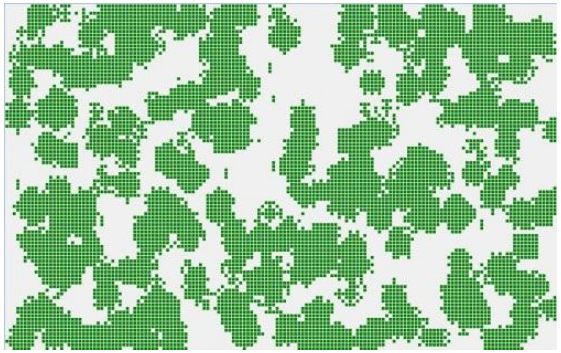


Figure C[1]: MCC particles growing step 5 in a lateral view on a simulated tablet

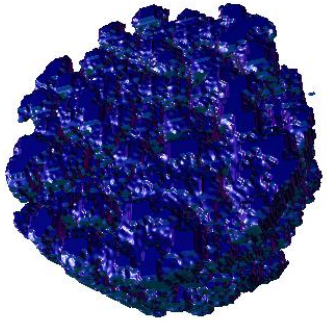


Figure C[2]: 3D visualization of MCC particles

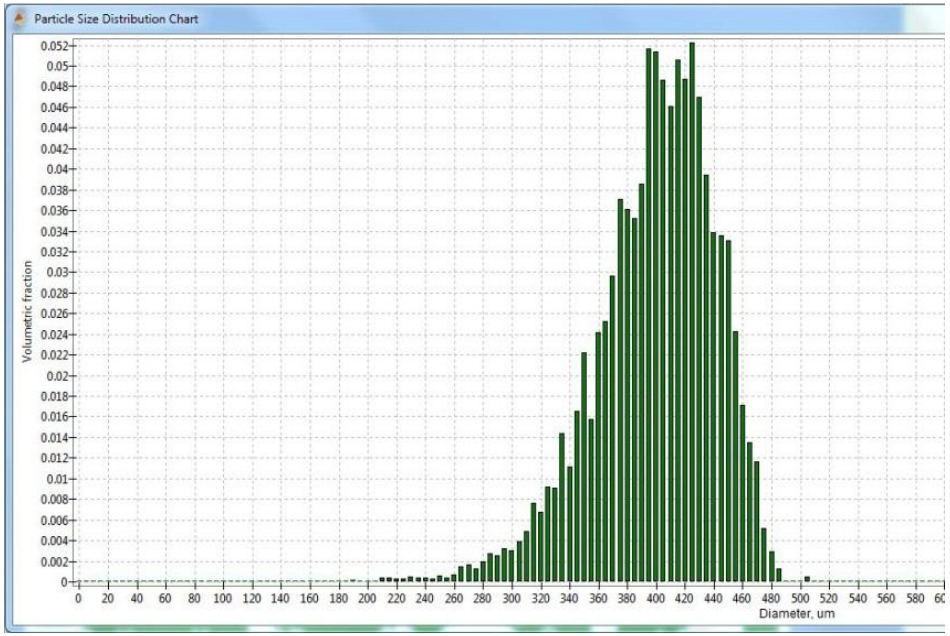


Figure c: Particle size distribution of MCC particles after growing step 5

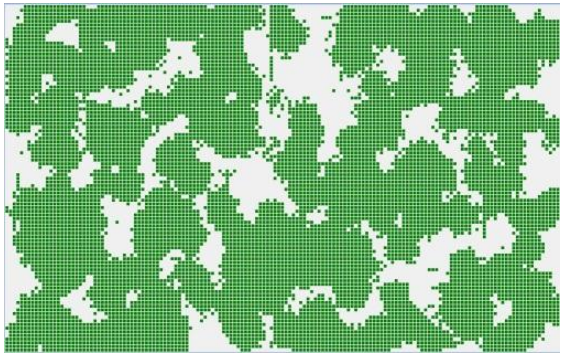


Figure D[1]: MCC particles growing step 6 in a lateral view on a simulated tablet

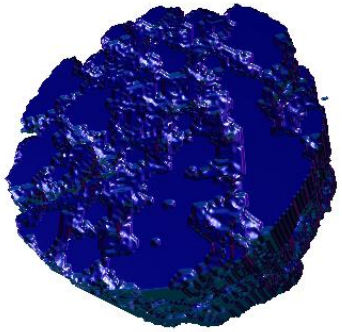


Figure D[2]: 3D visualization of MCC particles

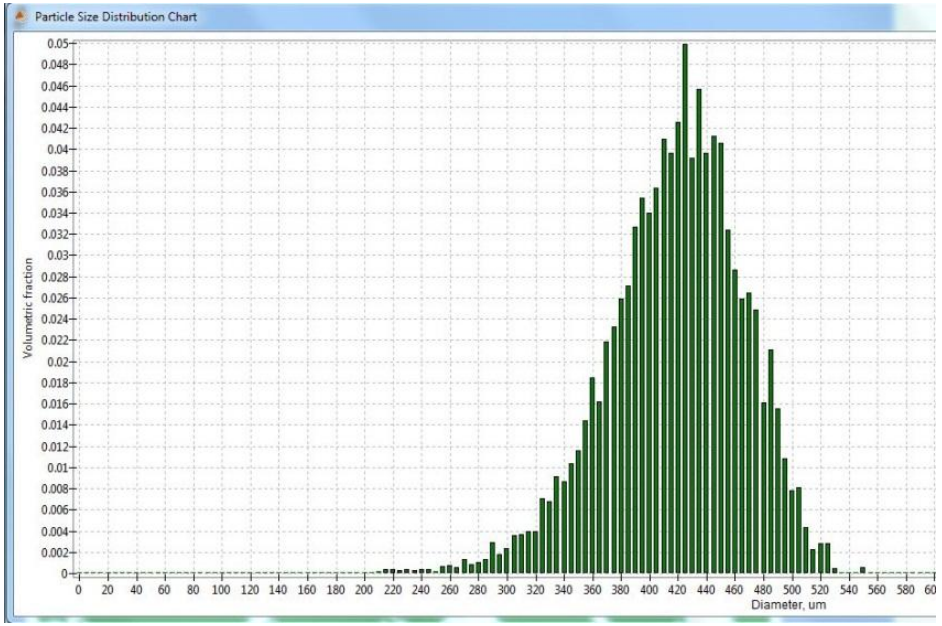
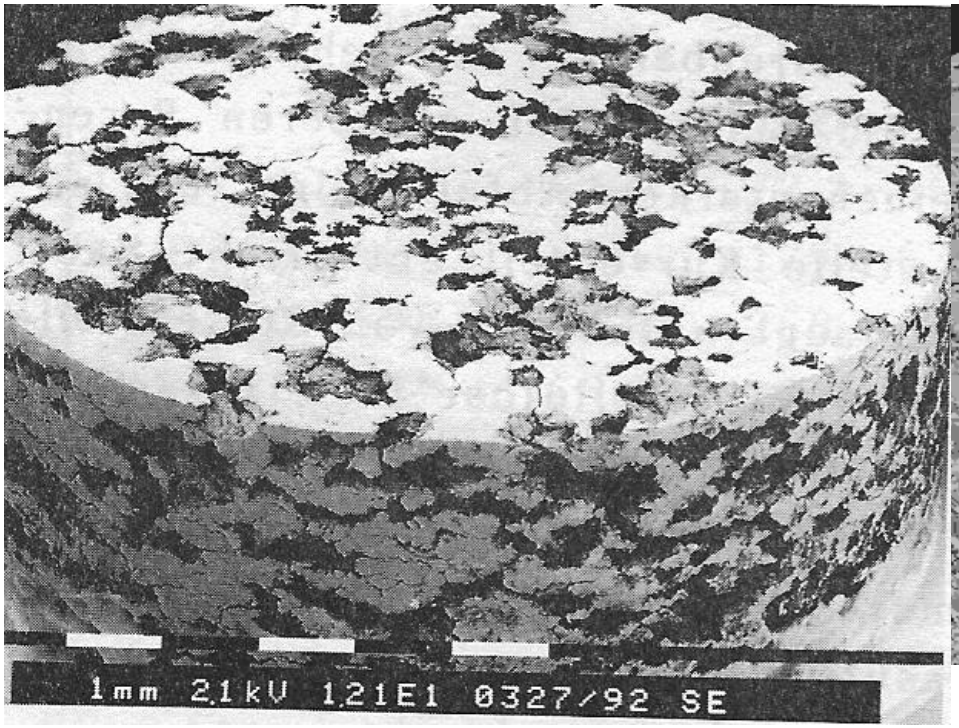


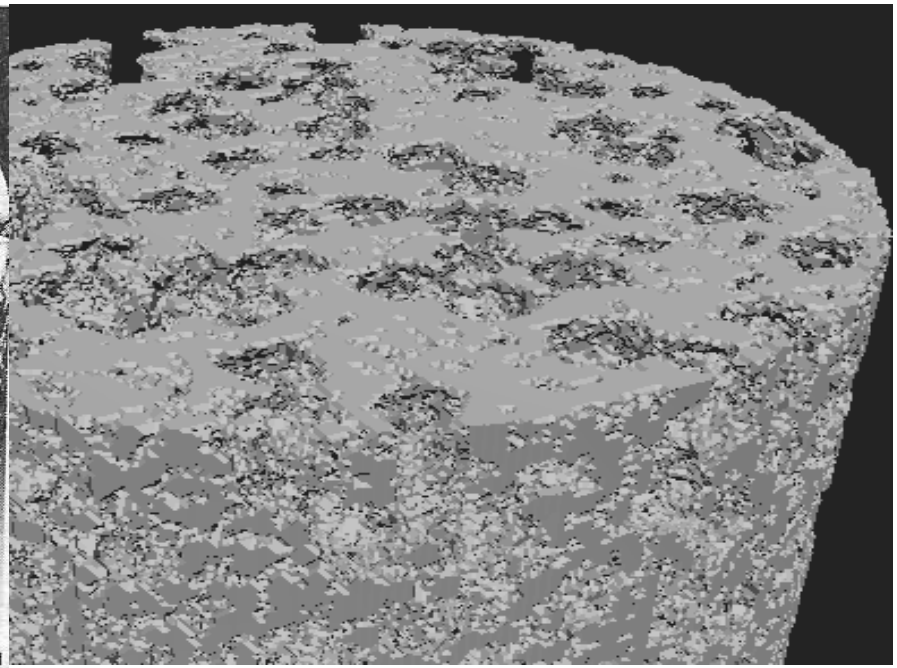
Figure d: Particle size distribution of MCC particles after growing step 6

Leached Matrix Controlled Release Tablet

500-710 µm



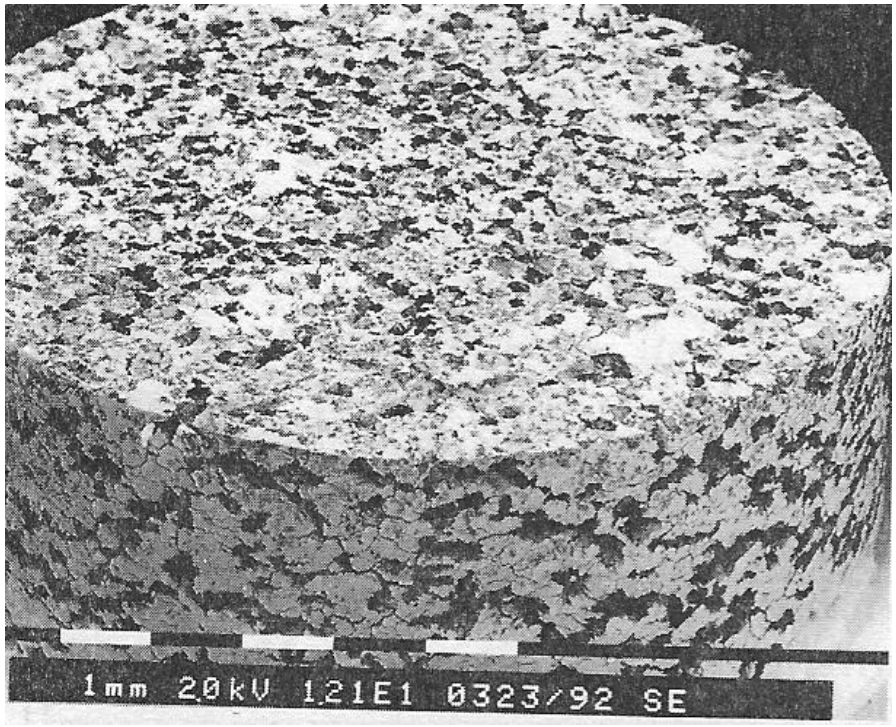
500-710 µm



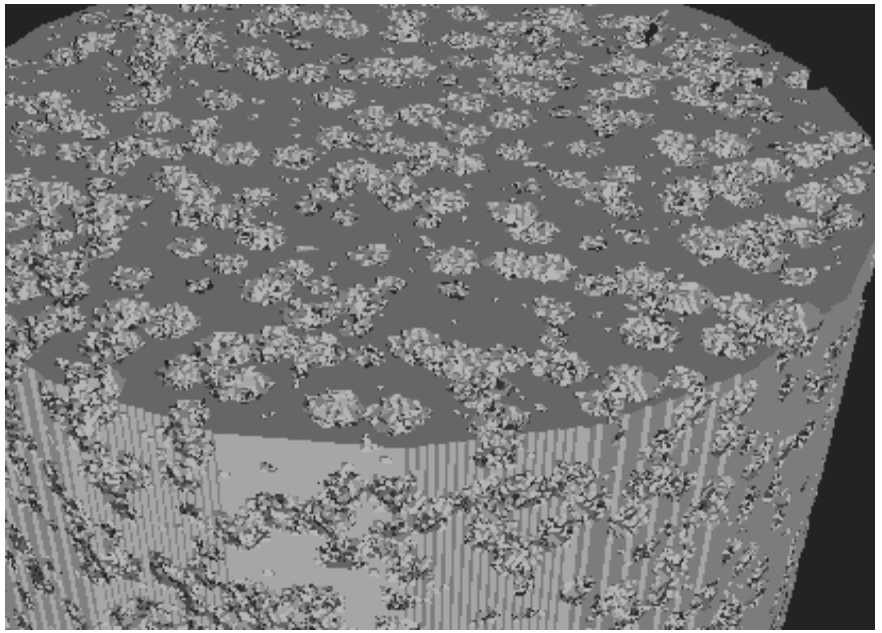
Real – left (PhD Thesis J.D. Bonny)
Computer Generated System - right

Leached Matrix Controlled Release Tablet

250-355 µm



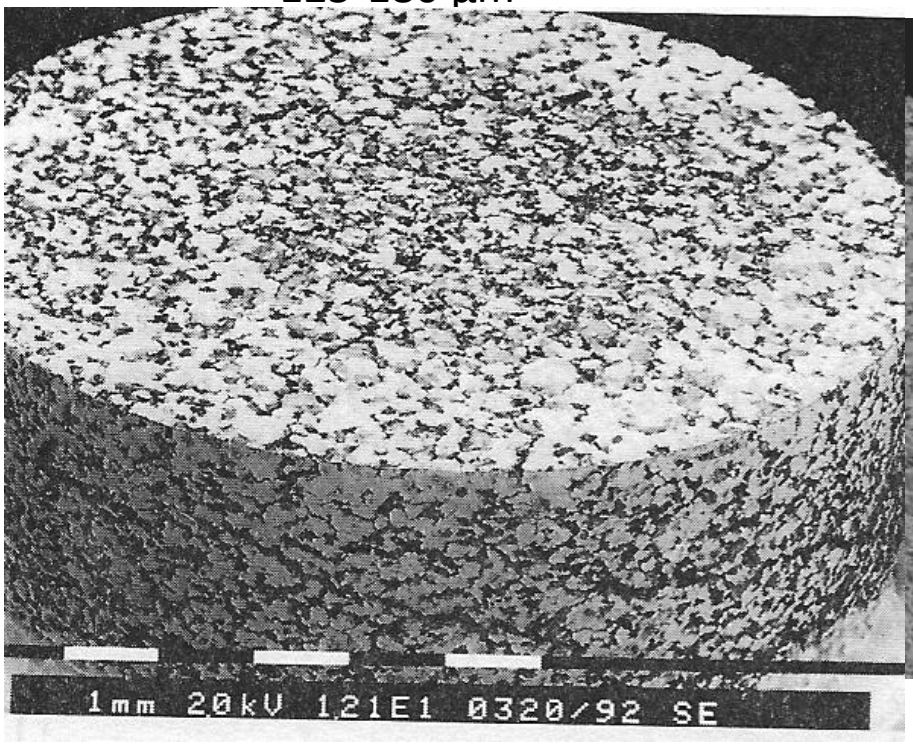
280-400 µm



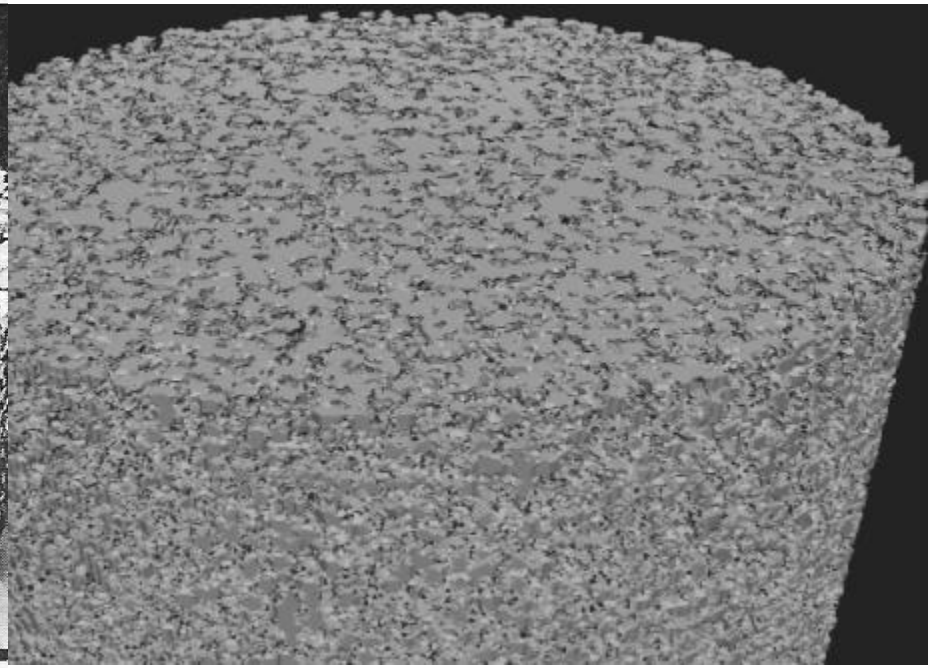
Real – left (PhD Thesis J.D. Bonny)
Computer Generated System - right

Leached Matrix Controlled Release Tablet

125-180 µm



150-200 µm



Real – left (PhD Thesis J.D. Bonny)
Computer Generated System - right

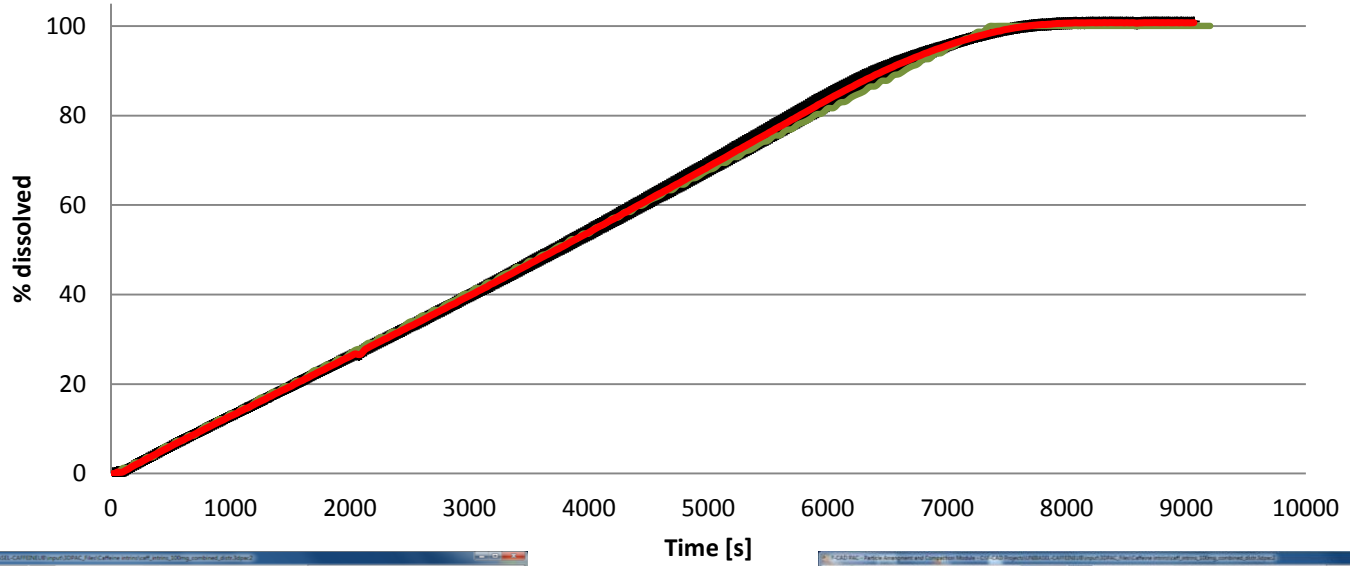
F-CAD GENERATED DISSOLUTION PROFILE

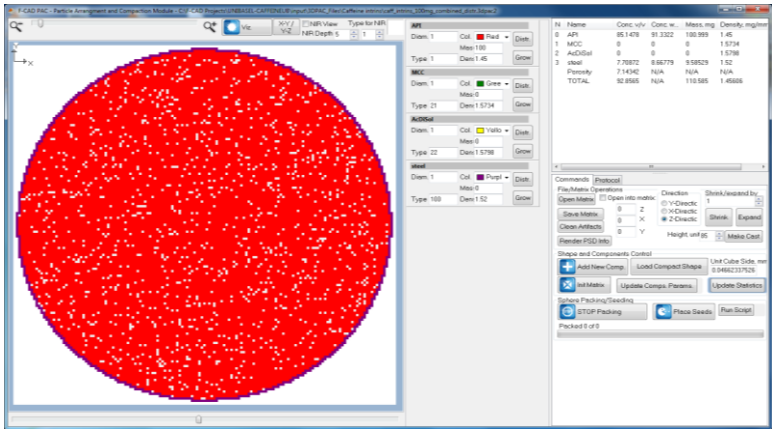
One more time: requirements

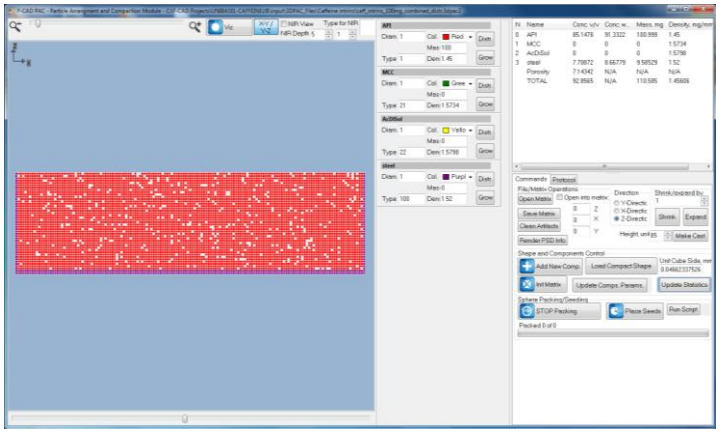
- Physico-chemical data of API:
  - Solubility of API
  - Particle size distributions of API
  - True density
  - **Intrinsic dissolution data (not just rate)**

Caffeine Intrinsic Dissolution (experimental vs. Calculated, overlapped plot)

200 mg Caffeine Pulvis

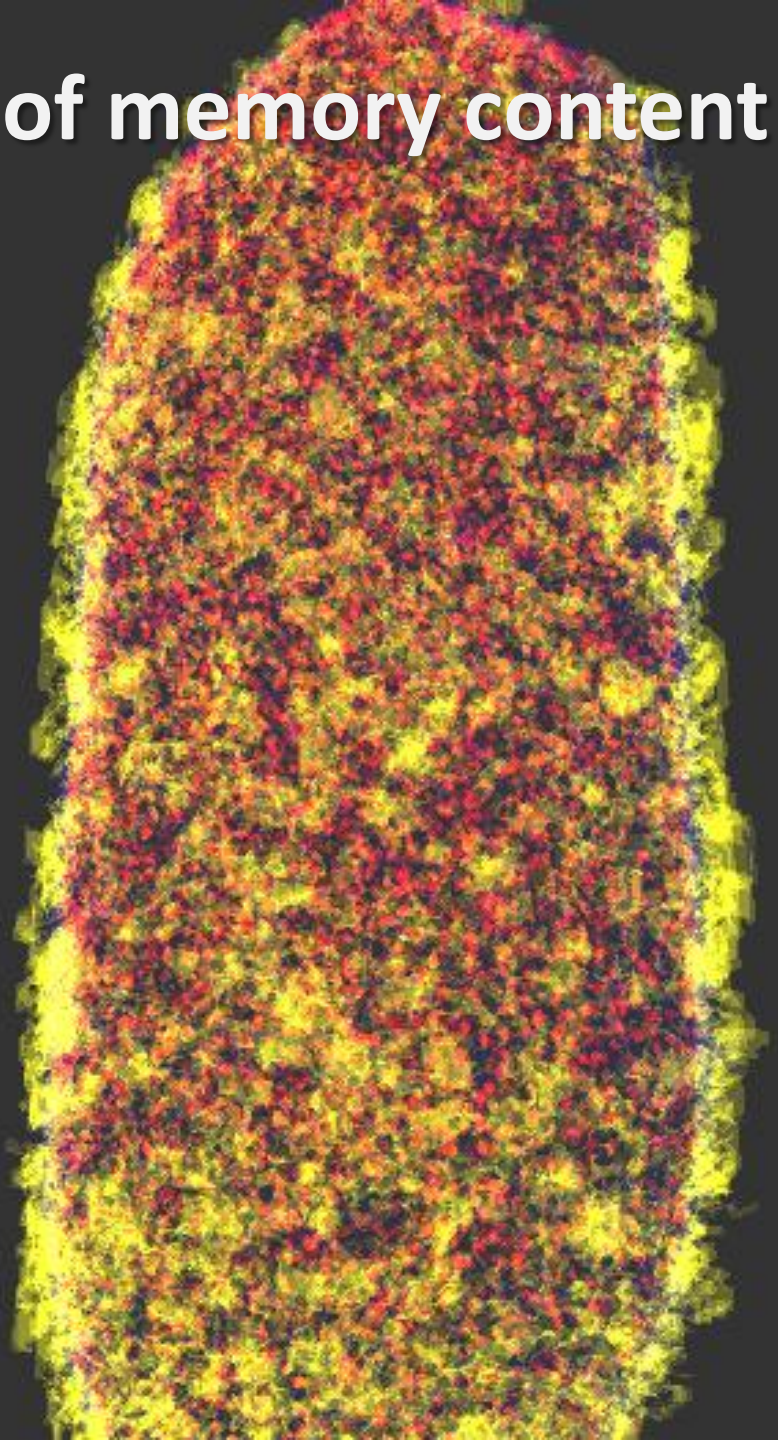




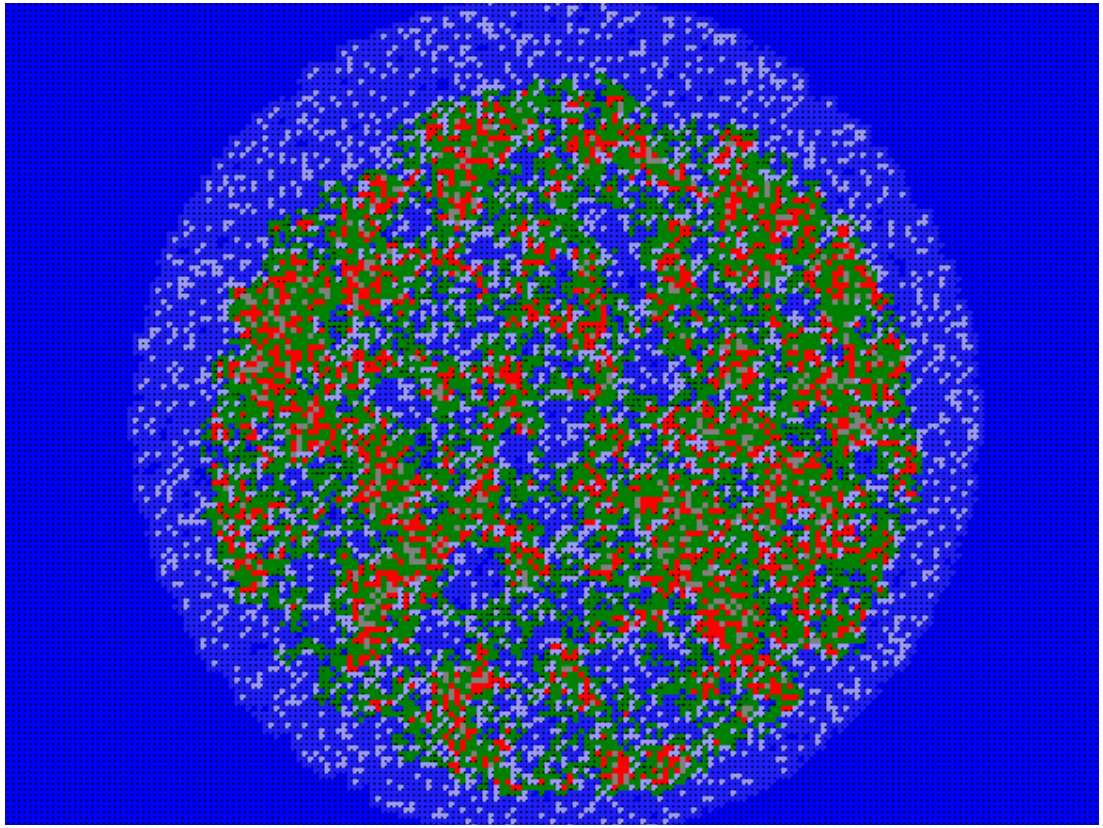


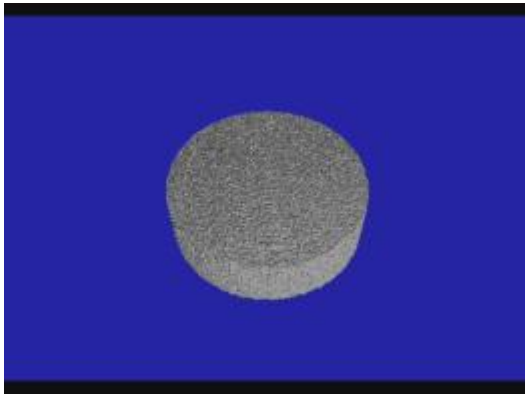
Data from Master thesis of David Tschirky, University of Basel

3D rendering of memory content



F-CAD Dissolution Profile Calculations





Rendering 3D Memory Content

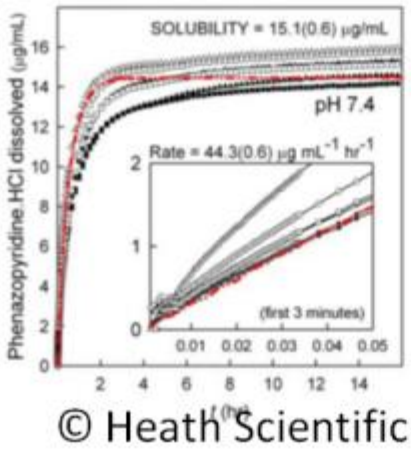
- Calculation of Release Stats., e.g. drug released, etc.
- Visual representation of process

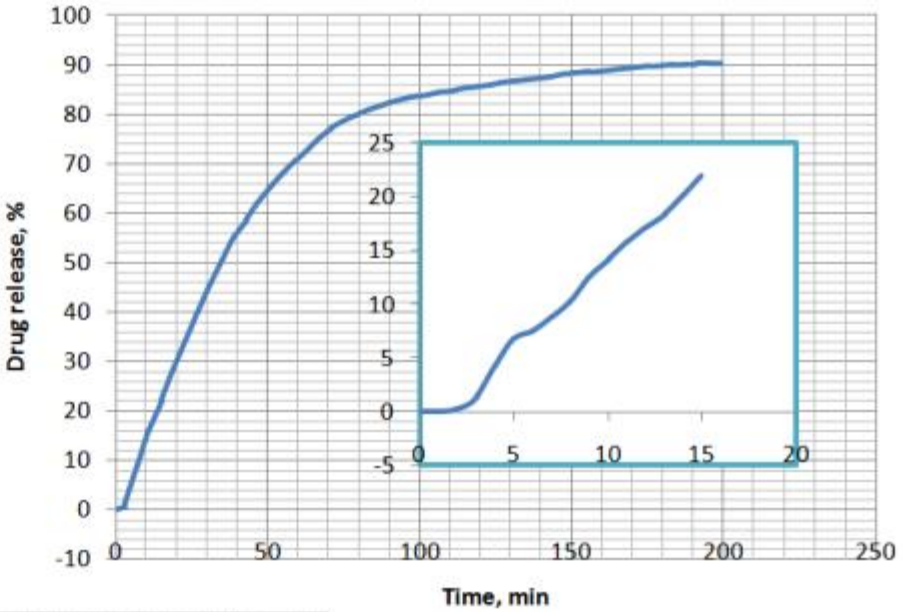
0 sec. 100 sec. 1800 sec.

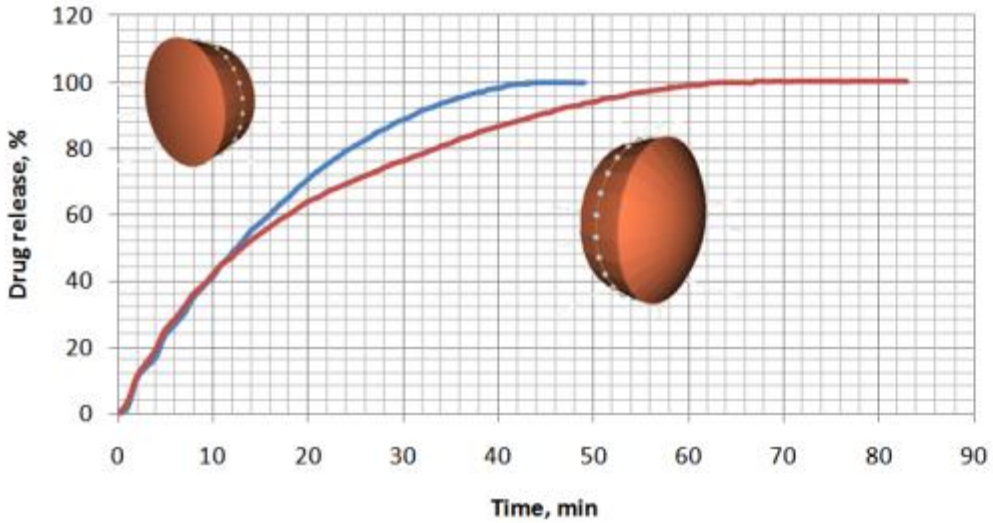




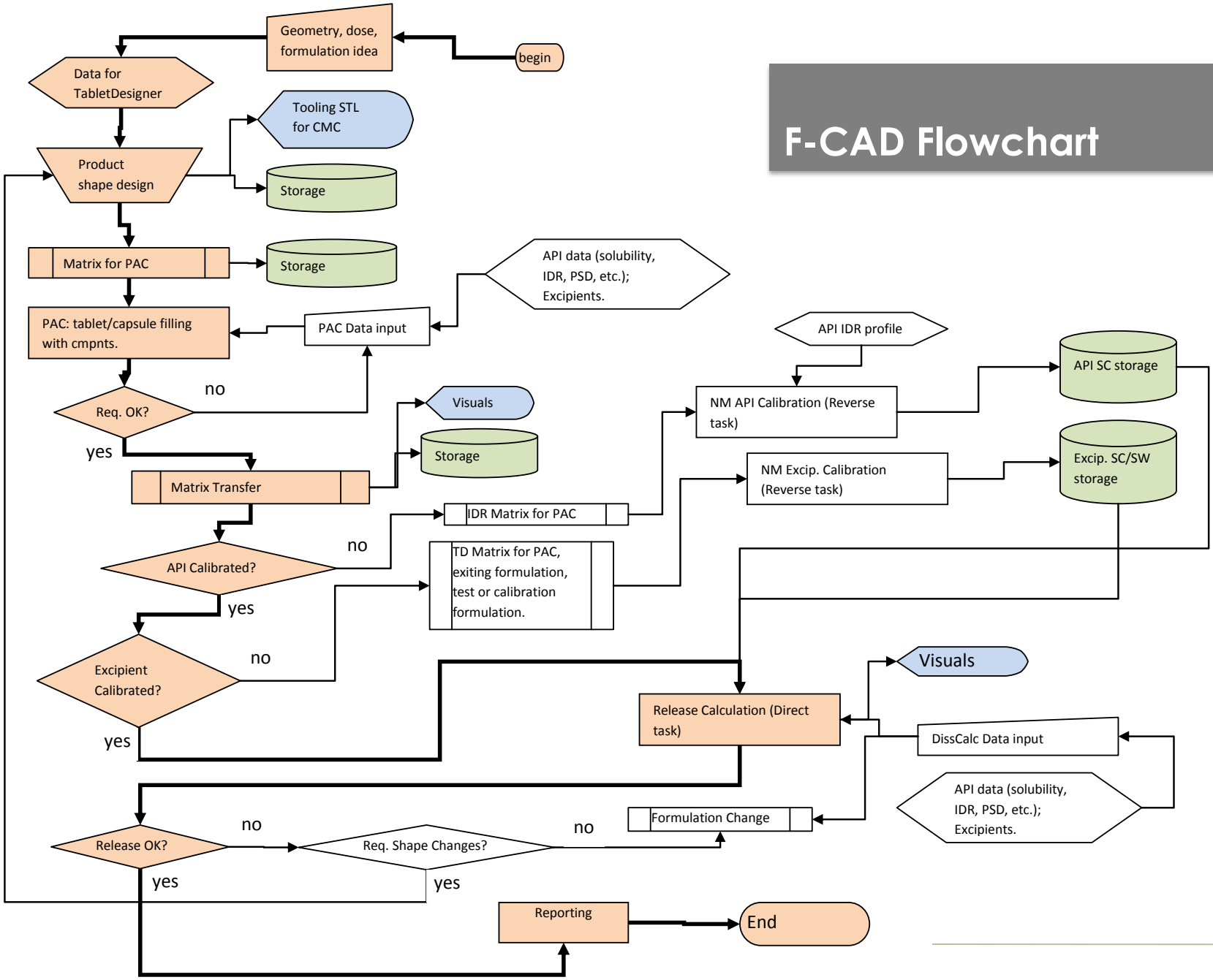
F-CAD DS – *in silico* Profiles

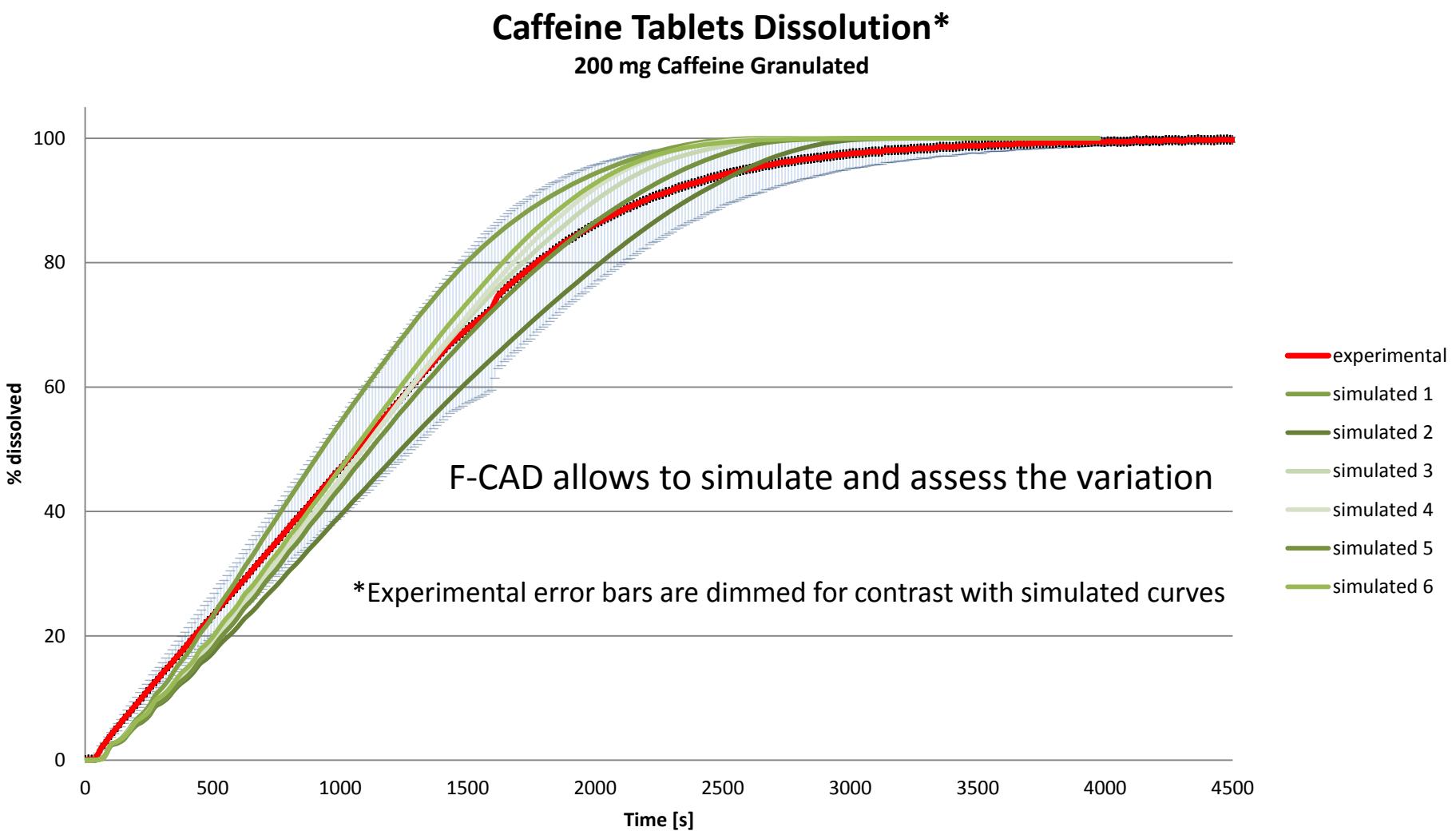






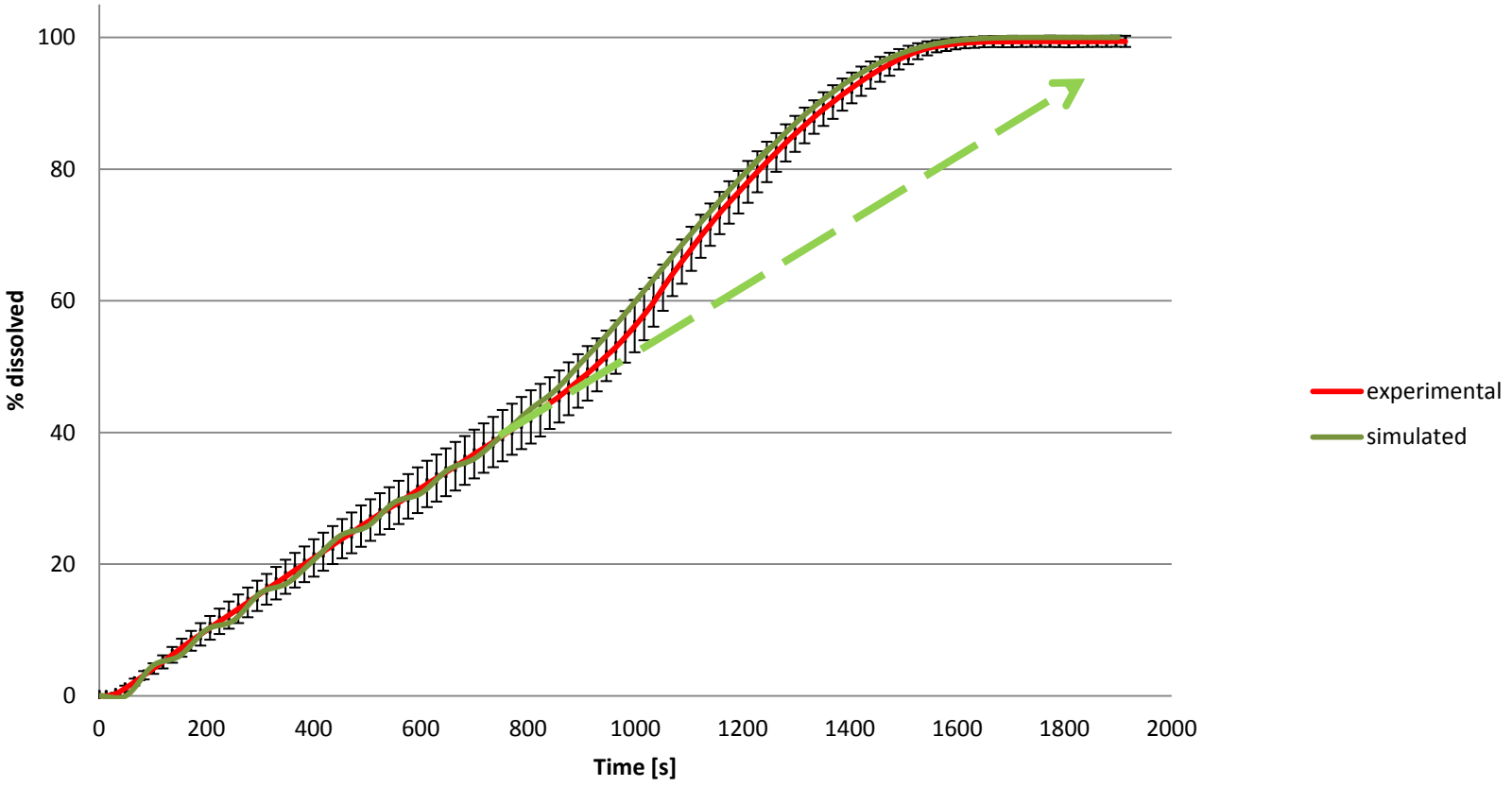
F-CAD Flowchart



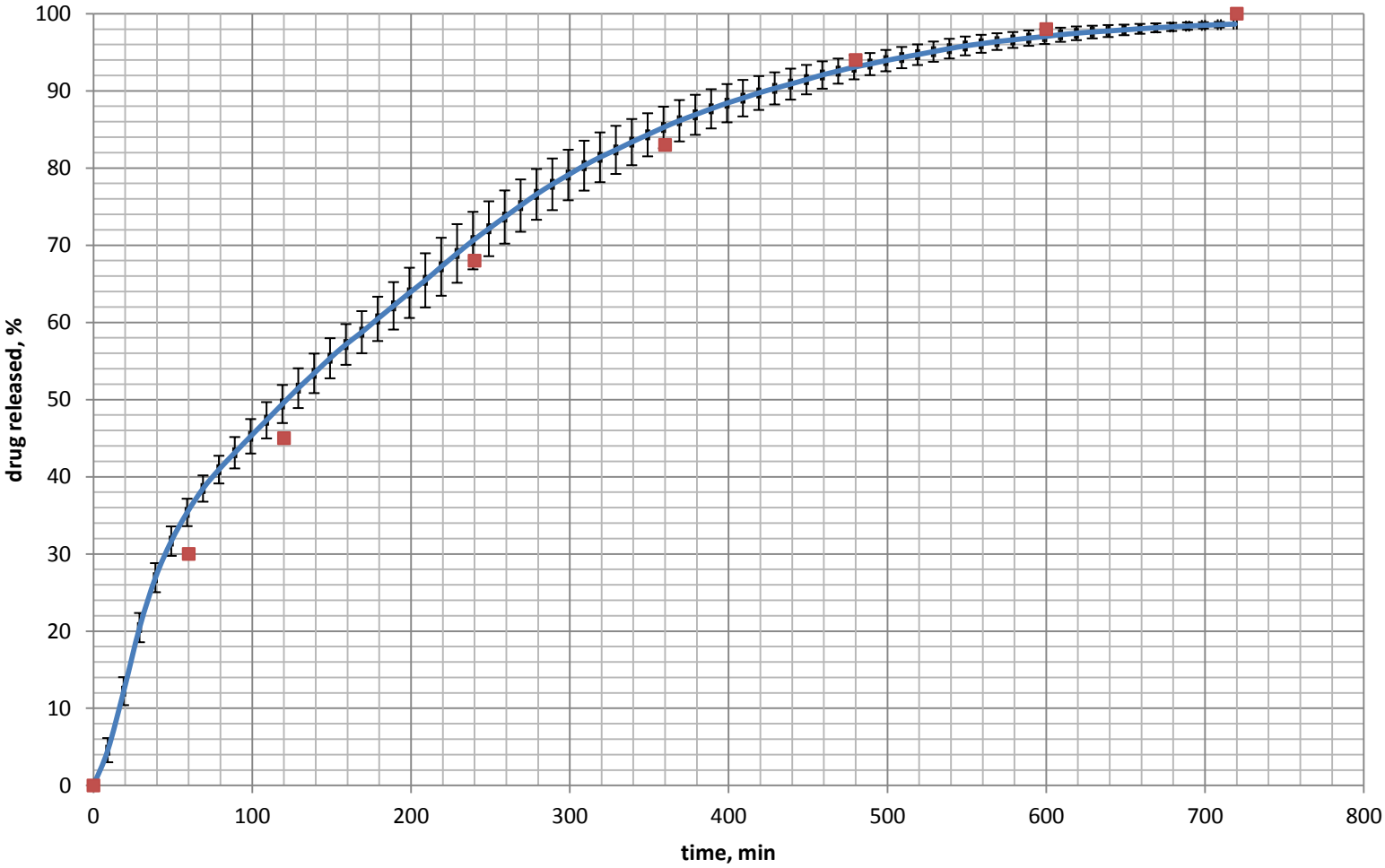


Data from Master thesis of David Tschirky, University of Basel

Influence of internal porosity

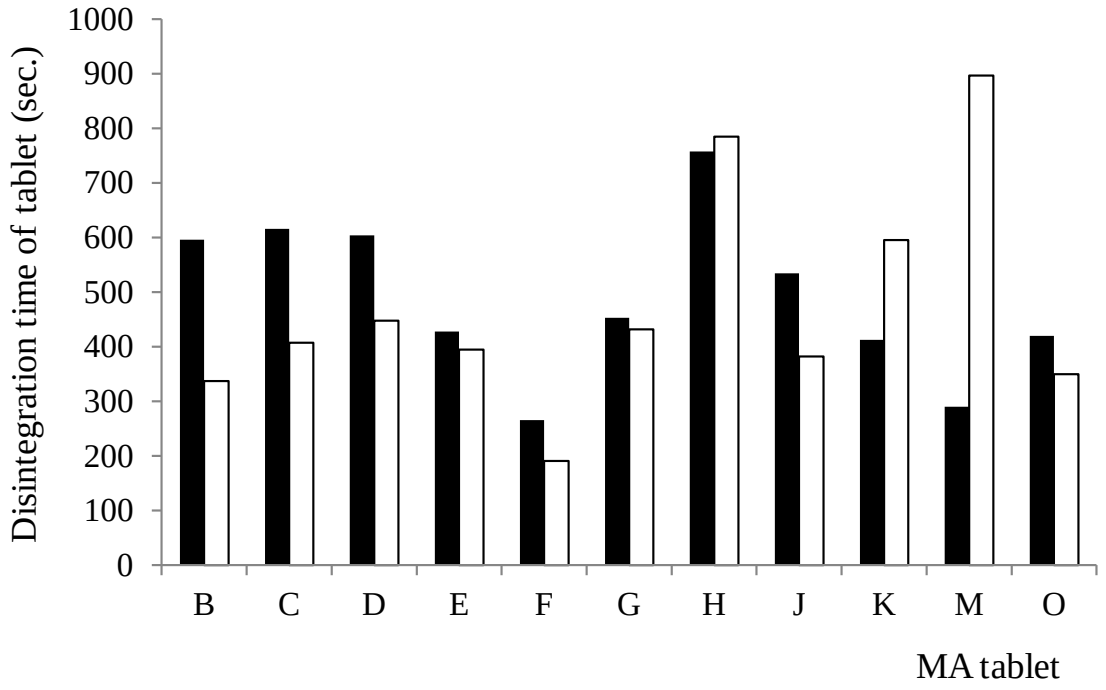


High solubility API/Prolonged Release



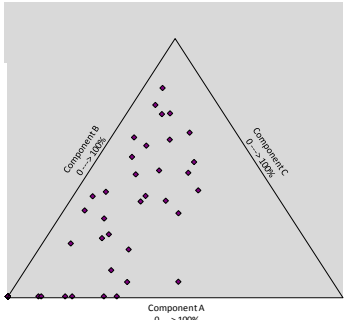
Design-Space Exploration Example

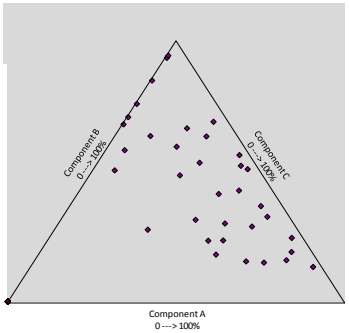
Tablet containing Mefenamic acid disintegration[1]:
Black- laboratory data
White – F-CAD experiment

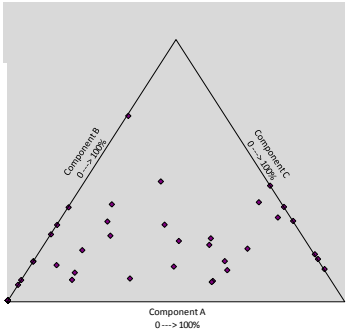


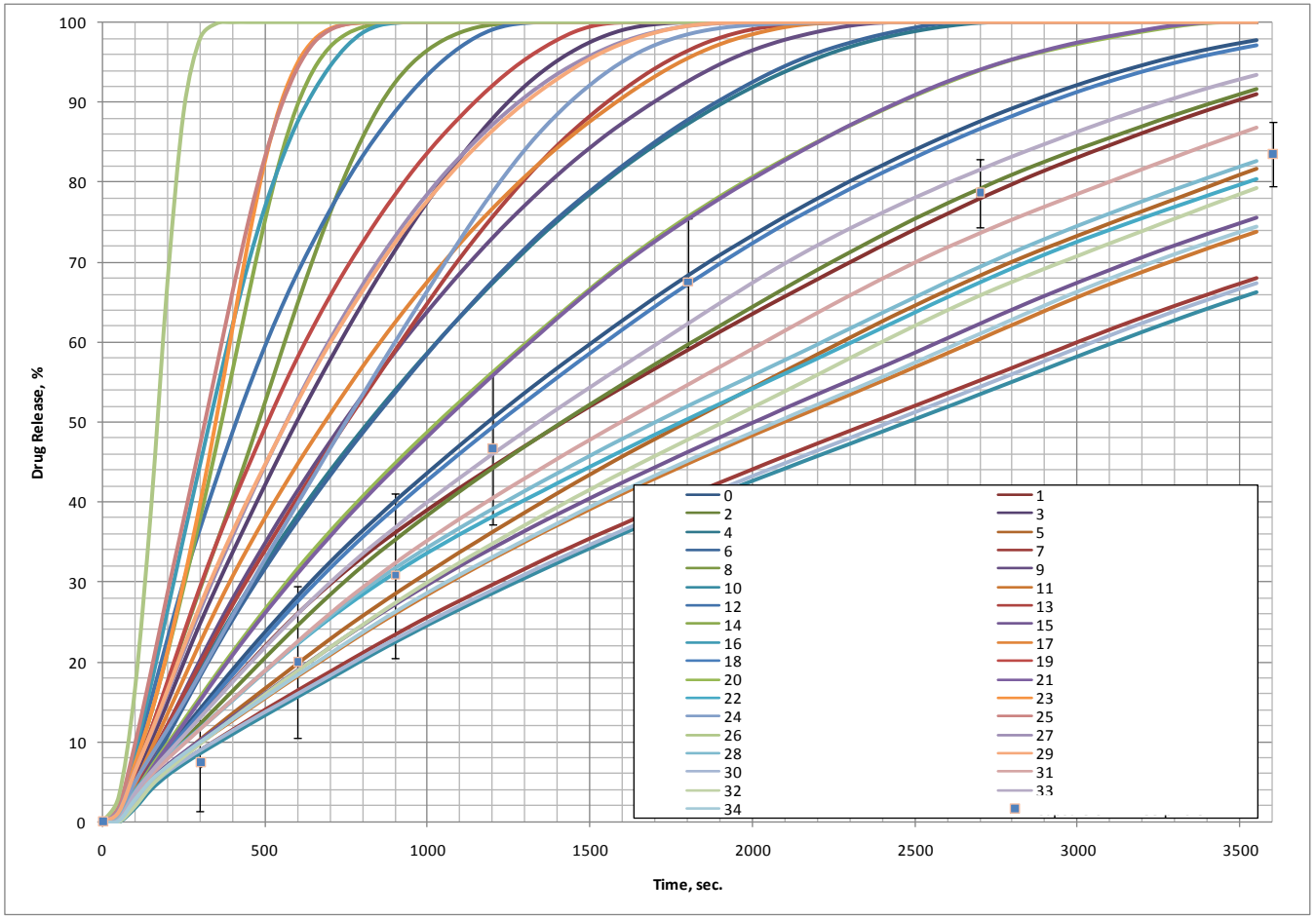
[1] Kimura et al. An Attempt To Calculate In Silico Disintegration Time of Tablets Containing Mefenamic Acid, a Low Water-soluble Drug. J Pharm Sci. 2013

Design-Space Exploration Example II



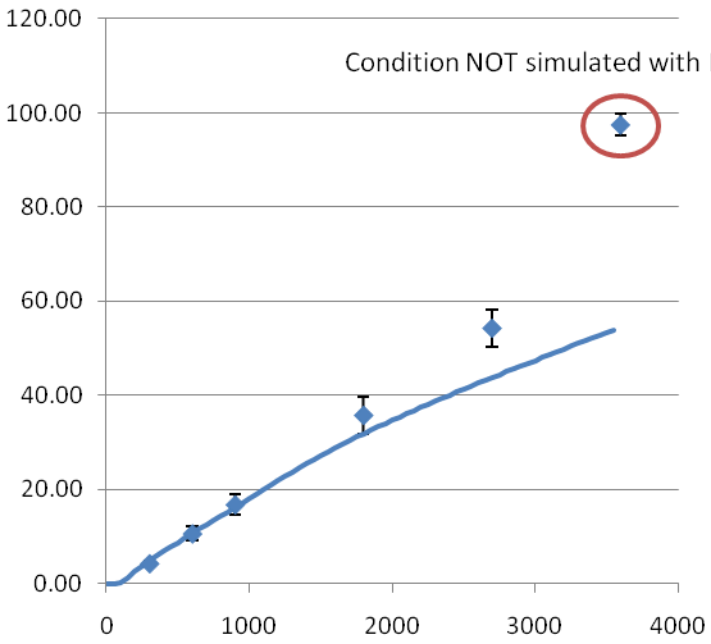


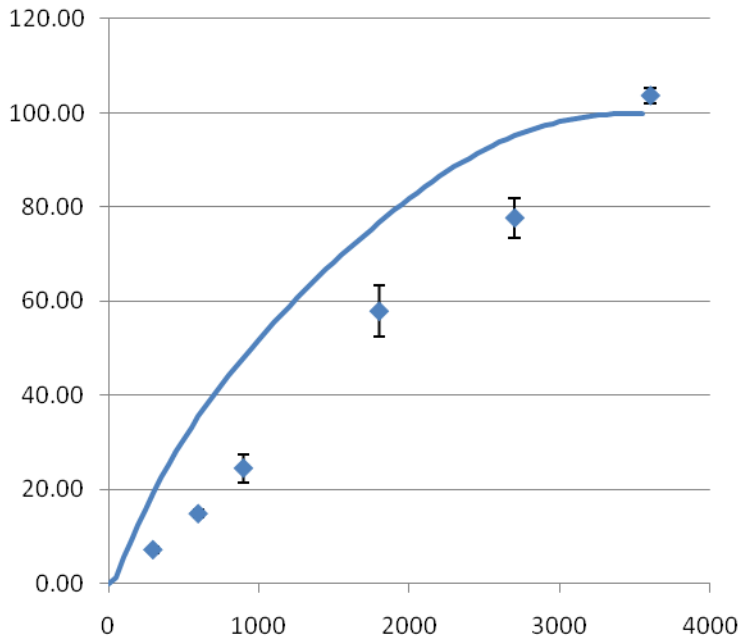




F-CAD Case-study

- API Solubility 10-20 mg/L (First Approximation)
- Dissolution in 2 different buffers for same formulation
- Solid curves: F-CAD calculated results
- Dots: experimentally-acquired results (after the calculation was done)





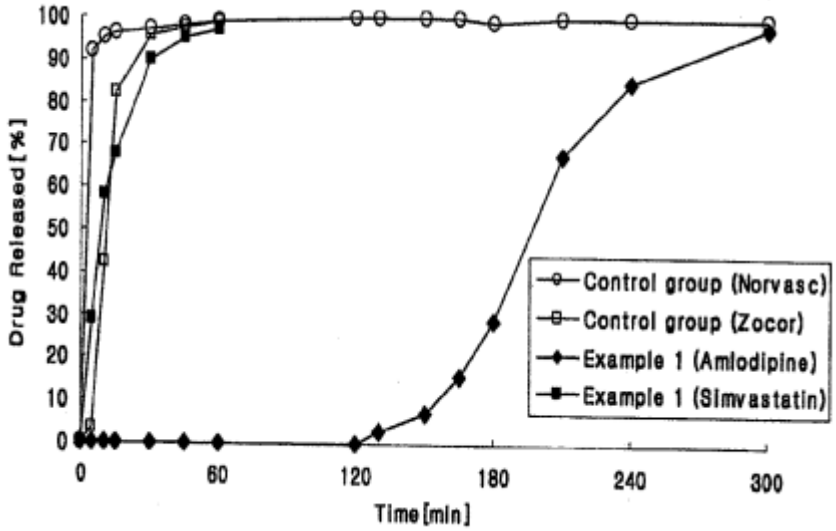
Troubles with Combinations

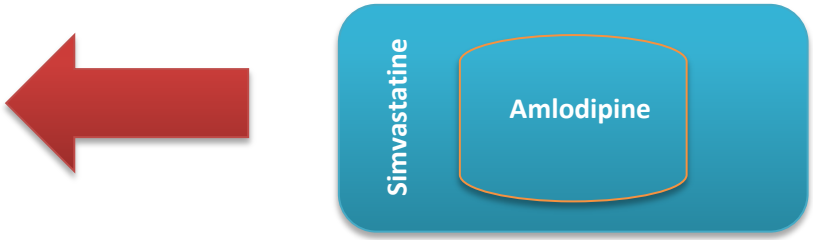
- Non-trivial formulations with specific complex functions
  - IR and modified release
  - Multi-API
  - Timed release to "switch" a biological response on or off
  - Etc.
- Initial design – difficult
- Prone to stability issues[1]
  - Drug-drug incompatibility
  - Drug-excipient incompatibility
  - Drug-drug-excipient incompatibility

S. Franz, The trouble with making combination drugs, Nature Reviews, Drug Discovery 5, 881-882 (2006)

The combination drugs debate: Incompatibility problems can be overcome
Rajesh Dubey, Avvaru Seshasayana, Satti Phanikumar Reddy, Suryakumar Jayanthi
PHARMACEUTICAL TECHNOLOGY EUROPE
Volume 21, Issue 9

Combined Drug Example





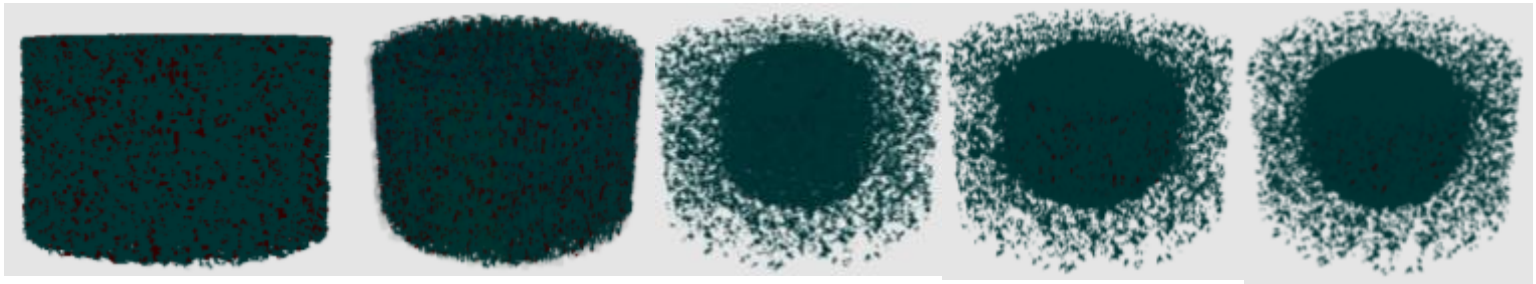
U.S. Pat. US2008241240 (A1)

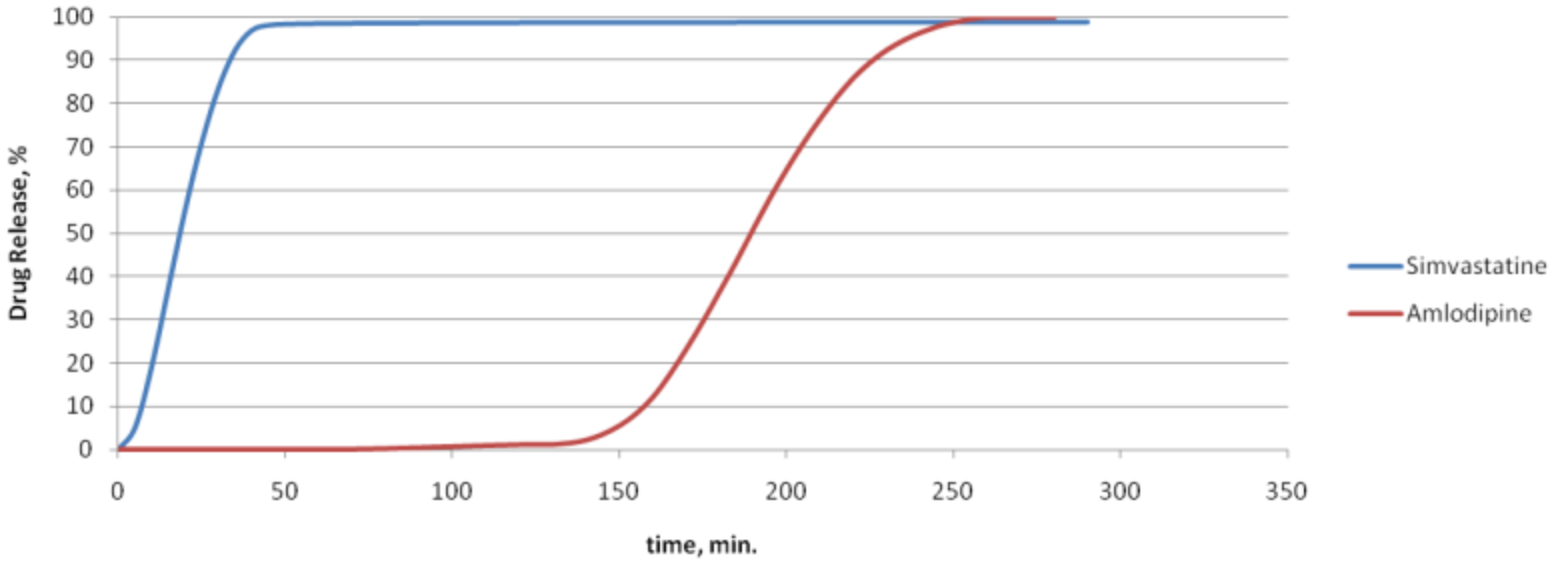
COMBINED PHARMACEUTICAL FORMULATION WITH CONTROLLED-RELEASE COMPRISING DIHYDROPYRIDINE CALCIUM CHANNEL BLOCKERS AND HMG-COA REDUCTASE INHIBITORS

KIM SUNG WUK [KR]; JUN SUNG SOO [KR]; JO YOUNG GWAN [KR]; KOO JA-SEONG [KR]; KIM JIN WOOK [KR]; YIM JU BIN [KR]; LEE JUN YOUNG [KR]

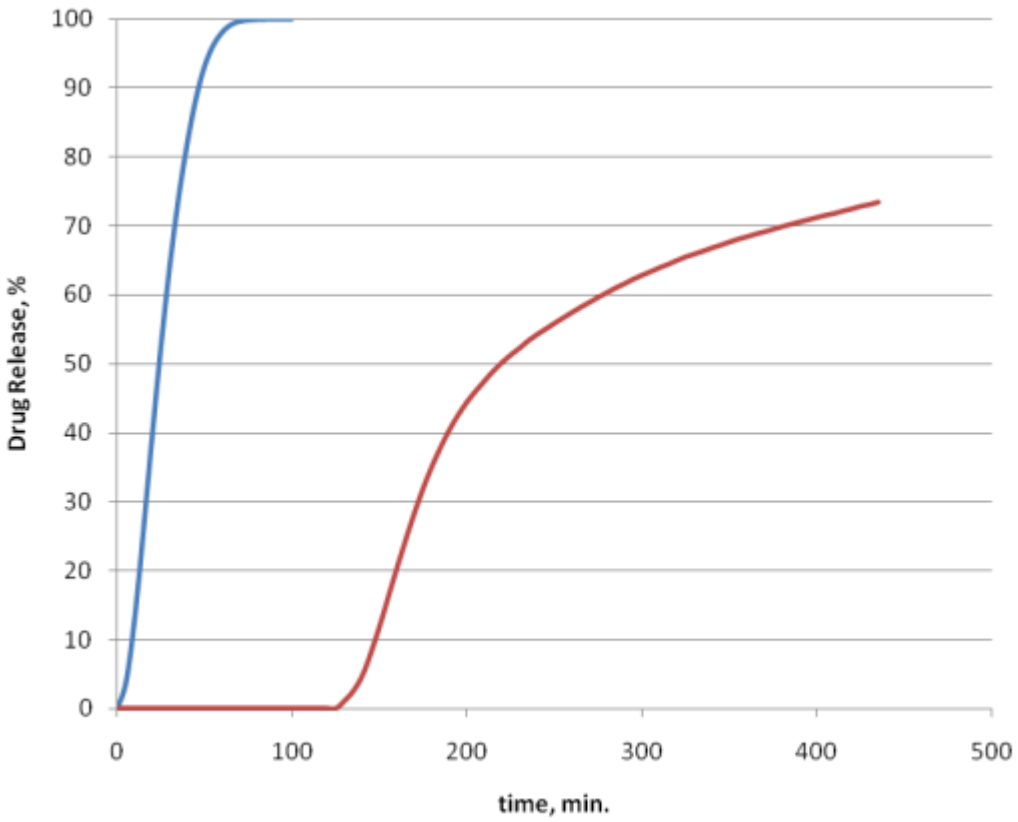
Name	%, v/v	%, w/w	Mass, mg	Density, mg/mm3
Amlodipine maleate	1.32	2.14	6.42	1.227
Simvastatine	4.53	6.67	20.00	1.115
MCC Inner	11.53	23.50	70.83	1.55
Carbomer 71G	2.10	3.32	10.00	1.2
HPMC Inner	0.38	0.66	2.00	1.326
HPMC Ph	1.39	3.32	10.00	1.82
MCC Outer	9.28	18.91	57.00	1.55
D-Mannitol	18.74	37.31	112.46	1.514
SSG	0.17	0.33	1.00	1.443
Butilated hydroxyanisole	0.01	0.01	0.04	1.117
HPMC Outer	0.95	1.66	5.00	1.326
Aerosil	0.10	0.33	1.00	2.634
Citric acid	0.29	0.66	2.00	1.762
MgSt outer	0.35	0.50	1.50	1.09
MgSt inner	0.17	0.25	0.75	1.09

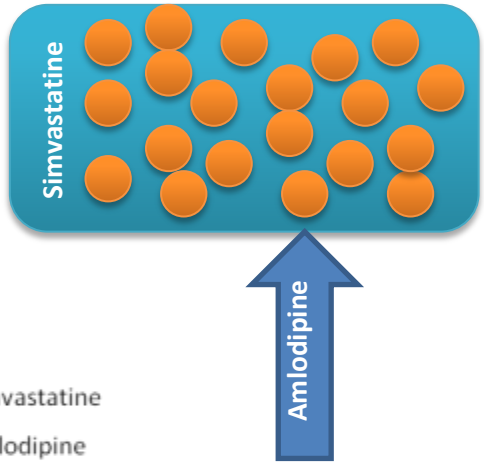
F-CAD-Generated output

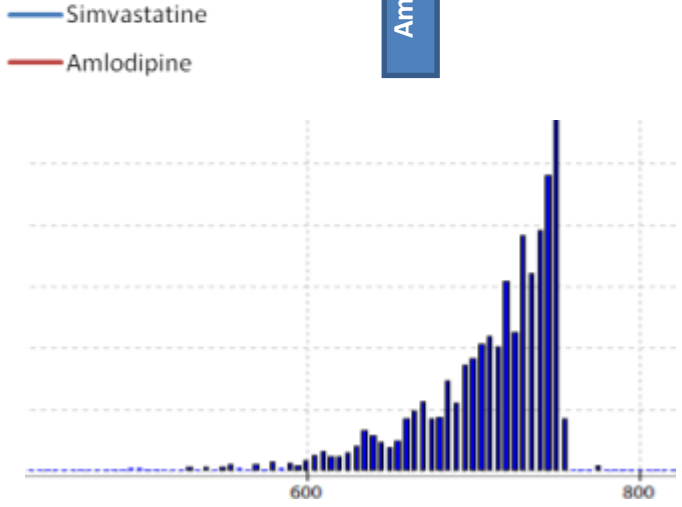




Similar Formulation with Pellets







Conclusions

- F-CAD is solving an engineering task in formulation design, enabling the
  - Physical-chemical effects are taken into an account through calibration
- F-CAD is generating dissolution profiles based on “specific” solubility of all of the components of a formulation (superposition)
- Component particle arrangement is playing one of the key roles in dissolution kinetics of a pharmaceutical compact
- Unit operations can be modeled though PAC
- Combination drug formulations are possible
- F-CAD as scientific tool
  - Study influence of spatial organization of solid particles on physico-chemical phenomena, for example, - dissolution or degradation?