CINCAP GmbH
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A Proposal to reduce significantly Public Health Costs: Development of Combination Drugs based on Generics using Virtual R&D techniques with the goal to improve Patient Compliance

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CINCAP GmbH, IFIIP GmbH
Switzerland

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Switzerland

CINCAP Technologies Overview

Formulation R&D

- F-CAD-based services
  - *In silico* formulation development
  - Development of tablet formulation from existing capsule formulation
  - Root Cause Analysis
  - TabletDesigner-software for formulation-bound trade dress design

F-CAD Robust Formulation!

Process Engineering

- Development and Application of custom-made Discrete Element Models (DEM) for simulation of particulate matter behaviour (coating, particulate flow behaviour, mixing, segregation, etc. models in customer-based geometries)
- HPC-based simulations at **INTERACTIVE RATES!**

NVIDIA Tesla Solve Tomorrow's Problems, Today!

Computer-Aided Education and Training Systems

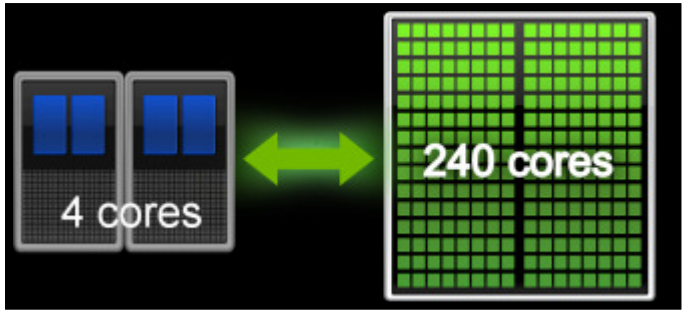
- Virtual Equipment Simulation (VES)
  - Continuous Education + Personalized Training
  - Minimum human error

VES Operator Training

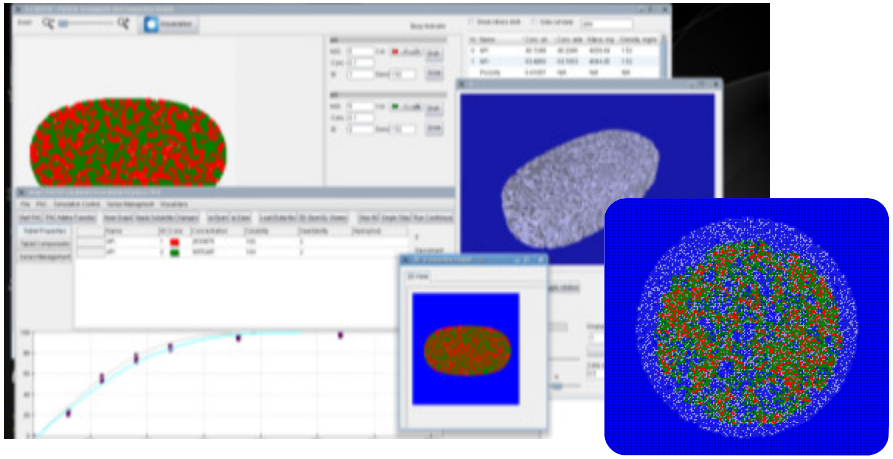
NVIDIA Tesla Computing Solutions

- Massively-Parallel Architecture, up to 512 multi-core single processor units
- Up to 4 TeraFLOPS computing capacity per ONE unit
- Scalable architecture

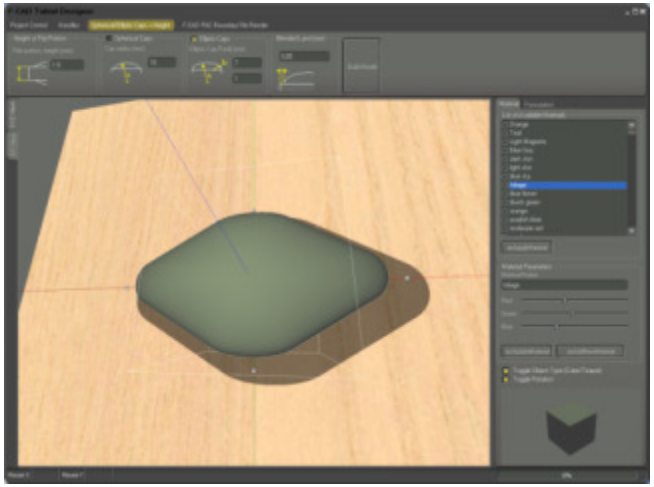
FLOPS – Floating Point Operations per Second



F-CAD Screenshots

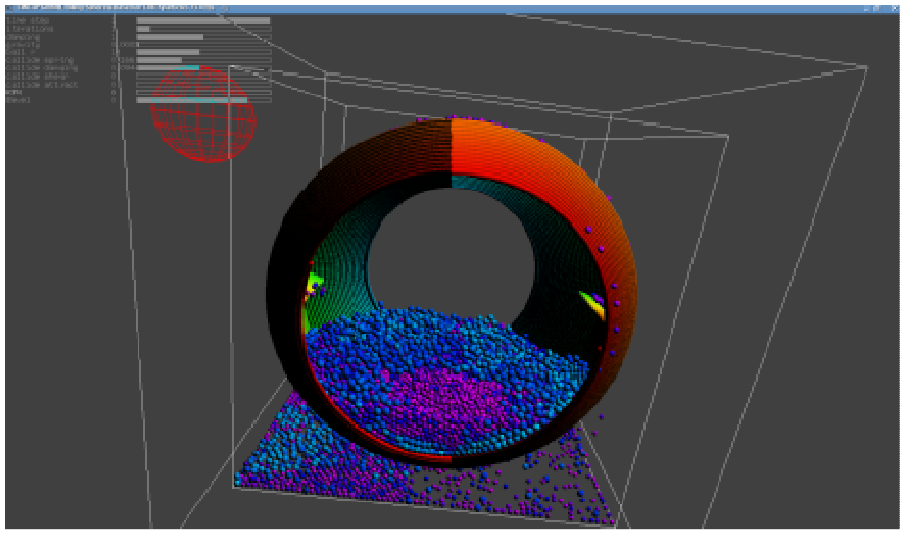


F-CAD TabletDesigner



VES Example

DEM Models



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

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

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

Solutions?

- New, innovative excipients with unique properties
- New tools for high throughput stability screening
- Computer-Aided Design tools

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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.

F-CAD Applications

- Feasibility study in case of a new product
- Existing product optimization
- Rapid 3D-design and rapid prototyping of a new dosage form, including tooling design
- Root Cause Analysis
- Unified solution for
  - Immediate and controlled release formulations
  - Support for different unit operations (granulation, milling, etc.)
  - Tablet size and shape design

  ... and much more.

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 swellability of the 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
- 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 (tablet, capsule)
- Required release specifications
  - Immediate release
  - Controlled release

General Workflow

TABLET DESIGNER

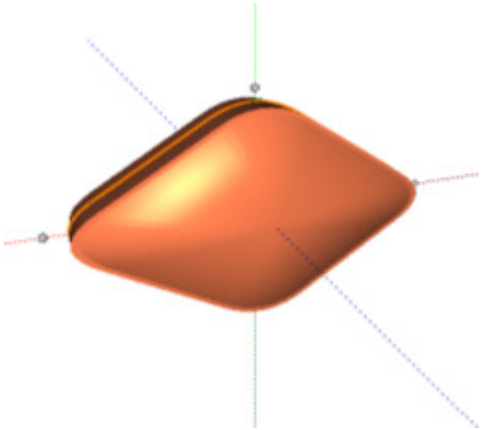
- Shape design
- Shape To Matrix Conversion

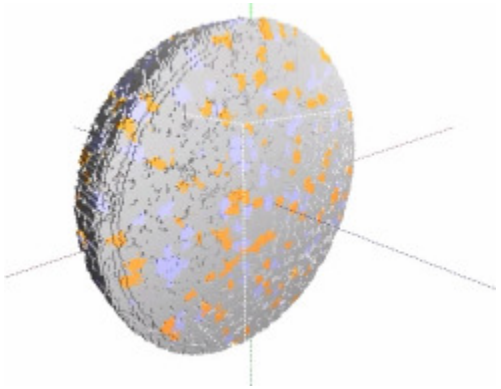
Particle Arrangement and Compaction (PAC)

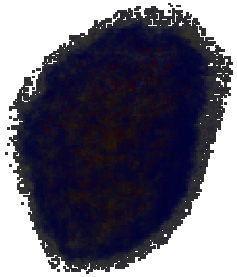
- Fill matrix with content

Dissolution Profile Calculation

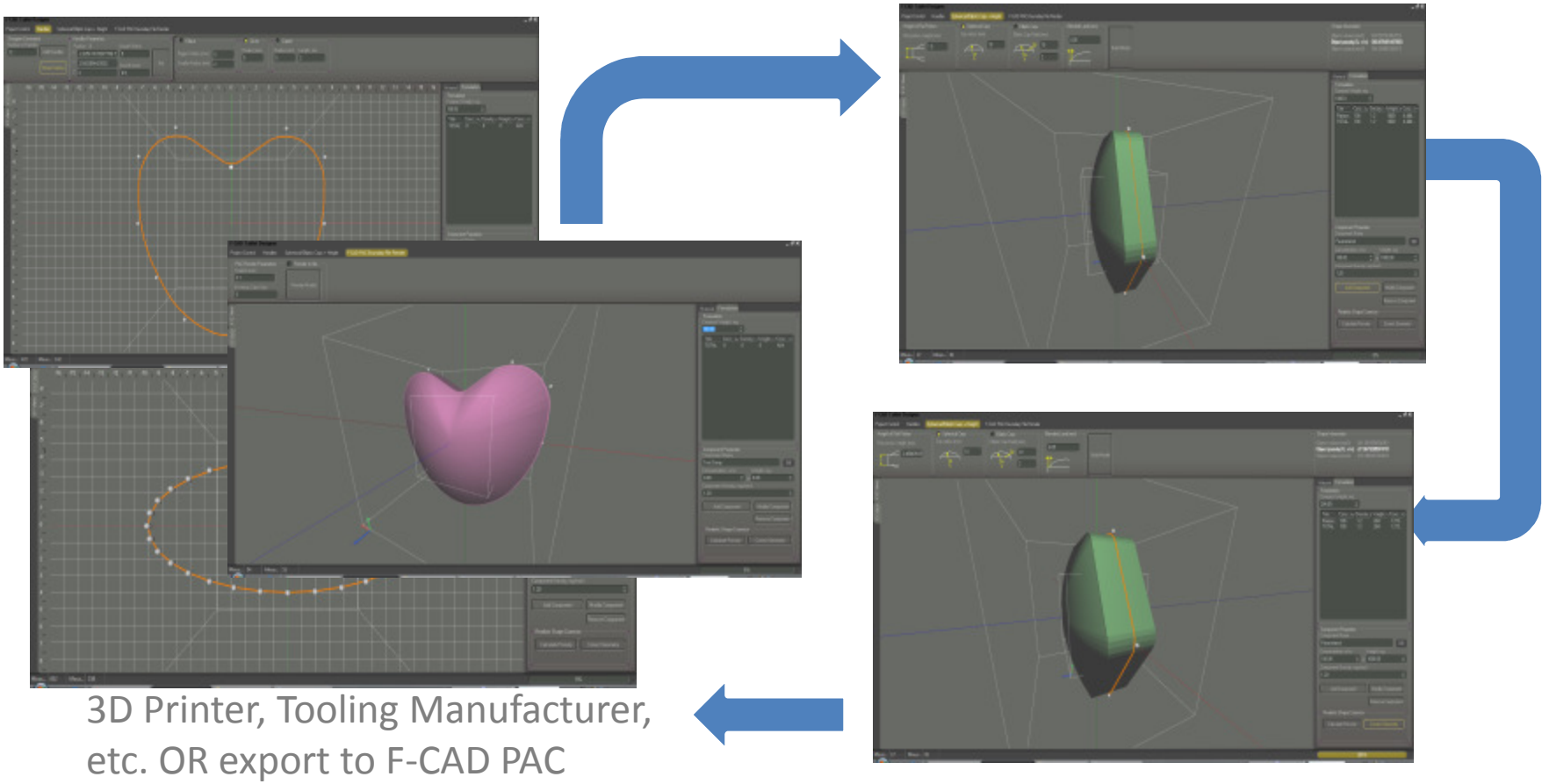
- Calculate the profile points per unit of time (e.g. sec, min)





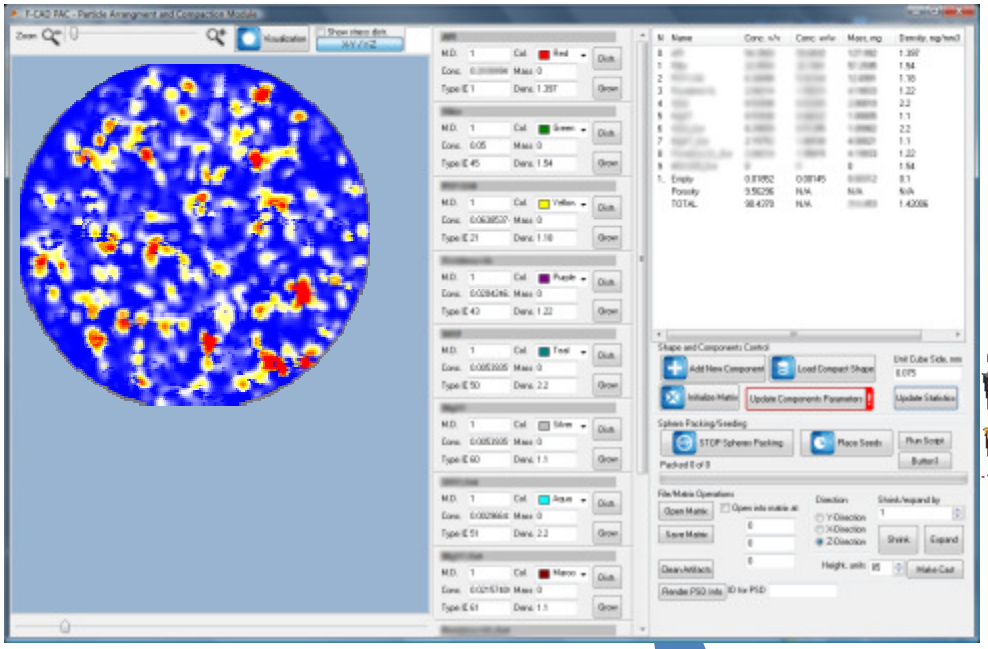


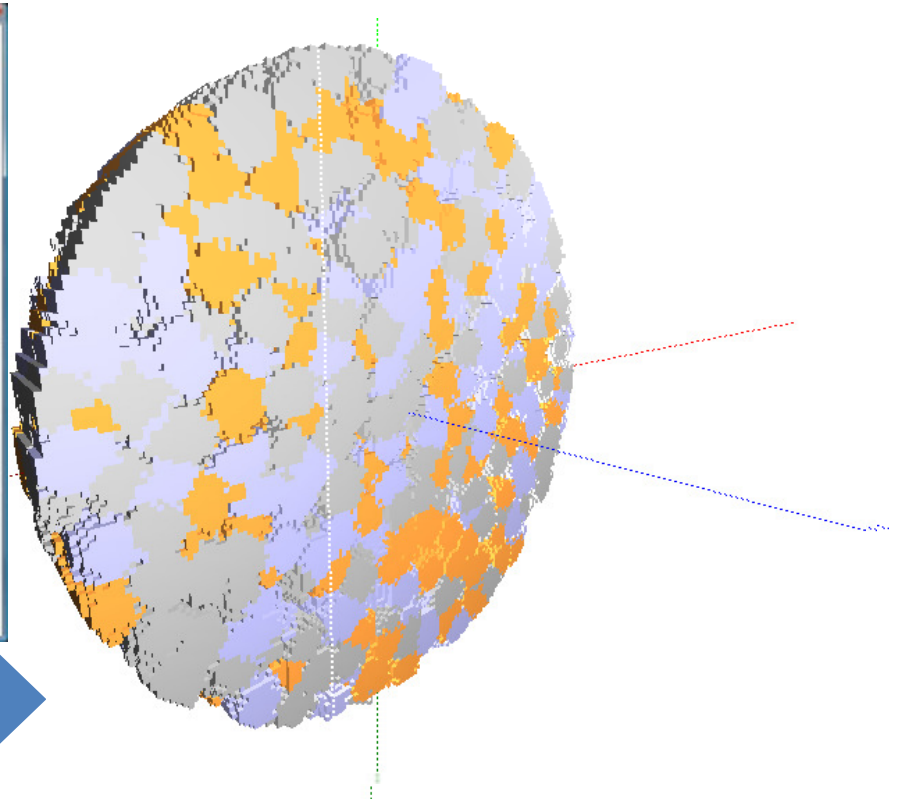
F-CAD Tablet Designer



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

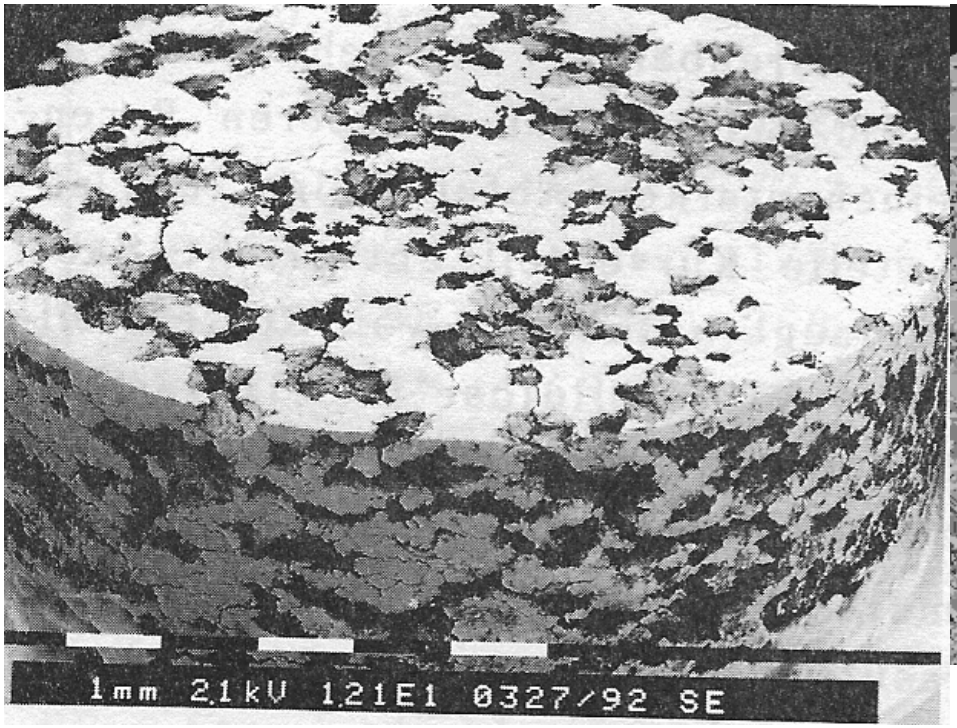
F-CAD PAC – Particle Arrangement and Compaction



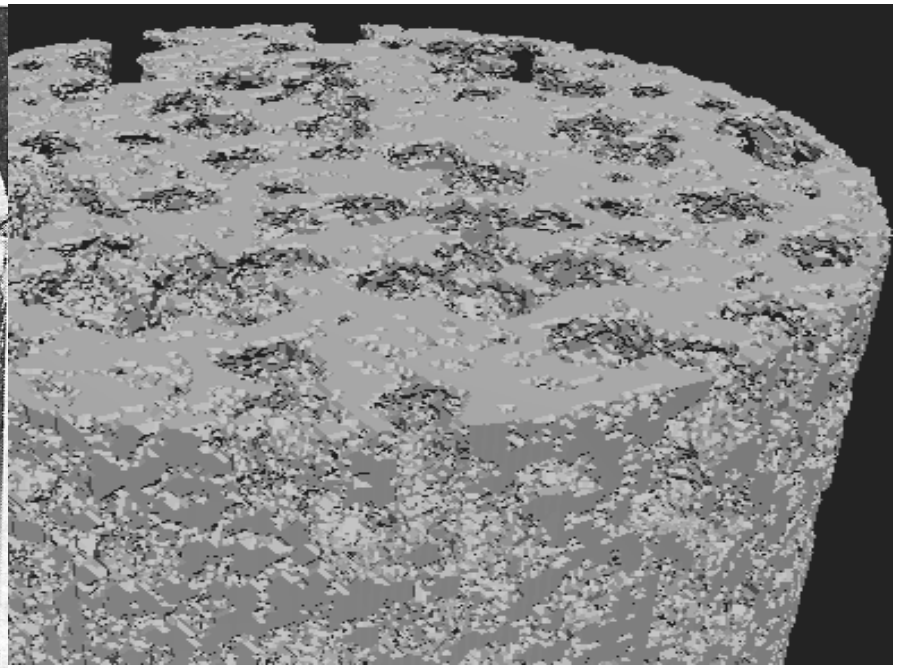


Leached Matrix Controlled Release Tablet

500-710 µm



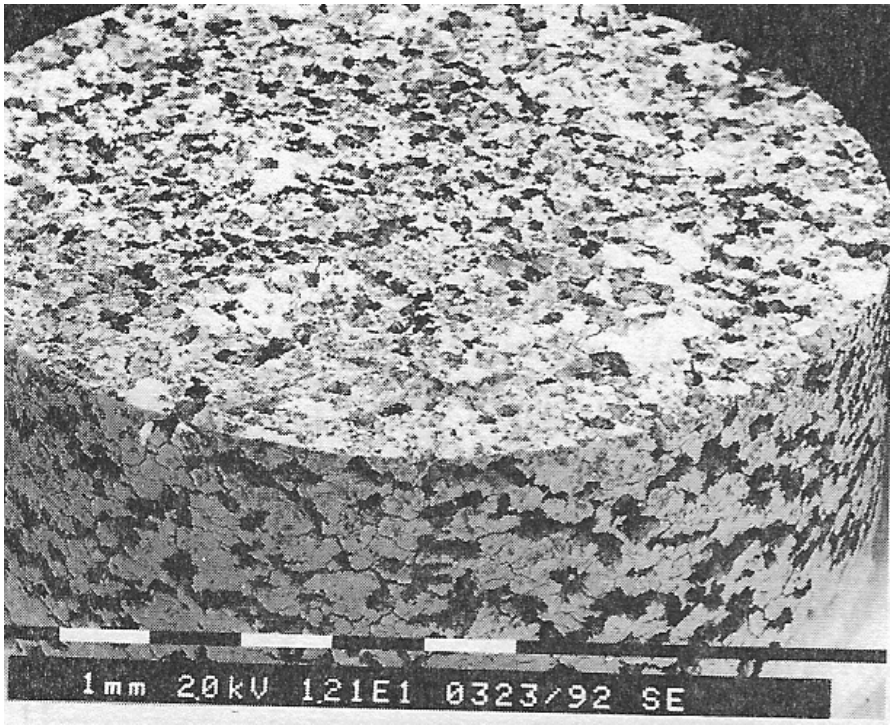
500-710 µm



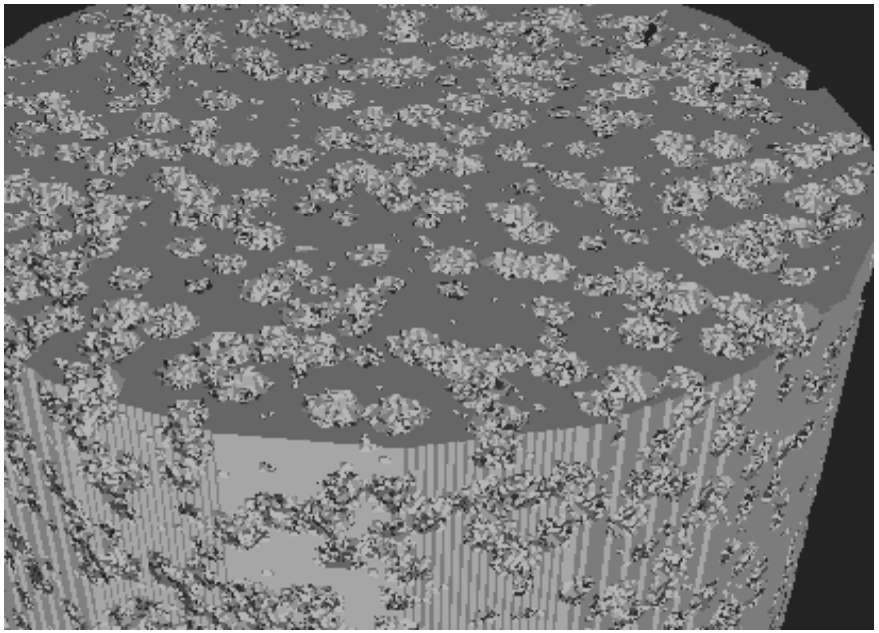
Real – left (PhD Thesis J.D. Bonny)
Computer Generated System - right

Leached Matrix Controlled Release Tablet

250-355 µm



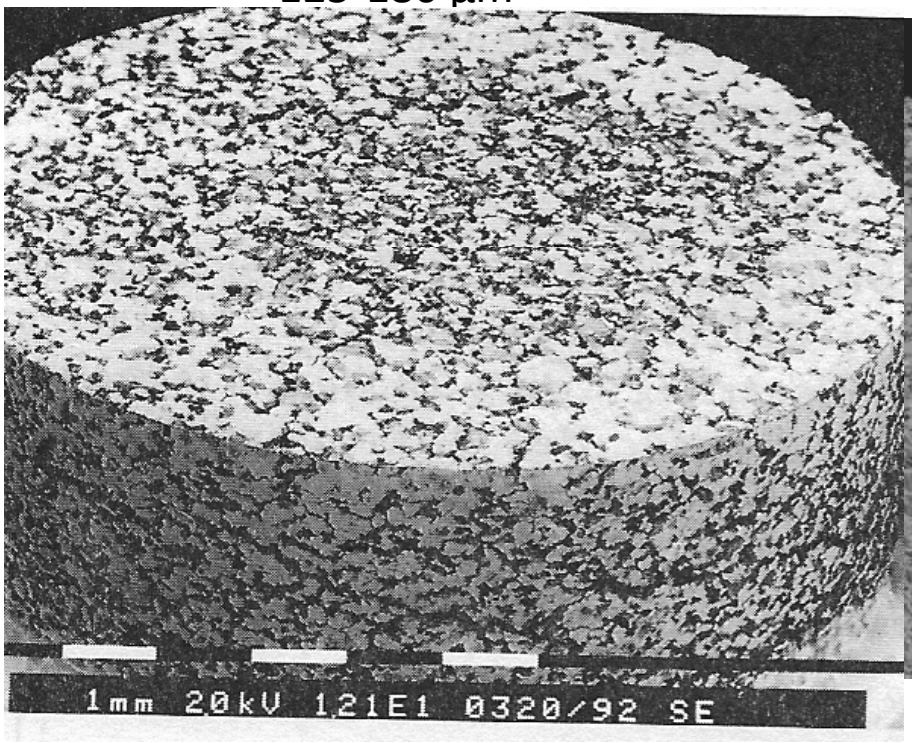
280-400 µm



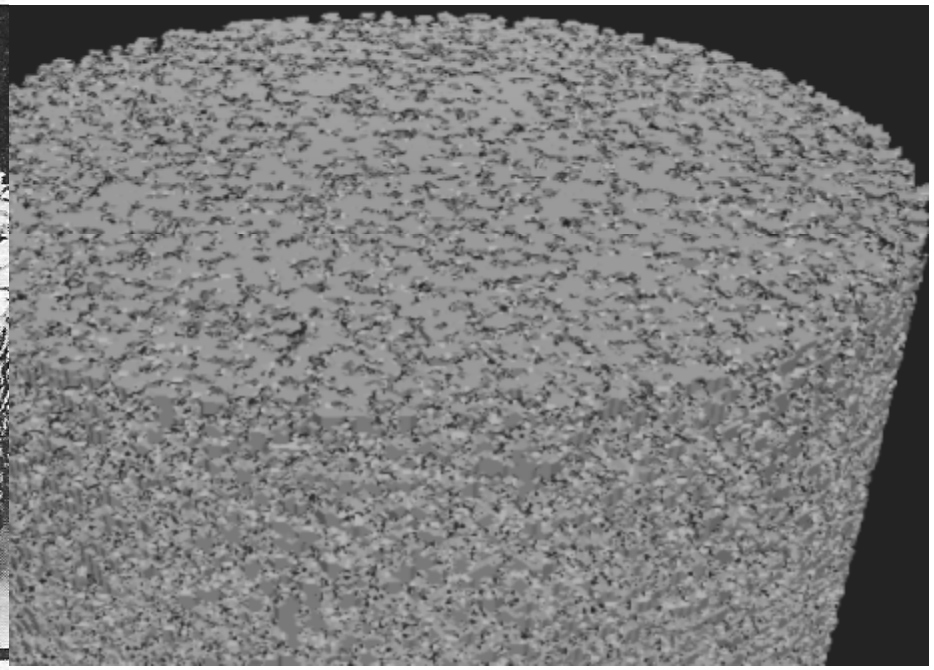
Real – left (PhD Thesis J.D. Bonny)
Computer Generated System - right

Leached Matrix Controlled Release Tablet

125-180 µm



150-200 µm

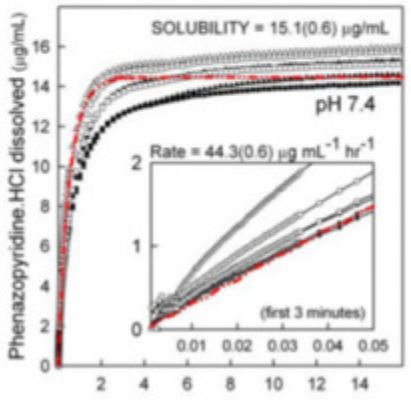


Real – left (PhD Thesis J.D. Bonny)
Computer Generated System - right

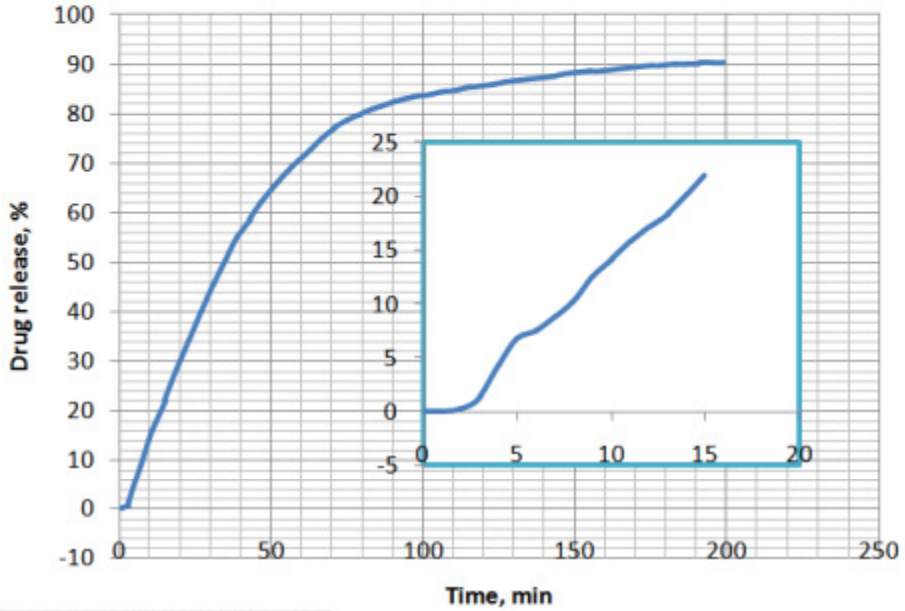
F-CAD Dissolution Profile Calculations

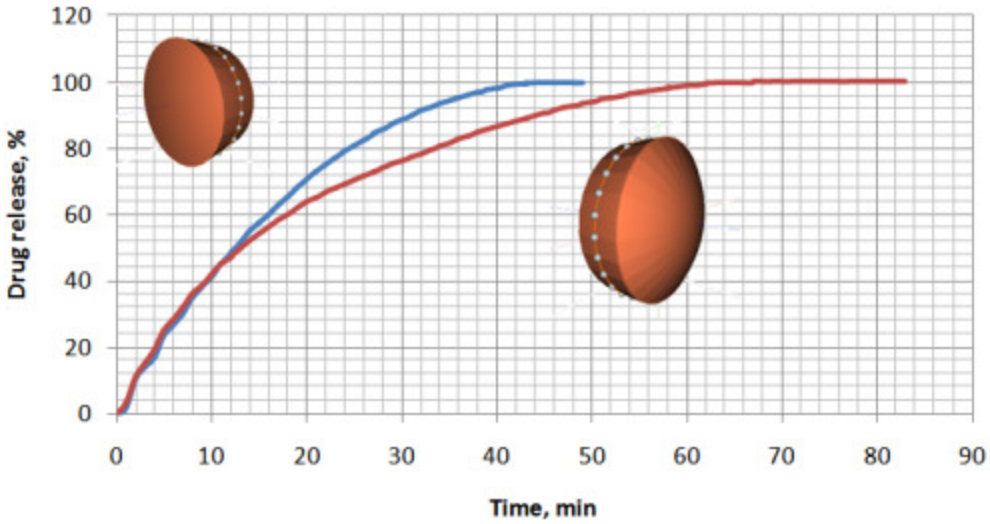
Periodic Sampling from calculation memory

F-CAD DS – *in silico* Profiles

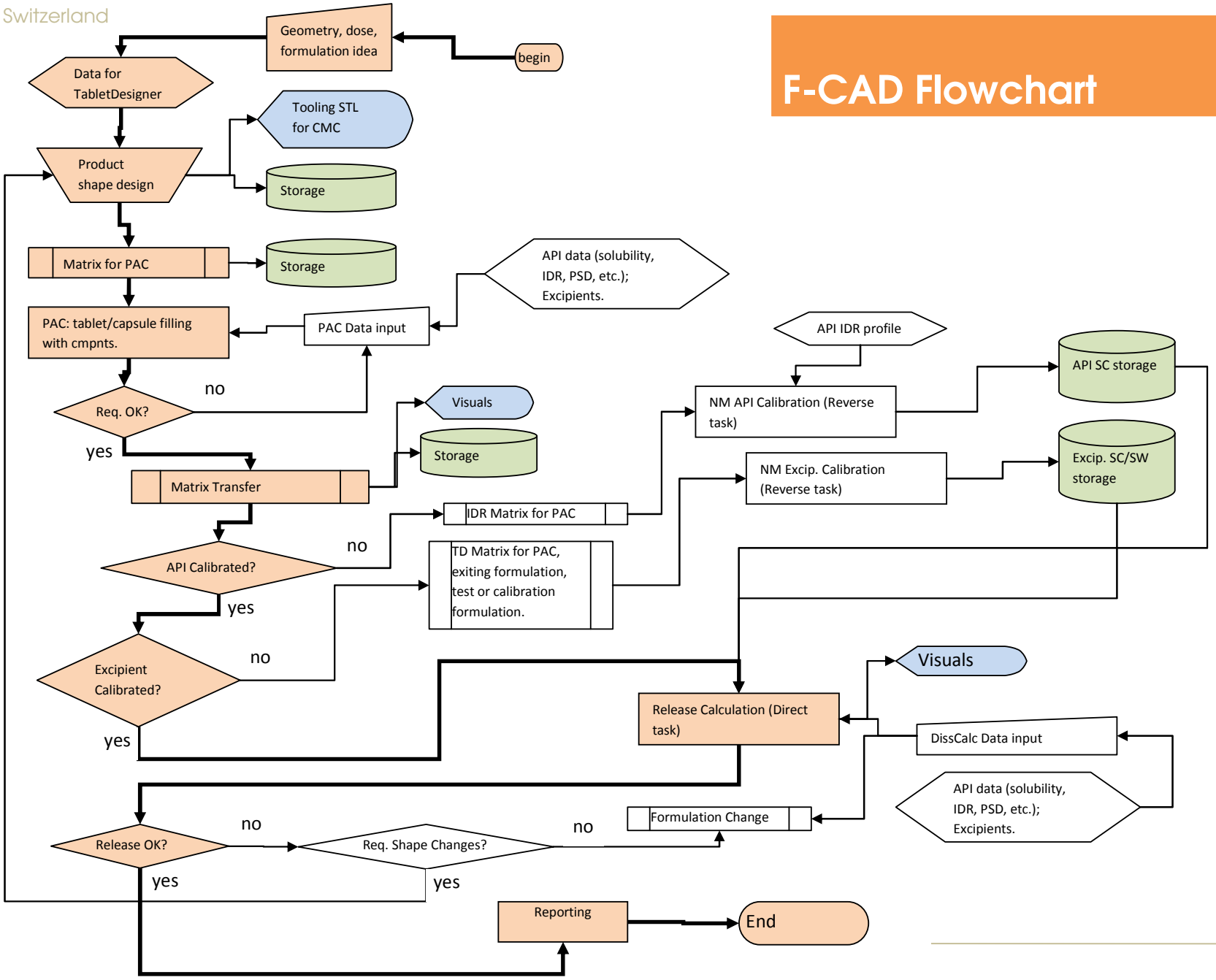


© Heath Scientific



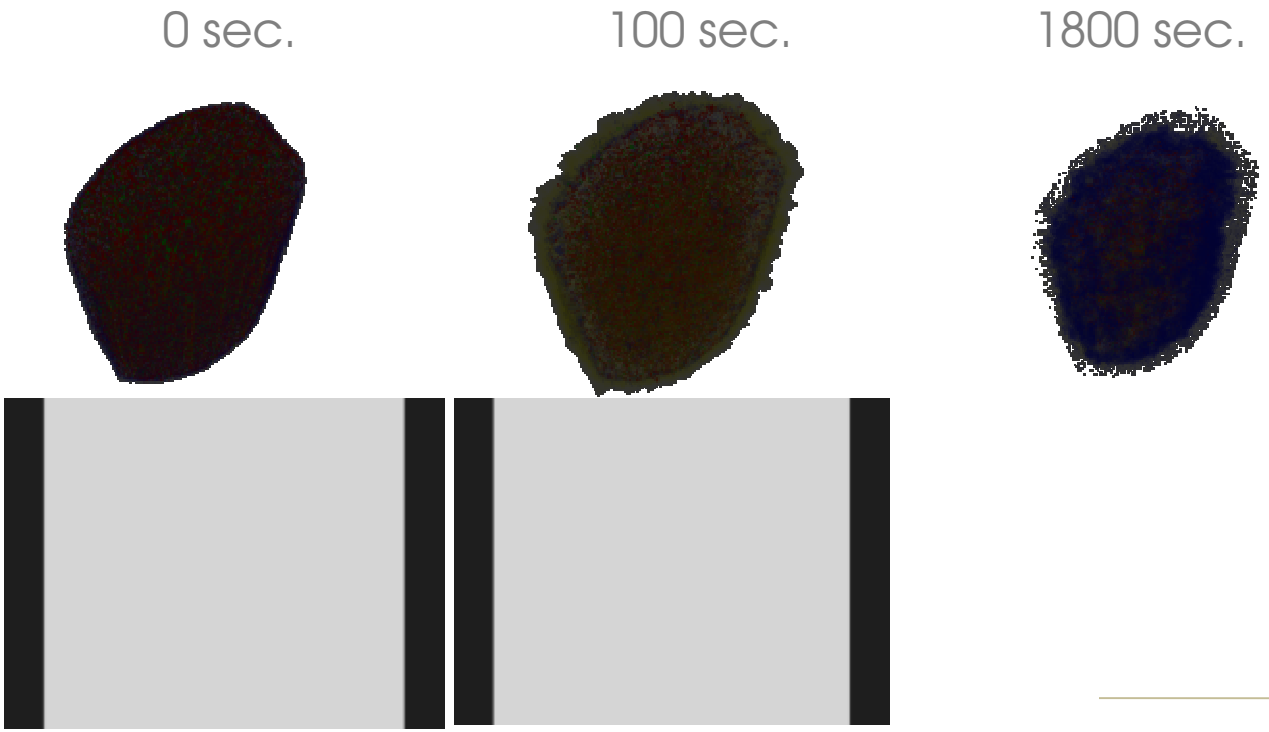


F-CAD Flowchart

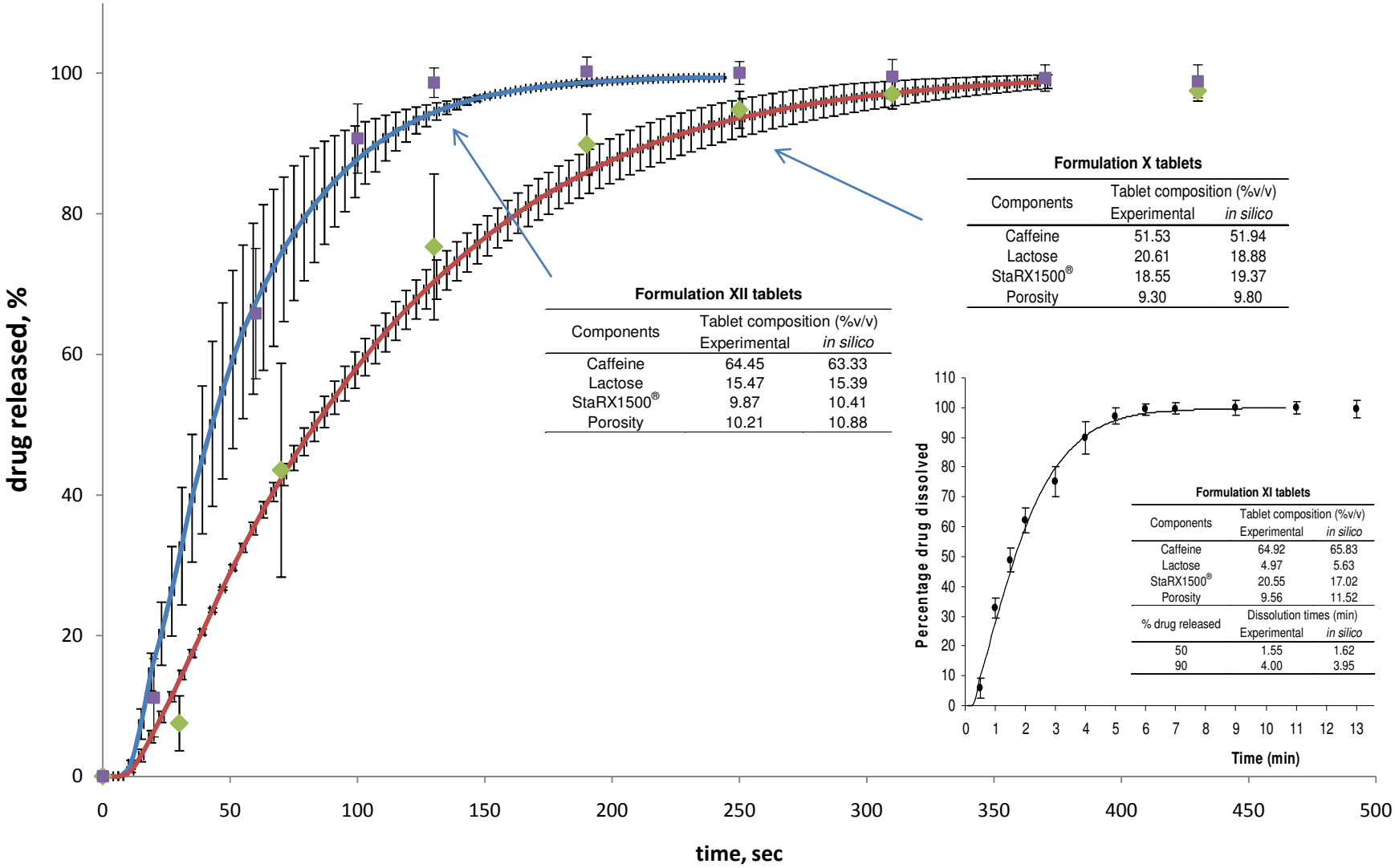


Rendering 3D Memory Content

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



Experimental vs. in silico dissolution profiles of different formulations with caffeine



Formulation XII tablets

Components	Tablet composition (%v/v) Experimental	*in silico*
Caffeine	64.45	63.33
Lactose	15.47	15.39
StaRX1500®	9.87	10.41
Porosity	10.21	10.88

Formulation X tablets

Components	Tablet composition (%v/v) Experimental	*in silico*
Caffeine	51.53	51.94
Lactose	20.61	18.88
StaRX1500®	18.55	19.37
Porosity	9.30	9.80

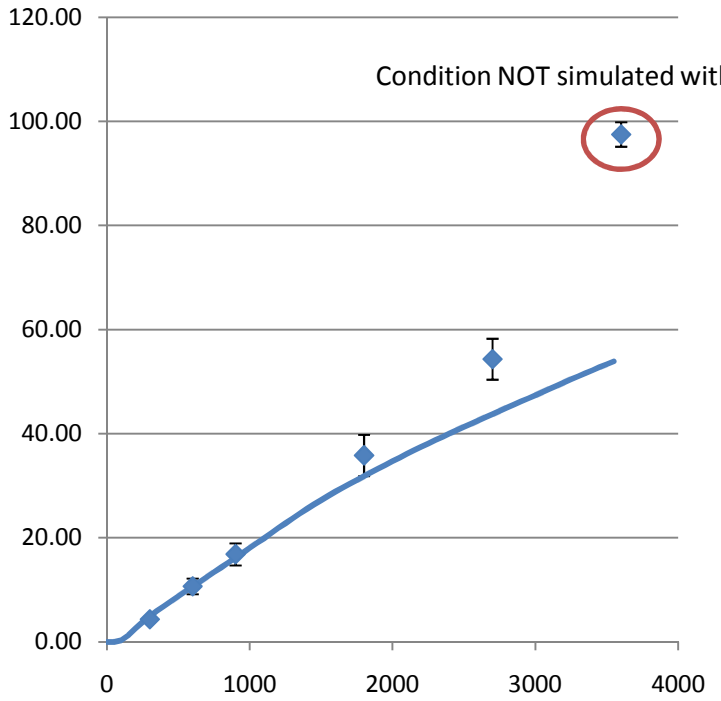
Formulation XI tablets

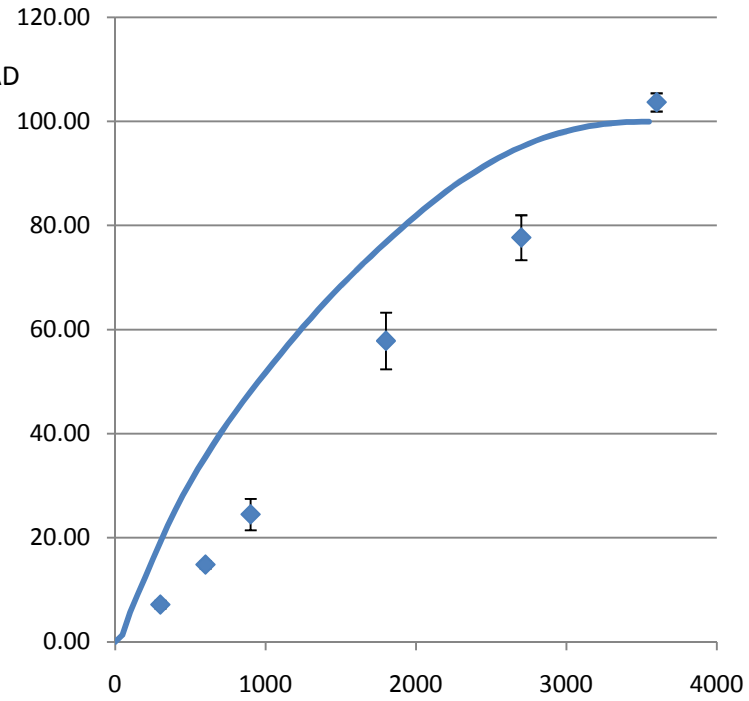
Components	Tablet composition (%v/v) Experimental	*in silico*
Caffeine	64.92	65.83
Lactose	4.97	5.63
StaRX1500®	20.55	17.02
Porosity	9.56	11.52
% drug released	Dissolution times (min) Experimental	*in silico*
50	1.55	1.62
90	4.00	3.95

"Krausbauer E.: Contributions to a science based expert system for solid dosage form design. PhD Thesis; University of Basel: Basel, 2007."

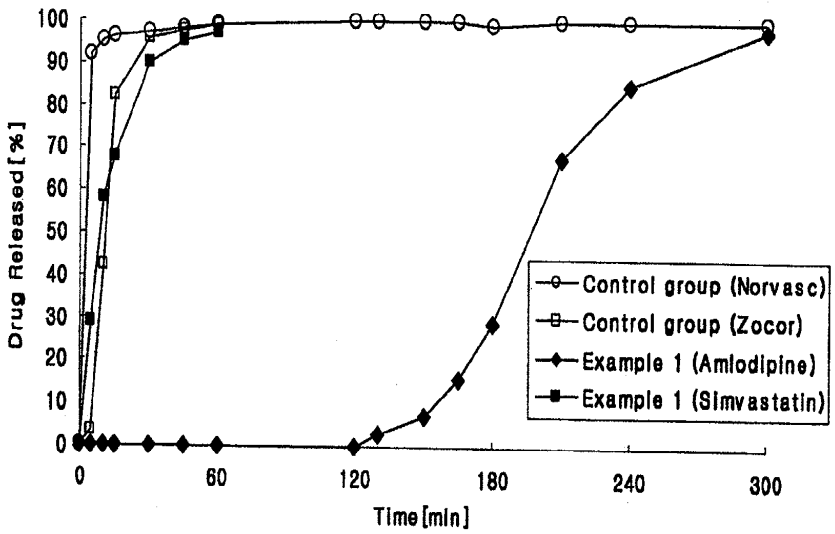
API Solubility 10-20 mg/L

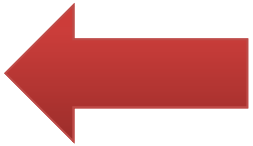
» API Solubility 10-20 mg/L (First Approximation)

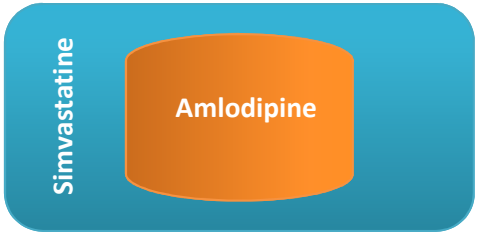




Combined Drug Example







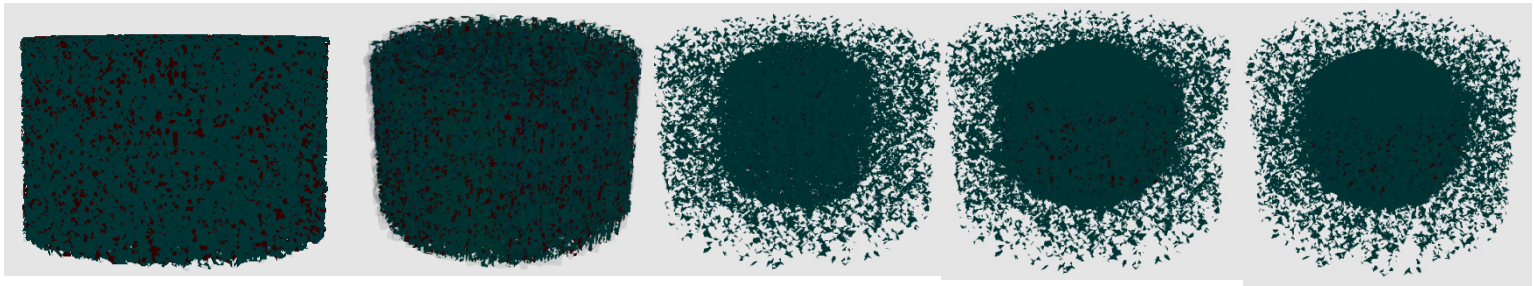
U.S. Pat. US2008241240 (A1)

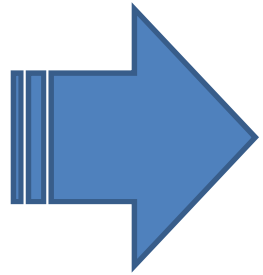
COMBINED PHARMACEUTICAL FORMULATION WITH CONTROLLED-RELEASE COMPRISING DIHYDROPYRIDINE CALCIUM CHANNEL BLOCKERS AND HMG-COA REDUCTASE INHIBITORS

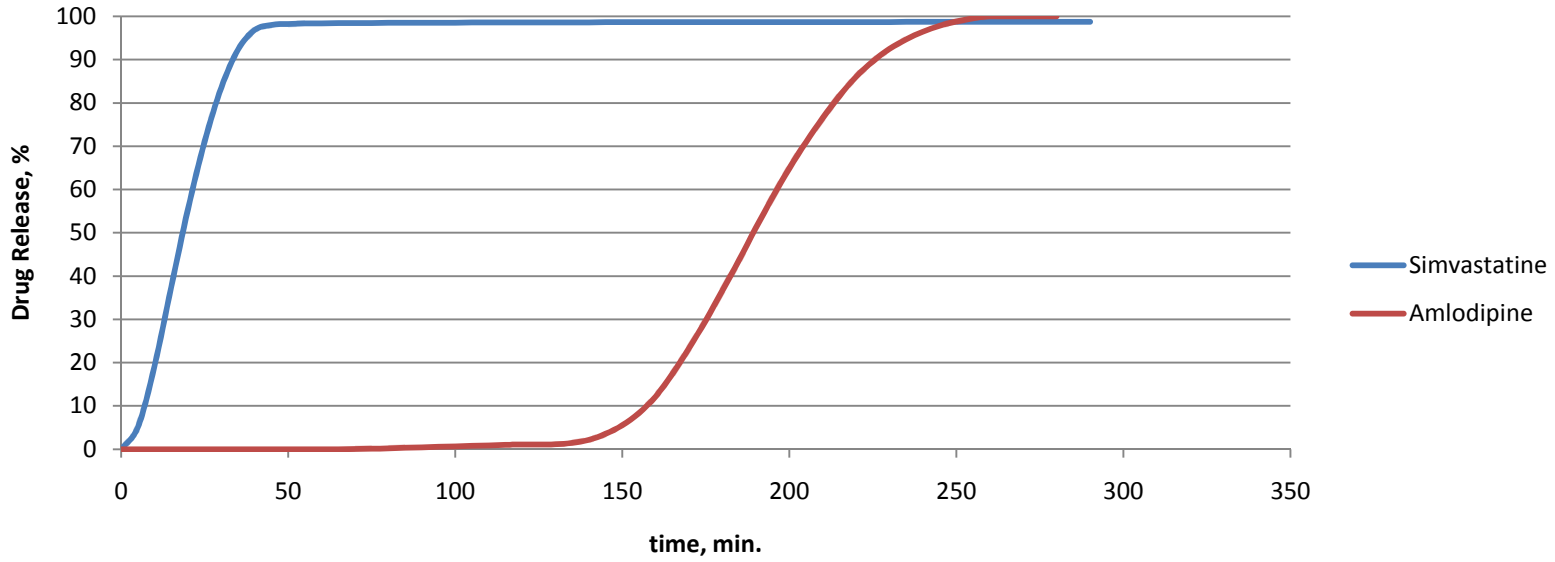
KIM SUNG WUK [KR]; JUN SUNG SOO [KR]; JO YOUNG GWAN [KR]; KOO JA-SEONG [KR]; KIM JIN WOOK [KR]; YIM JU BIN [KR]; LEE JUN YOUNG [KR]

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

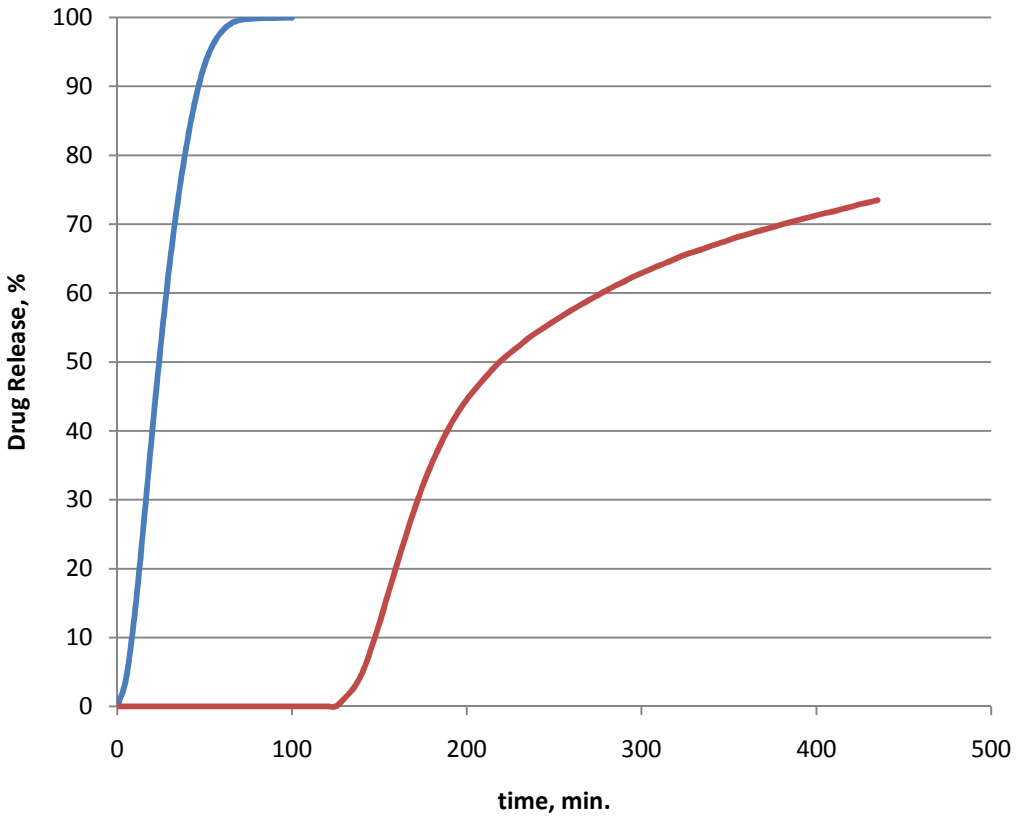
F-CAD-Generated output

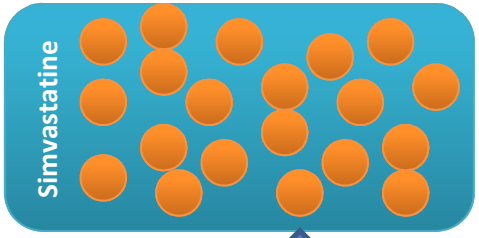


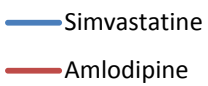


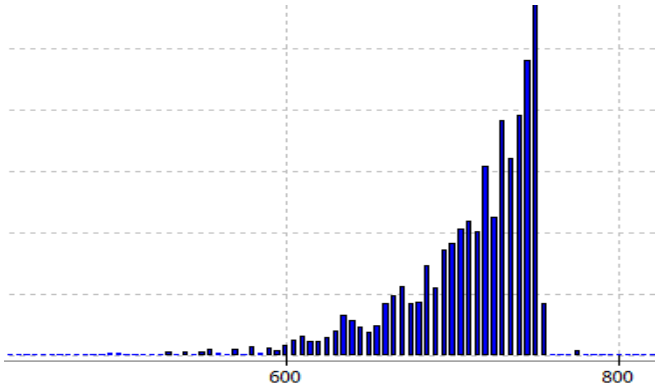


Similar Formulation with Pellets









About CINCAP

- The Center for Innovation in Computer-Aided Pharmaceutics, CINCAP GmbH is mainly focusing on the novel, science-based software products to assist in design, development and production of modern pharmaceutical products.

- CINCAP main activities include:
  - Development of the computer-aided formulation design software and technologies, along with scientific research in pharmaceutical process technology, process optimization and modeling. The corresponding software product of CINCAP is **F-CAD.**
  - Research and development of reliable process simulators of existing pharmaceutical machinery for different unit operations. This concept and technology is also known as **Virtual Equipment Simulators (VES).**
  - Additional services rendered at CINCAP include design and development of HPC-solutions for computationally intensive problems in process simulation (Discrete Element Modeling); pharmaceutical, medical, and biological fields of science and technology.
  - Design and construction of mass-parallel high-performance computing (HPC) hardware systems.

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Thank you for your attention!

Video Demonstrations + Audience Q&A