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"Right, First Time" Concept & Workflow based on F-CAD (Formulation Computer-Aided Design)

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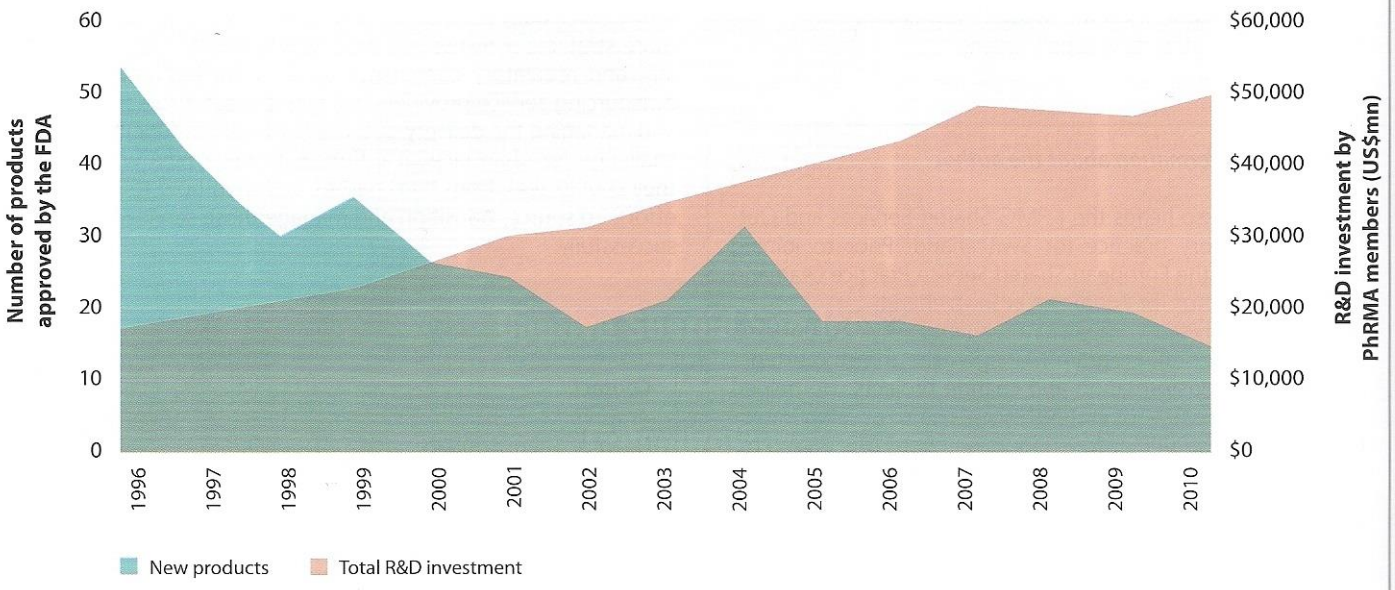
Formulation Computer-Aided Design (F-CAD): Key for "Right, First Time" Workflow to speed -up Time to Market

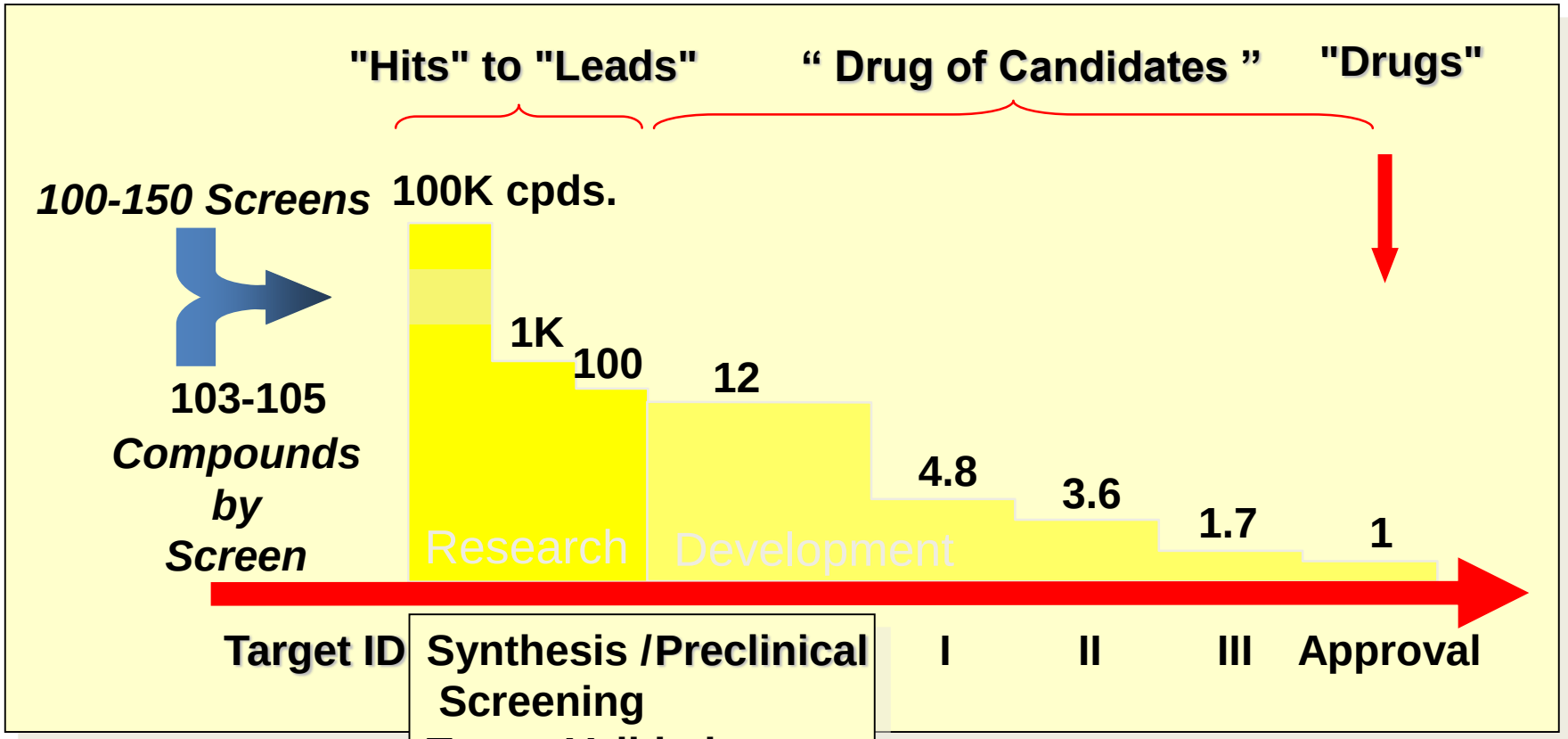
The drug development process

Graph shows declining product approval despite increasing R&D investment. R&D investment figures only include company-financed R&D. *Source: PhRMA member survey 2011 and Nature Drug Discovery* [1]



[1] **Mullard**, A, *Nature Reviews Drug Discovery 10*, 82-85 (February 2011)

Attrition rate of drugs tested



Formulation Computer-Aided Design (F-CAD): Key for "Right, First Time" Workflow to speed -up Time to Market

Sharp rise in the attrition rate between 1990 and 2004*):

Drug companies are removing in Clinical Phase III more compounds from the pipeline at all levels of testing!

Different reasons: 1) Lack of Efficacy 2) Safety 3) Commercial/ Financial 4) Not disclosed

Lack of Quality by Design at all levels?

*) S. Schreder, SWISS PHARMA 34 (2012) p.19

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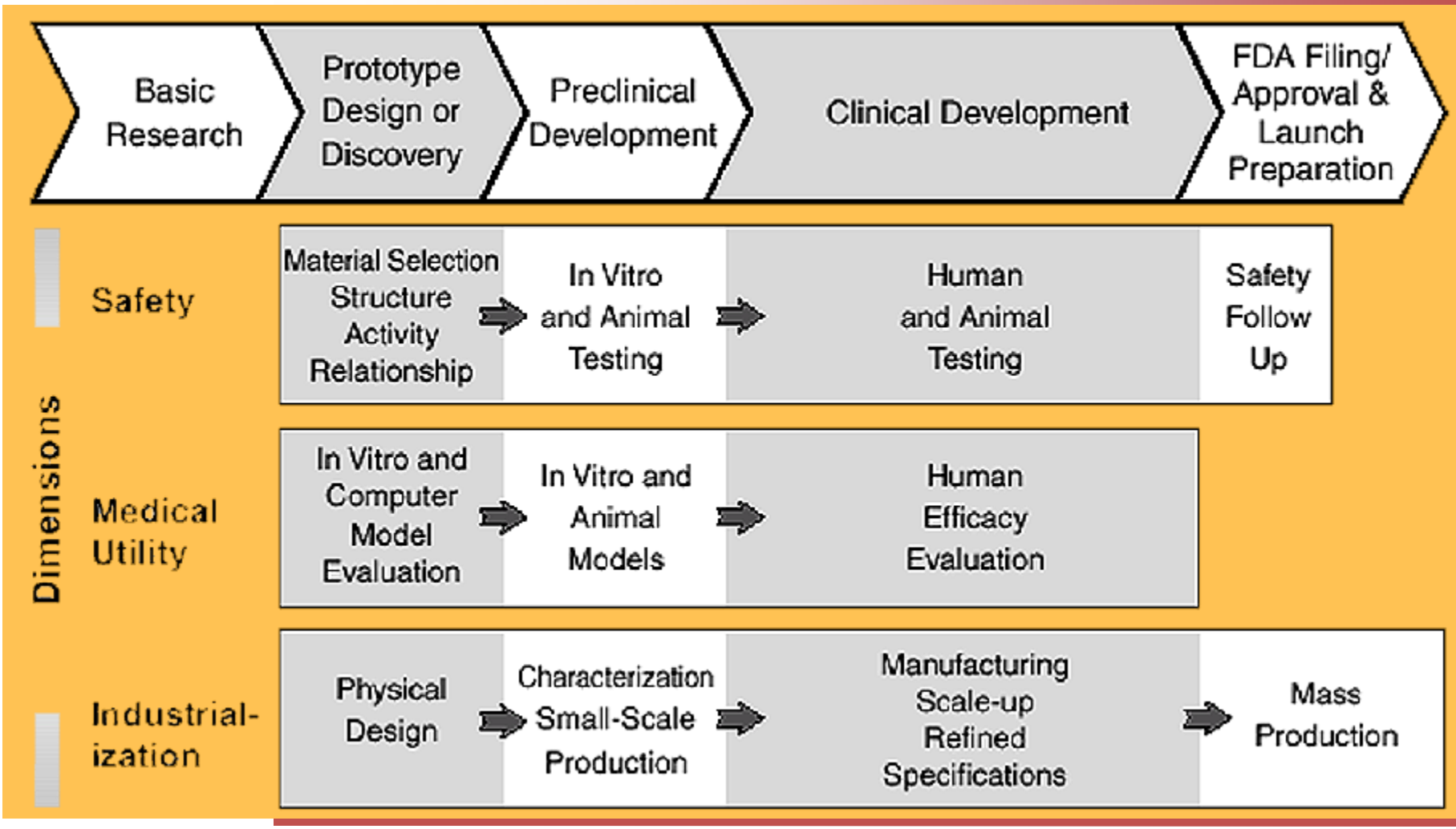
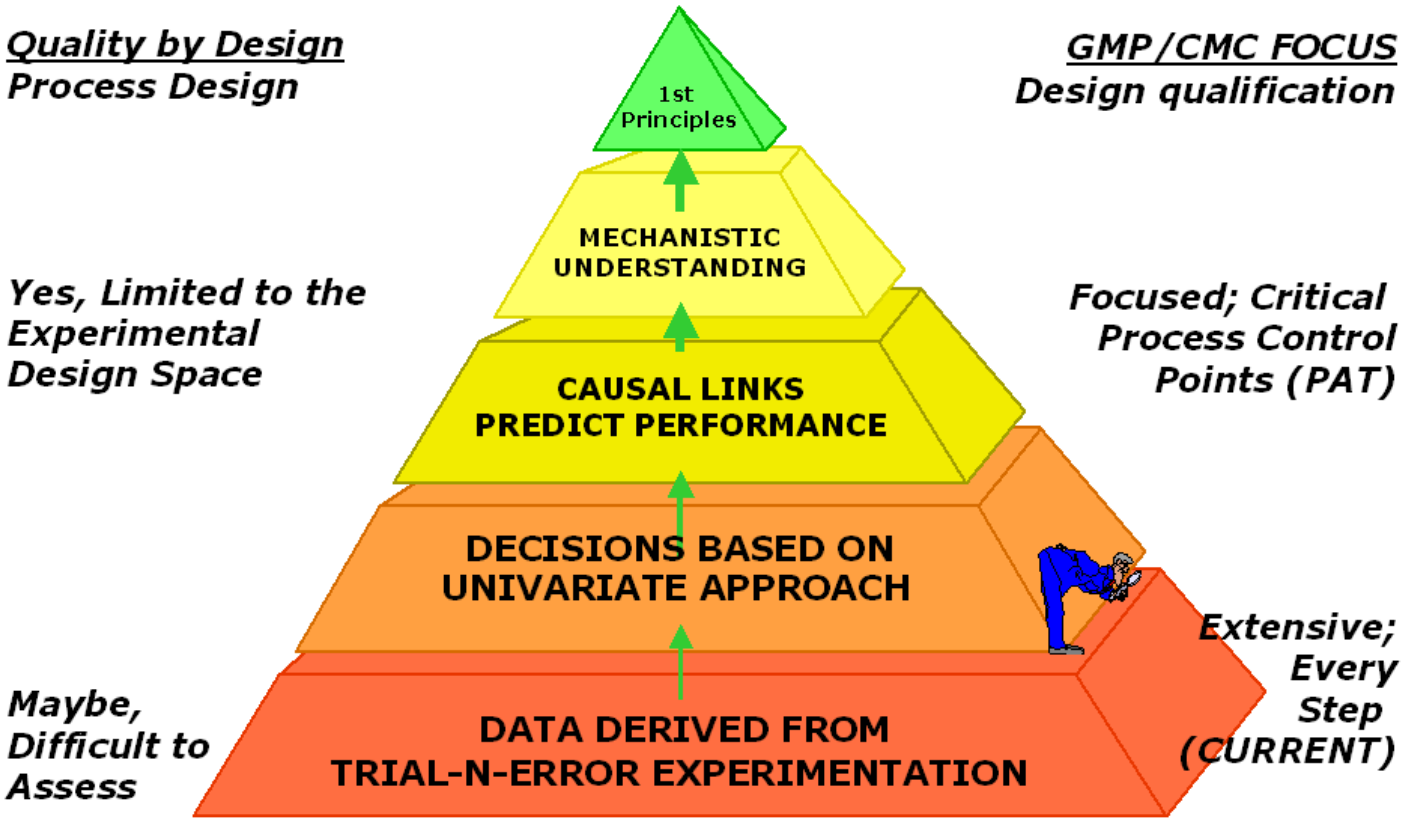
FDA Whitepaper March 2004
Three Dimensions of the Critical Path



Quality by Design

Product and Process Quality Knowledge: Science-Risk Based cGMP's



Conventional workflow for clinical trials

Early Phase: Service dosage form (in general capsules)

↓

Change to tablets & Bioequivalence Testing

↓

Scale-Up Exercise

↓

Mass-production of final marketed form (Two-sigma quality)

Right-First-Time Workflow

Market ready tablet dosage form (instead of service form)

↓

Small-scale Production

↓

Scale-Up Exercise (computer-assisted)

↓

Mass-production of final marketed form (six-sigma quality)

Formulation Computer-Aided Design (F-CAD): Key for "Right, First Time" Workflow to speed -up Time to Market

Regulatory Issues:

ICH Q 8 (R2)

Design space exploration with F-CAD eliminates risk for undesired time extension

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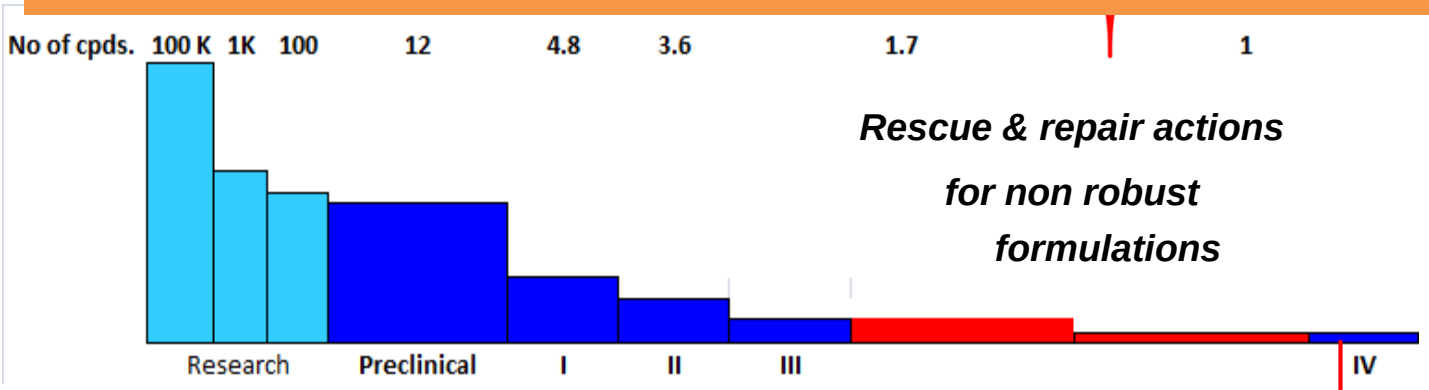
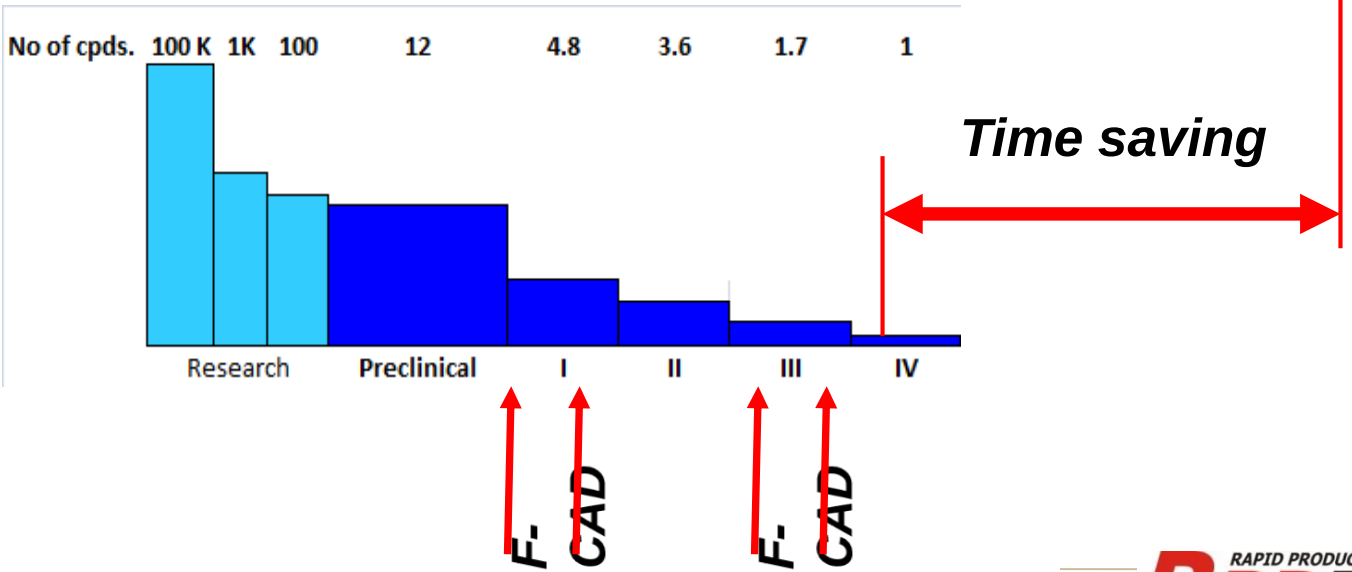
Conventional versus Right First Time (RFT) Workflow

Conventional workflow



RFT workflow



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F-CAD

Computer-Aided Formulation Design

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.

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Anticipated market ready tablet formulation

Steps:

1)

-> Selection of the drug substance:

-> for a comprehensive test-> check all classes of BCS

-> Physico-chemical properties of the drug substance needed

-> Choice of chemical/physical compatible excipients

-> Choice of the strength of the tablet formulation, e.g. 5 strengths

-> Choice of the dissolution profile ->immediate release and/or -> controlled release

2)

-> Application of F-CAD

-> In-silico evaluation of the Design Space according to ICH Q8 (R2): Sensitivity Report (excipients, process variables) on dissolution profile

3)

->Choice of the best in-silico dosage form (different strengths) for Phase 1 Clinical Study for laboratory validation and clincal manufacturing.

-> Normal chem. stability program (incl. Dissolution rate, disintegr. Time)

-> Accelerated Stability Test Program for Formulations: 1. results after 1-2 weeks.

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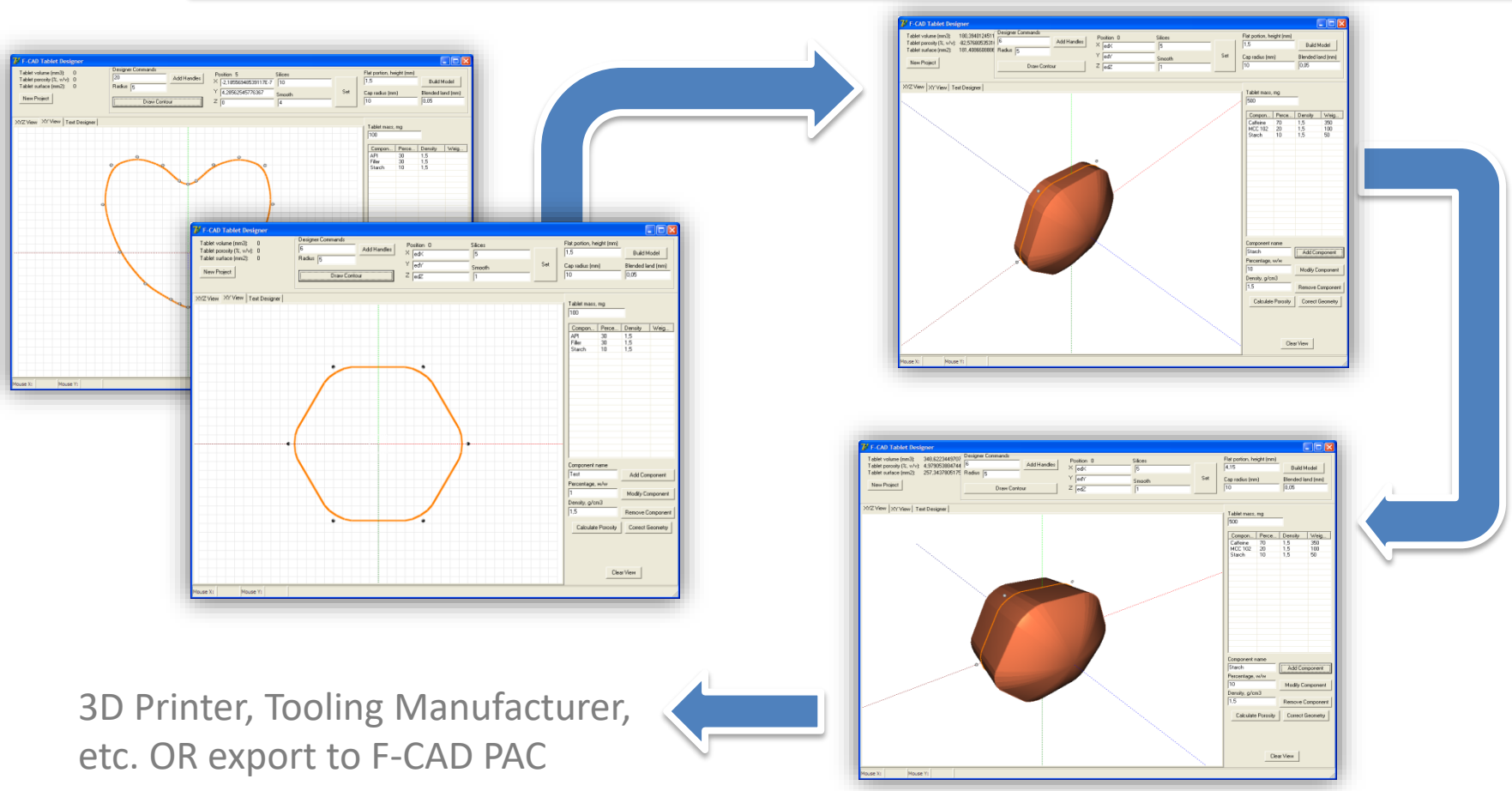
F-CAD Tablet Designer



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

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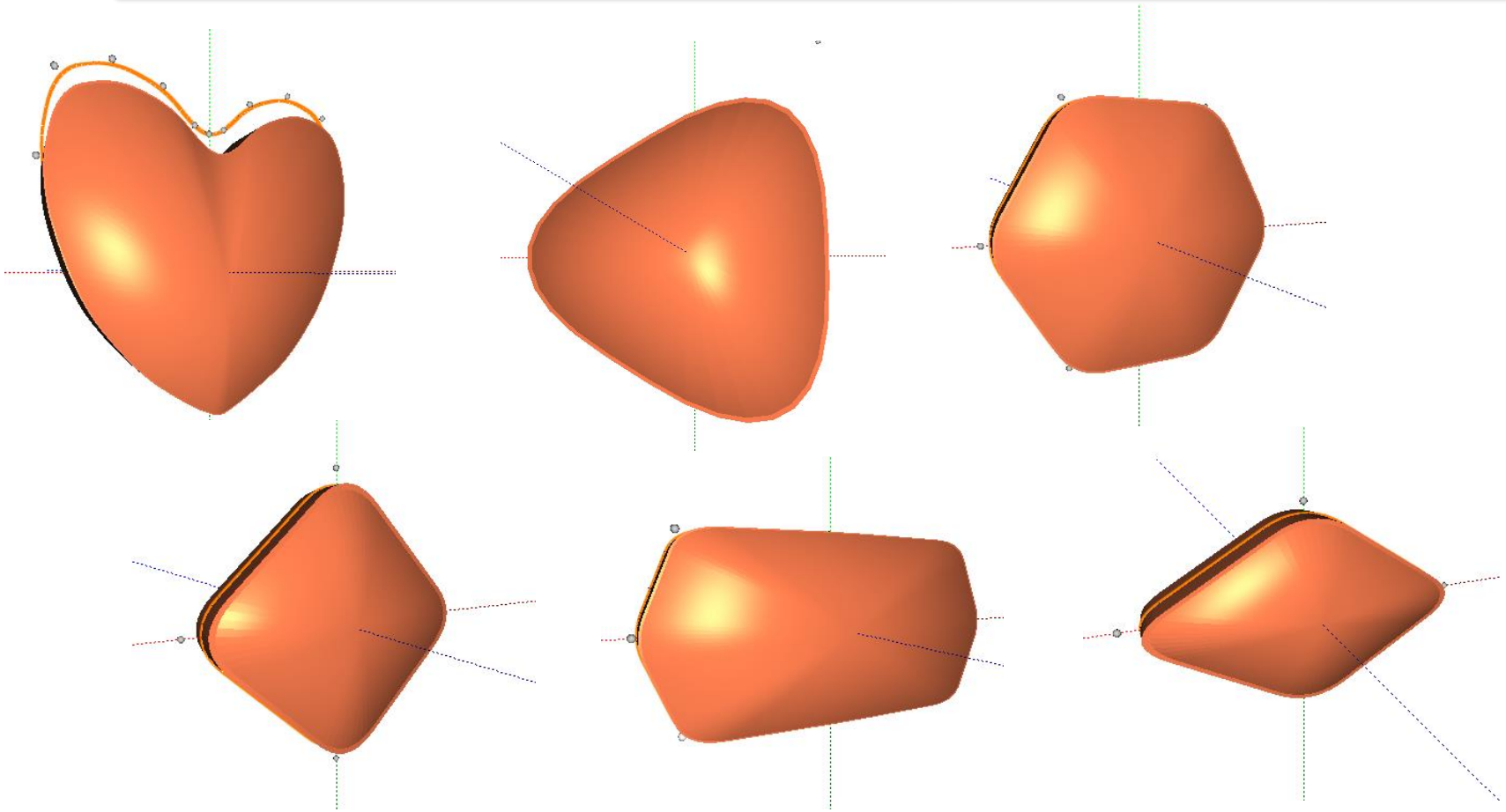
Custom Shapes with F-CAD Tablet Designer



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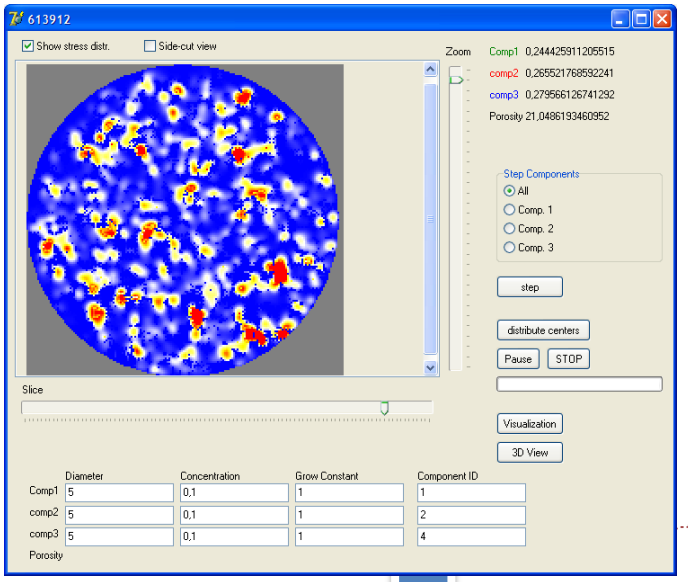
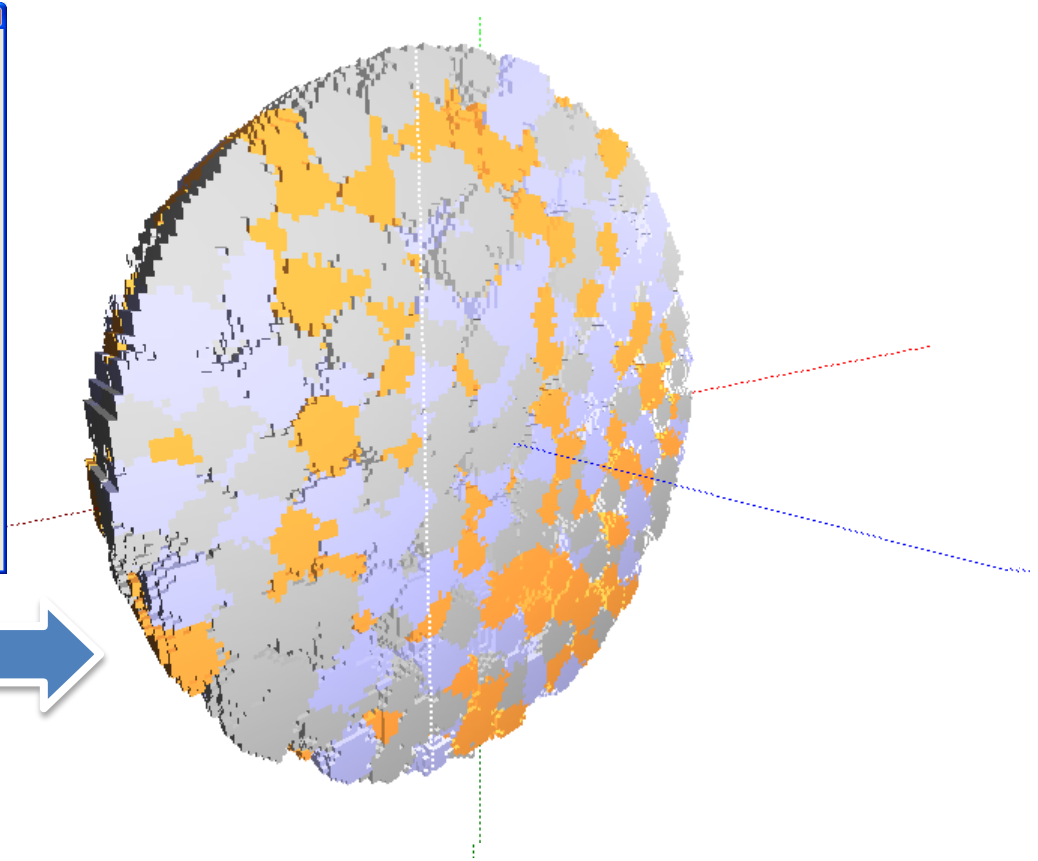
F-CAD PAC – Particle Arrangement and Compaction





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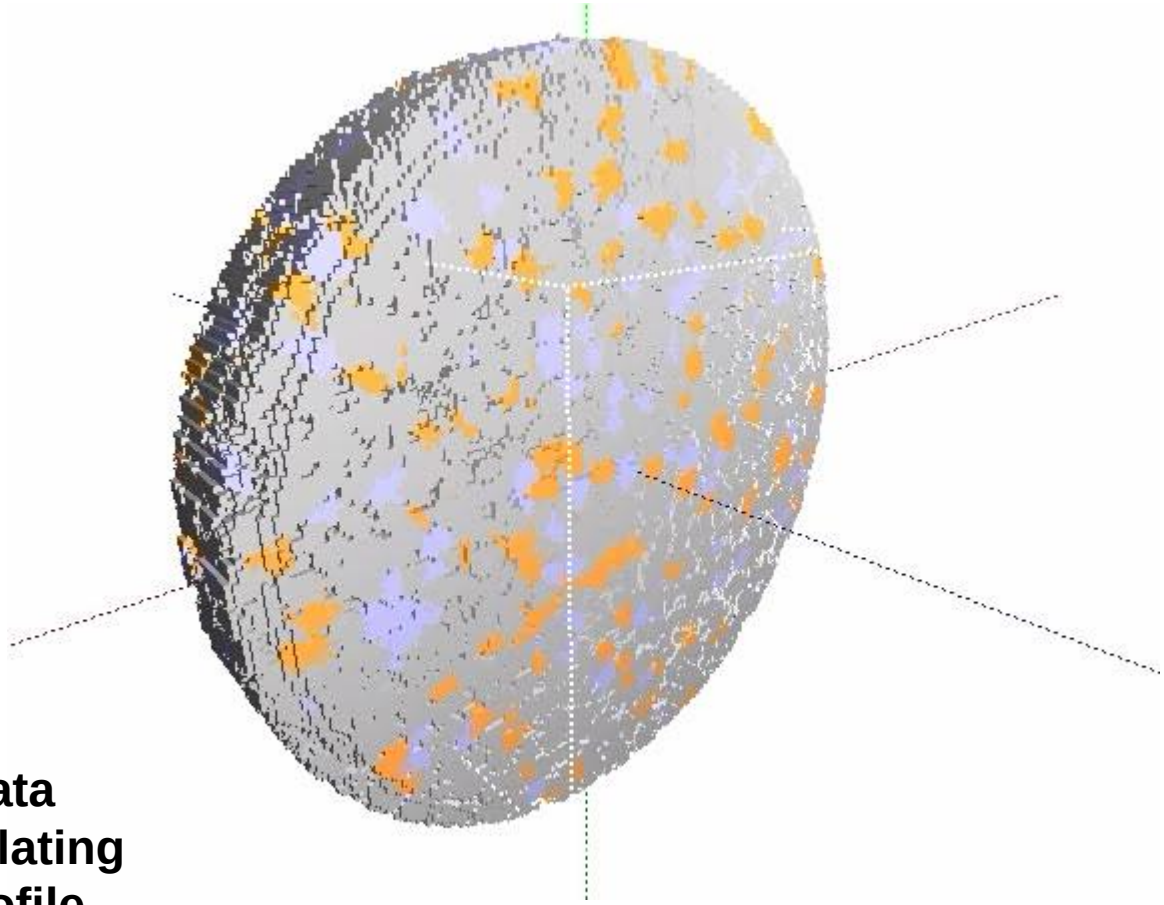
Resulting compact



**First Principle,
i.e. Cellular Automata
approach for calculating
dissolution rate profile**

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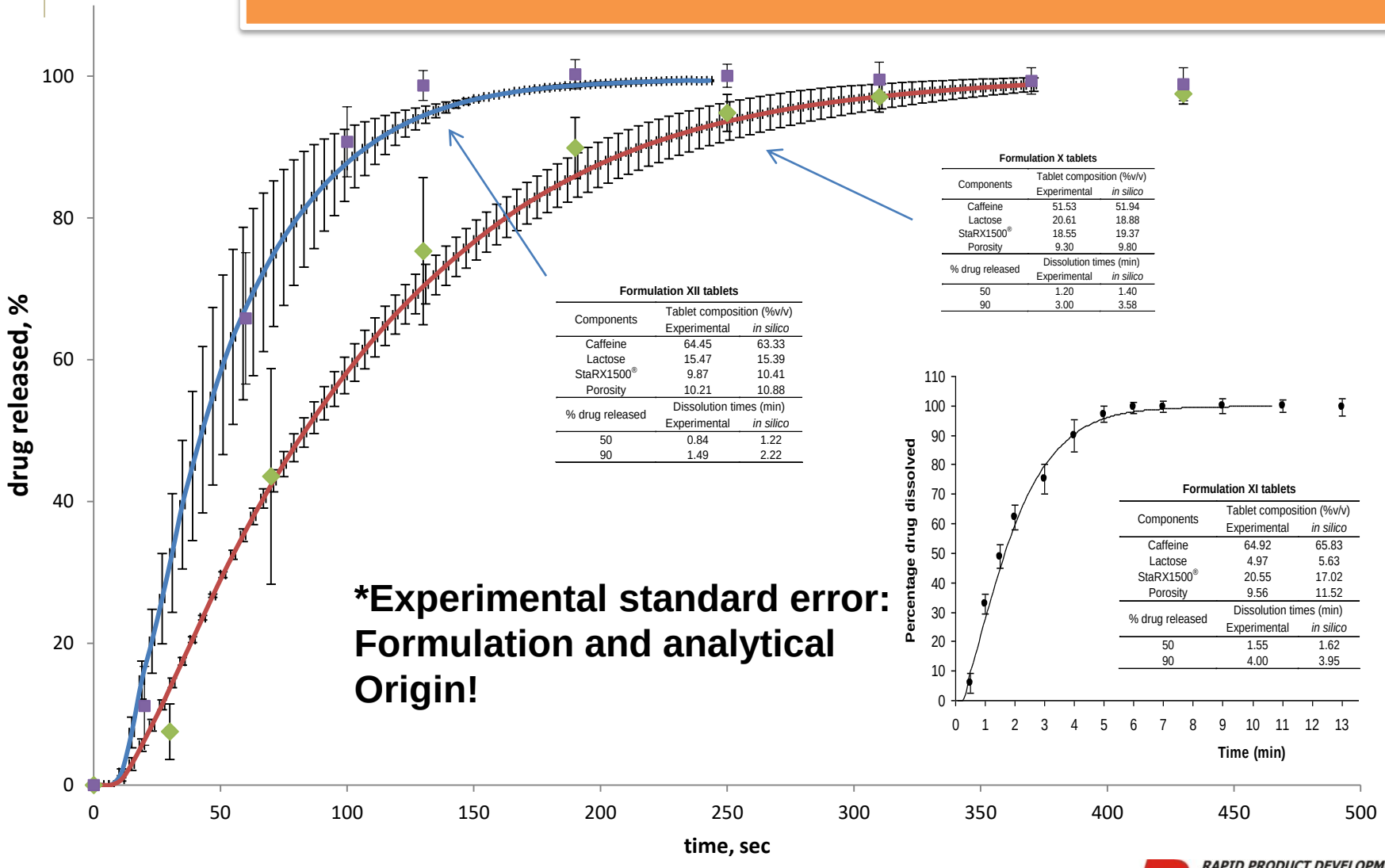
Experimental vs. in silico dissolution profiles of different formulations with caffeine: Experimental * and in-silico formulation standard error due to random arrangement of drug particles in the tablet



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
% drug released	Dissolution times (min) Experimental	*in silico*
50	0.84	1.22
90	1.49	2.22

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
% drug released	Dissolution times (min) Experimental	*in silico*
50	1.20	1.40
90	3.00	3.58

***Experimental standard error: Formulation and analytical Origin!**

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

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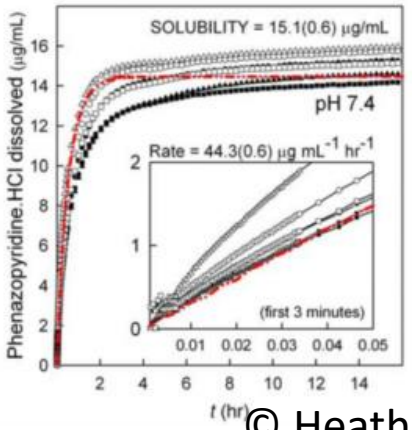
F-CAD – *in silico Dissolution Profiles:* 1) Reproducibilty of details (see zoom) 2) Effect of tablet shape



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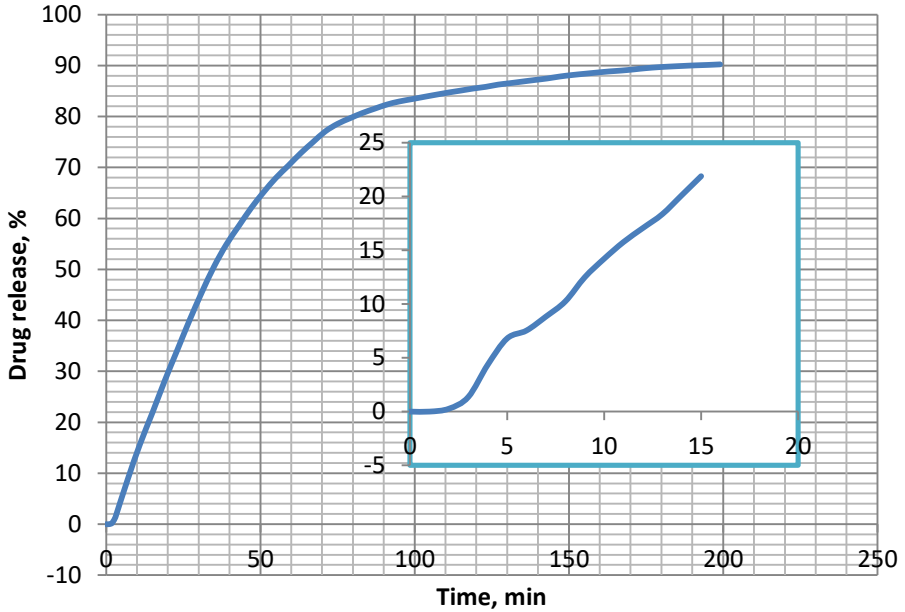

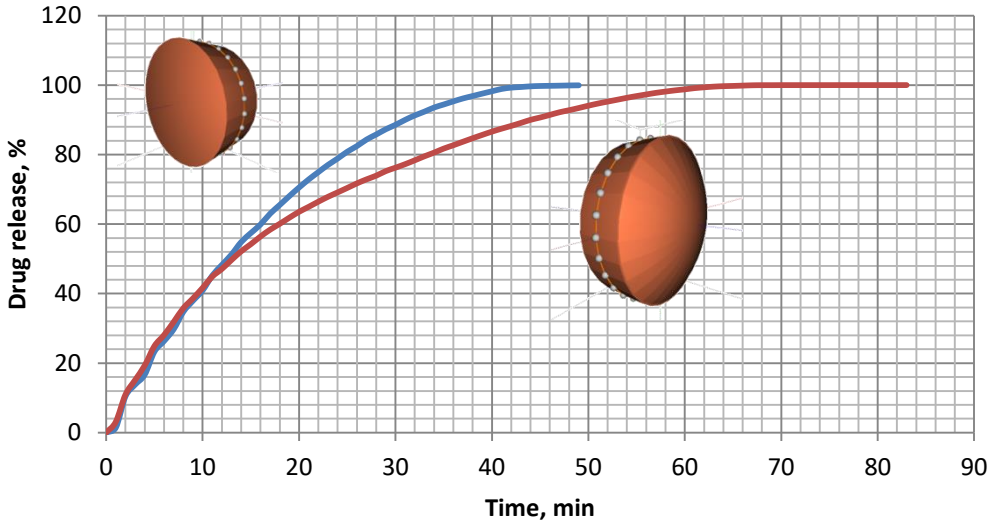

î 1) Initial dissolution detail

<- 2) Effect of tablet shape

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Percolation Theory and F-CAD

F-CAD is cabable to detect Percolation thresholds in a tablet formulation, which can be the source of the variability of a tablet property such as the dis-integration time , see PhD Thesis Go Kimura ,eLink:
at http://edoc.unibas.ch/diss/DissB_9886

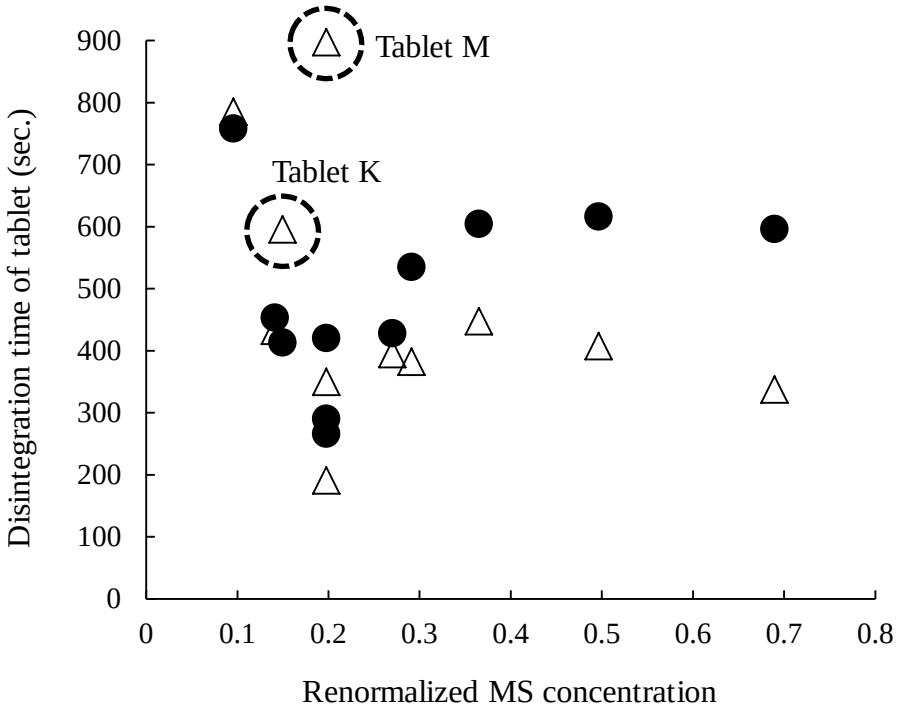

Fig. 68 of PhD thesis: Experimental disintegration time (●) and F-CAD values (△) as
a function of the renormalized MS (= Maize starch as disintegrant) concentration.

!

F-CAD and Quality by Design

- **F-CAD enables and facilitates to comply with the requirement of ICH Q8 (R2) at affordable costs!**

- Screening for robust formulation
- Setting up acceptance criteria for raw materials
- Analyse scale-up/scale-down issues and prevent problems

Summary: Goals of F-CAD

- Superior quality of formulations than with existing approach
- Possibility to quantify the robustness of the formulation
- Possibility to define specifications based on science
- Reduction of time to market
- Boosting formulation and process technology understanding
- F-CAD is able to detect percolation thresholds within the design space exploration according to ICH Q8 (R2)
- Computer aided design of formulations similar to aircraft design
- Savings comparable to the savings of the aircraft industry

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Thank you for your attention!

Audience Q&A

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