Paracelsus (1493-1541) Father of the Application of scientific method to development of formulations

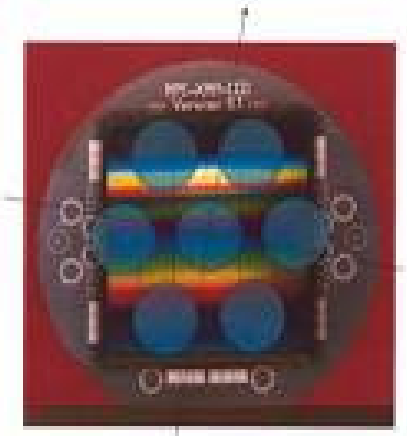
R&D Scientific Colloquia No5

14:00-15:30 – Tuesday 28 July 2009;

Neuchatel: Cervin A/B

Cologne : Room DE PMRLG R008.2

Leuven : Room BE PMRLB R004



In-silco development of solid and liquid formulations.

Prof. Dr. Hans Leuenberger

Center for Innovation in Computer Aided Pharmaceutics - CINCAP
Institute for Innovation In Industrial Pharmacy - ifiip
BASEL, SWITZERLAND

Will give a presentation on an innovative approach to the development of solid and liquid dosage formulations entitled:

Quality by Design Based on *in-silico* Testing of Formulations

"Formulations can now be designed and tested with high performance computers and corresponding software i.e. *in-silico.* The fact, that laboratory experiments can be replaced by *in-silico* experiments, will dramatically speed-up formulation work flow in the pharmaceutical industry. Can this approach be applied to the development of our Next Generation Products?

Don't miss this valuable opportunity: Mark your calendars

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Quality by Design based on *in-silico* Testing of Formulations

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Contents of presentation

- What is a formulation? What is a functional excipient?
- History: Formulations, Recipes, Tradition
- PAT (Process Analytical Technology) Initiative and Quality by Design (QbD)
- The SIGMA Concept, 20%/80% Rule
- PwC Pharma 2020: Virtual R&D
- Percolation Theory, Cellular Automata
- F-CAD, F-CAD Modules
- Powder for inhalation, Spray Freeze Drying
- F-CAD for liquid formulations,

What is a formulation?

- A pharmaceutical **formulation** is the **process** in which the **active drug** substance(s) and selected **auxiliary substances**, having a specific function (**functional excipients**) are combined to produce a **final medicinal product**.

- In this context, it has to be kept in mind, that a formulation means more than a composition of different substances such as the drug substance and excipients, but includes specifically the manufacturing process to obtain the so called final marketed "**dosage form**".

- A synonym of a formulation is a **recipe.**

What is a functional excipient?

- A functional excipient in a tablet has to perform a certain task such as a "filler" or to induce the disintegration of a tablet being in contact with gastric juice or e.g. water.
- Some excipients are "multi-tasking", i.e. are capable to take care of more than one function.
- Microcrystalline Cellulose (MCC) is often used in direct compaction and thus serves as a filler and binder.
- The function is related to the physico-chemical property of the excipient.
- The physico-chemical property dos not depend alone on the chemical composition but also on the physical state (different crystalline structure, polymorphism)

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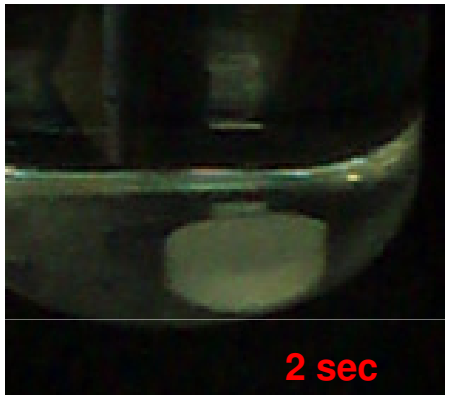
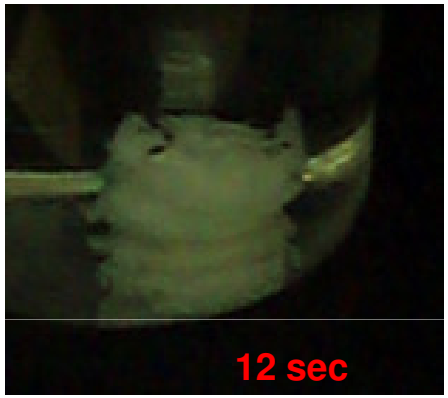
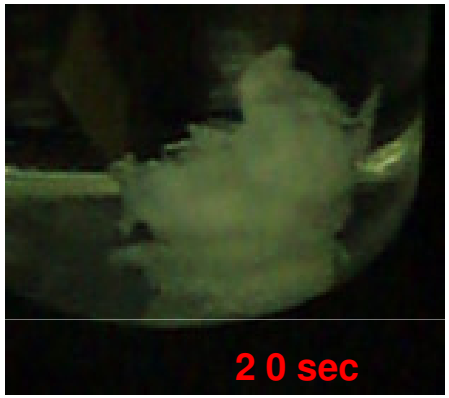
Different behavior of MCC (Cellulose I,II):

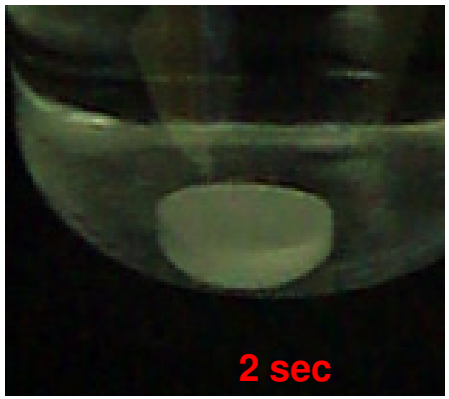
MCC Rapid (Cellulose II)

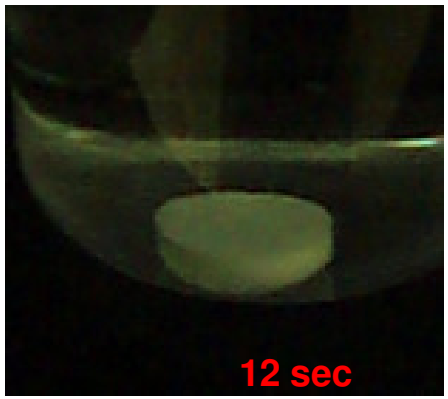


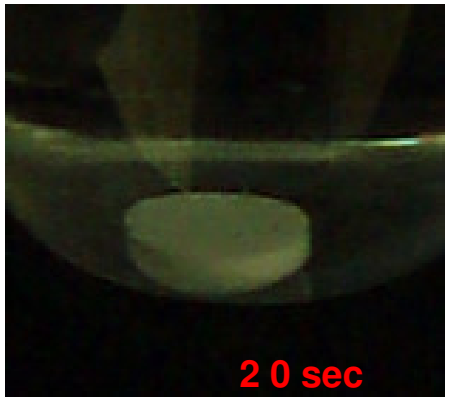




MCC (Cellulose I)







Relative density = 0.88

Formulations, Dosage Form

Liquid Formulations:
Oral liquid dosage forms, sterile liquid dosage forms for injection,
Liquid dosage forms for inhalation, eye droplets, topical liquid dosage forms (sprays) etc.

Semi-solid Formulations:
Ointments, pastes in general for topical use, especially skin, rectal, vaginal use, especially suppositories, ovula etc.

Solid Formulations:
If possible, preferred due to its high stability and long shelf life (3-5 years),
Tablets, film coated tablets, matrix or membrane controlled release drug delivery systems,pellets, powders, powders for inhalation etc

History: Formulations, Recipes, Tradition

- Pharmaceutical **recipes** are known since **mankind exists**. It has been reported that already in ancient Egypt a **collection of recipes** was written down, which can be considered as one of the first **pharmacopoeias**.
- The **recipes** have been based on **empirical knowledge**.
- A **collection of recipes**, a pharmacopoeia , was considered to be **a holy text**, like a bible .
- In Egypt, the **medical doctor** was also **a priest ,** playing a **powerful role** in society, supervising that the tradition is kept in place.
- In ancient Rome, the Greek physician ***Galen*** (130 a.c – 200 a.c) collected recipes for different health disorders according to the existing tradition and knowledge.

History: Formulations, Recipes, Galenics

- ***Galen*** born in Pergamon, Minor Asia, was an excellent physician, anatomist, physiologist, philosopher and lexicographist.
- ***Galen*** became the personal medical doctor of the Roman imperator Augustus. Rome at that time was the center of power in Europe.
- Galen's collection of recipes became so famous, that the knowledge , how to prepare medicinal products has been defined as ***Galenics***, Galenical Science.
- The preparation of such medicinal products has been considered as an ***Art*** due to its ***complexity.***
- The ***complexity*** ,and the ***holy tradition*** played an important role ***not to challenge*** the existing collection of recipes.

It is dangerous to challenge a tradition

- It has been always ***dangerous to challenge a tradition,*** especially, if the tradition is **linked to power .**

- ***Paracelsus*** (1493-1541) was then one of the first to challenge this tradition by introducing a scientific approach concerning quality and quantity of the drug substance.

„It depends on the quantity
If an active substance is a poison or
a medicinal drug“.

Modern times

- it has to be kept in mind, that ***medicinal products*** have been manufactured by industry only ***since the late 19th century.***
- The ***chemistry of the drug substance*** played a major role. The ***drug substance not the formulation*** is now in the ***focus!***
- ***Only since the 1950s*** of the last century ***processes*** as ***part*** of a ***formulation*** such as e.g. the moist agglomeration of powders have been investigated by physicists, mechanical and chemical engineers introducing a more ***scientific approach.***

The FDA starts to challenge the contemporary approach concerning development and manufacturing of medicinal products by introducing the PAT (Process Analytical Technology) and Quality by Design (QbD) Initiative.

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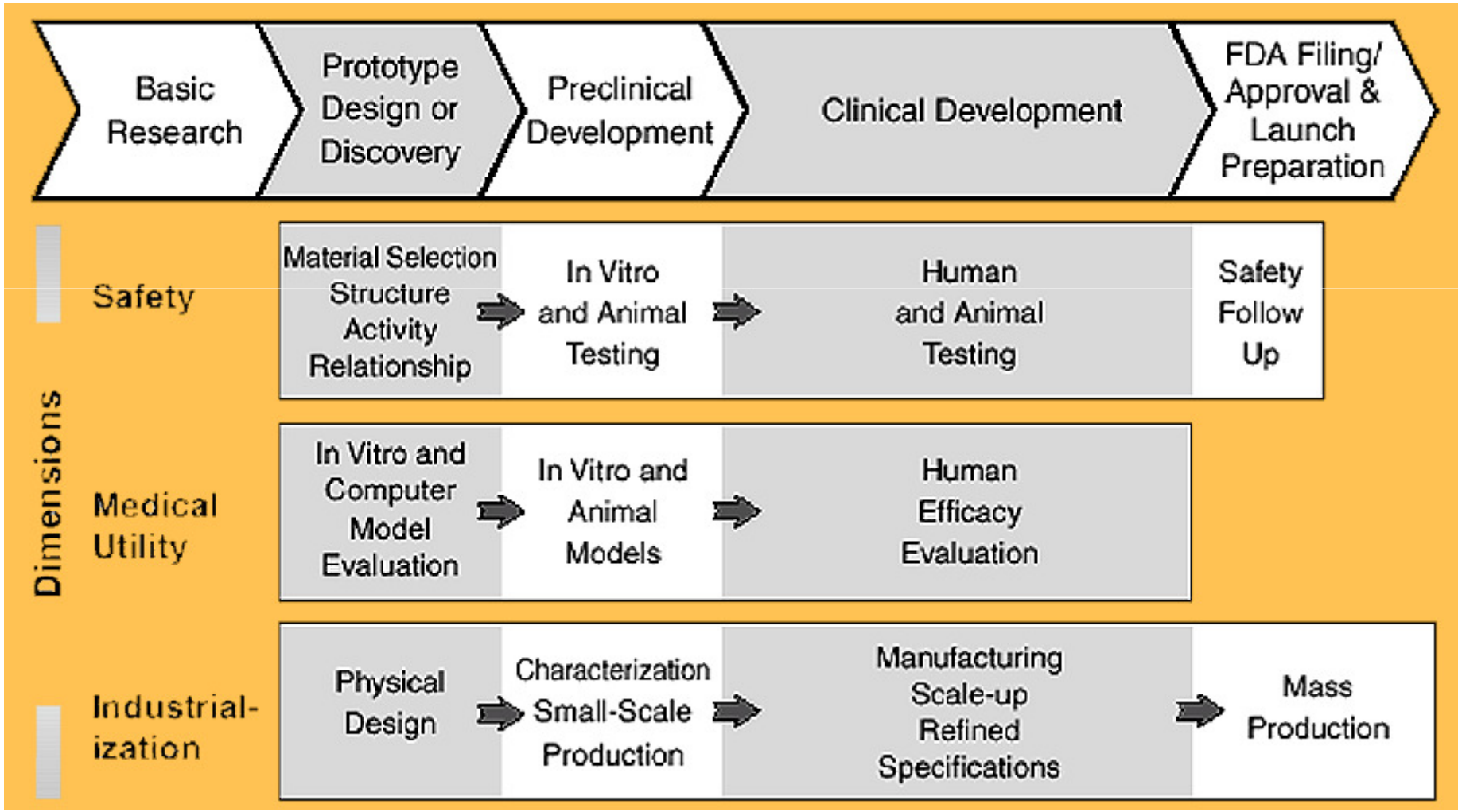
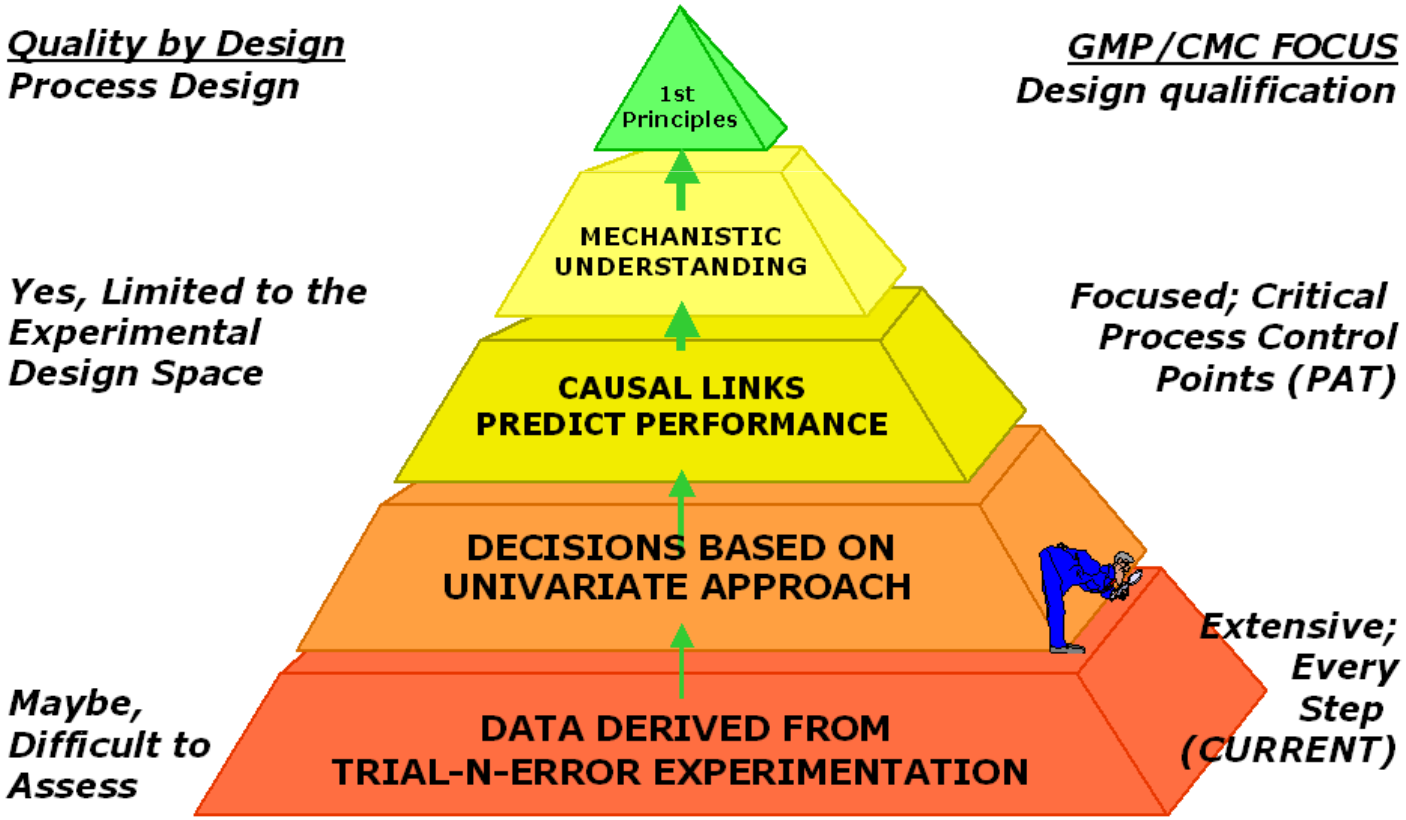
FDA Whitepaper March 2004
Three Dimensions of the Critical Path



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



PAT (Process Analytical Technology) Initiative and Quality by Design (QbD)

- What means PAT, i.e. Process Analytical Technology?
- The basic idea: not to test – in the Quality but to build-in the Quality, i.e. "**Quality by Design**"!
- **PAT has been much better accepted by the responsible persons in Manufacturing than in the Development Departments**
- What are the reasons?

PAT (Process Analytical Technology) Initiative and Quality by Design (QbD)

- The name of PAT with focus on **Analytical** is somehow unfortunate, which was soon realized by FDA

- Thus the first idea came up to instrument all processes by appropriate means such as NIR Technology, i.e. NIR Spectroscopy, NIR Imaging, Therahertz Spectroscopy and many more analytical techniques often based on Chemometrics using corresponding software packages.

- Thus the "in-line", "on-line" and "at-line"-measurements of the relevant properties has lead to the temptation to continue to "test-in" the quality!

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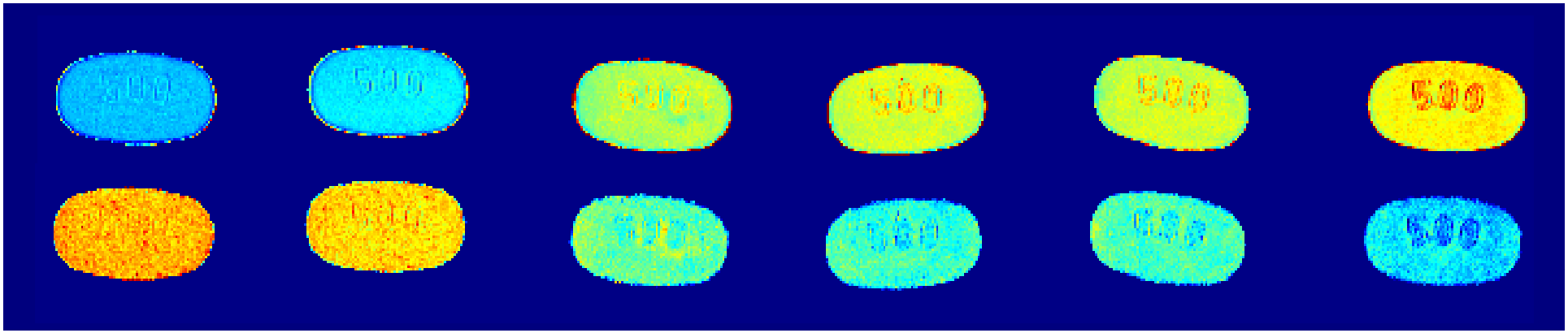
Near Infrared Spectroscopy/Imaging and Terahertz Pulsed Spectroscopy/Imaging for the Analysis of Solid Dosage Forms

Dissertation Lene Maurer, 2. Juni 2008



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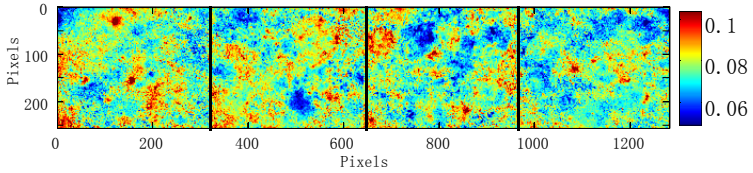
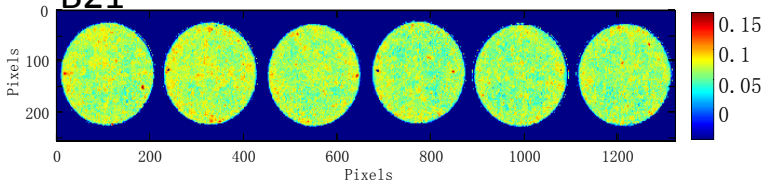
NIR Imaging: distribution of the drug and auxilliary substances

Tablettenschichten (abgefräst), B11

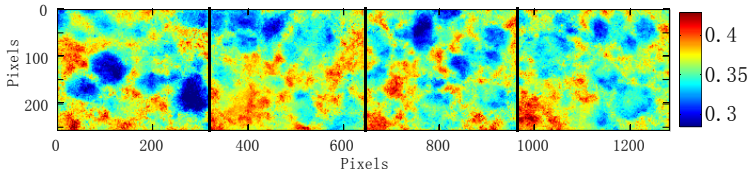
Tablettenflächen (abgefräst), B16-B21

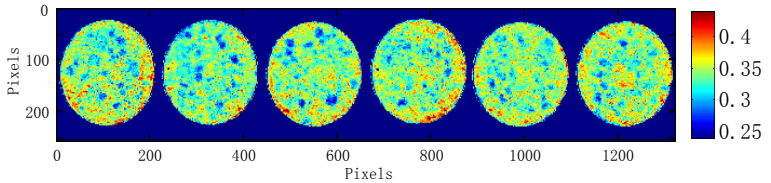
Wirkstoff



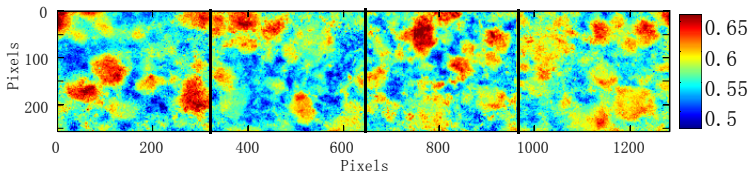


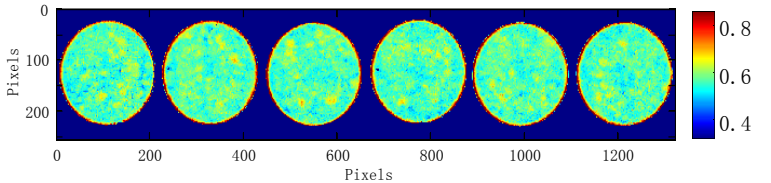
Hilfsstoff 1





Hilfsstoff 2





PLS-DA distribution maps

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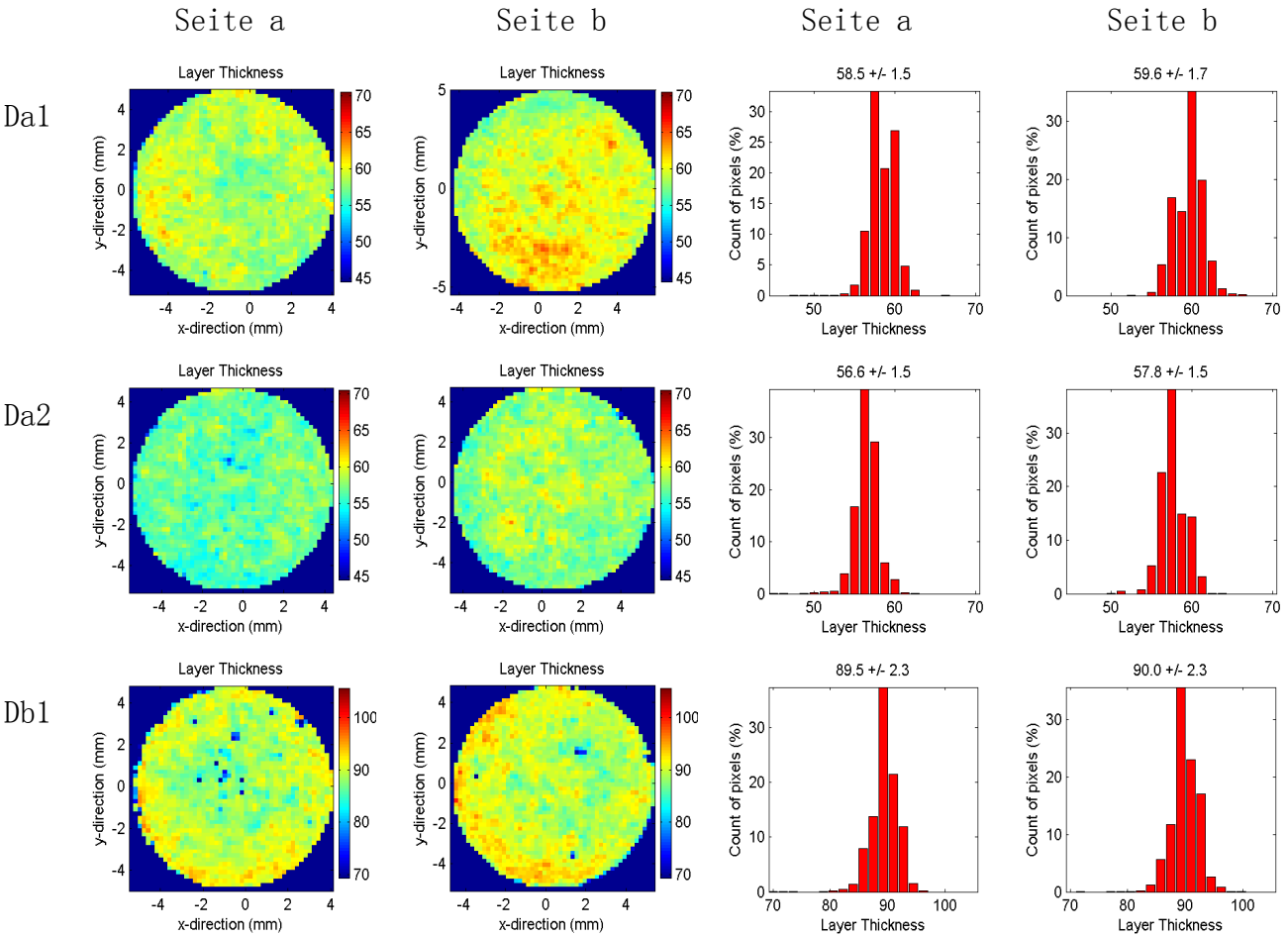
Terahertz Pulsed Imaging: Coated Tabs

Different thicknesses of the coating

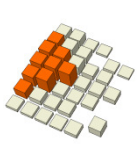


PAT (Process Analytical Technology) Initiative and Quality by Design (QbD)

- However to **"test-in"** the quality was not the idea of FDA! On the over hand, it is important to monitor a process, which allows to analyse its behaviour!

- In the mean time many companies have instrumented in an excellent way their process equipment which will lead to a better process understanding and as a consequence to a higher quality.

- Thus If a process works in best conditions, it is possible to accept this result as to **"build-in " the quality.**



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Advanced Powder Technol., Vol. 16, No. 1, pp. 3–25 (2005)

Also available online - www.vsppub.com

Invited review paper

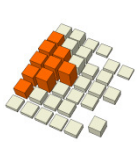
Pharmaceutical powder technology — from art to science: the challenge of the FDA's Process Analytical Technology initiative

H. LEUENBERGER* and M. LANZ

Institute of Pharmaceutical Technology, Pharmacenter of the University of Basel, Klingelbergstrasse 50, 4056 Basel, Switzerland

Quality by Design (QbD) is however the primary task of the Development Department!

- To achieve **QbD** it is essential that this happens in the **early phase of development**!
- The problem is that in the preclinical phase there maybe simultaneously 12 product candidates in the pipe-line and nobody knows, which of the twelve candidates will be successful!
- Which of the twelve candidates has which priority? Thus if all **12 are equal**, do we have **some** of them, which **are more equal**? How do we attribute the available human and money resources for these 12 candidates? How can we measure the performance of our development work/process?



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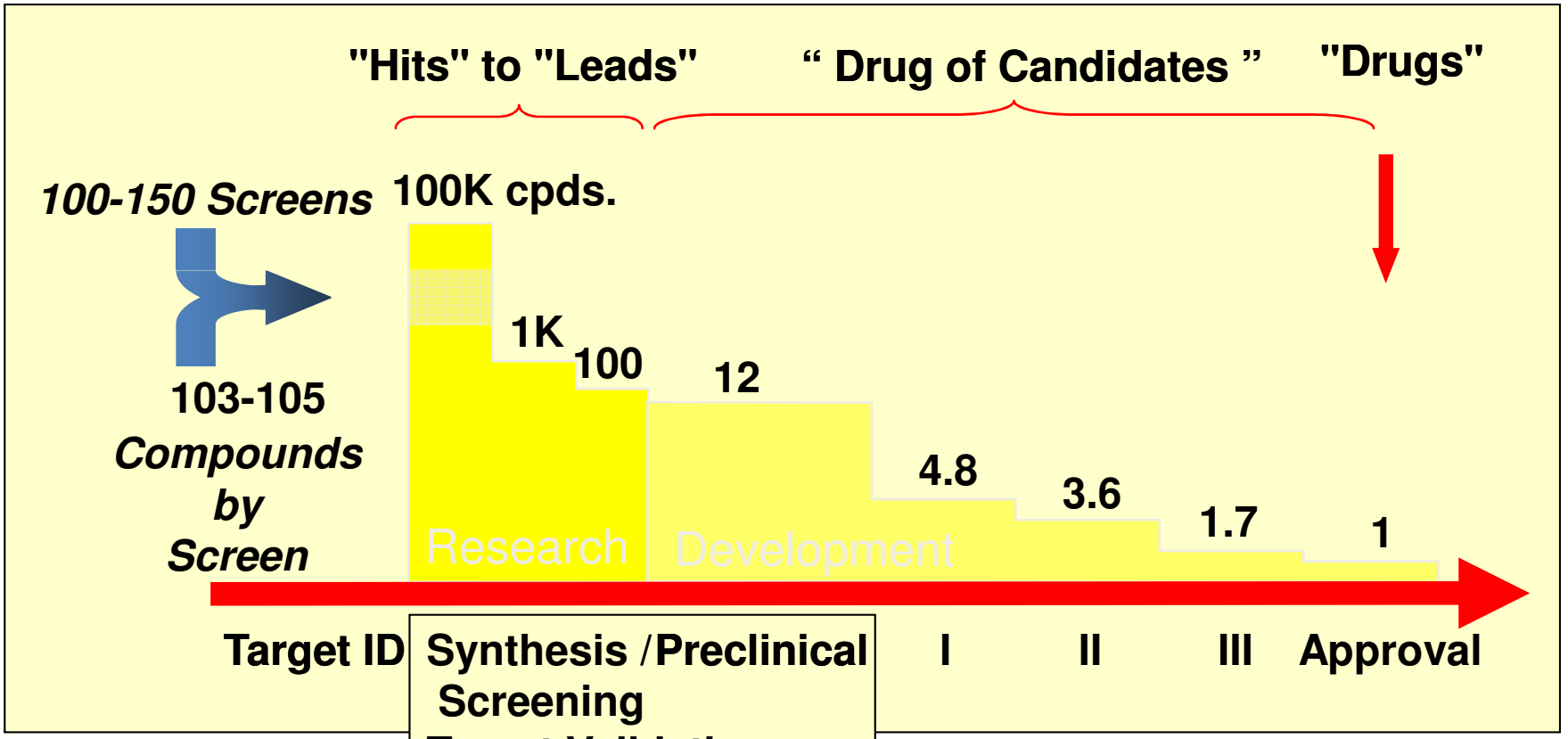
Preclinical Phase:12 Drug Candidates !

Slide: A. Hussain, FDA



How to share the resources in case of 12 drug candidates?

- Due to the limited resources the following rule became popular: **the 20%/80% rule**
- This rule is a common practise in the pharmaceutical industry
- Thus **with 20% of time and effort** allocated to a project **80% of the goals** should be **achieved!**
- What about the **performance** ? How do we measure performance? Let us look at the **SIGMA CONCEPT!**

PAT (Process Analytical Technology) Initiative and Quality by Design (QbD) – Can we afford it ?

- Is it possible to reduce time to market and to enhance product quality?
- The Sigma Concept
- Goal: Six Sigma Performance

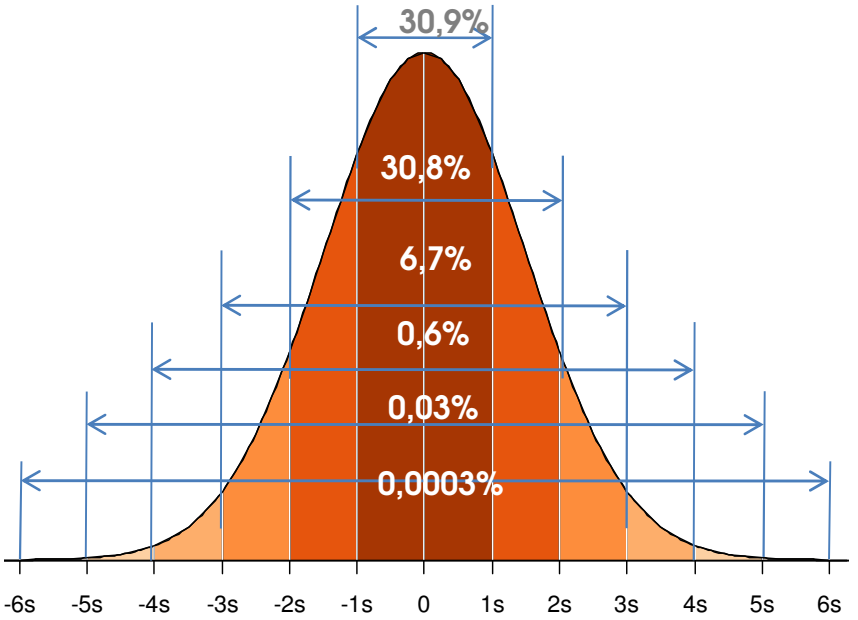
Performance of a process → Sigma value

Sigma	Yield, %	Defects, %	DPMO
1	30,9	69,1	690000
2	69,2	30,8	308000
3	93,3	6,7	66800
4	99,4	0,6	6210
5	99,97	0,03	320
6	99,9997	0,0003	3,4

Source: Kurt Haubner, www.sixsigma.de

Normal distribution - Gauss!

$$f(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{x^2}{2\sigma^2}}$$



Source: Jeremy Kemp, adapted

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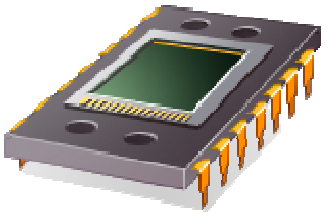
The SIGMA Concept

Champion: Chip industry



6 Sigma performance:

amount of defective samples = 3.4 DPMO

Performance

Pharmaceutical Industry ~ 2 Sigma

i.e. > 20% defectives in case of the **dynamical** Sigma Value, which has been adopted during the phases of early development, i.e. in thePreclinical Phase up to the decision point of defining the final marketed dosage form in the Clinical Phase I, II or even III?

i.e. ca. 4.5% defectives (snap-shot evaluation of the final dosage form (**static** Sigma Value!)

Common approach to keep costs under control

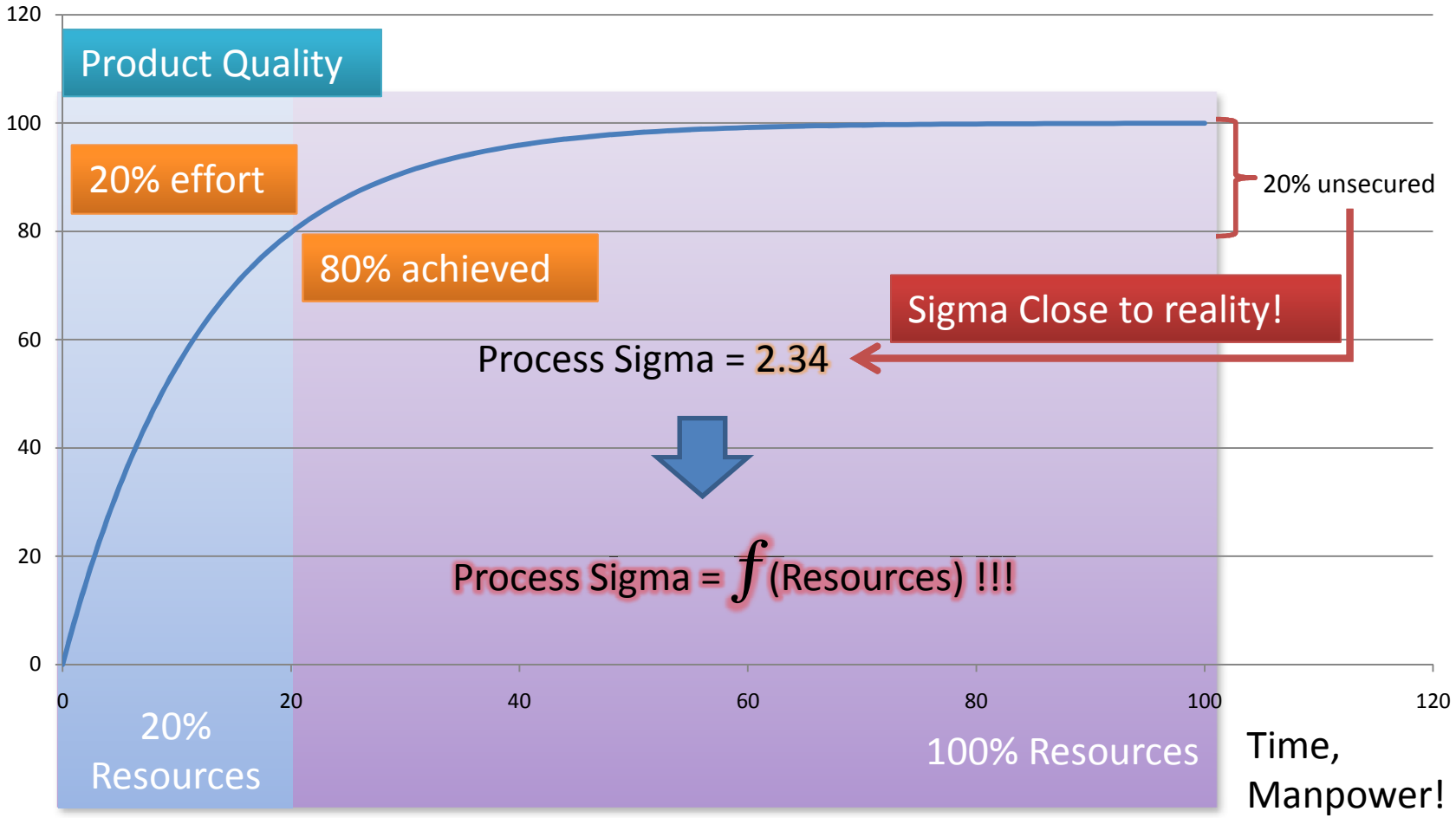
The 20% / 80% Rule:

With 20% of time and effort dedicated to a project
80% of the goals can be achieved!

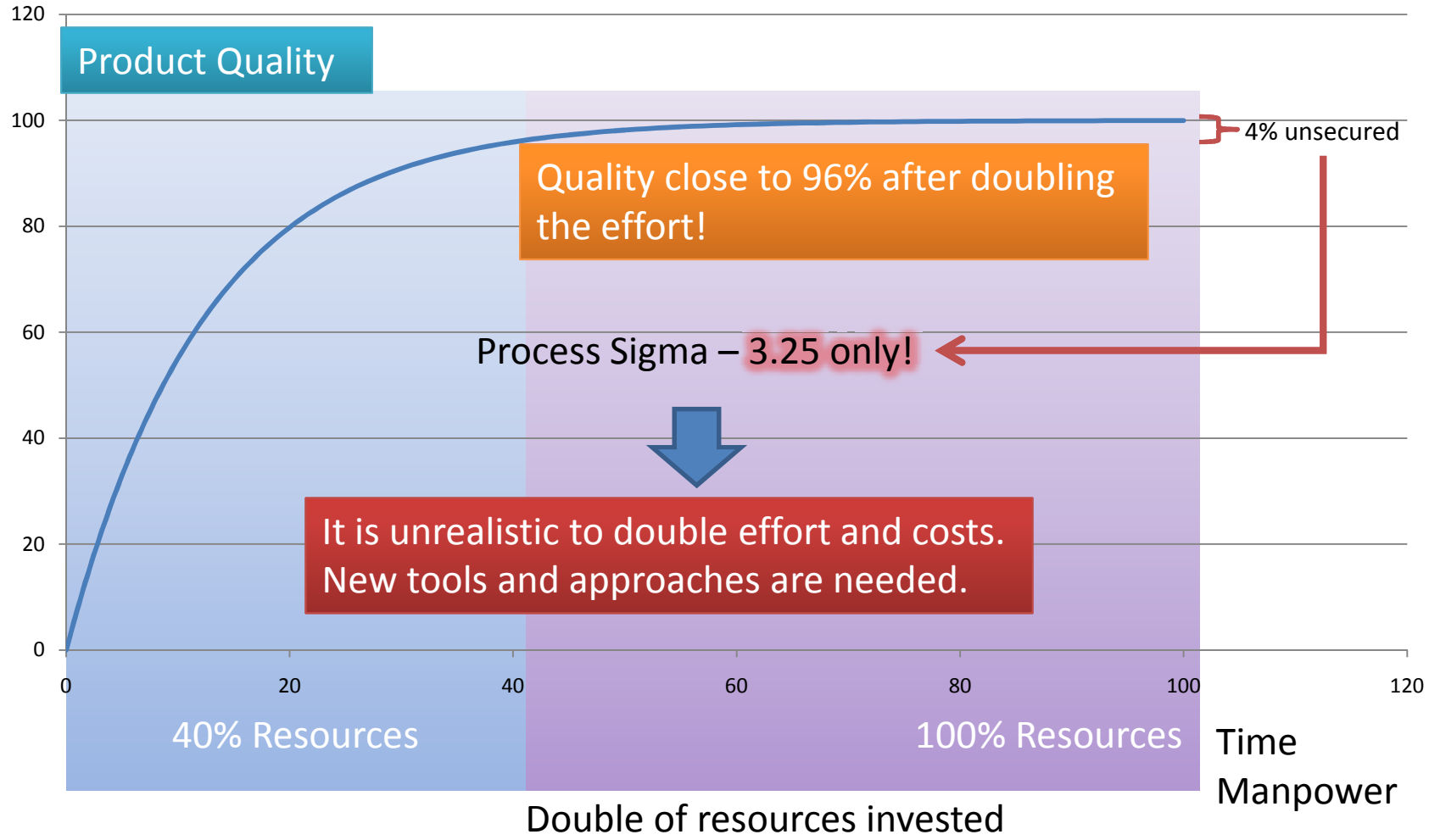
Is this approach adequate for an optimal Quality by Design?
Can we afford a 6 Sigma Quality? What is the Quality in case of the 20%/80 % Rule?

Let us make an estimate!

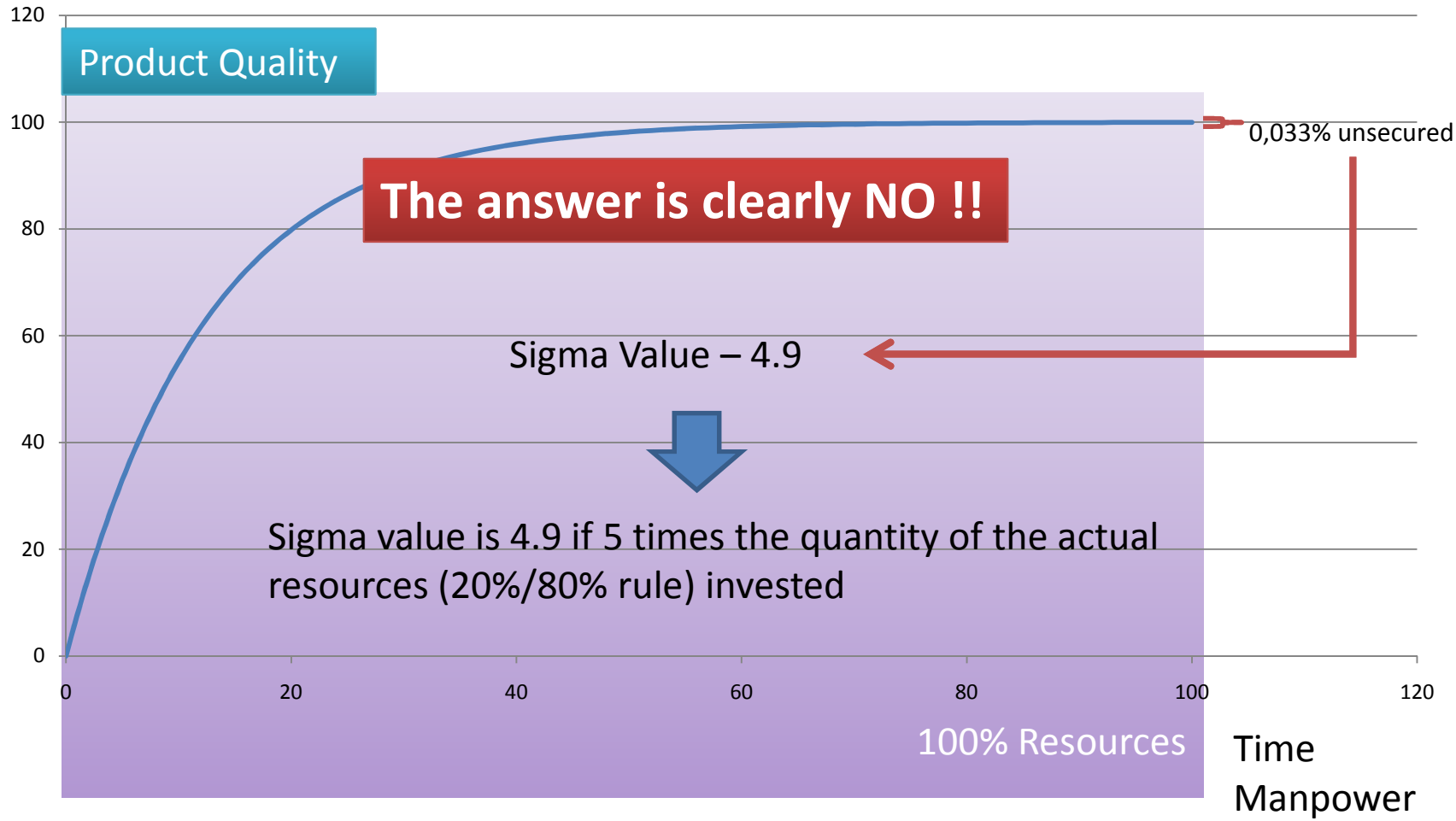
Sigma Value – function of resources



Can we afford to double effort and costs?!



Can Six Sigma be achieved with conventional tools?



PwC Pharma 2020: Vision e-Development

- SEE the study of PricewaterhouseCoopers :
- **PwC PHARMA 2020 – Virtual R&D**

- **Is it possible to introduce special e-tools to facilitate the work of development?**
- **We think: YES**

- Is it possible to copy e.g. the concepts of the aircraft industry, using „in-silico" Computer-aided design?
- Let us compare the aircraft building industry with the development of a solid dosage form!

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Aircraft and drug formulation: similarities

- Development and production of a **vehicle** that
- **delivers the drug substance**
  - precisely at the **right time**
  - in the **right quality**
  - in the **right quantity**
  - to the **right site** in the body.

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Designing aircraft: *in silico* approach

Boeing 777: 100% digitally designed using 3D solids technology

- The consequences were dramatic:
  - Elimination of > 3000 assembly interfaces, without any physical prototyping
  - 90% reduction in engineering change requests (6000 to 600)
  - **50% reduction in cycle time for engineering change request**
  - **90% reduction in material rework**
  - 50x improvement in assembly tolerances for fuselage.

How can we do that for pharma?

Source: http://www.cds.caltech.edu/conferences/1997/vecs/tutorial/Examples/Cases/777.htm

New tools and approaches are needed!

- Personally I know only one e-tool, which may fulfill this task:
- F-CAD, Formulation Computer-Aided Design by CINCAP, let us have a look:
- F-CAD is different from any existing e-tool such as
  - Expert System
  - Artificial Neural Network
  - Collection of existing formulations etc

New tools and approaches are needed!

- The Concept of F-CAD developed by CINCAP

- F-CAD is based on
  - Physical laws
  - **Percolation Theory**
  - Process Understanding
  - Particulate Formulation Design
  - And uses a sophisticated Algorithm taken from nature, i.e.
  - The Cellular Automata Approach
  - What are Cellular Automata?

Percolation Theory

- For a ***real understanding*** of a ***formulation***, it is a prerequisite to know ***Percolation Theory.***
- ***Remember:*** Formulation means ***Composition*** of active and auxilliary substances ***and Process(es)!***
- The most important points of Percolation Theory are the existance of ***critical concentrations of a substance*** in a ***composition***
- A ***critical concentration*** of a substance ***means***: the substance ***percolates*** the ***system*** (2D, 3D). A ***critical concentration = Percolation Threshold!***

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Site and bond percolation thresholds for 2 dimensional lattices

Site and bond percolation threshold:

Two neighbouring sites being occupied

can be **only** connected with **one bond**.

Lattice	Site	Bond
Honey	0.696	0.653
Square	0.593	0.500
Triangular	0.500	0.347

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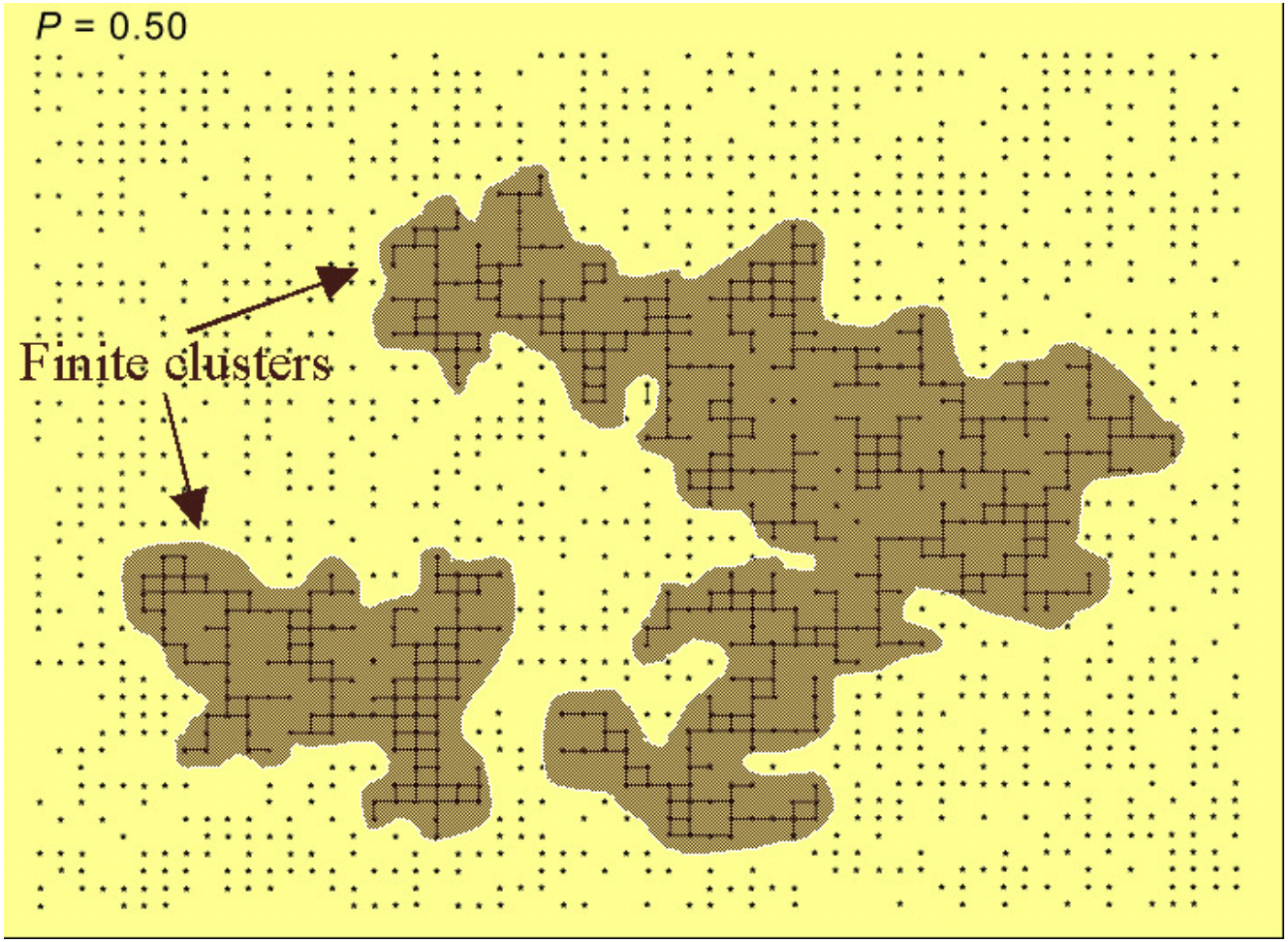
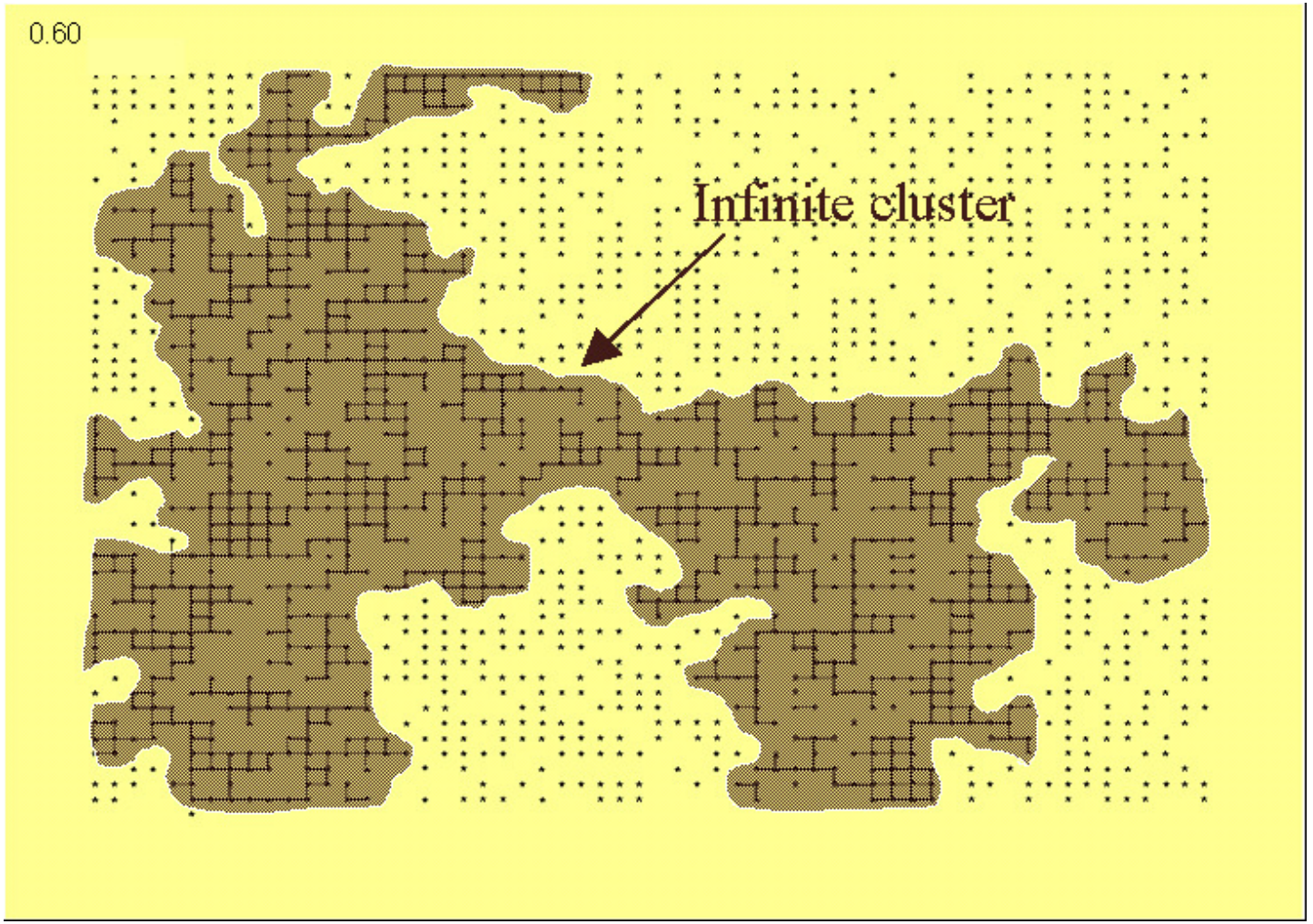
2-dimensional square lattice occupation probability P = 0.50



P= 0.60, i.e. above Percolation Threshold:



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3 D percolation thresholds

Critical concentration p_c

- ***critical site occupation probability***
- ***percolation threshold, for 3 dimensional lattices***

Grid	p_c	Coordination number z
Diamond	0.428	4
Simply cubically	0.312	6
Cubic-body-centered	0.245	8
Cubic-face-centered	0.198	12

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What means a Cellular Automata Approach?

What are Cellular Automata?

» Cellular Automata (C.A.) are simple mathematical idealizations of natural systems following ***First Principles***

» In fact, C.A. can be considered as discrete idealizations of partial differential equations used to describe natural systems such as „Fick`s Laws" in case of diffusional effects.

»Thus with relatively simple rules of C.A. can discribe complex textures in nature such as on a marine shell or the complex B.-Z. oscillating chemical reaction (see next slide).

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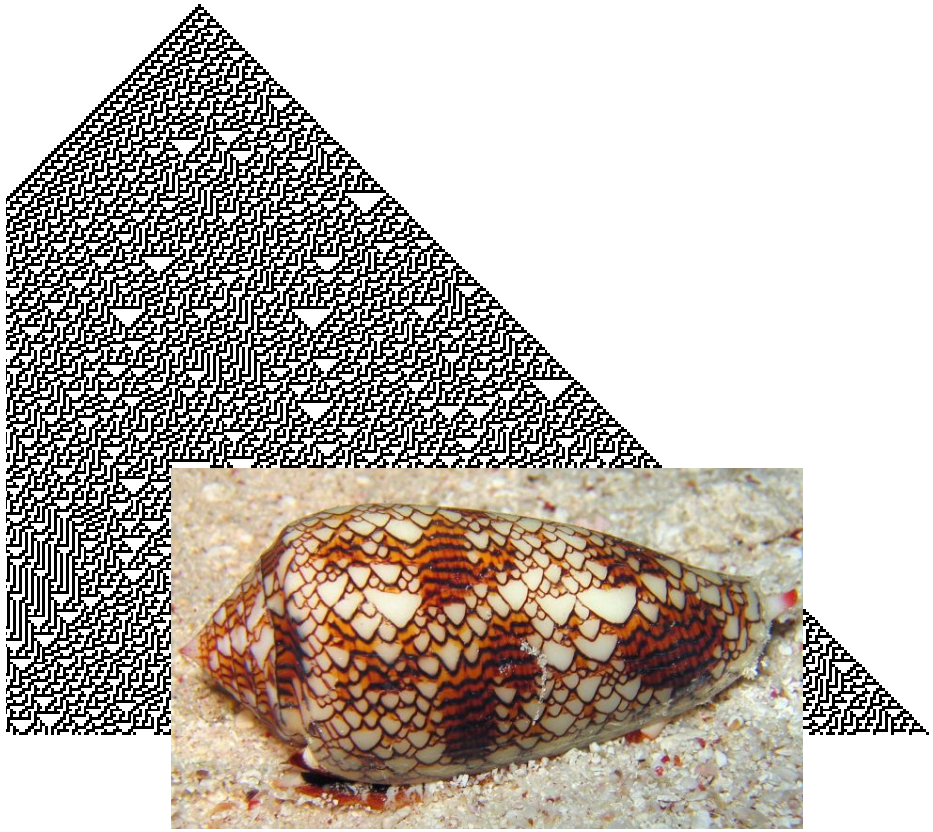
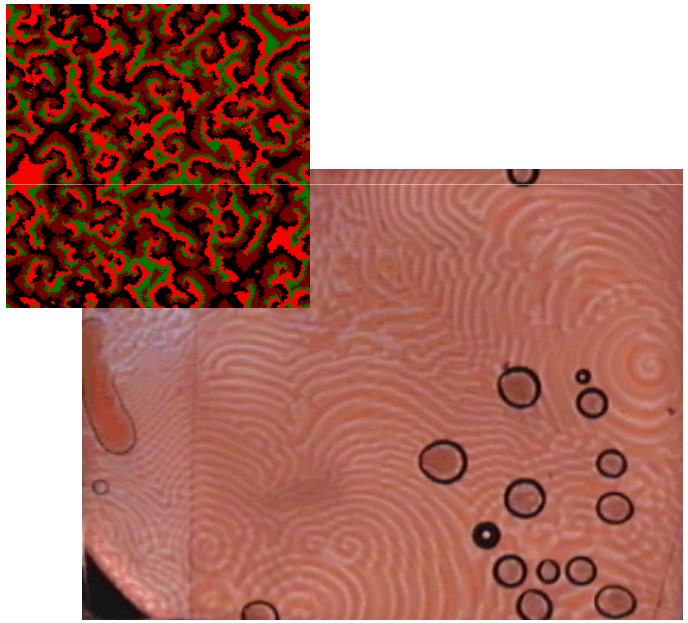
Cellular automata and modeling of natural phenomena



www.directopedia.org



Belousov-Zhabotinski Reaction

C.A.:What is in common with Percolation Theory?

The Concept of F-CAD:

F-CAD and its special tool C.A. need for the description of the tablet a (3D) Lattice like in case of Percolation Theory.

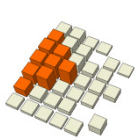
Percolation Thresholds p_c need to be known in 3D for developing a robust formulation. This can be calculated by C.A.

Thus it is necessary to define a 3D lattice and a very large number of particles (> 100 000 , better 1 000000) located on this lattice: i.e. Particles representing 1) the active substance, 2) the excipients involved, 3) the pores (particles representing void space!) of the tablet, 4) representing liquid droplets of water (in case of the drug dissolution process to be described)

What is needed to perform a C.A. calculation?

F-CAD needs:

A supercomputing facility
A special core algorithm to describe the process taking place locally at the site of the particle investigated:
i.e. At the site of the drug particle exhibiting a specific water Solubility
i.e. At the site of a excipient particle exhibiting a specific solubility (such as Lactose) or swellability (such as Maize Starch) etc
i.e. At the site of a pore, at the site of the surface of the tablet etc.



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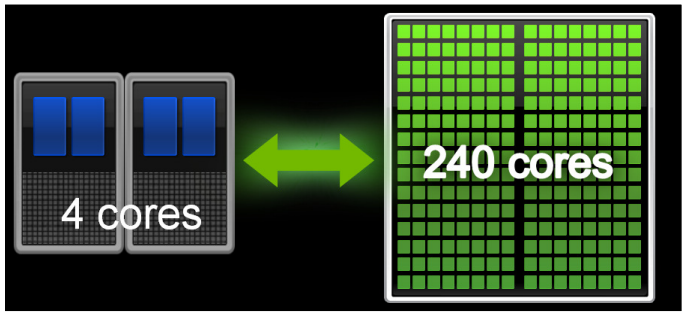
NVIDIA Tesla Computing Solutions

- Massively-Parallel Architecture, up to 240 multi-core single processor units
- 4 TeraFLOP computing capacity per ONE unit
- Scalable architecture

CINCAP F-CAD and CINCAP DEM are utilizing the TERAFLOP power of NVIDIA Tesla!



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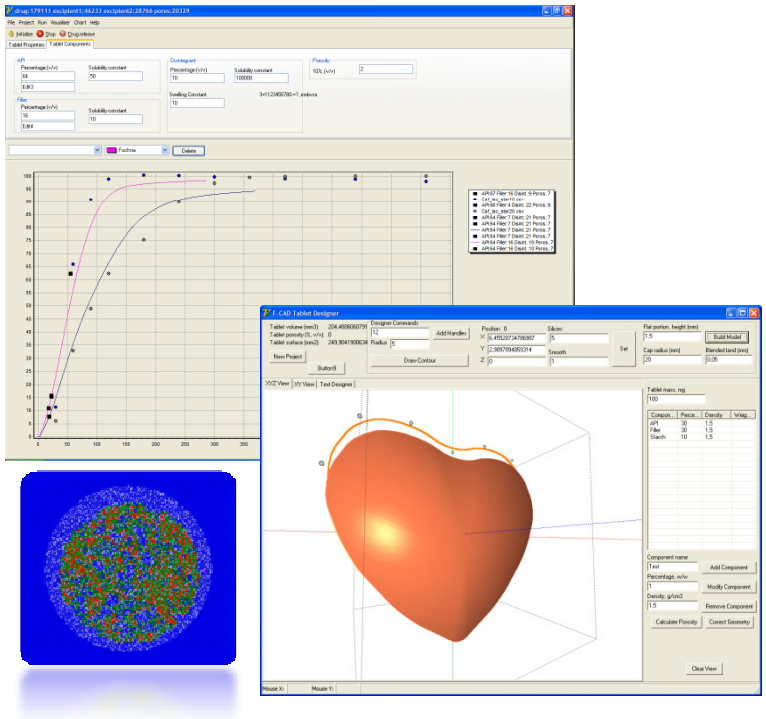
VES and F-CAD Screenshots



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Orientation: Quality by Design (QbD)

Formulation R&D

- F-CAD
  - *In-Silico* formulation development
  - Risk assessment and mitigation
  - Cost reduction

F-CAD Robust Formulation!

Production

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

VES Operator Training

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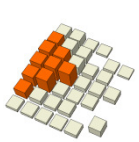
F-CAD

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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Benefits of F-CAD

- Significant development **costs reduction**
- **Real connectivity** between marketing and pharma R&D and production depts.
- Higher end-product quality – **Quality By Design** (QbD)
- Knowledge and experience management
- 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.

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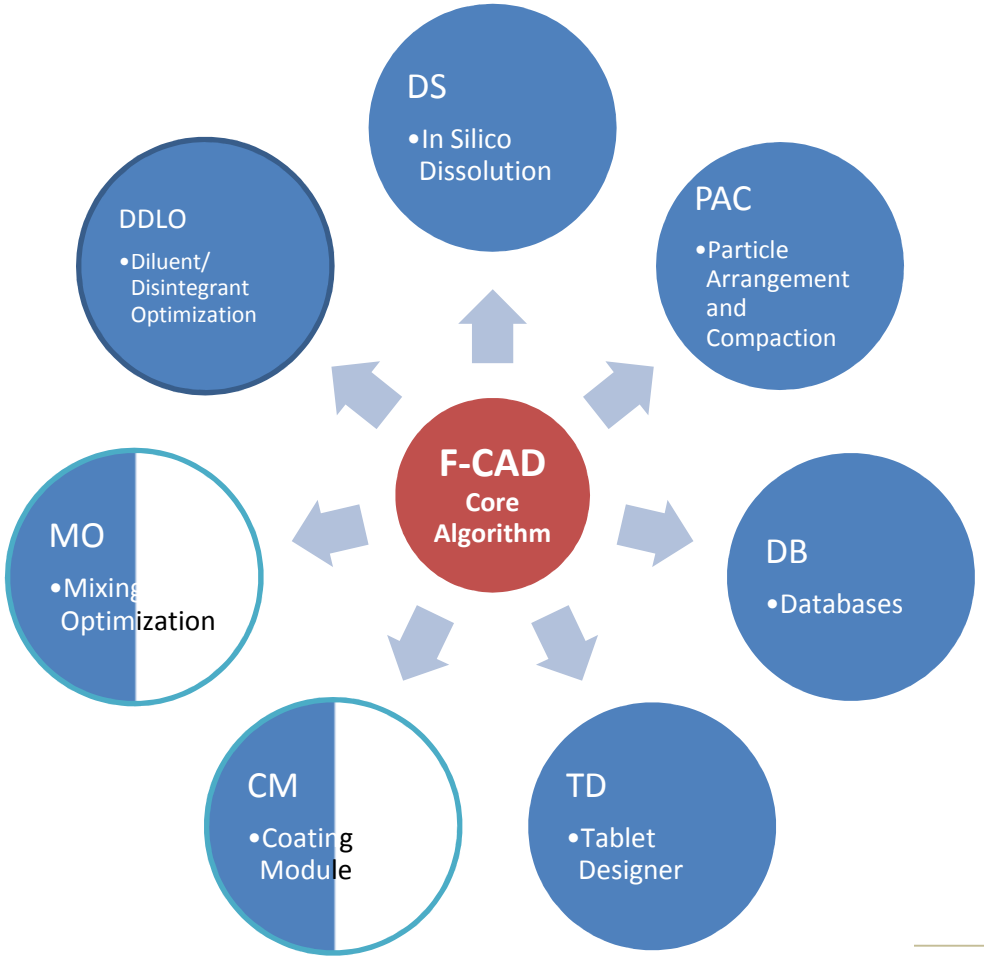
F-CAD Modules



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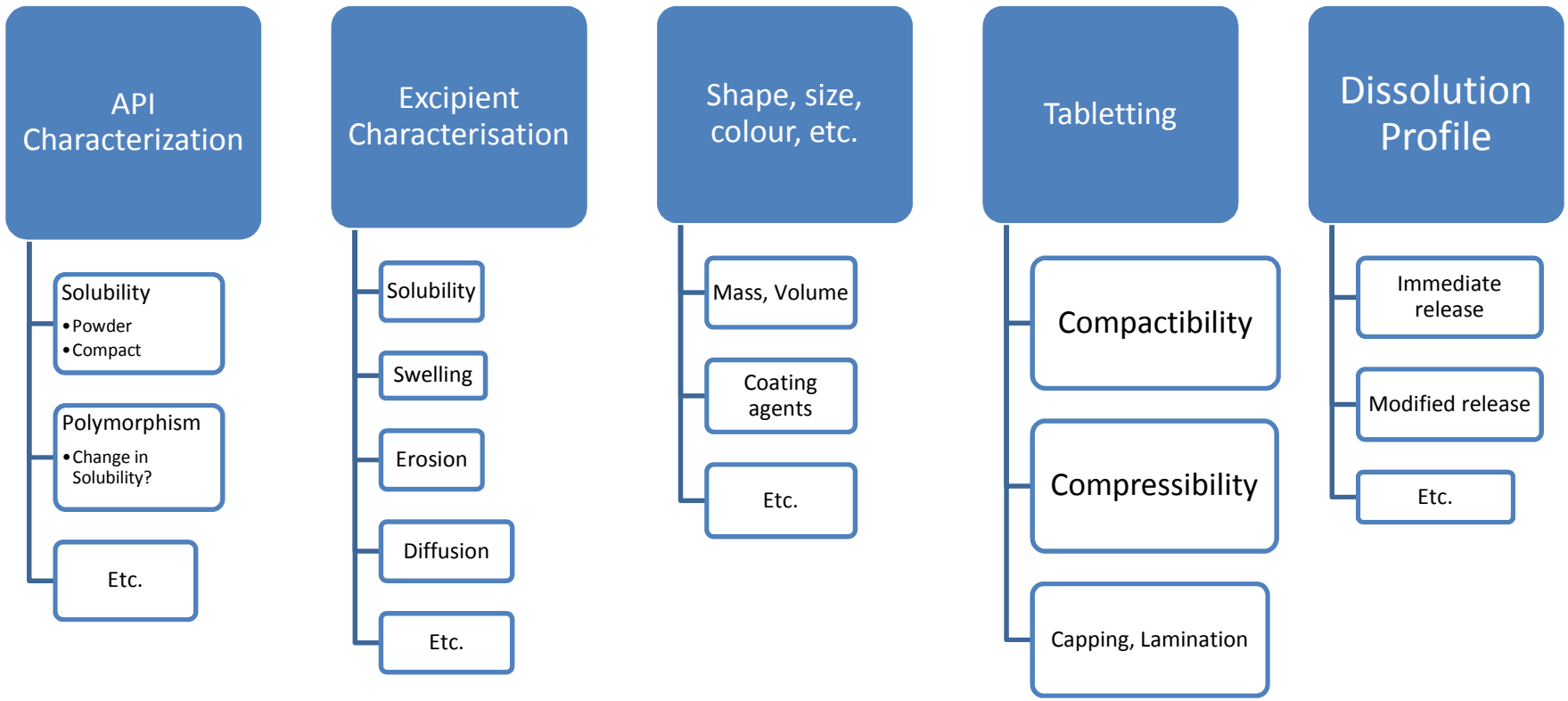
Formulation development with F-CAD



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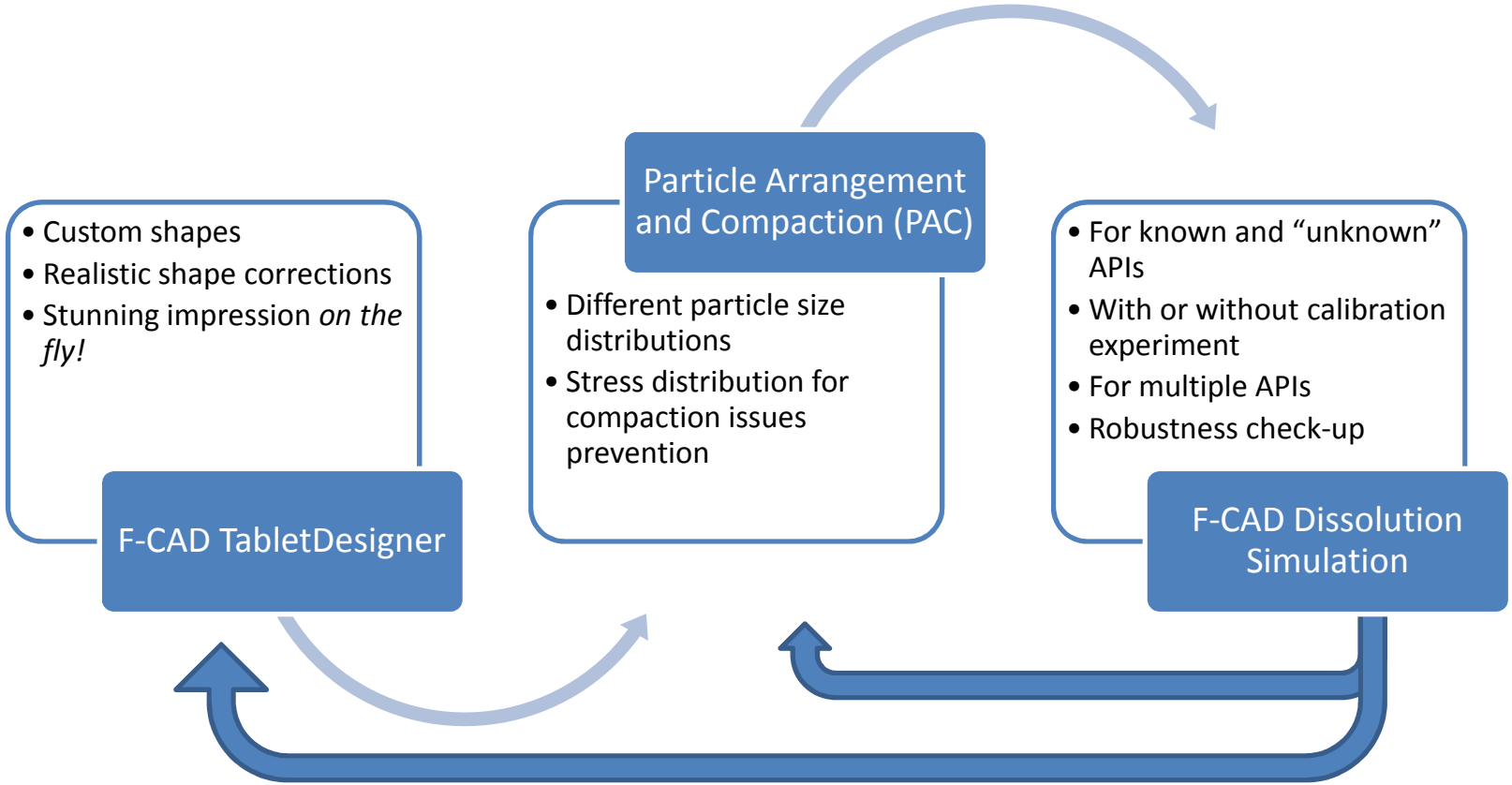
F-CAD - QbD

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

F-CAD modelling process



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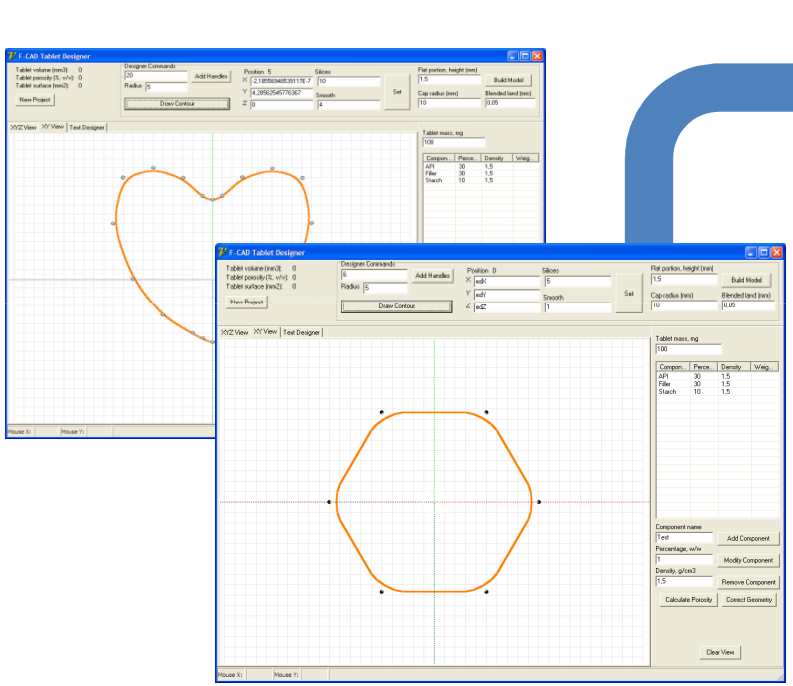
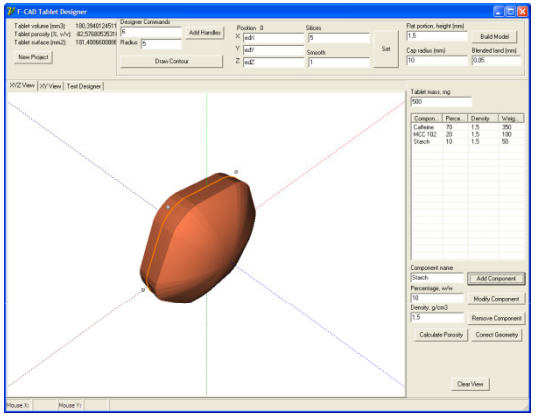
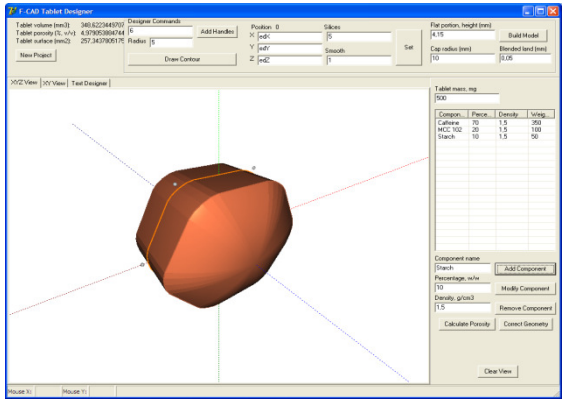
F-CAD Tablet Designer







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

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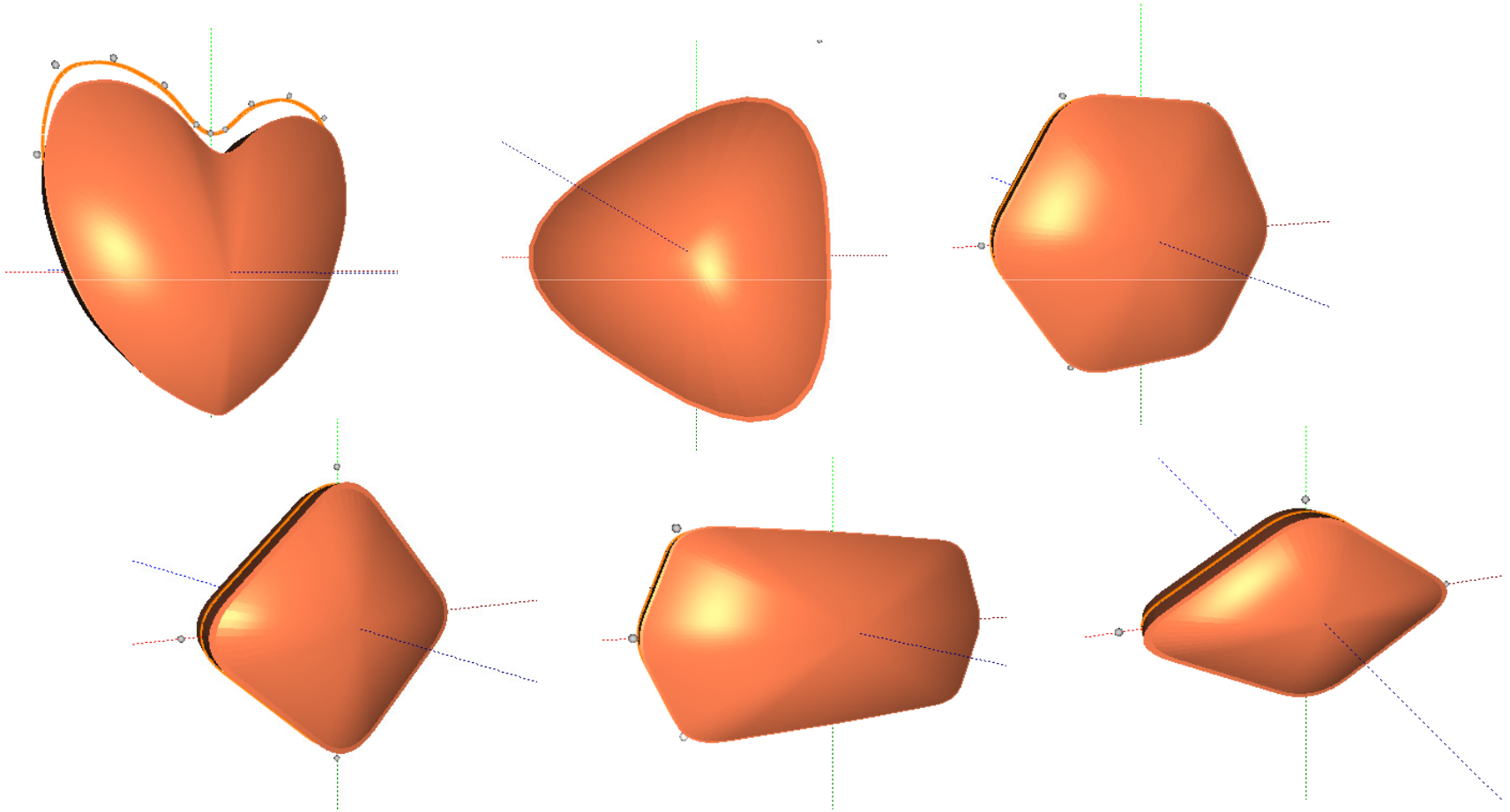
Custom Shapes with F-CAD Tablet Designer



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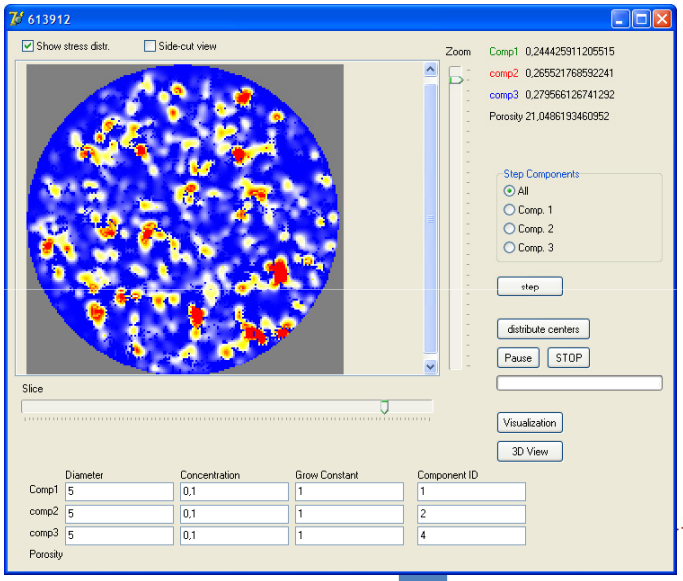
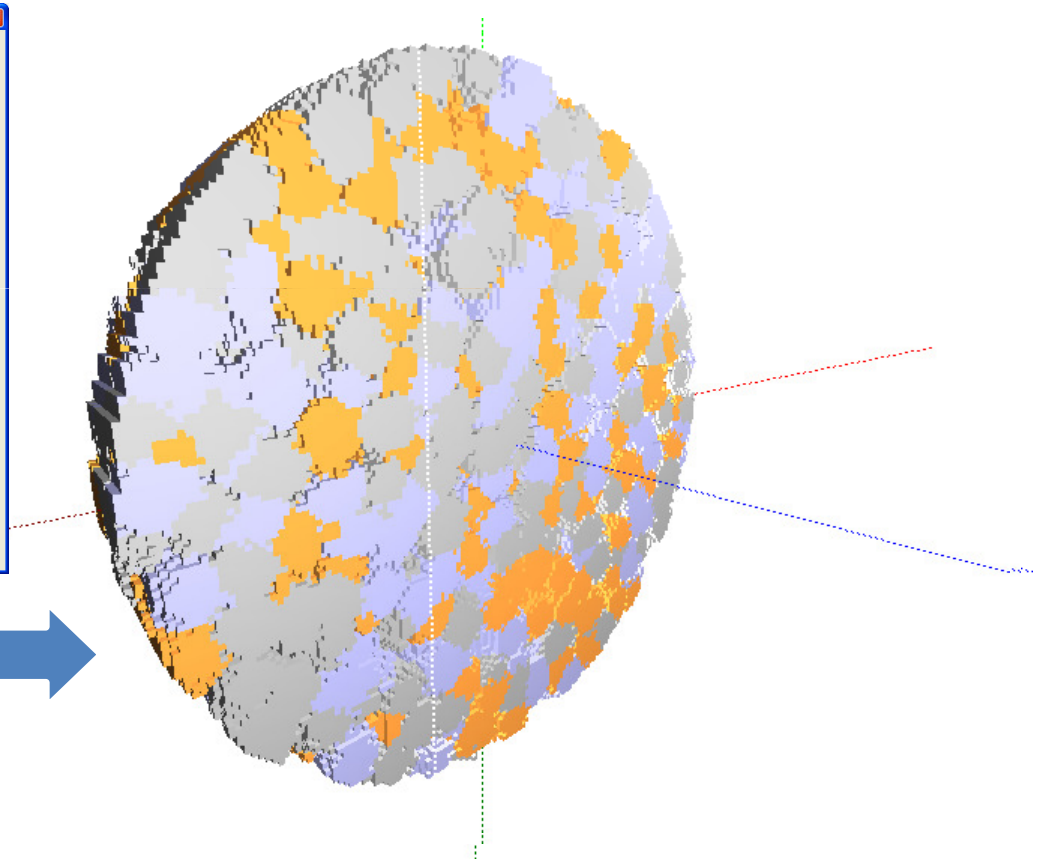
F-CAD PAC – Particle Arrangement and Compaction





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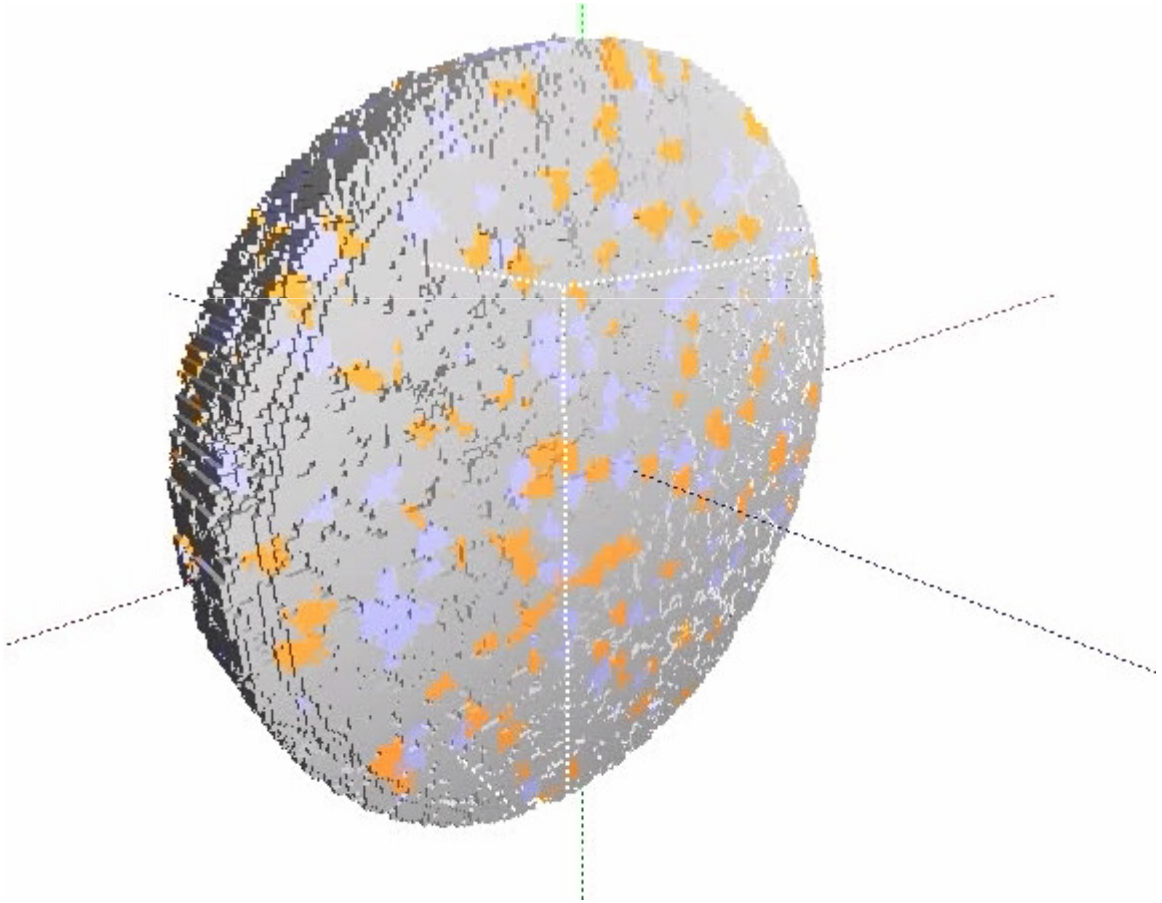
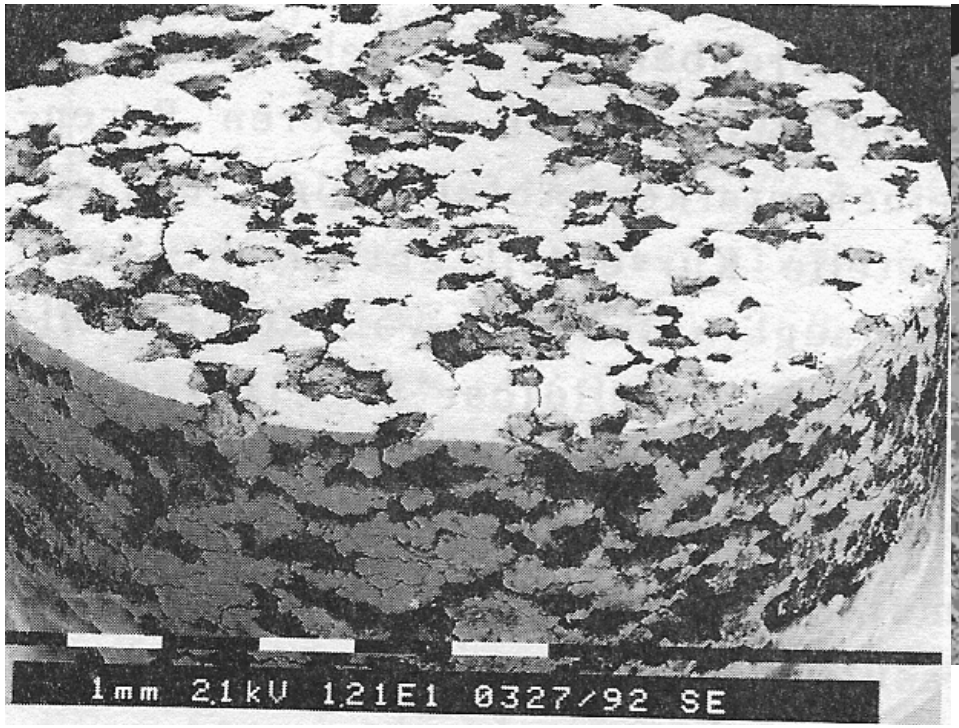
Resulting compact

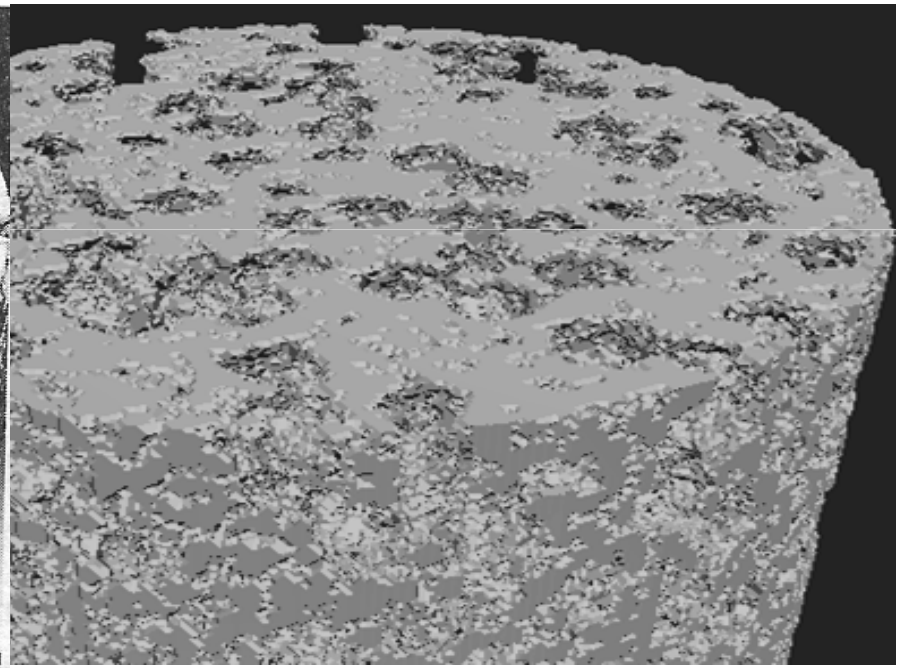


Leached Matrix Controlled Release Tablet

500-710 µm



500-710 µm



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

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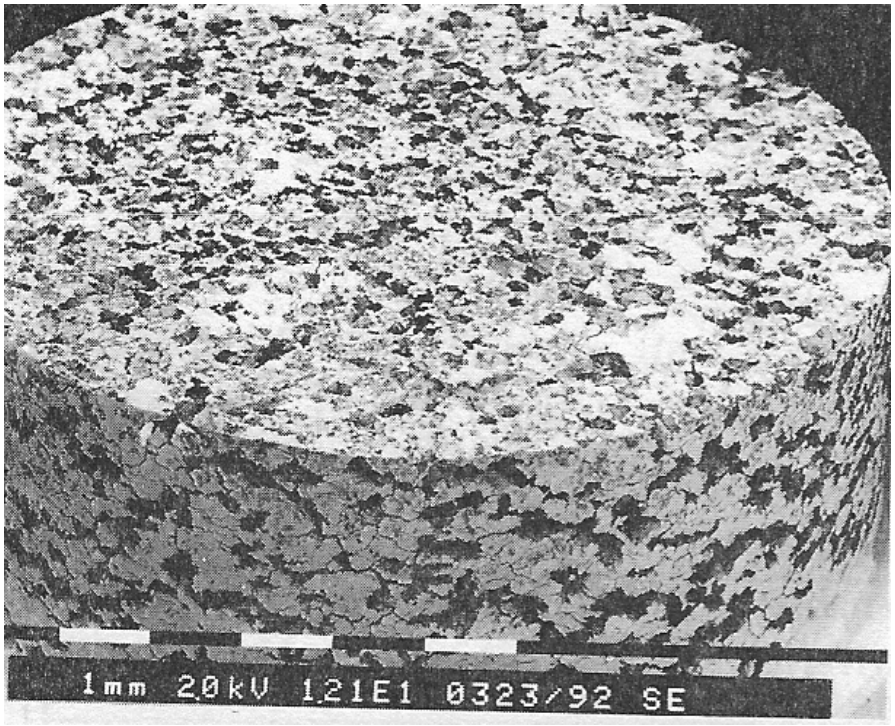
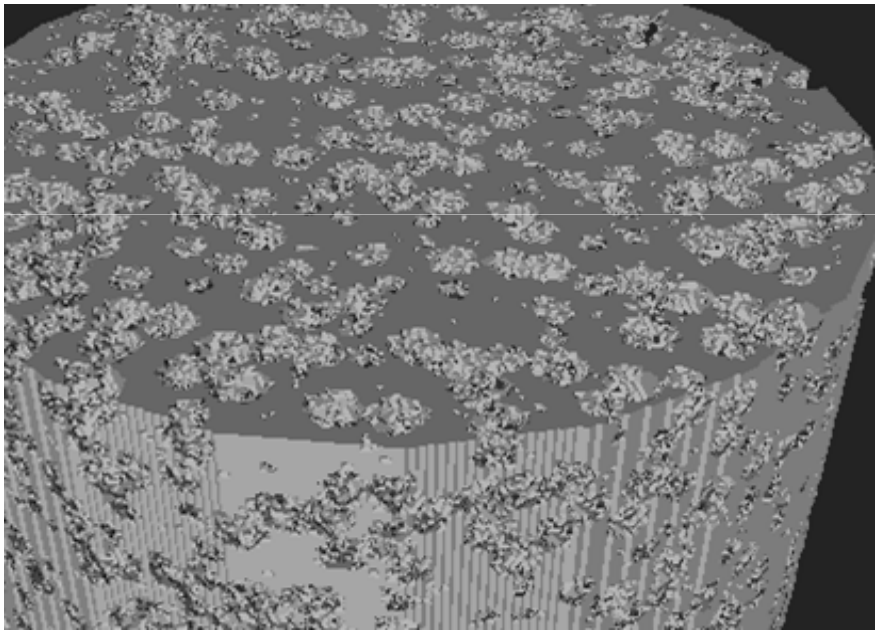
Leached Matrix Controlled Release Tablet

250-355 µm



280-400 µm



Real – left (PhD Thesis J.D. Bonny)
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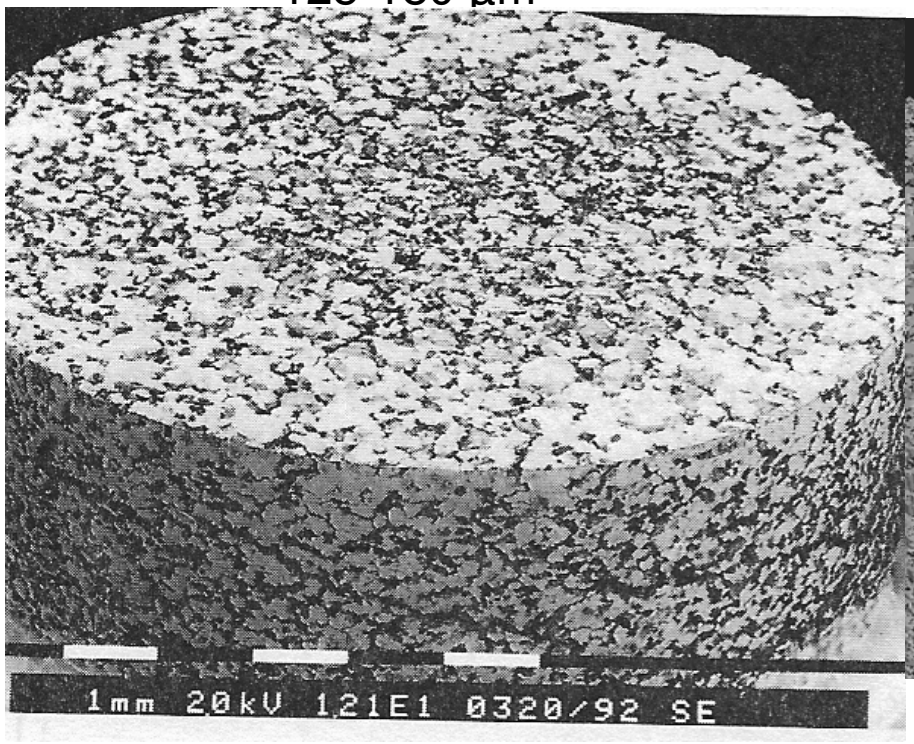
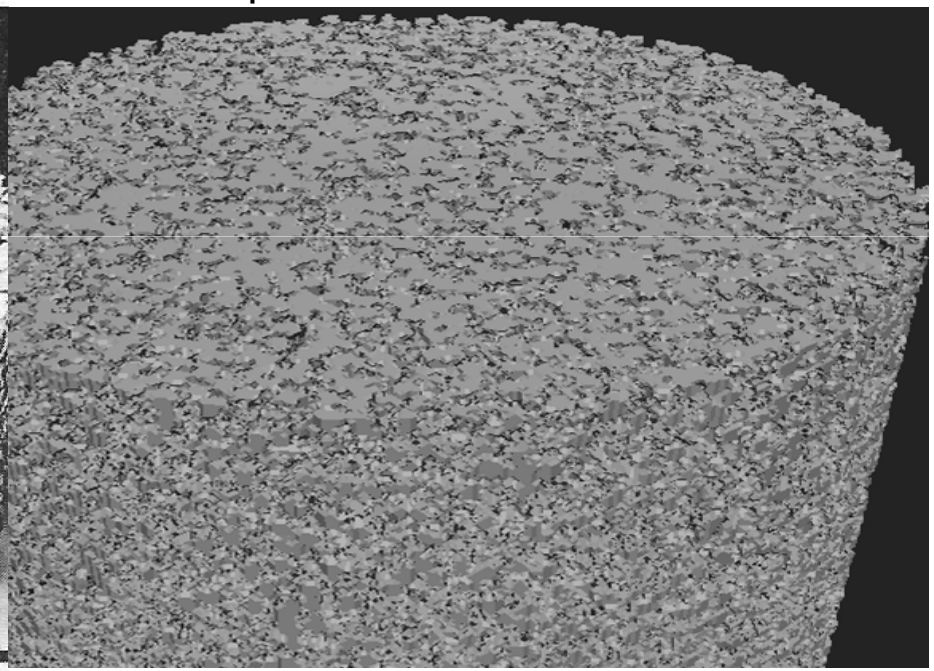
Leached Matrix Controlled Release Tablet

125-180 µm



150-200 µm



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

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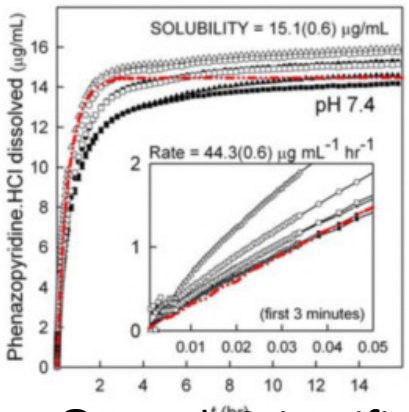
F-CAD DS – *in silico* Profiles



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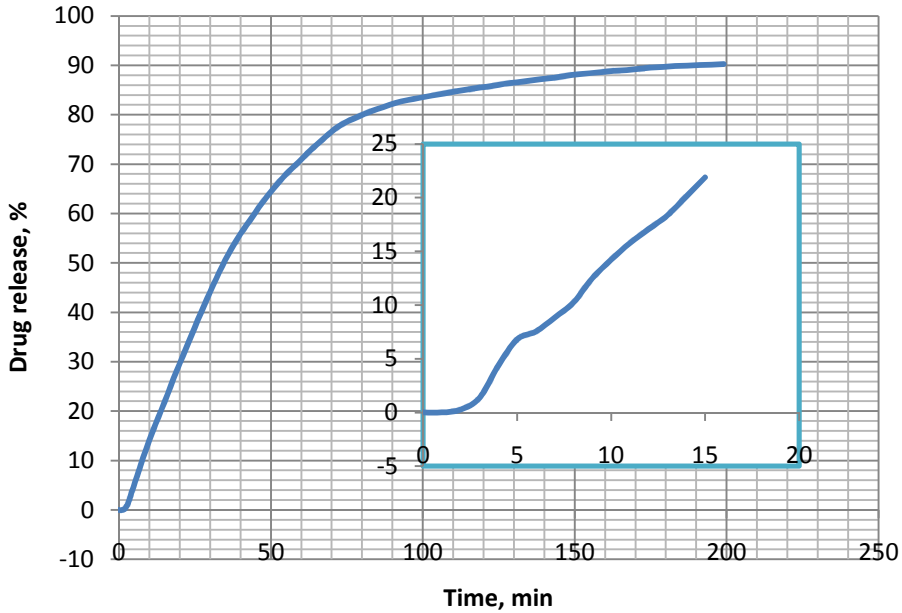

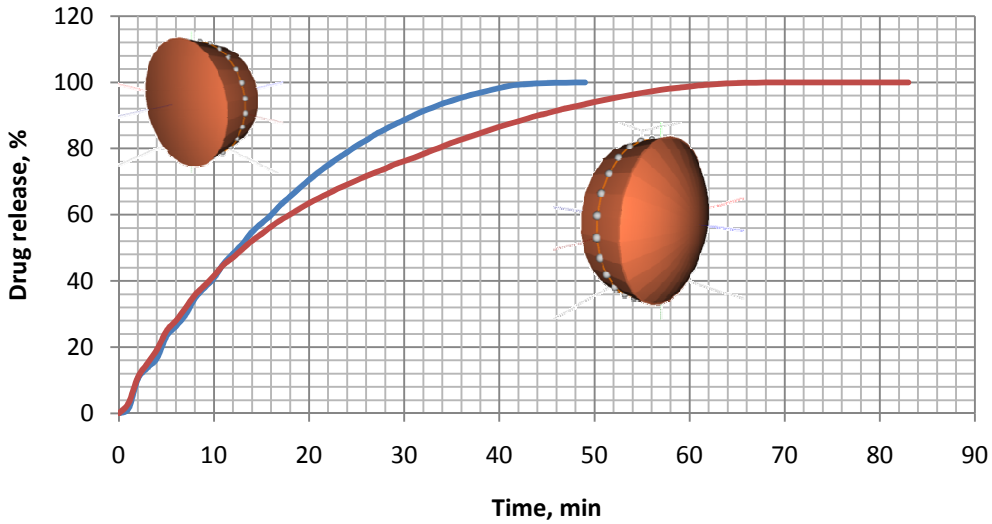

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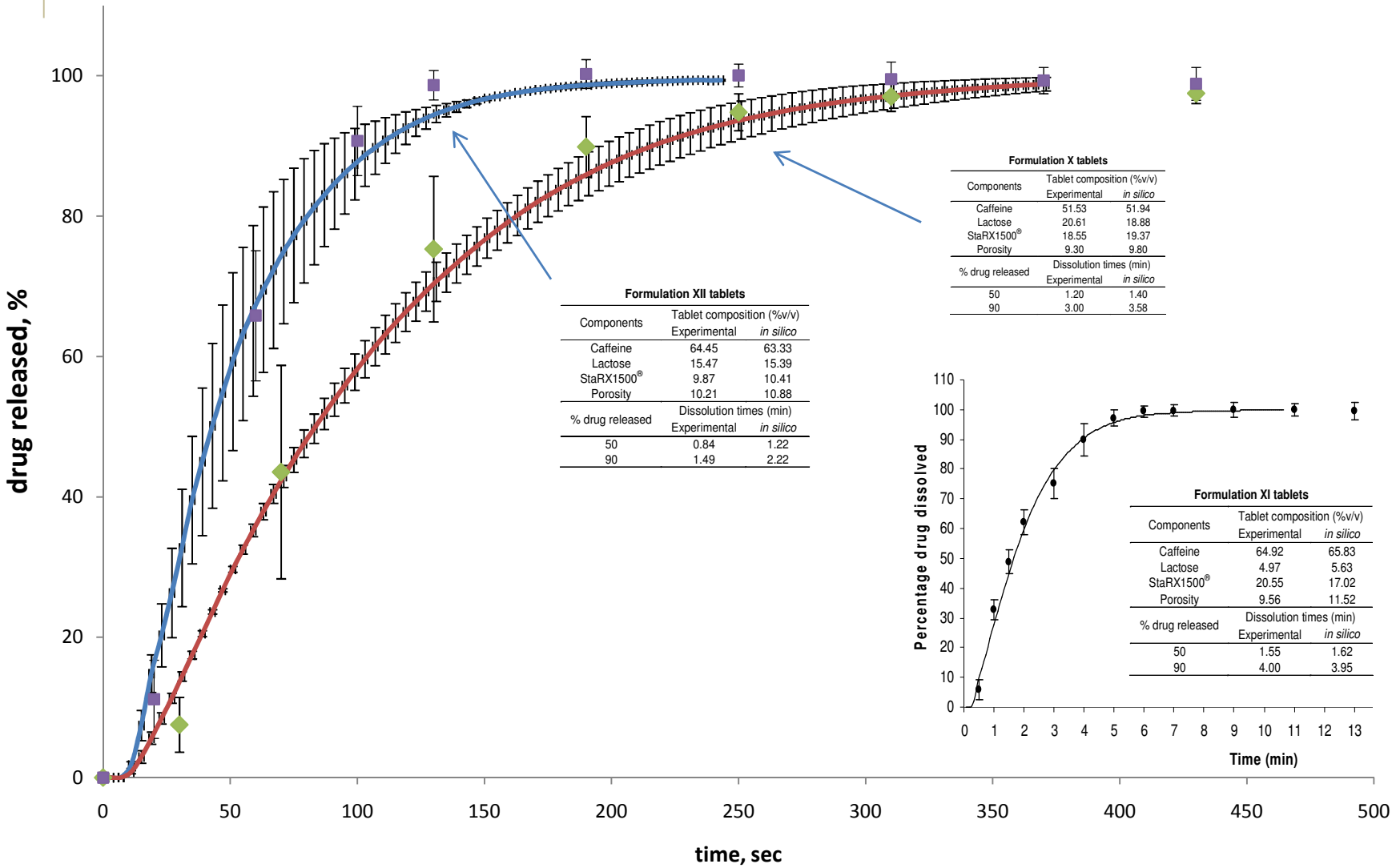
Experimental vs. in silico dissolution profiles of different formulations with caffeine



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
% 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

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."

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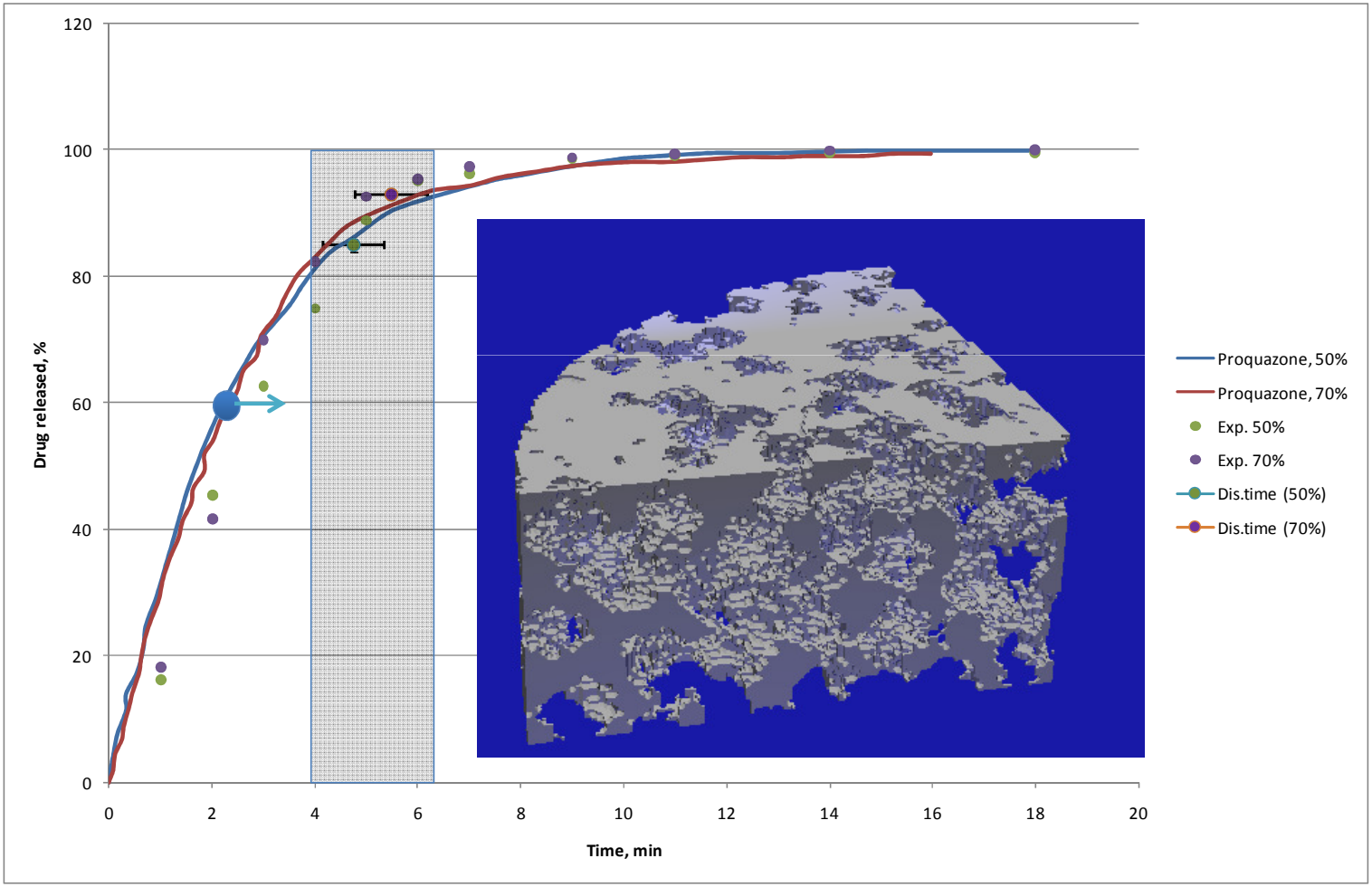
Tablet disintegration time and specific time point before disintegration



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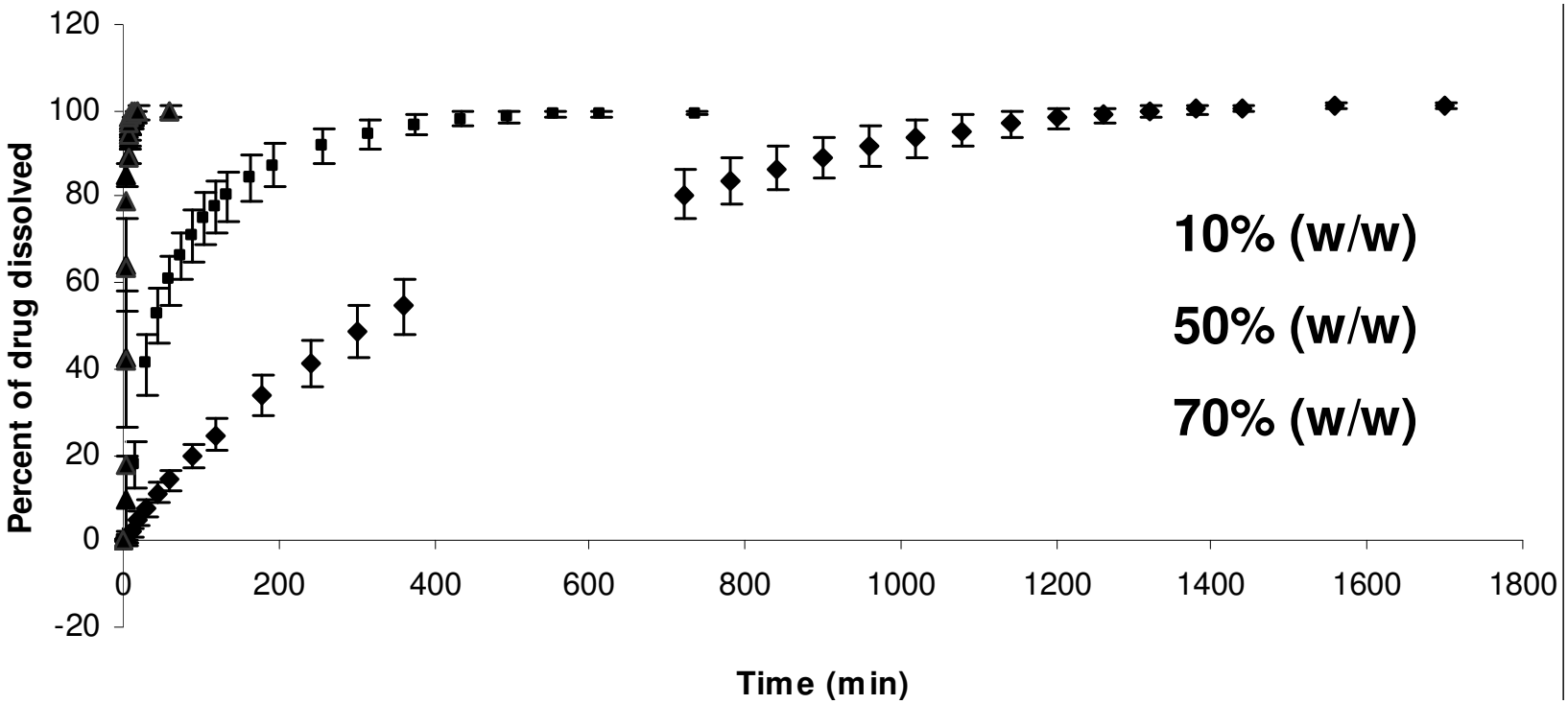
Drug A: Dissolution rate of capsule formulations

Capsule formulations were not robust being sensitive to the drug load (16, 79 and 109 mg, respectively 10% w/w, 50% w/w and 70% w/w.



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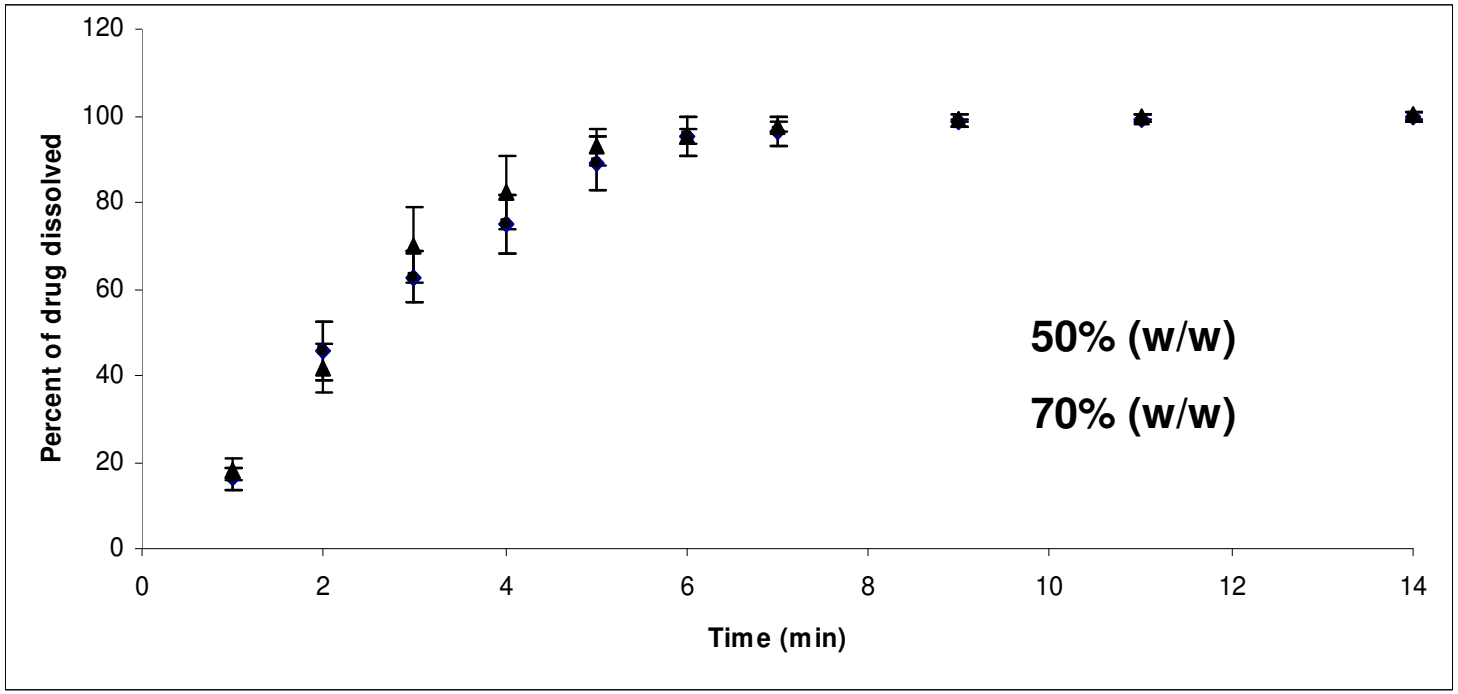
Drug A: Dissolution rate of tablet formulations

Tablet formulation have been robust and not sensitive to the drug
Load: 77mg, 109 mg drug substance, respectively 50% w/w, 70% w/w.
Reference: PhD Thesis Johannes von Orelli



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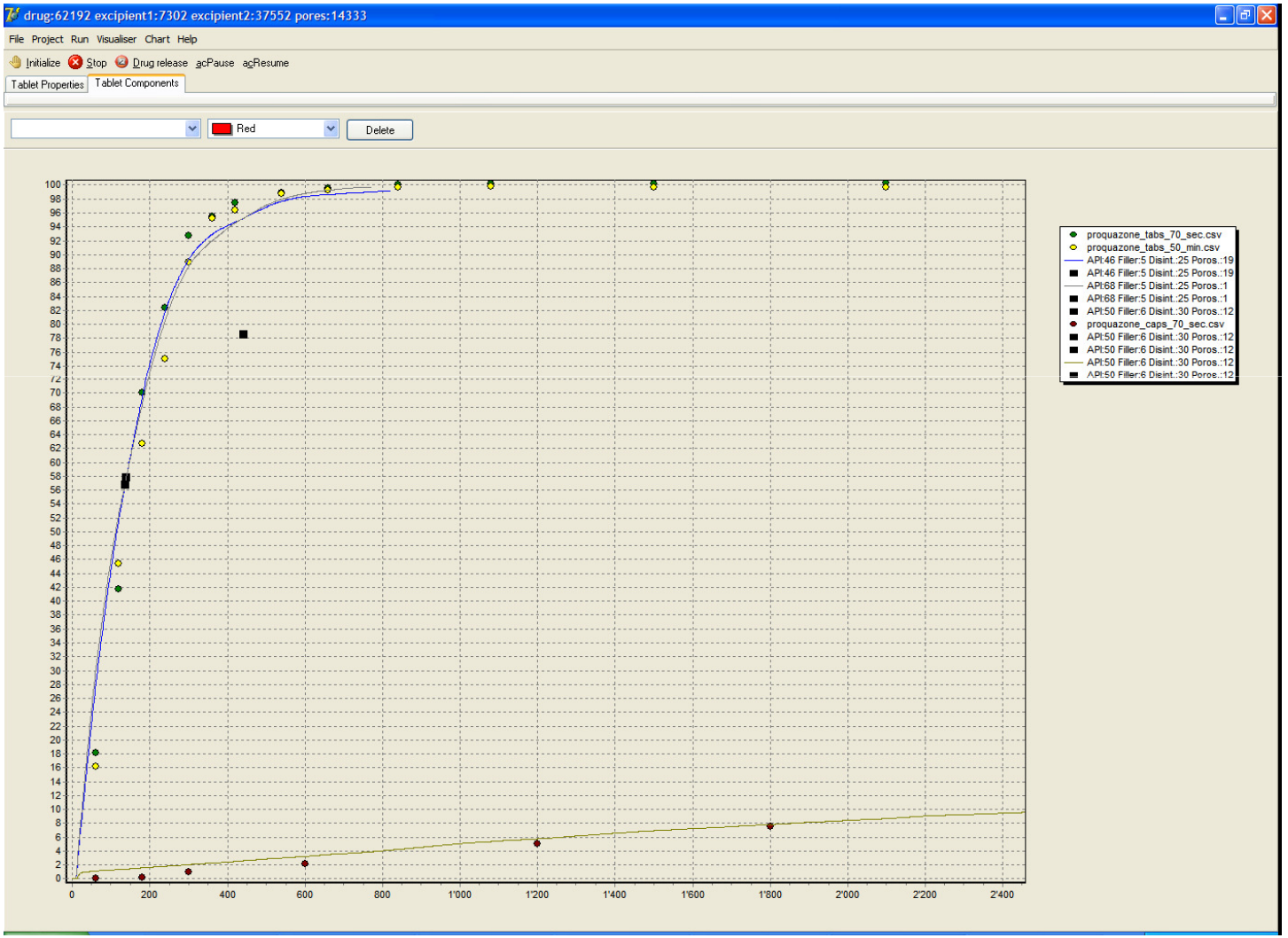
Capsule/Tablet simulation



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One for All

- F-CAD Core Algorithm
  - PAC
    - Calculation of stress distribution
    - Multi-layered tablets
  - DS
    - Extended release
    - Immediate release
    - Combination drugs
  - Coating (under development)
    - Bridging
    - Peeling
    - Roughness
  - Flowability in hoppers, feeders of arbitrary geometries (under development)

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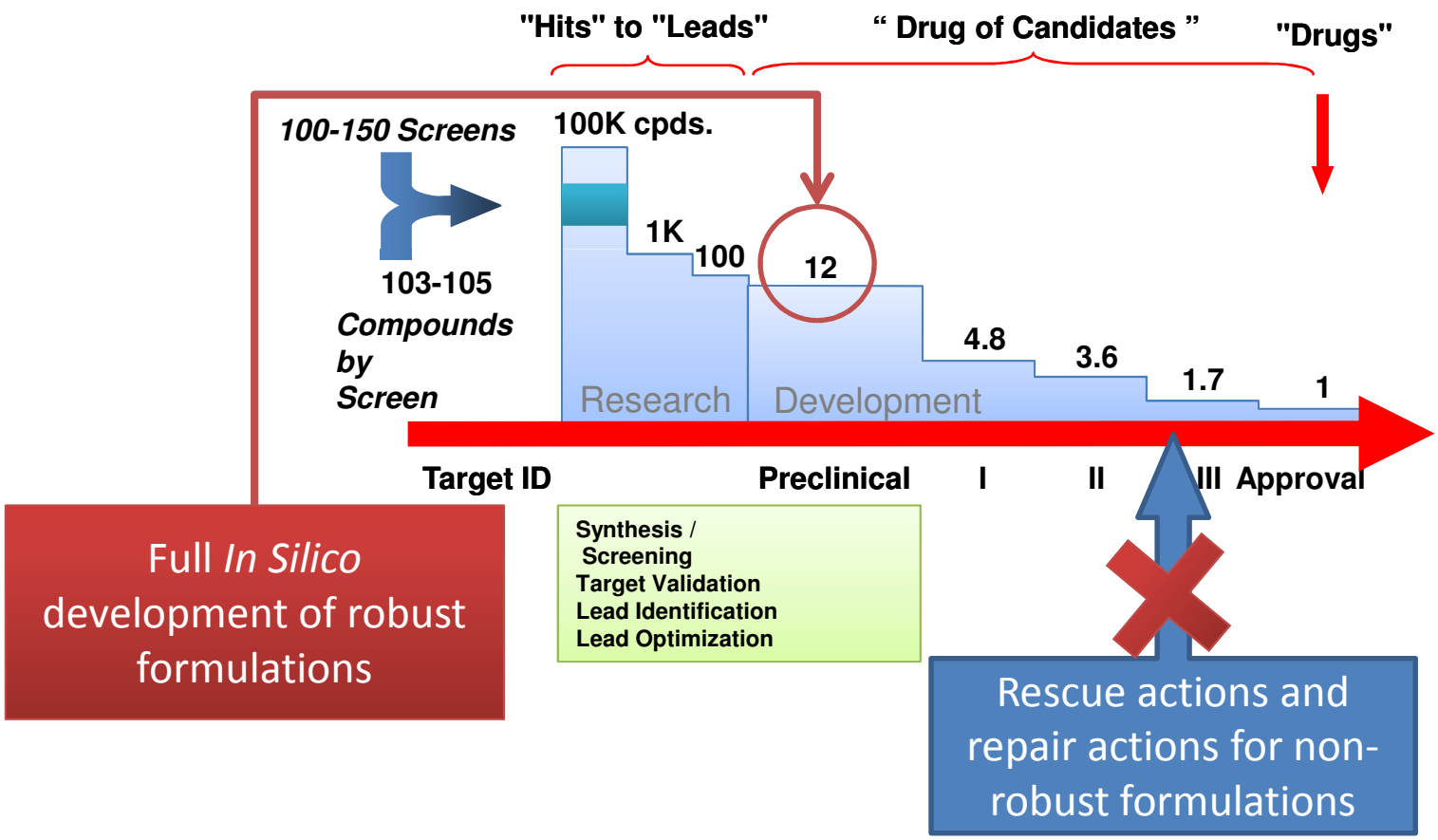
F-CAD Realms

- Marketing
  - Shape, colour, size design
- R&D Support
  - In-silico robust formulation design
- Manufacturing Support
  - In-silico Scale-up and Launch Support
- Finance
  - Cost assessment
- Risk management
  - Risk assessment and mitigation

Computing formulation quality

- If we use computation do we still need experimental trials?
  - Yes. However, not for screening but confirmation
- If it is so good, can I substitute human scientists with it?
  - No. However, free your scientists from innovation hurdles induced by costly, time-consuming lab tests
- I have my know-how (technology, physical and chemical effect, etc.), can I integrate them into computational algorithms without going deep into mathematical or computational science?
  - You can and you have to! You can naturally use and enter all your available know-how(s), previously obtained experimental data to boost up versatility of your computed models.

Slide: A. Hussain, FDA



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Powder for inhalation

- **Special devices for inhalation of powders**
- **Special size fraction of the powder:**
  optimal 1- 6 μm aerodynamic diameter
- **Carrier often lactose (larger size)**
- **Drug attached , then detached**
- **Solid with longer shelflife**

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Spray Freeze Drying as a novel process

- **Idea: spherical particles with a high porosity (up to 80% V/V)**
- **Idea: better flowability**
- **Idea: Physical diameter larger than aerodynamic diameter**
- **Idea: drug and carrier formulated**
- **Idea: immediate and controlled release**

- **PROCESS: 1) Freezing, 2) Drying step**

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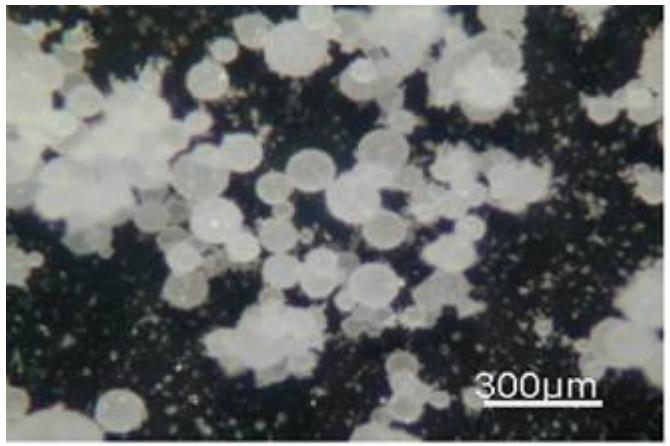
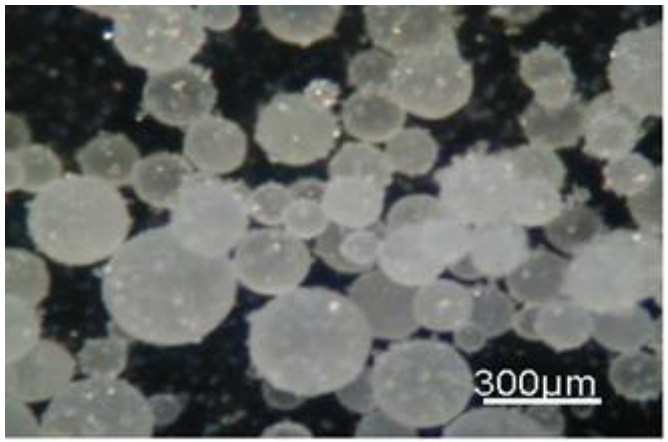
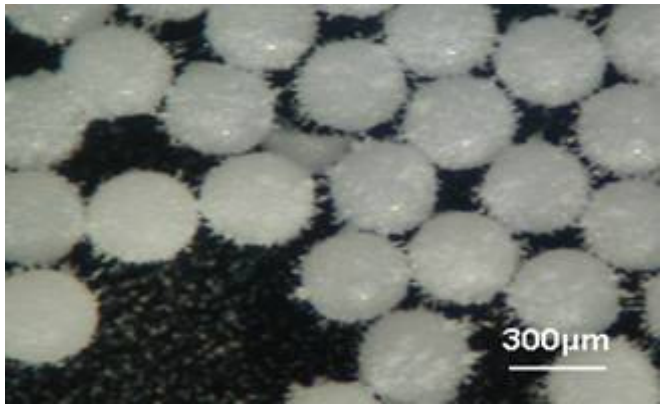
Spray Freezing



1. Ultrasonic nozzle



2. Binary nozzle



3. Prilling nozzle

Subsequently
Drying in a fluidized bed
at low temperature
e.g.
- 20 °C (Lyophilisation)

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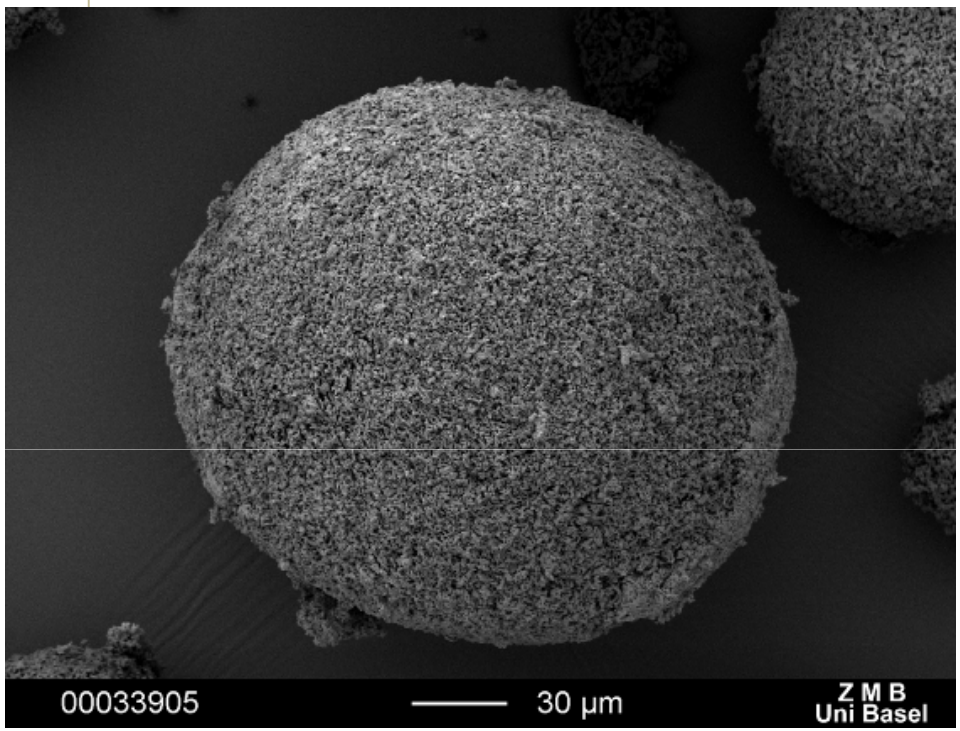
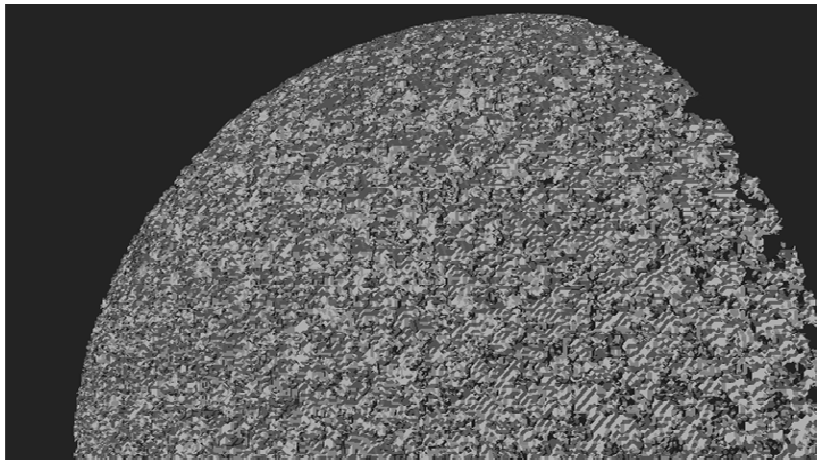
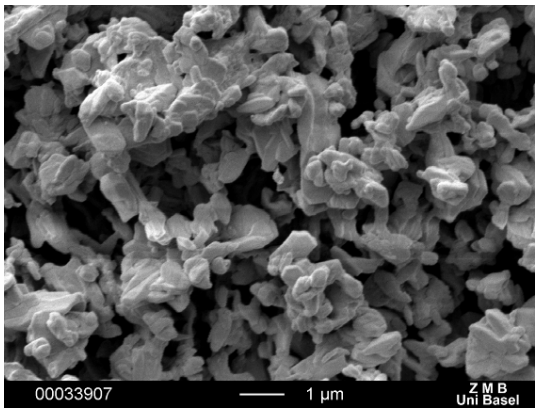
F-CAD applied for biologicals

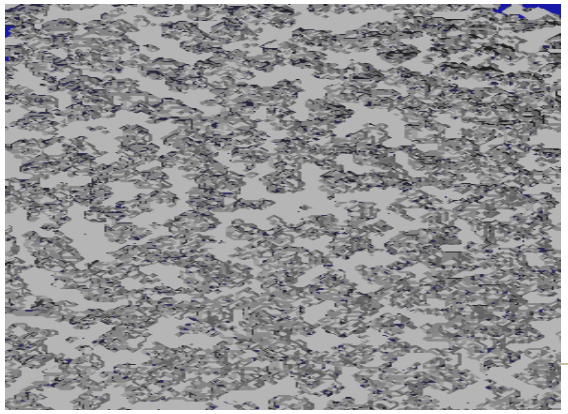


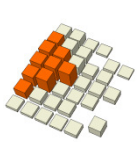


Spray freeze dryed Mannitol pellets with ca. 80% porosity as a drug Carrier, Left: PhD Thesis M. Plitzko; Right: Computer generated nano - comp. pellets by F-CAD (www.cincap.ch).

Nanocomposite Pellets as drug carriers for instant soluble Injections Or for Inhalation of Biopharmaceuticals, see www.ifiip.ch







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CINCAP DEM Features

- NVIDIA Tesla HPC-powered
- Fully-customizable core-engine for specific applications
- Uses standard soft-body collision DE-Model
- Import of any rigid machine geometries, e.g. coaters, mixers, etc.
- Possibility to read all/single particle statistic, trajectories, etc.

- All simulations are working at **INTERACTIVE RATES!!!**

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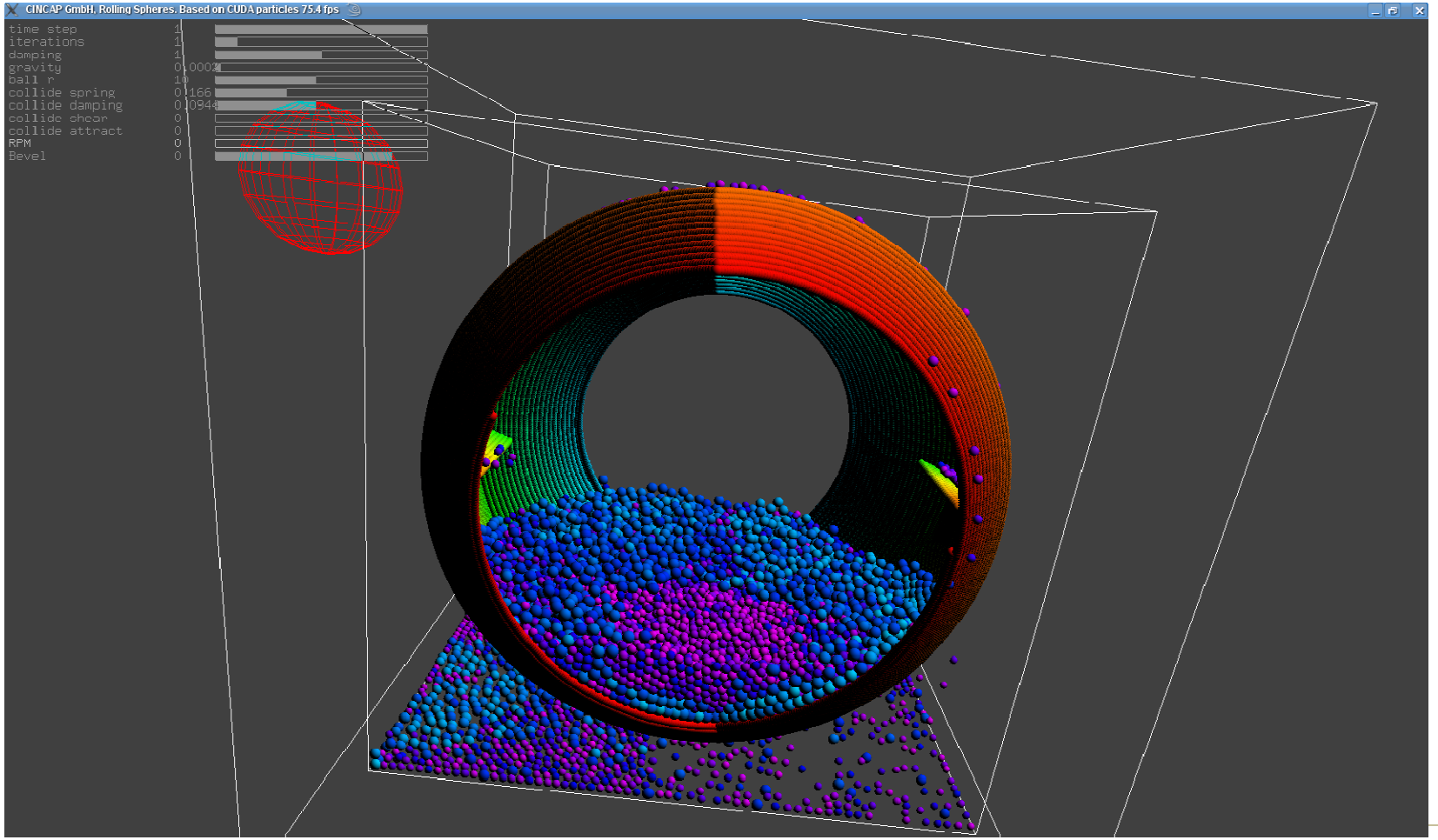
Different Particle Size Distributions



Liquid Formulations, Classification by application

Oral liquids:

- Emulsions
- Syrups
- Solutions
- Suspensions
- Instant preparations

Liquids for topical applications:

- Nasalia
- Ocularia
- Auricularia
- Dermatologica
- Parenteralia
- Rectal liquids
- Vaginal liquids
- Inhalations
- Instant preparations

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F-CAD for liquid formulations

Idea/Model:

- **Liquid = Nanosized Powder System**
- **Nanosized clusters = special physical and chemical properties!**
- **Nanosized clusters = special biological and pharmacological properties?**

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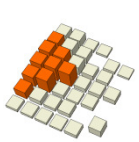
F-CAD for liquid formulations

Idea/Model:

Nanosized cluster formulations:

- **What are the relevant properties, parameters for the optimal formulation?**
- **Do we find these properties in the pharmacopoea?**
- **What are the basics of liquid formulations, of solutions?**



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Physical pharmacy of liquids

Hanson Solubility Parameters: $\delta^2_{total} = \delta^2_{disp} + \delta^2_{pol} + \delta^2_{hyd}$ **[MPa]**

Liquid	V/cm3 mol-1	δ_{disp}	δ_{pol}	δ_{hydr}	δ_{total}
Hexane	131.6	14.9	0.0	0.0	14.9
Octane	163.5	15.5	0.0	0.0	15.5
Benzene	89.4	18.4	0.0	2.0	18.6
Dioxane	85.7	19.0	1.8	7.4	20.5
Octanol	157.7	17.0	3.3	11.9	21.0
Ben.Alc.	103.6	18.4	6.3	13.7	23.8
Ethanol	58.5	15.8	8.8	19.4	26.5
DMSO	71.3	18.4	16.4	10.2	26.7
Water	18.0	15.6	16.0	42.3	47.8

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Dielectric Spectroscopy

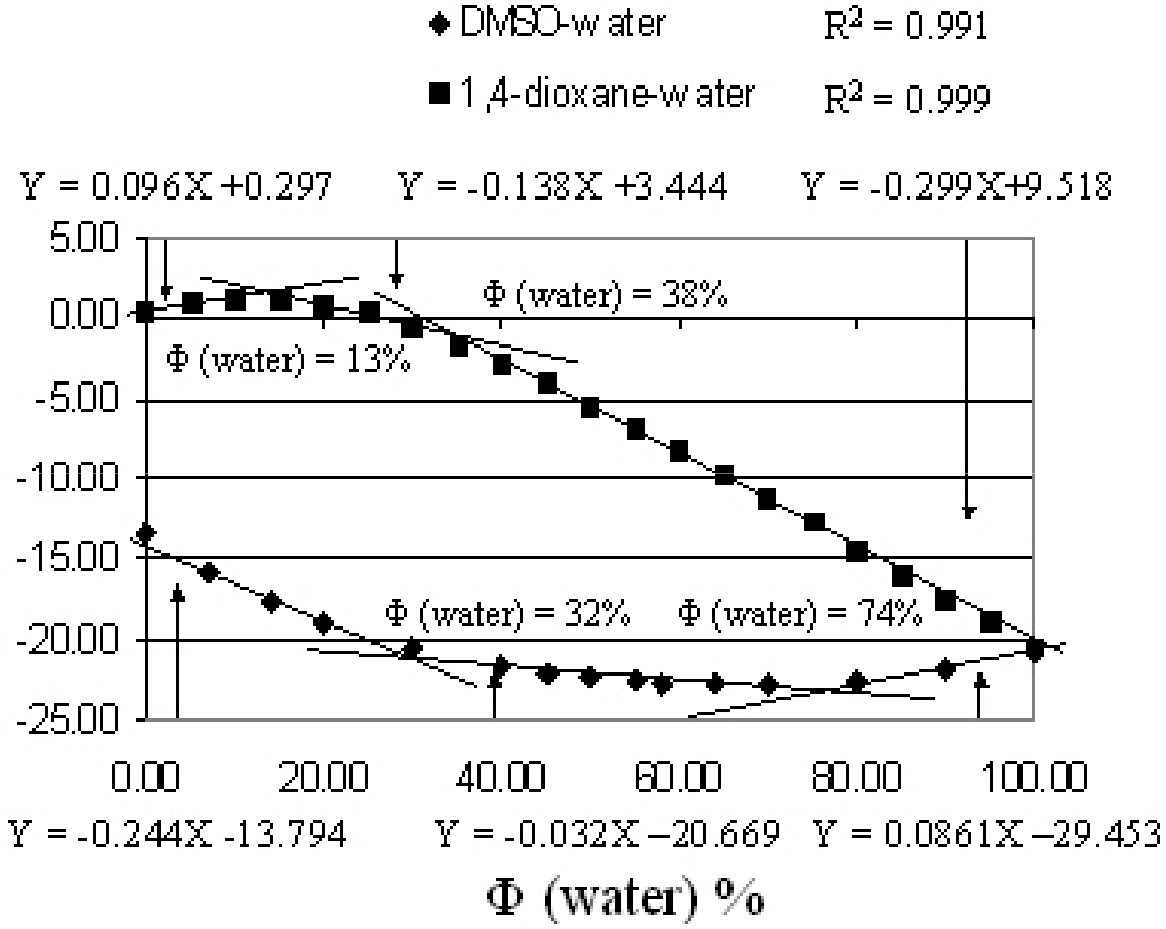
For liquids (& solids) Generalized Clausius-Mosotti-Debye Equation:

$$\frac{\varepsilon - 1}{3\frac{E_i}{E} + (\varepsilon + 2)} \frac{M}{\rho} = \frac{N_A}{3\varepsilon_0}\left(\alpha + \frac{\mu_g^2}{3kT}\right)$$

E_i/E

E_i = internal, **local** electric field

E = external electric field



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DMSO-Water system as a drug carrier?

DMSO – Water system as a drug carrier:

- Often standard test for first pharmacological trial in animals
- DMSO as solubilizing agent in parenteralia
- DMSO is an impressive transdermal carrier
- Nobody knows the optimal ratio DMSO/water as drug carrier
- Studies concerning pharmacokinetic and pharmacodynamical effects of DMSO in a liquid formulation?
- Role / effect of percolation thresholds in the DMSO/water carrier system?

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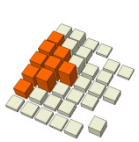
Summary: Goals of F-CAD

- 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
- Computer aided design of formulations similar to aircraft design
- Savings comparable to the savings of the aircraft industry



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F – CAD applications for

- Marketing
  - Shape, colour, size design
- R&D Support
  - In-silico robust formulation design
- Manufacturing Support
  - In-silico Scale-up and Launch Support
- Finance
  - Cost assessment
- Risk management
  - Risk assessment and mitigation

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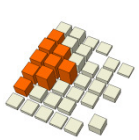
How will the Quality by Design Initiative Affect Formulation Development and Manufacturing?

CONCLUSIONS

- **MANUFACTURING**
  - More at-line, on-line and in-line IN – PROCESS TESTING
  - GOAL: Parametric release of the batches
- **PHARMA R&D**
  - New tools are necessary to achieve a SIX SIGMA PERFORMANCE
  - I am convinced that e-DEVELEOPMENT will have a future
  - In order to save money and to increase the quality of the formulations and processes



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Thank you for your attention!

Audience Q&A

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About CINCAP

- The Center for Innovations in Computer-Aided Pharmaceutics, CINCAP GmbH is a start-up enterprise 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 computationally intensive software for process simulation; pharmaceutical, medical, and biological fields of science and technology.

- CINCAP GmbH is incorporated in Switzerland (BL) as Limited Liability Company.
- Founders: Prof. Hans Leuenberger, Dr. Maxim Puchkov