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**New Formulation Paradigm: Solid Dosage Form Design
“in-silico” and Training with Virtual Equipment
Simulators like the Aircraft industry**


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Aircraft and drug formulation: similarities


- » Development and production of a **vehicle** that
- » **delivers the drug substance**
 - precisely at the
 - in the
 - in the
 - to the

right time
right quality
right quantity
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>

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Principle of "in-silico" Solid Dosage Form Design:




Tablet: 100% digitally designed using F-CAD in 3D.

The Goal of F-CAD is to achieve similar savings in the pharmaceutical area

- » F-CAD is based on (3D) Percolation theory and on Cellular Automata
- » What is Percolation Theory? A brief introduction
- » What means a Cellular Automata model approach? A brief description
- » F-CAD: Achievements

F-CAD: Formulation – Computer Aided Design

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What is percolation theory?

A brief introduction

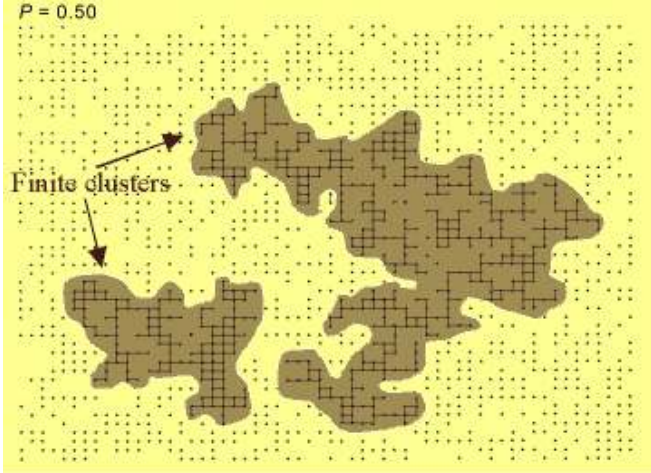
Percolation Theory is very suitable for the description of powder systems and its behaviour!

Powder systems like pharmaceutical solid dosage forms represent disordered chaotic systems, which need a special attention!

For more details see:
Leuenberger, H.; The application of percolation theory in powder technology (Invited review); *Advanced Powder Technology*; **10**:323-353 (1999)
Pharmaceutical Powder Technology - From Art to Science: The Challenge of FDA's PAT Initiative. Leuenberger Hans, Lanz Michael. *Advanced Powder Technol.* 16 (1), 2005, 3-25. ISSN 0921-8831

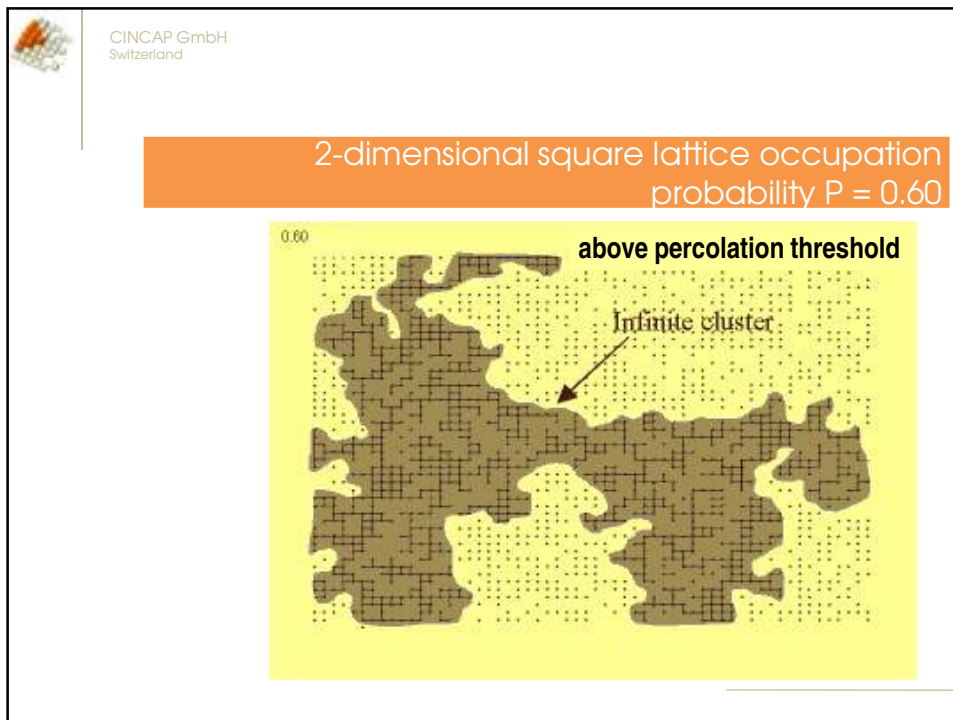
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2-dimensional square lattice occupation probability $P = 0.50$



$P = 0.50$

Finite clusters



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Percolation theory

Basic equation - percolation theory

$$X = S|p - p_c|^q$$

X = property of the system
 S = Scaling factor
 p = occupation probability of the lattice sites
 p_c = Percolation threshold (critical concentration of excipient, e.g. disintegrant)
 q = critical exponent (Process-dependent universal value)

Example values:
 $p_c = 0.315$ v/v (fibrous disintegrant)
 $q = 0.41$ (water uptake process)

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P_c needs to be calculated numerically, e.g. by CA.

$$X = S|p - p_c|^q$$

S = scaling factor
q = critical exponent
 p_c is related to the microscopic structure!

Universal critical exponent q **depends only on** Euclidean/fractal dimension of the process!

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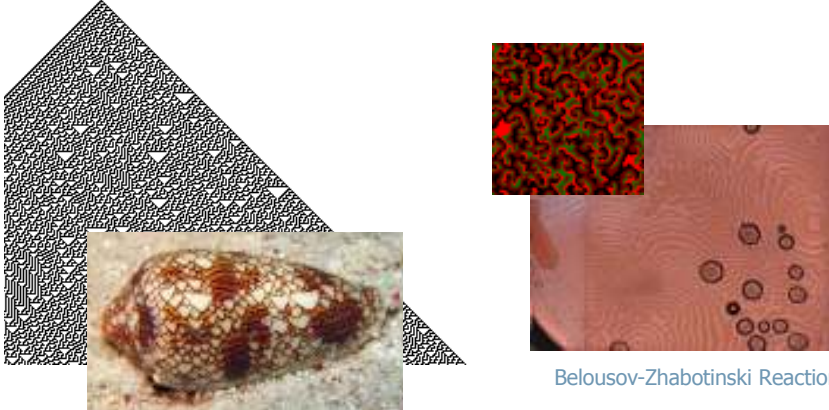
What means a Cellular Automata Approach?

- » What are Cellular Automata?
- » Cellular Automata (CA) are simple mathematical idealizations of natural systems (Stephan Wolfram, Prof. In Mathematics, Princeton University)
- » In fact, CA can be considered as discrete idealizations of partial differential equations used to describe natural systems such as „Fick's Laws“ in case of diffusion effects.

Thus with relatively simple CA-rules can describe complex textures in nature such as on a cone shell or the complex Belousov-Zhabotinsky oscillating chemical reaction (see next slide).

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Cellular automata and modeling of natural phenomena



www.directopedia.org


Belousov-Zhabotinski Reaction

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The concept of F-CAD

- » F-CAD is different from any existing e-tool such as:
 - Expert System
 - Artificial Neural Networks
 - Collection of existing formulations etc
- » F-CAD takes into account
 - Physical laws
 - Percolation Theory
 - Disordered Particulate Systems
 - Applying Cellular Automata Rules

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What is in common with Percolation Theory?

F-CAD and Percolation Theory:

- » 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 CA
- » Thus it is necessary to define a 3D lattice and a very large number of particles (>100 000, better 1000000) located on this lattice, i.e. particles representing:
 - the active substance,
 - the excipients involved,
 - the pores (particles representing void space) of the tablet
 - liquid droplets of water (in case of the drug dissolution process to be described)

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What is needed to perform a CA 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:
 - at the site of the drug particle exhibiting a specific water solubility
 - at the site of a excipient particle exhibiting a specific solubility (such as lactose) or swellability (such as maize starch) etc.
 - at the site of a pore, at the site of the surface of the tablet etc.


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Benefits of F-CAD

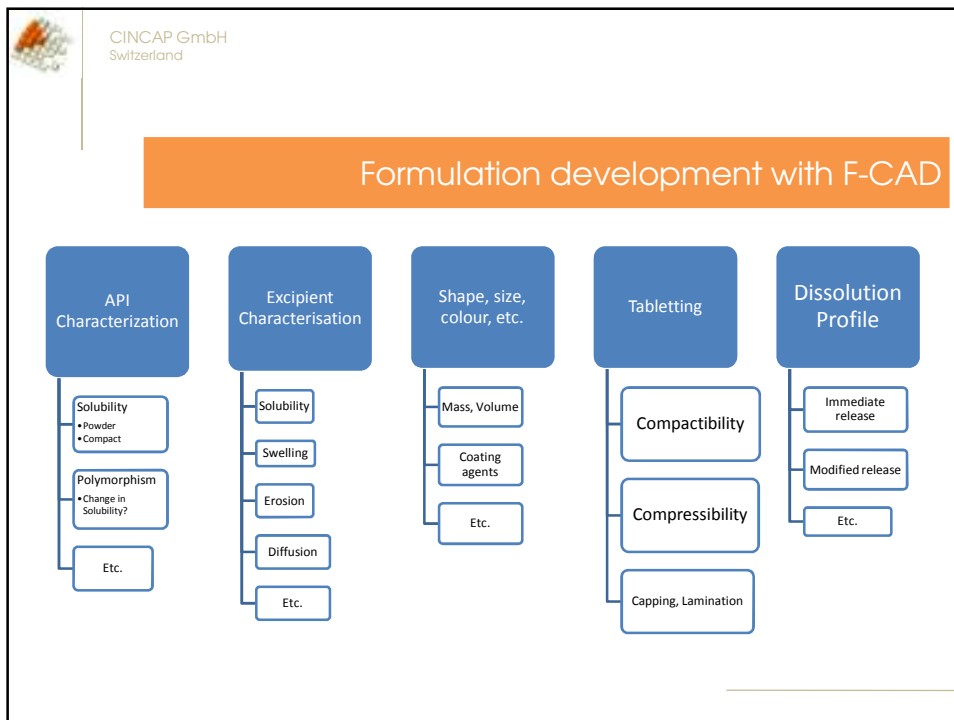
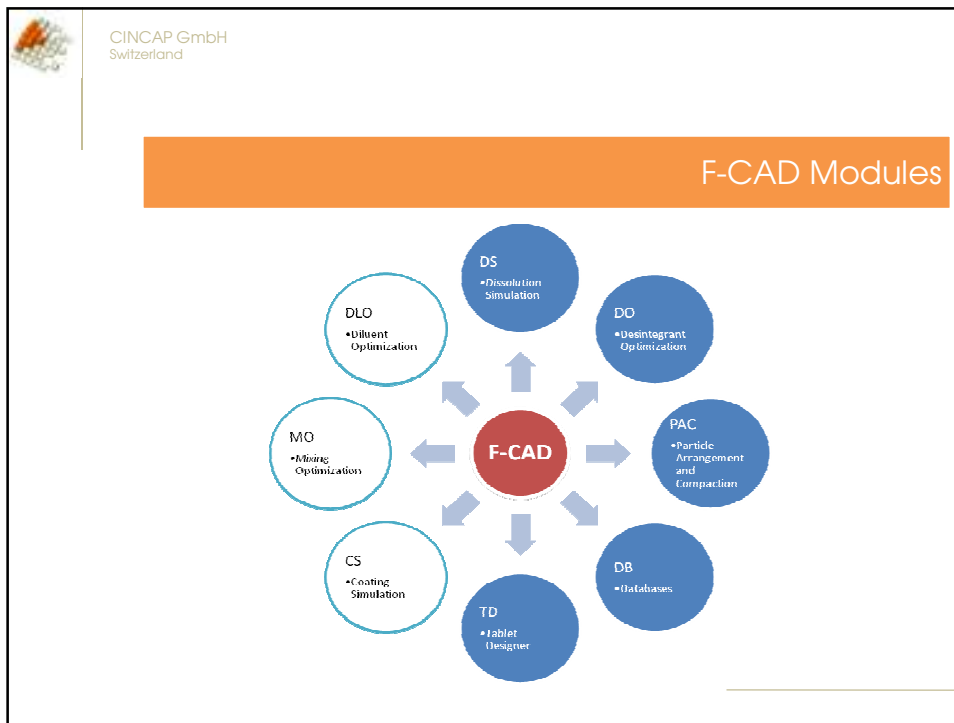
- » Significant **costs reduction** in pharmaceutical R&D
- » **Improved connectivity** between marketing and pharma R&D and production depts.
- » Higher end-product quality – **Quality By Design (QbD)**
- » Knowledge and experience management
- » Unified solution for
 - Immediate and controlled release formulations
 - Support for different unit operations (granulation, milling, etc.)
 - Tablet size and shape design
 - ... and much more.

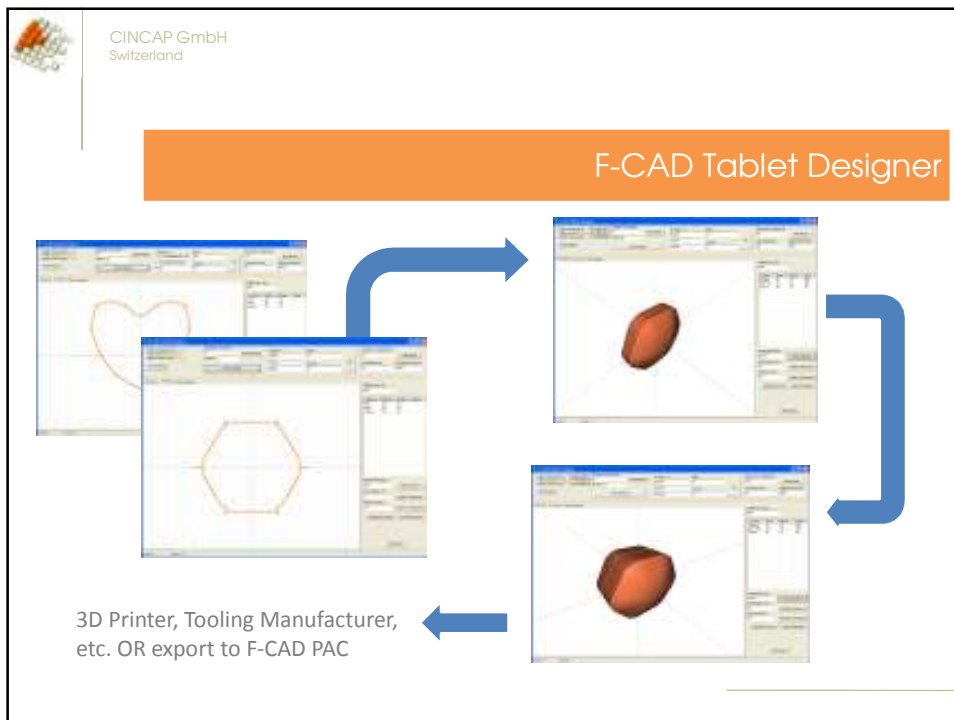
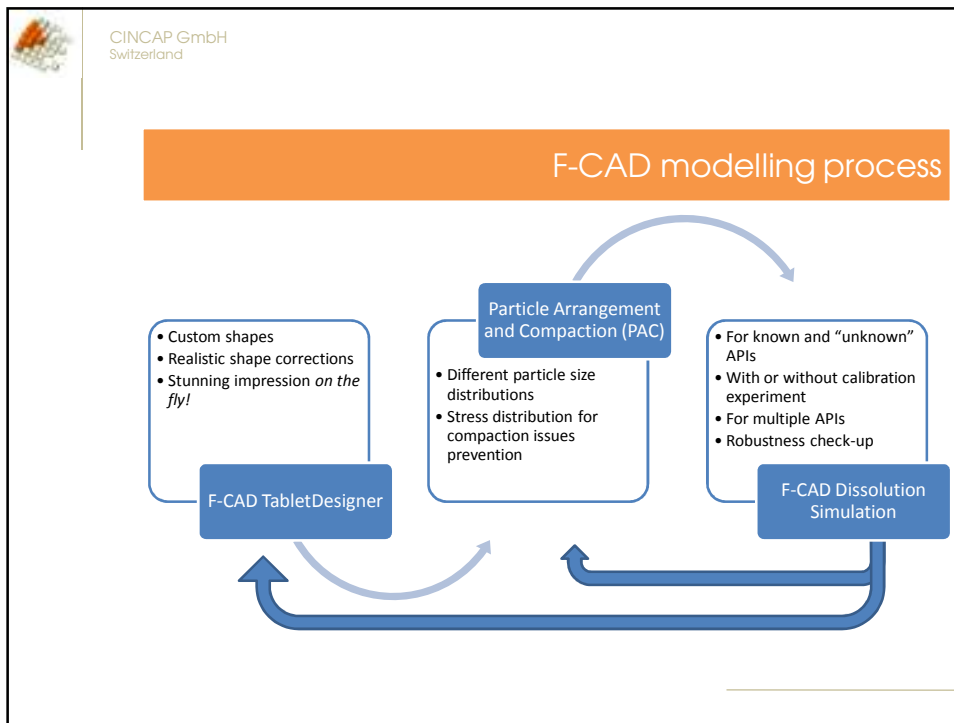


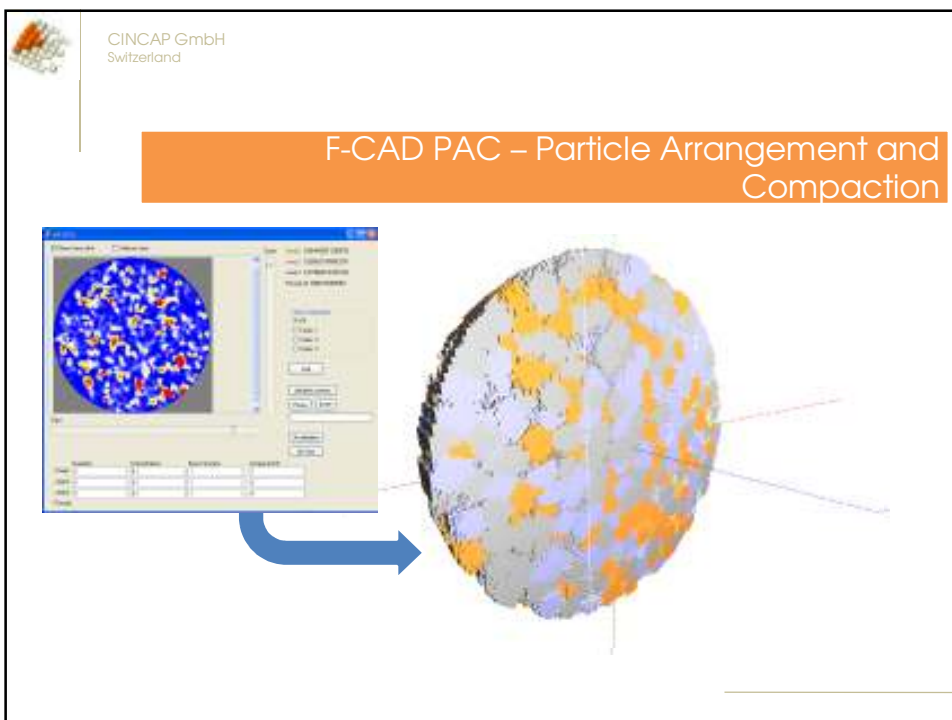
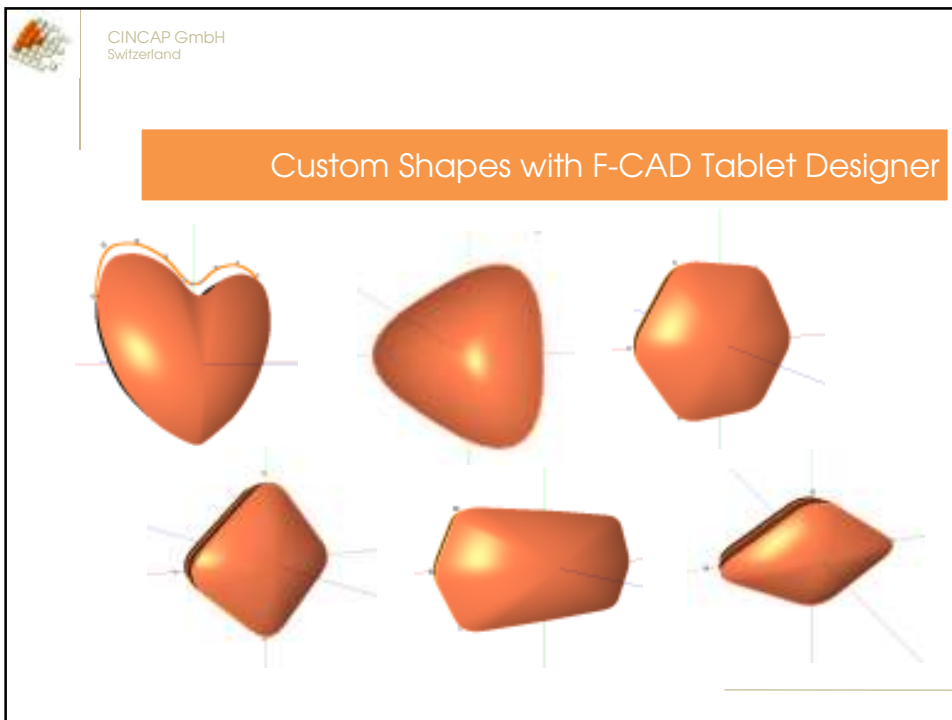
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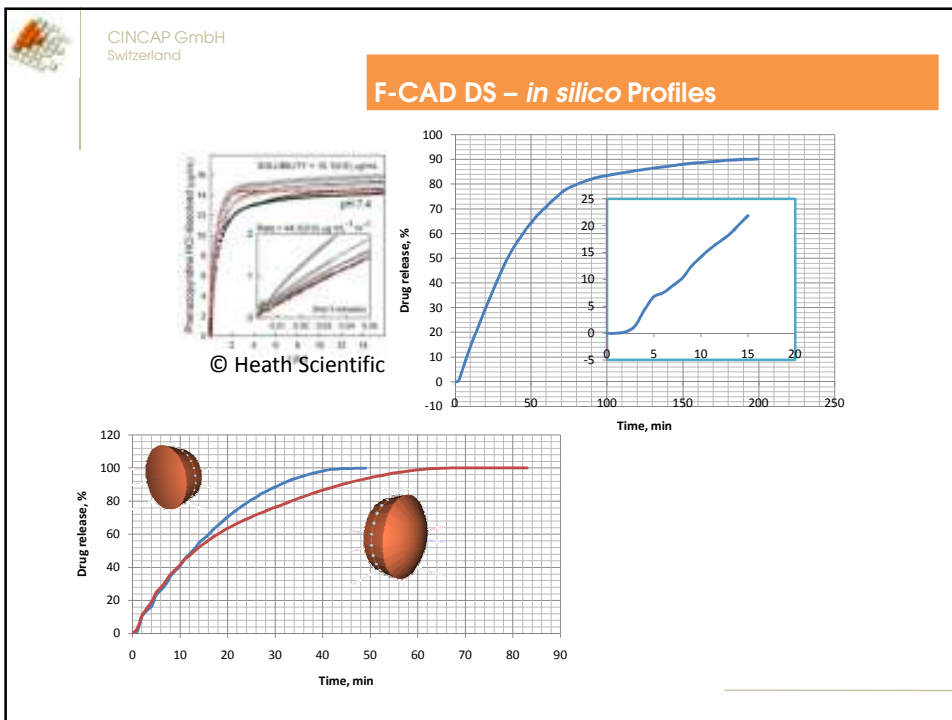
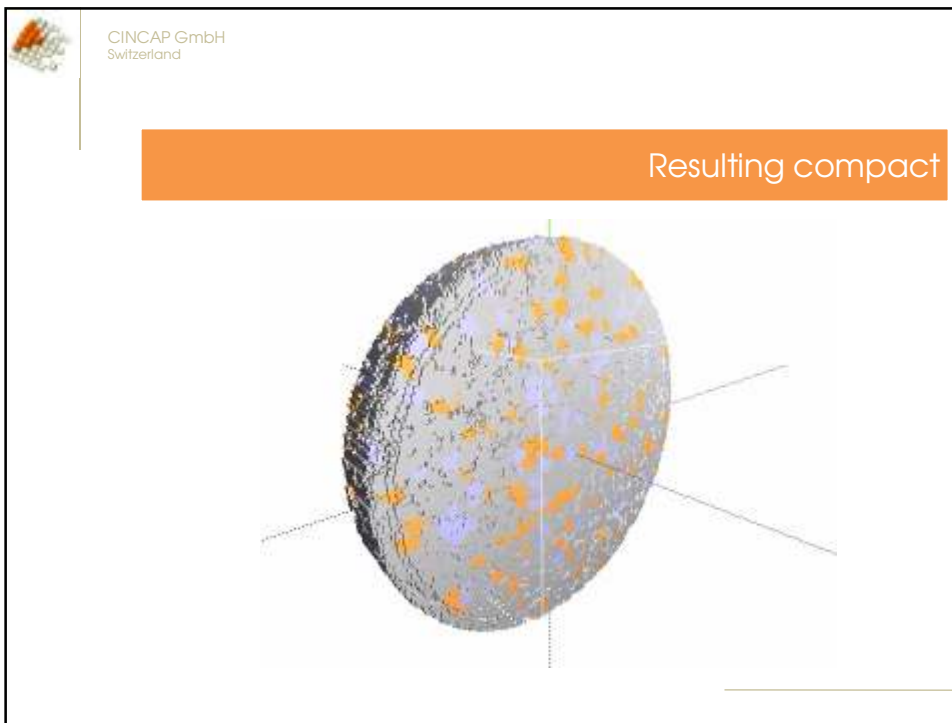
F-CAD Selected Features

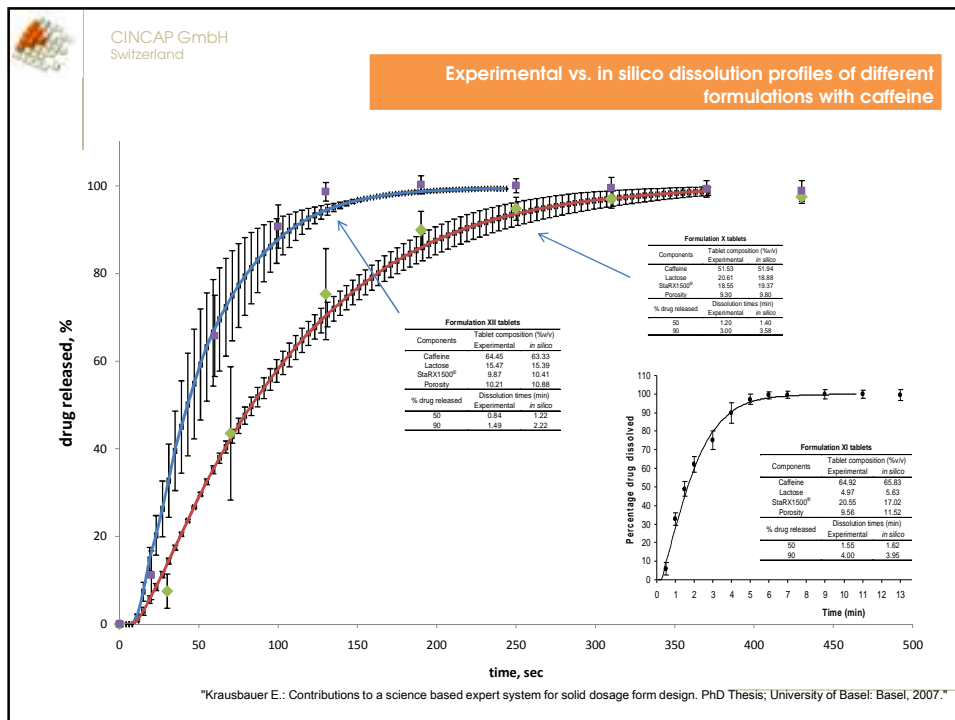
- » Formulation design with F-CAD starts with final-product desired properties, such as shape, dissolution rate, etc.
- » F-CAD is tablet shape sensitive.
 - F-CAD can be used to find out differences in dissolution profiles for different shapes of tablets with identical composition.
- » Different particles 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 Input Data

- » Solubility of all components
- » Particle size distributions of the components
- » Swellability/hydrophobicity of components if applicable
- » Tablet geometry

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F-CAD and VES Screenshots

The image displays four distinct elements related to pharmaceutical simulation and equipment:

- A software window showing a graph with a curve, likely representing a process parameter over time.
- A 3D visualization of a heart-shaped object, possibly a tablet or a specific component.
- A circular visualization showing a distribution of particles or data points.
- A photograph of a physical 'MiniGlyt simulator' piece of equipment, which includes a control panel with buttons and a digital display, a vertical stainless steel mixing column, and a weighing scale.

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Orientation: Quality by Design (QbD)

Formulation R&D


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

Production

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


**F-CAD
Robust
Formulation!**

**VES
Operator
Training**

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Virtual Equipment Simulators (VES) in order to reduce human failures


- » What do you do for a continuous training and education of your production floor operators in order to improve process quality?
- » What happens when you start to use new equipment?
- » What do you do if your collaborators feel frustrated using the operation manual?
- » How to train your personnel to correctly respond to critical situations without putting at risk the quality of your product?
- » How to fulfil the requirements of continuous education as requested by authorities such as FDA, etc?

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What are VES?

- » VES are modeling process's behavior, its form and visual appearance.
- » "... like a flight simulator?"
- » **Comparable to the effectiveness of flight simulator to pilot training!**






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VES Includes

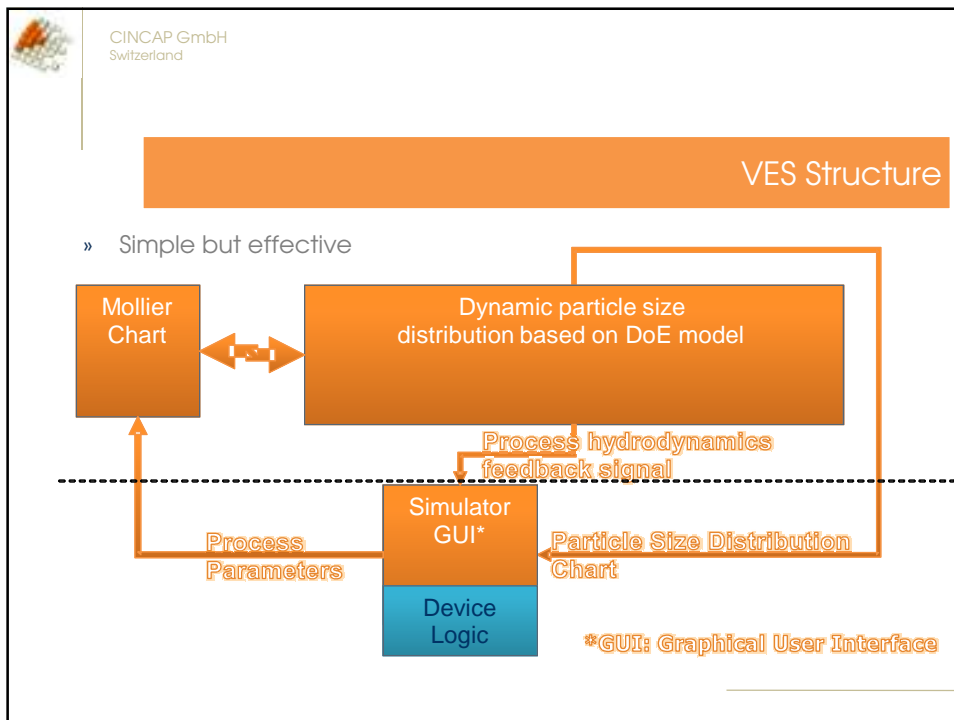
- » Real interactive animation → i.e. reproducing visual appearance
- » Process Simulation with wider range of possible situations, allowing prediction and exploratory learning
- » Strong mechanistic model for 1:1 process description



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Virtual Equipment Simulators (VES)

- » VES is an ideal tool to get a better process understanding (Process Analytical Technology)
- » VES is an ideal tool to explore the limits of the process without putting to danger operators and product
- » VES is an ideal tool for training especially to reduce human failures during real operation
- » VES can be used in case of small and large equipment



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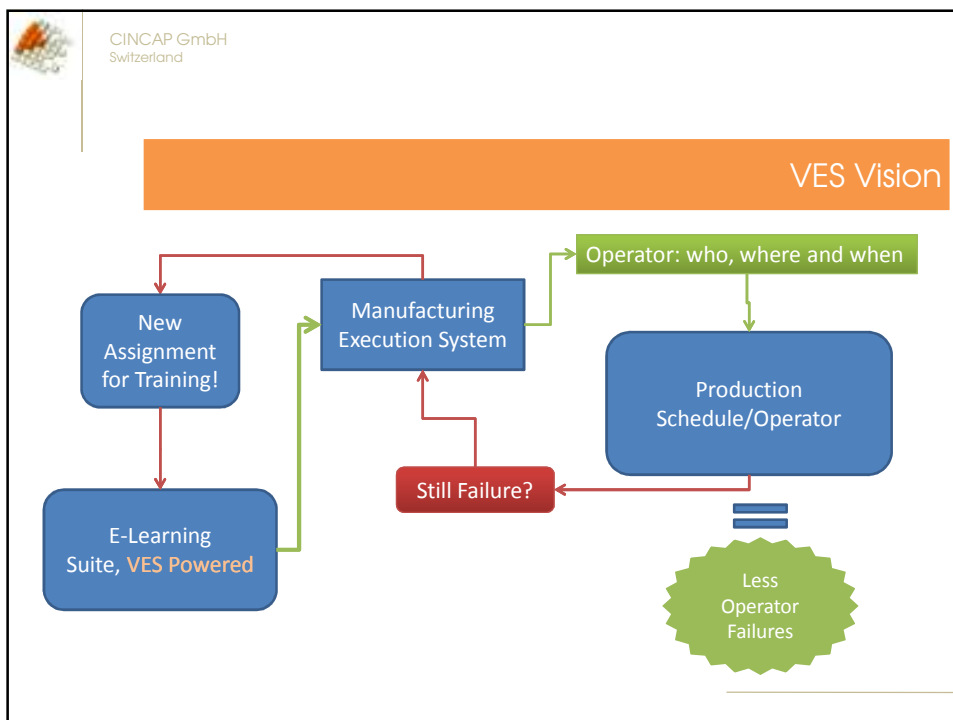
VES, is it only for Fluid Beds?


» Answer:

NO!

» Any type of machinery:

- Coating pans
- Mixers, Blenders
- Tablet Presses
- Capsule Fillers
- Etc.
- Laboratory equipment:
 - Assays
 - HPLC, Mass specs, etc...






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Virtual Equipment Simulators (VES) Advantages

- » Personnel training
 - Possibility of real personalized individual training
 - Self-identifying weaknesses and improving skills
 - Personalized “learning path”
- » Business perspective
 - Reducing human errors
 - Better process understanding leading to a higher quality
 - Facilitated troubleshooting with equipment vendor




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Conclusions

In silico design endeavours are likely to be expected due to the power of informatics in the areas:

- » **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

These conclusions are in agreement with the concepts described in: “Pharma 2020: The vision. Which path will you take?*”
PricewaterhouseCoopers (www.pwc.com/pharma)



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Thank you for your attention!

Audience Q&A
