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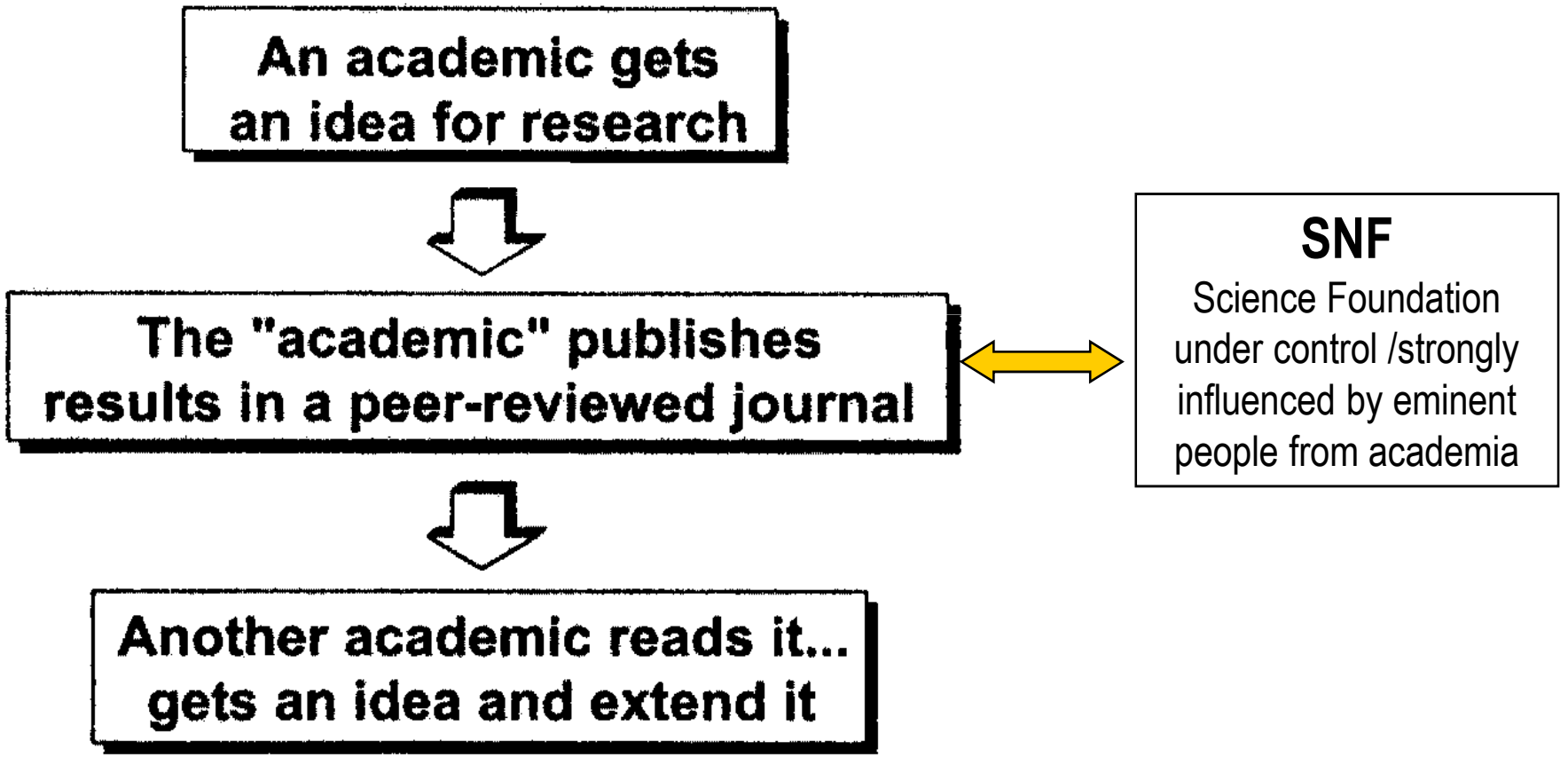
www.PharmTech.unibas.ch

# The signification of FDA's PAT initiative for Academia

Hans Leuenberger

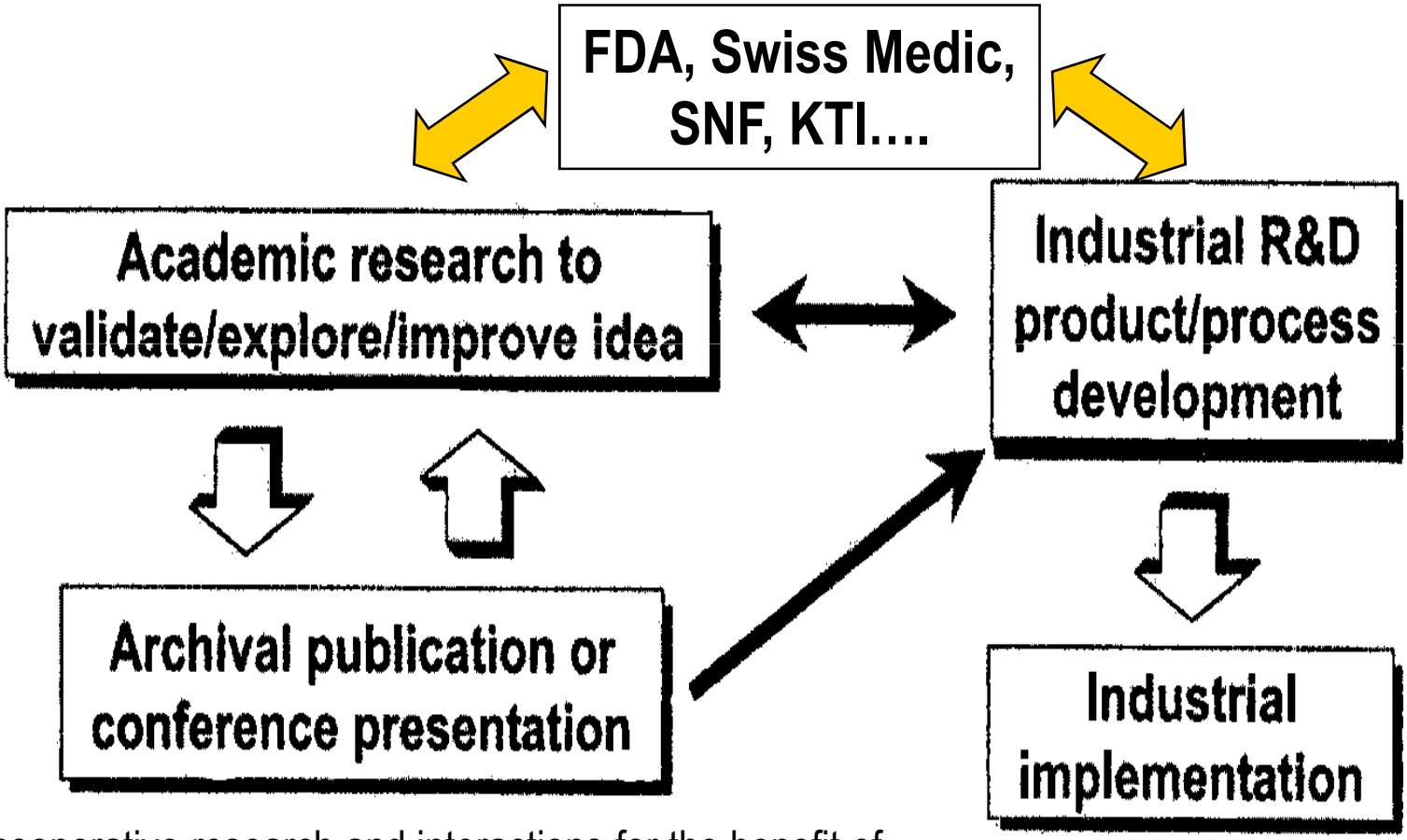
Institute of Pharmaceutical Technology
Pharmacenter of the University Klingelbergstrasse 50
CH-4056 Basel
Switzerland

# The role of academia I (wide-spread-model)




A "closed-loop" model of academic research

# The role of academia II




Model of cooperative research and interactions for the benefit of patients (policy of the Institute of Pharm. Technology of the University of Basel)

# Research and Teaching Policy

**at the Institute of Pharmaceutical Technology**

- Problem oriented, derived from needs.
  (Applied and Basic Research):
- Themes, Projects in Research and Teaching can easily be linked to FDA‘s PAT Initiative and to the Risk based assessment of GMP inspections.
- Close Cooperation with the Industry
  (Pharma, Equipment Manufacturers) and FDA.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# Clean Room in the Pharmacenter

for Research & Teaching in Pharmaceutical Technology (Sterile Dosage Forms)

# FDA`s PAT Initiative

FDA pushes forward the Process Analytical Technology Initiative
www.fda.gov/cder/OPS/PAT.htm

for very good reasons:

- To be competitive with other industries the variability of pharmaceutical processes needs to be reduced!

# The SIGMA Concept I

**FDA pushes forward the PAT Initiative for very good reasons:**

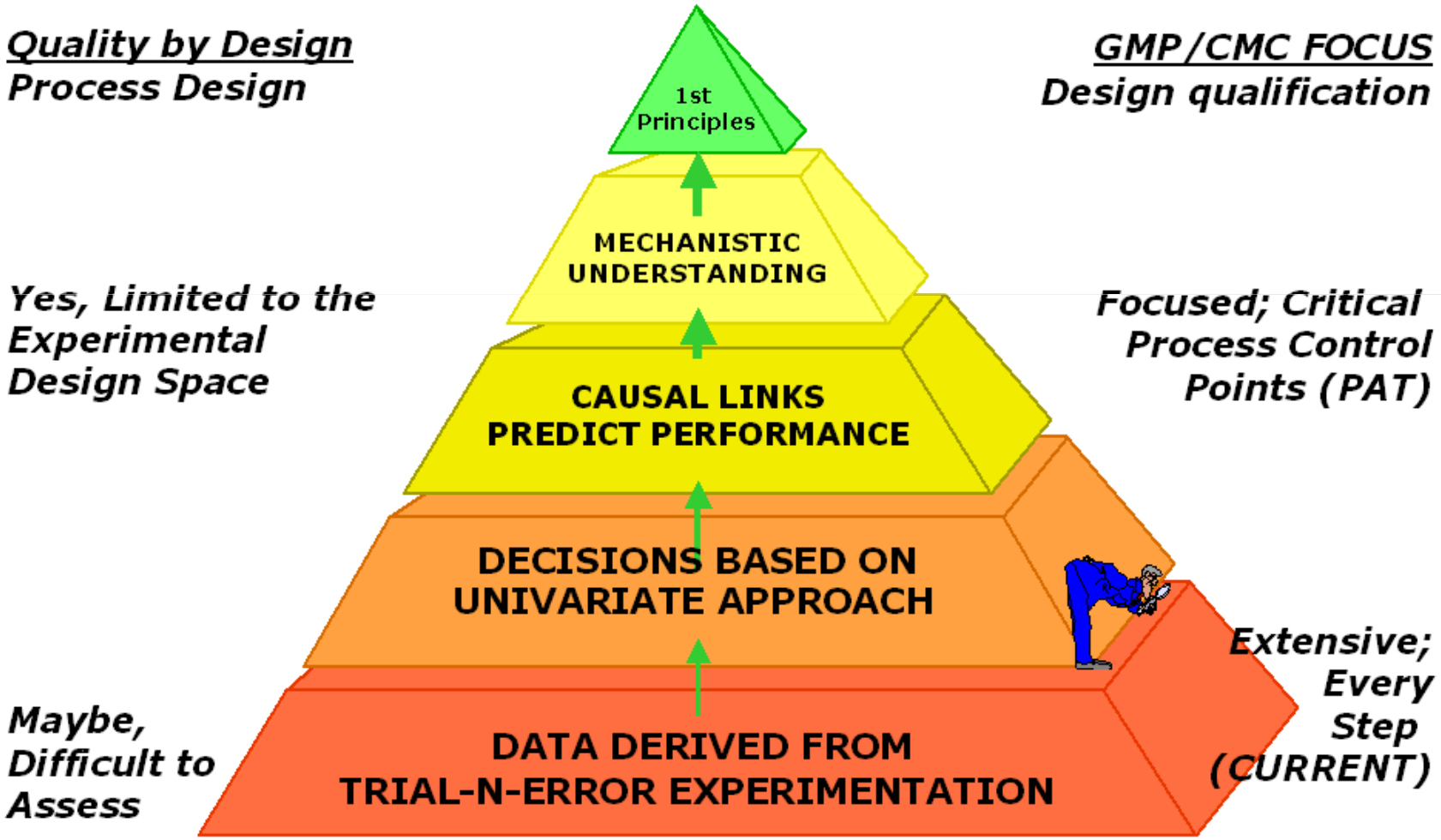
- The variability of most pharmaceutical processes needs to be reduced.
- The performance of a process can be described by its Sigma value.

# The SIGMA Concept II

- The champion is the chip industry with a six Sigma manufacturing performance
  - i.e. with an amount of defective samples ≤ 2 ppb.

- The performance of the pharma-ceutical industry is around 2 Sigma
  (≤ 4.6 % defectives).
  ("static" values)

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



# Beyond PAT:

**“Innovation or Stagnation” –**
**FDA Whitepaper March 2004 :**

- We need superior development science to address these challenges - to ensure that basic discoveries turn into new and better medical treatments.
- We need to make the effort required to create better tools for developing medical technologies.

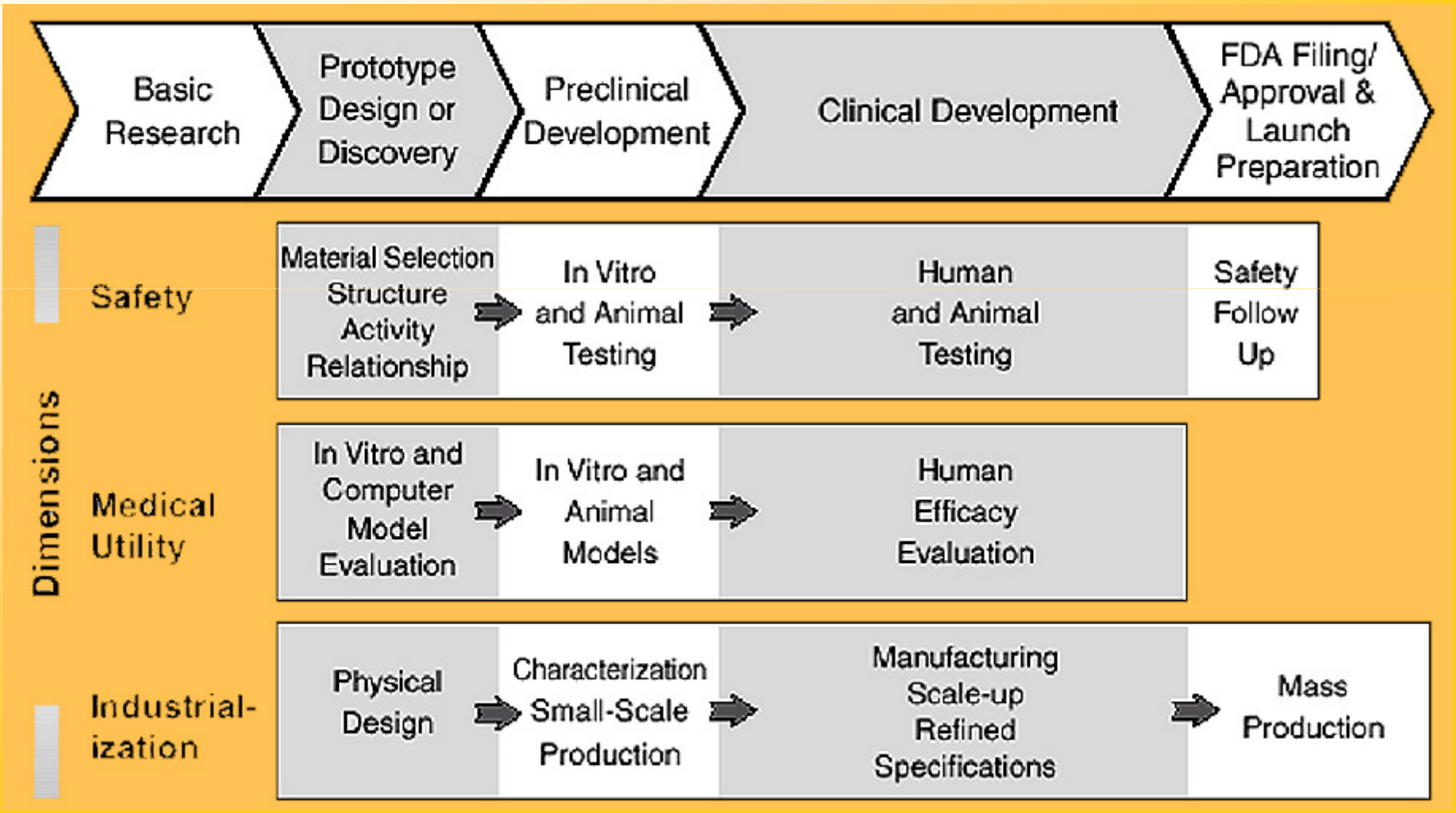
# FDA Whitepaper March 2004

- The medical product development process is no longer able to keep pace with basic scientific innovation.
- Only a concerted effort to apply the new biomedical science to medical product development will succeed in modernizing the critical path.

# FDA Whitepaper March 2004:
# Three Dimensions of the Critical Path

| | | |
|---|---|---|
| **Assessing Safety** | **Show that product is adequately safe for each stage of development** | • **Preclinical: product safe enough for early human testing Eliminate products with safety problems early**<br>• **Clinical: show that product is safe enough for commercial distribution** |
| **Demon-strating Medical Utility** | **Show that the product benefits people** | • **Preclinical: Select appropriate design (devices) or candidate (drugs) with high probability of effectiveness**<br>• **Clinical: Show effectiveness in people** |
| **Industria-lization** | **Go from lab concept or prototype to manufactura ble product** | • **Design a high-quality product**<br>- Physical design/Characterization/Specifications<br>• **Develop mass production capacity**<br>- Manufacturing scale-up/Quality control |

# FDA Whitepaper March 2004
# Three Dimensions of the Critical Path



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# Presentation of Selected Research Activities at the Institute of Pharmaceutical Technology

For more details:

Publication list and Annual Report of the Institute of Pharmaceutical Technology at

**www.PharmTech.unibas.ch**

# Formulation Research

- In the following typical examples of critical issues are listed.
- It is evident that the list cannot be a comprehensive one.

# Formulation Research

- The choice of a Capsule or Tablet Formulation for early Clinical Trials (Dose Range Finding):

The choice is often not rational, and based on

1) „marketing“ issues or
2) on the capsule formulation used in early clinical trials, just kept to save „time to market“.

# Formulation Research

**Preformulation Work**

- Due to Dose Range Finding in Early Clinical Studies → low dose and high dose formulations are needed.
- Thus it is necessary to change from a Drug (D/E) in Excipient to an Excipient in Drug Formulation! → Who cares whether it is a D/E – or E/D formulation?

# Formulation Research

**Preformulation Work**

- However it is generally accepted, that the pharmaceutical properties of an O/W Emulsion is very different from a W/O Emulsion!!

# Formulation Research

**Preformulation Work**

- Thus it is surprising that in Solid Dosage Form Design,
- nobody seems to be highly alerted if we change from a Drug in Excipient to an Excipient in Drug Formulation!

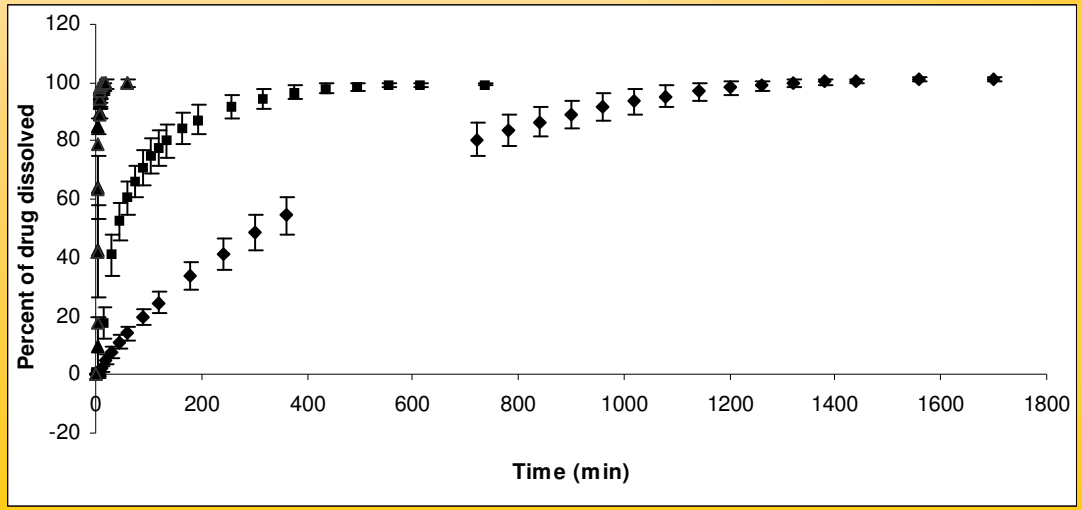
# Formulation Research

## Choice of a Capsule or Tablet Formulation

- Example:
  In case of drug A the following differences in the dissolution behaviour for a capsule and for a tablet formulation as a function of dose was found:

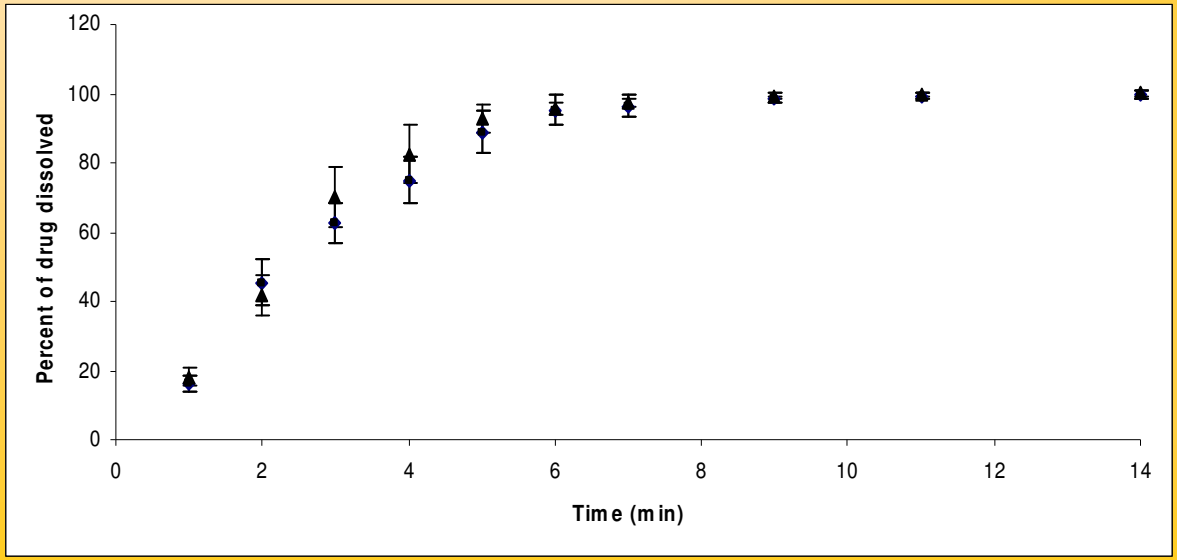
# Drug A: Dissolution rate of capsule formulations

- 10% (w/w), 50% (w/w) and 70% (w/w) of the drug!
- Capsule formulation not robust and sensitive to the drug load (16 mg, 79 mg and 109 mg).
  - 10%(w/w) Drug embedded in hydrophilic excipients,
  - 70%(w/w) excipients embedded in hydrophobic drug!



# Drug A: Dissolution rate of tablet formulations

Drug A: Dissolution rate of tablet formulations containing 50% (w/w) and 70% (w/w) of the drug substance! Tablet formulation is robust and not sensitive to the drug load (77mg, 109 mg).



# Formulation Research

**Conclusion: Keep in Mind the Application of Percolation Theory**

- The Impact of Percolation Theory on the Properties of a Formulation is not yet generally recognized.
- The following slide shows a typical example in case of the preparation of a lactose-corn starch granule formulation.

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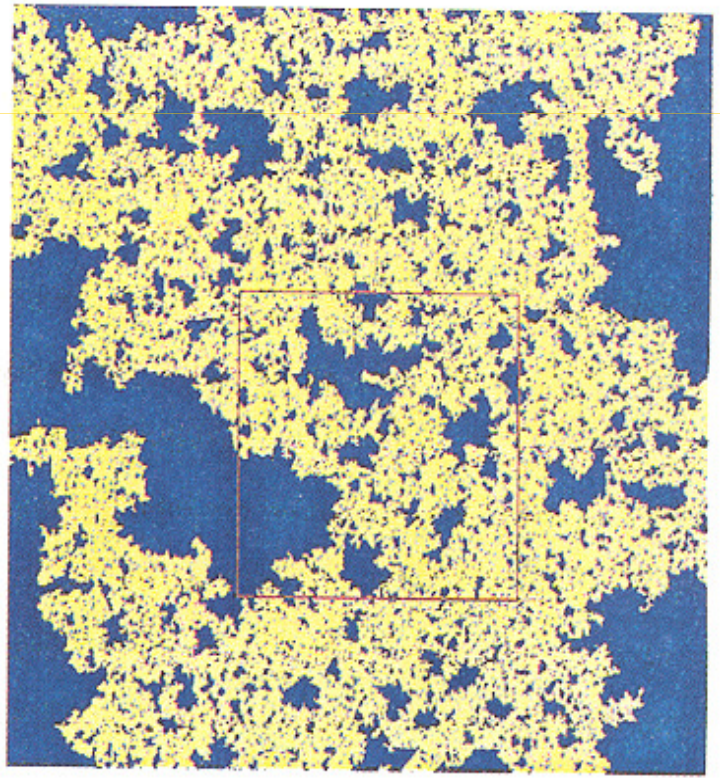
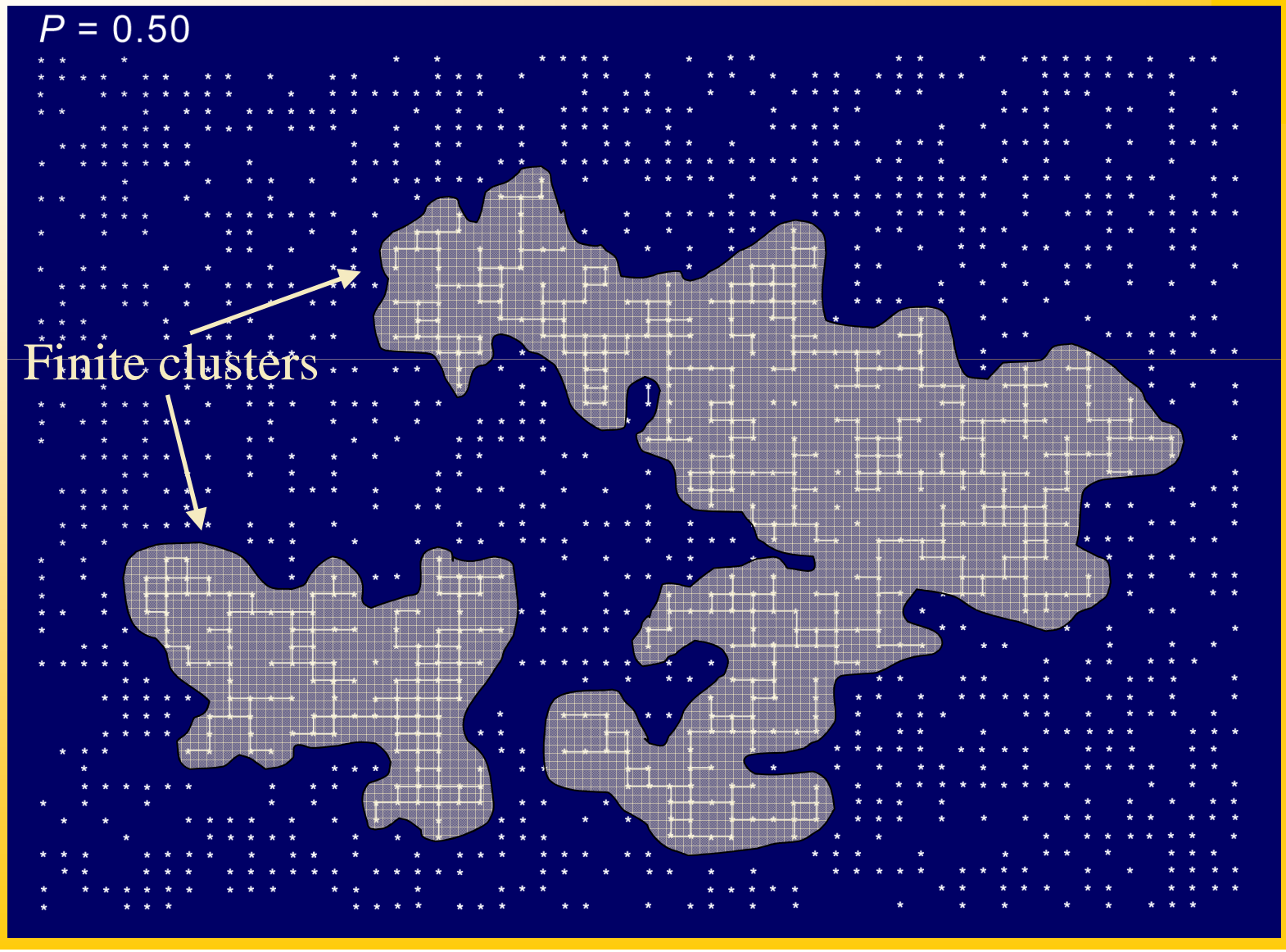
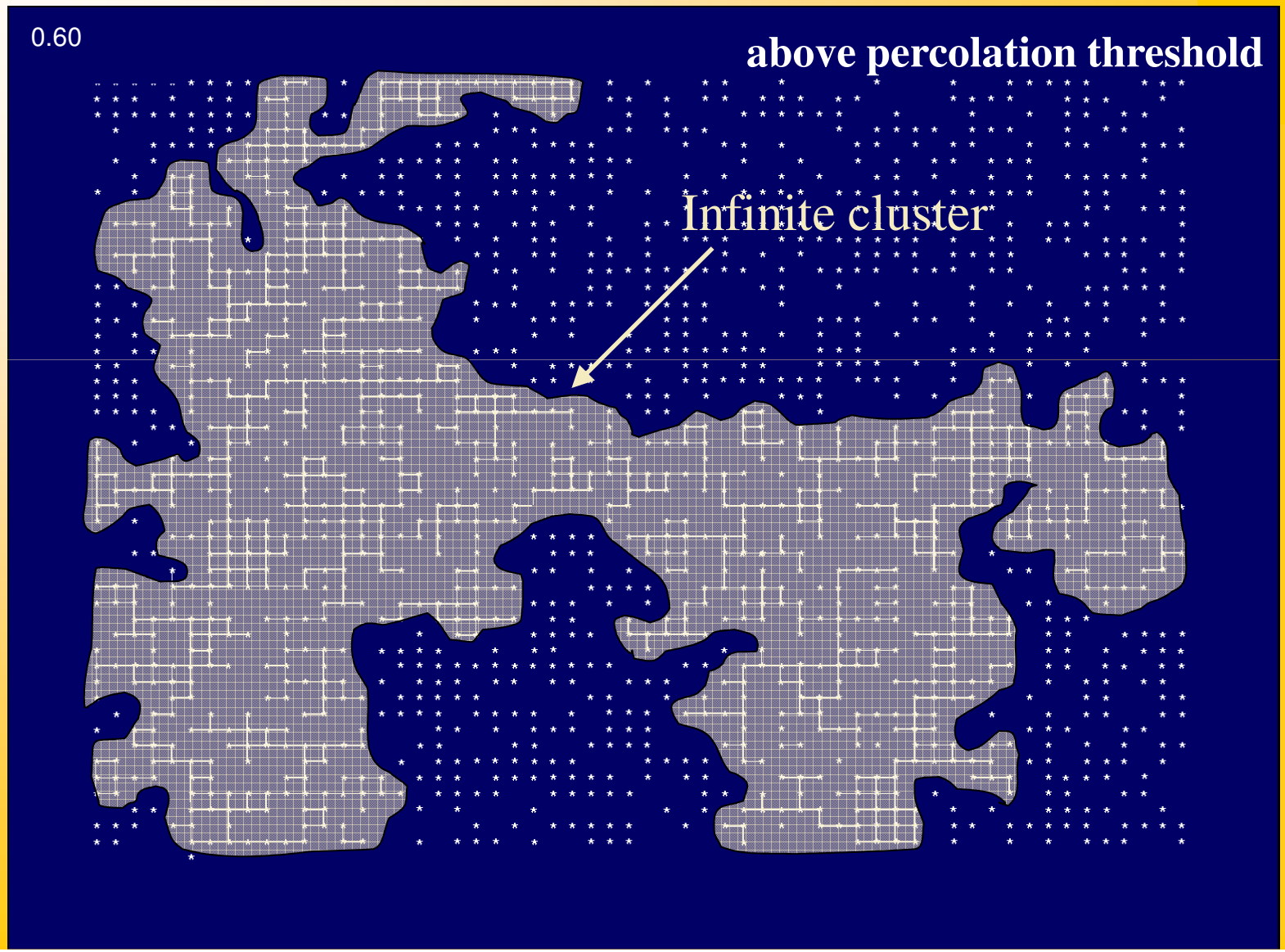
# Percolation Theory and Robust Formulations



# 2-dimensional square lattice occupation probability P = 0.50



# 2-dimensional square lattice occupation probability P = 0.60



# Percolation Theory

- Site occupation probability p with threshold $p_c$
- Basic equation: Property X

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

S = scaling factor

q = critical exponent

# Order in the Chaos!

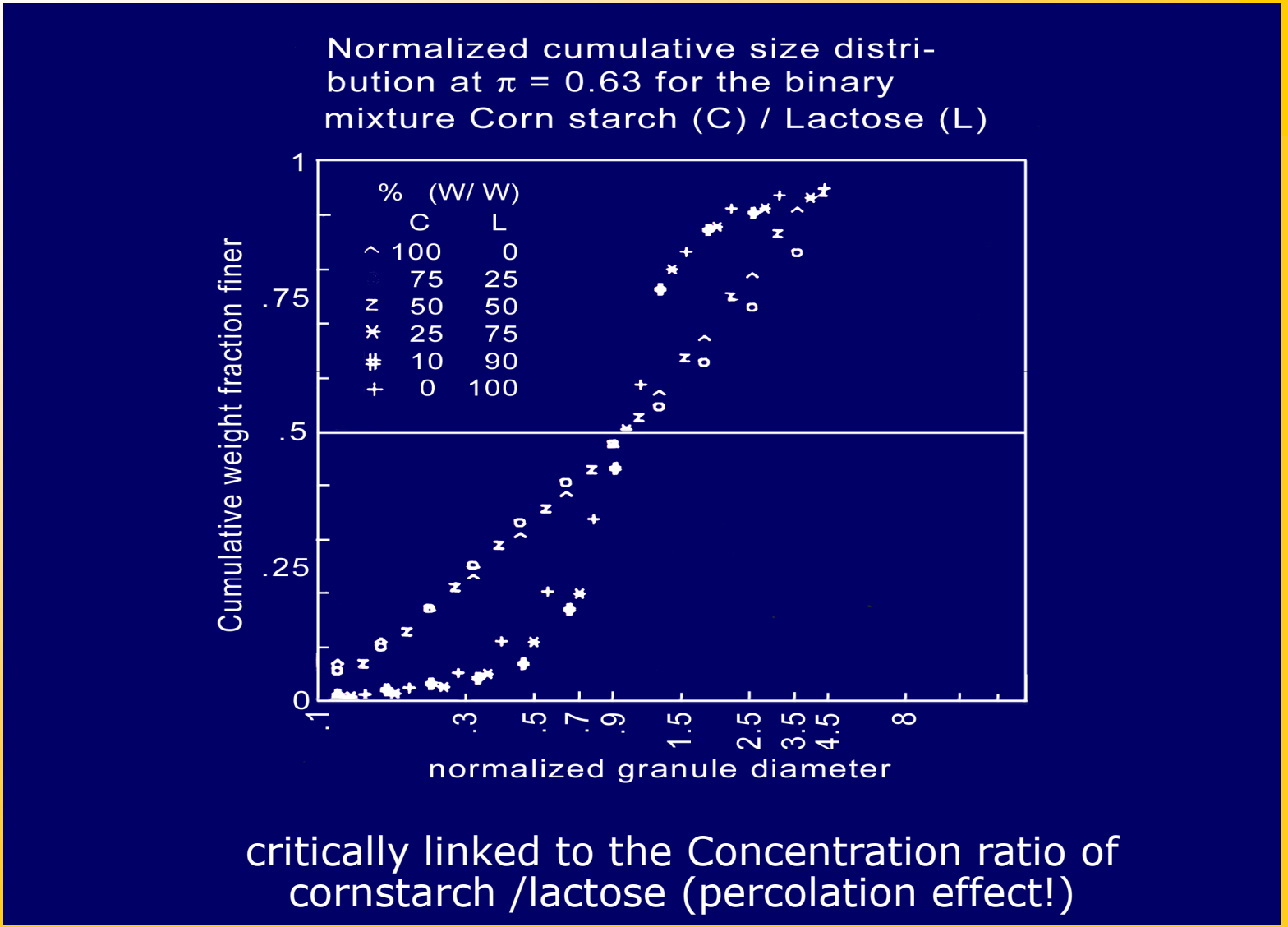
$$X = S\,|p - p_c|^{q}$$

S = scaling factor

q = critical exponent

- The **universal** critical exponent q depends only on the euclidean/fractal dimension of the process!
- $p_c$ is related to the microscopic structure.

# Linear & S-shaped granule size distribution




critically linked to the Concentration ratio of cornstarch /lactose (percolation effect!)

# Identification of critical processes

- In the following typical examples of critical processes are listed.
- It is evident that the list cannot be a comprehensive one.

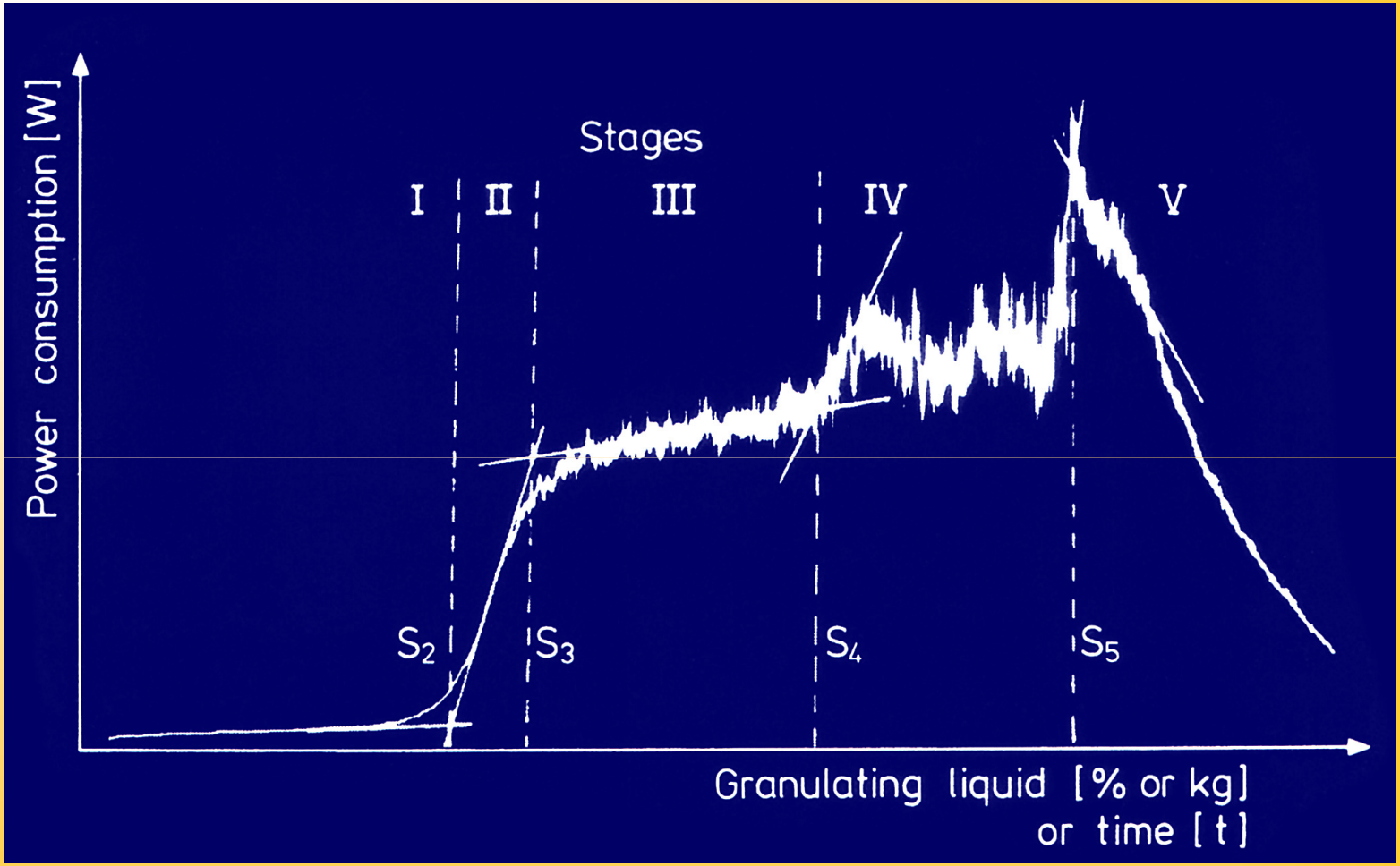
# Identification of critical processes

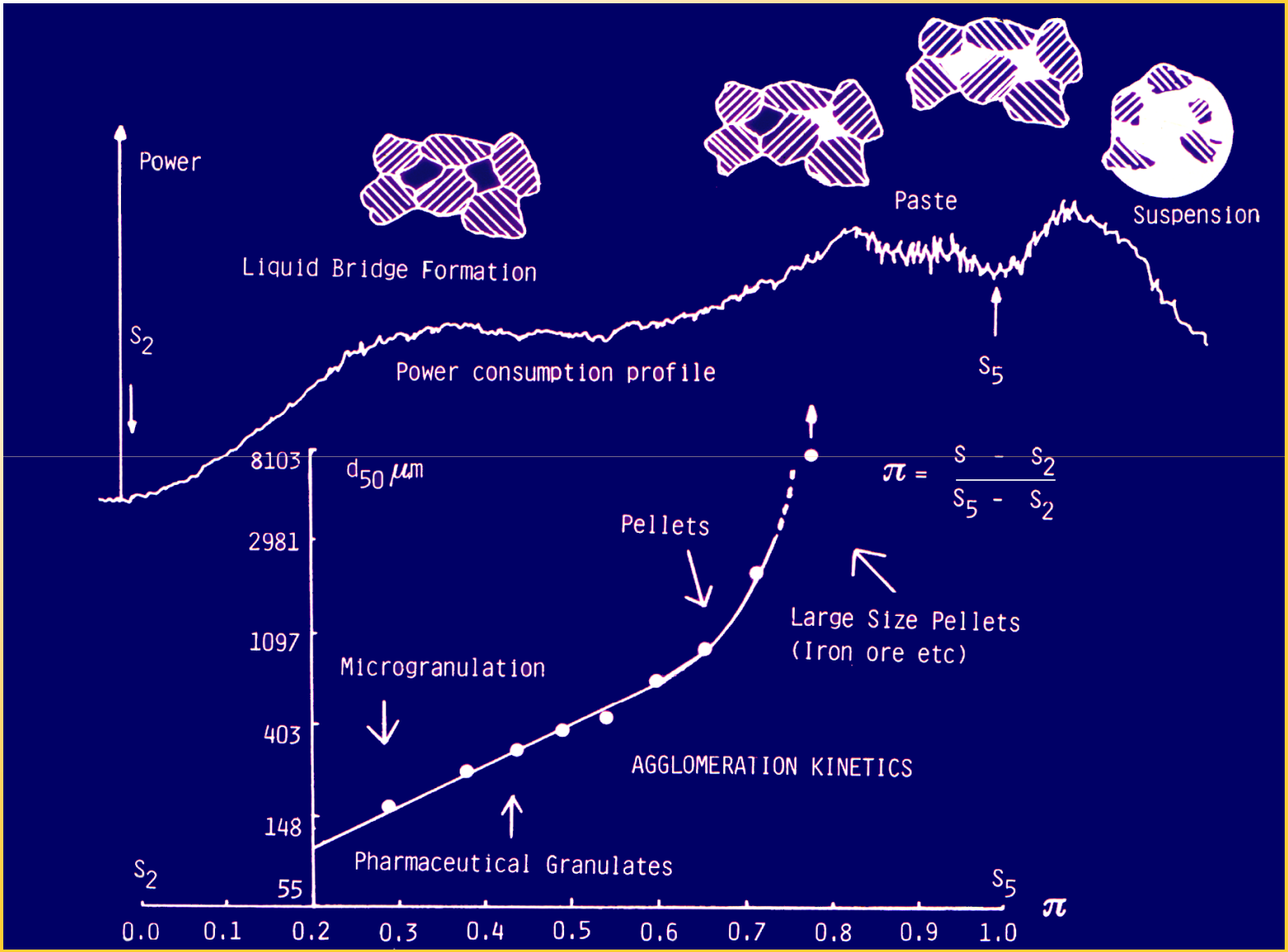
## 1. Wet agglomeration

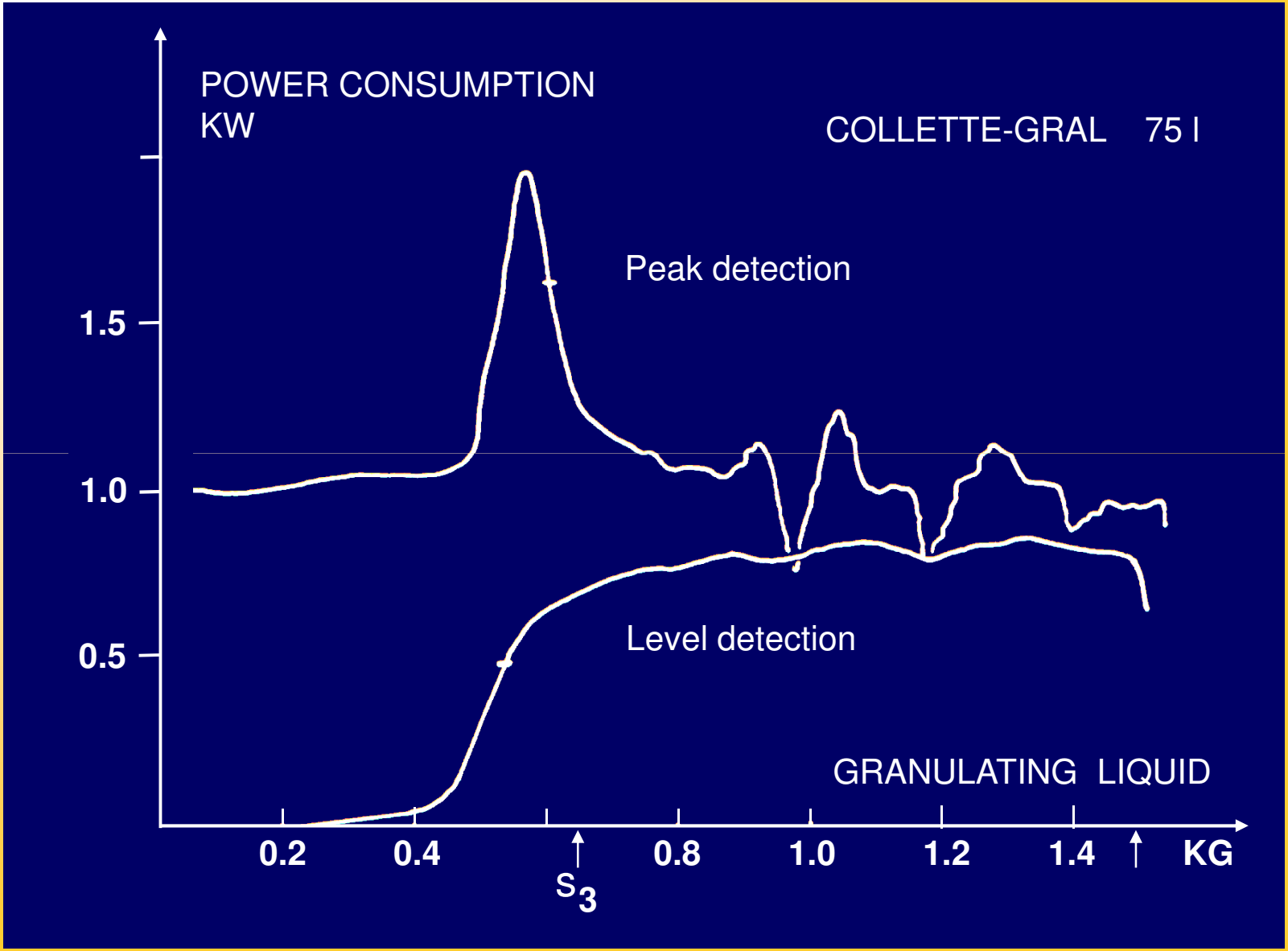
- A problem in the wet agglomeration process is the „endpoint“ or the correct amount of granulating liquid needed.

→ Leuenberger H., New Trends in the Production of Pharm. Granules: The classical batch concept and the problem of scale-up / Batch versus continuous processing.

Eur. J. Pharm. Biopharm. 52(3), 2001, 279-296.


Power consumption [W]
Stages
I
II
III
IV
V
S2
S3
S4
S5
Granulating liquid [% or kg]
or time [t]


Power
Liquid Bridge Formation
Paste
Suspension
$S_2$
Power consumption profile
$S_5$
8103
$d_{50}\,\mu m$
2981
1097
403
148
55
Pellets
Large Size Pellets
(Iron ore etc)
Microgranulation
AGGLOMERATION KINETICS
Pharmaceutical Granulates
$\pi = \frac{S - S_2}{S_5 - S_2}$
$S_2$
$S_5$
$\pi$
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0


POWER CONSUMPTION
KW
COLLETTE-GRAL 75 l
Peak detection
Level detection
1.5
1.0
0.5
GRANULATING LIQUID
0.2
0.4
0.8
1.0
1.2
1.4
KG
S3

# Wet agglomeration process - manual and automatic mode

| Type of mode | yield (% w/w) 90 - 710 µm | % undersize < 710 µm | undersize < 90 µm |
|---|---|---|---|
| Manual mode n = 20 batches | 81.03 ± 2.42 | 88.30 ± 2.05 | 6.80 ± 0.51 |
| Automatic mode n = 18 batches | 91.45 ± 0.36 | 96.80 ± 0.31 | 5.40 ± 0.35 |

# Identification of critical processes

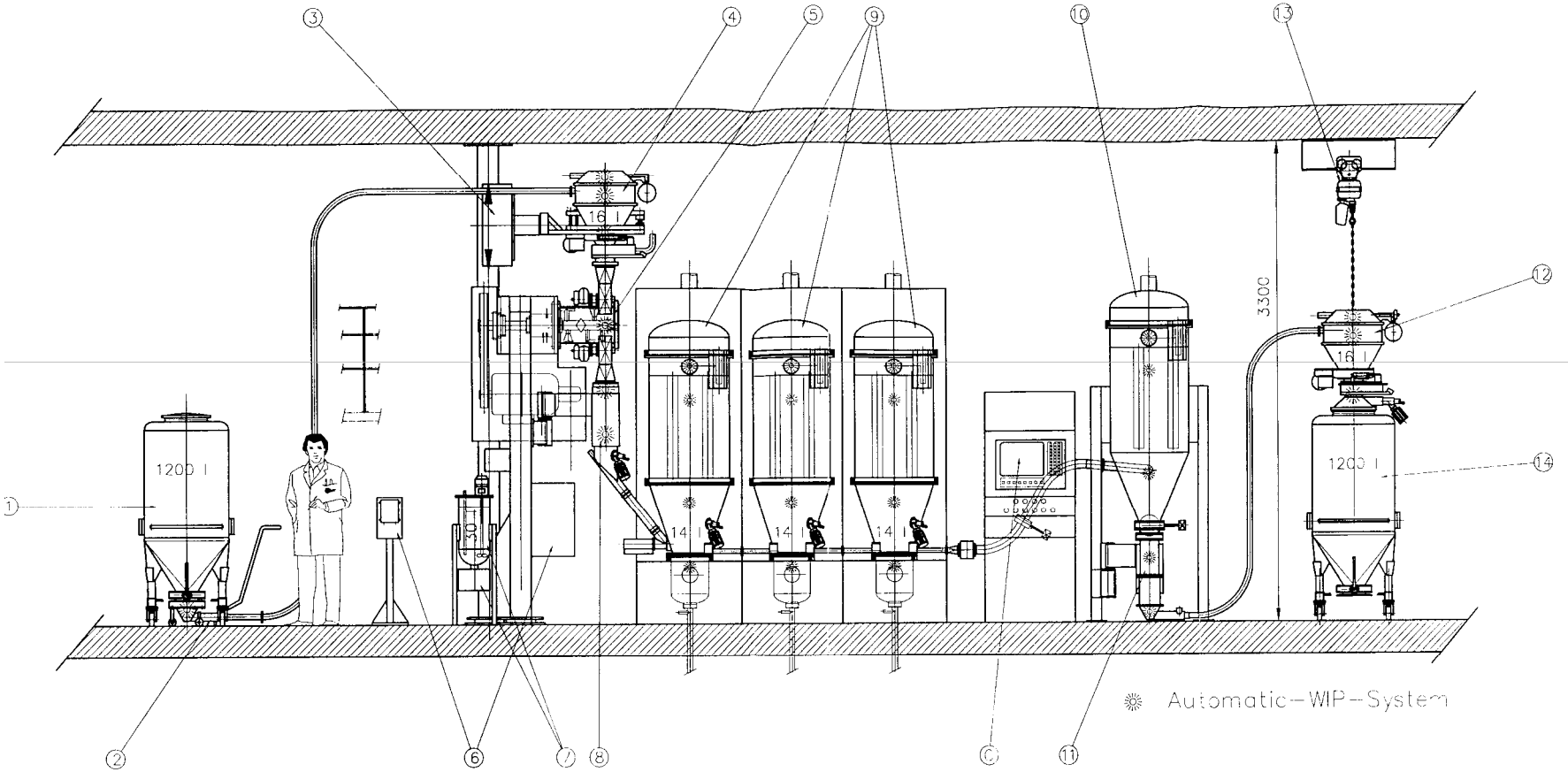
## 2. Scale-up exercise

- the major problem consists in the fact, that the formulation is optimised on a small scale equipment, but is no longer optimal on a large scale equipment.

  →Leuenberger H., New Trends in the Production of Pharm. Granules: The classical batch concept and the problem of scale-up / Batch versus continuous processing.

  Eur. J. Pharm. Biopharm. 52(3), 2001, 279-296.

# How to avoid conventional scale-up




The Glatt® Multicell ™ equipment for small and large batches

# Glatt®
# MULTICELL™

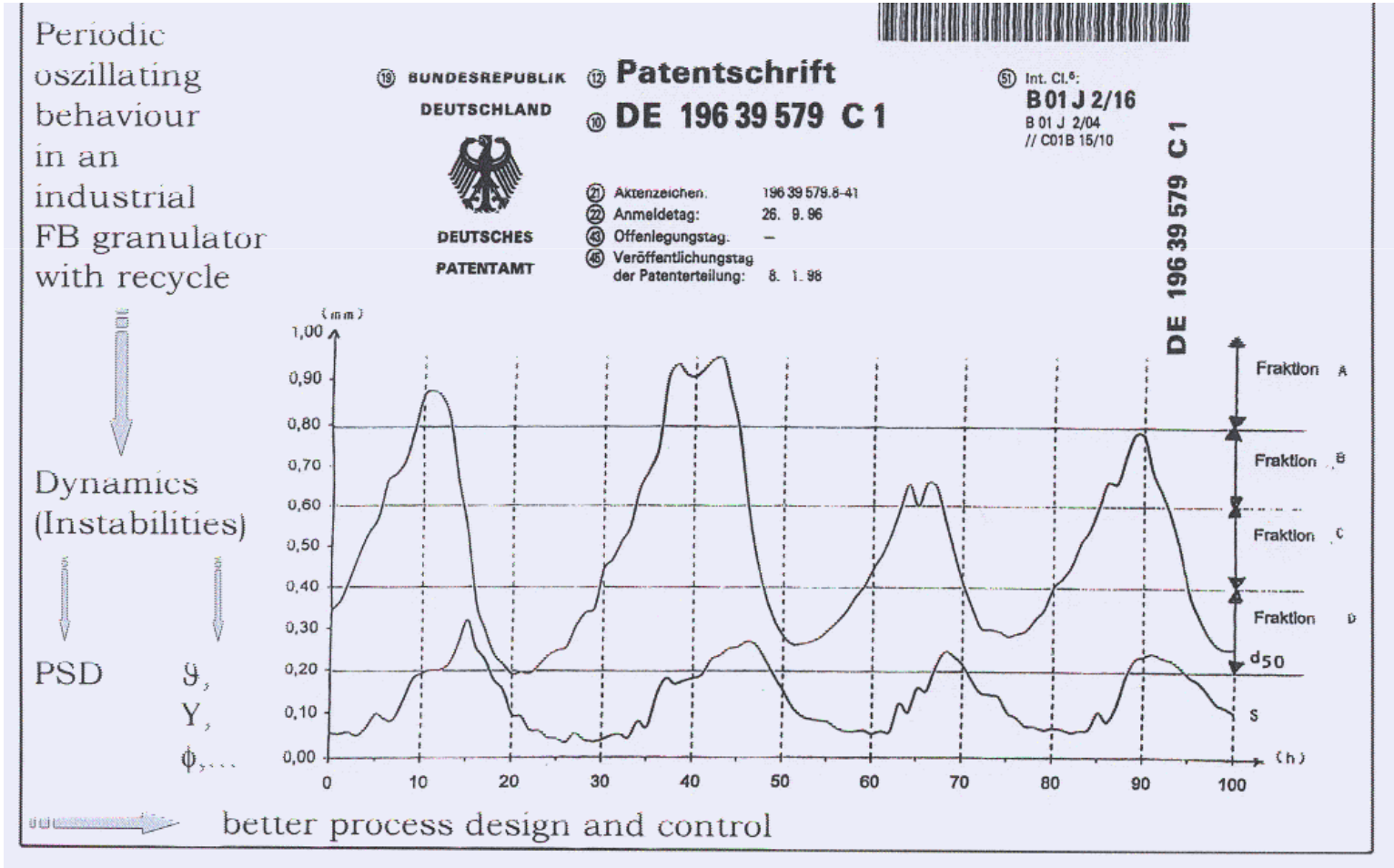
Pfizer - Goedecke

Technology Center

Freiburg, Germany

# Real continuous or preferably a quasi-continuous process?

Problem of a dynamic instability in the real continuous granulation process



# Identification of critical processes

**Scale-up exercise:**

**high speed tabletting machines**

- In case of scale-up concerning the tableting process novel test methods are needed such as the Presster™ equipment, simulating high speed tableting machines, see

  www.mcc-online.com

→ **Effect of Dwell – Time!**

# Identification of critical processes

**3. Classical Lyophilization**

- the major problem:

→ the freezing and lyophilization process of a solution filled in vials is in general far from being robust,

→ creating an important variability from batch to batch but also from vial to vial within a batch.

# Identification of Classical Lyophilisation as a critical process

- The major problem:

→The reason for the high variability is the bad heat transfer between the supporting plate and the vials.

# Atmospheric Spray Freeze Drying as an Alternative

- The idea:

→to avoid the critical freezing step of the classical lyophilisation process by spray freezing of droplets in a cold air stream of –50 °C.

→to dry the frozen droplets in a cold air stream of – 20° C at atmospheric pressure.

# Atmospheric Spray Freeze Drying as an Alternative

- Advantages:

→Process is faster due to the better heat transfer and has a lower variability.

→It is possible to combine the advantages of Nano- and Microtechnology.

.

# Atmospheric Spray Freeze Drying as an Alternative

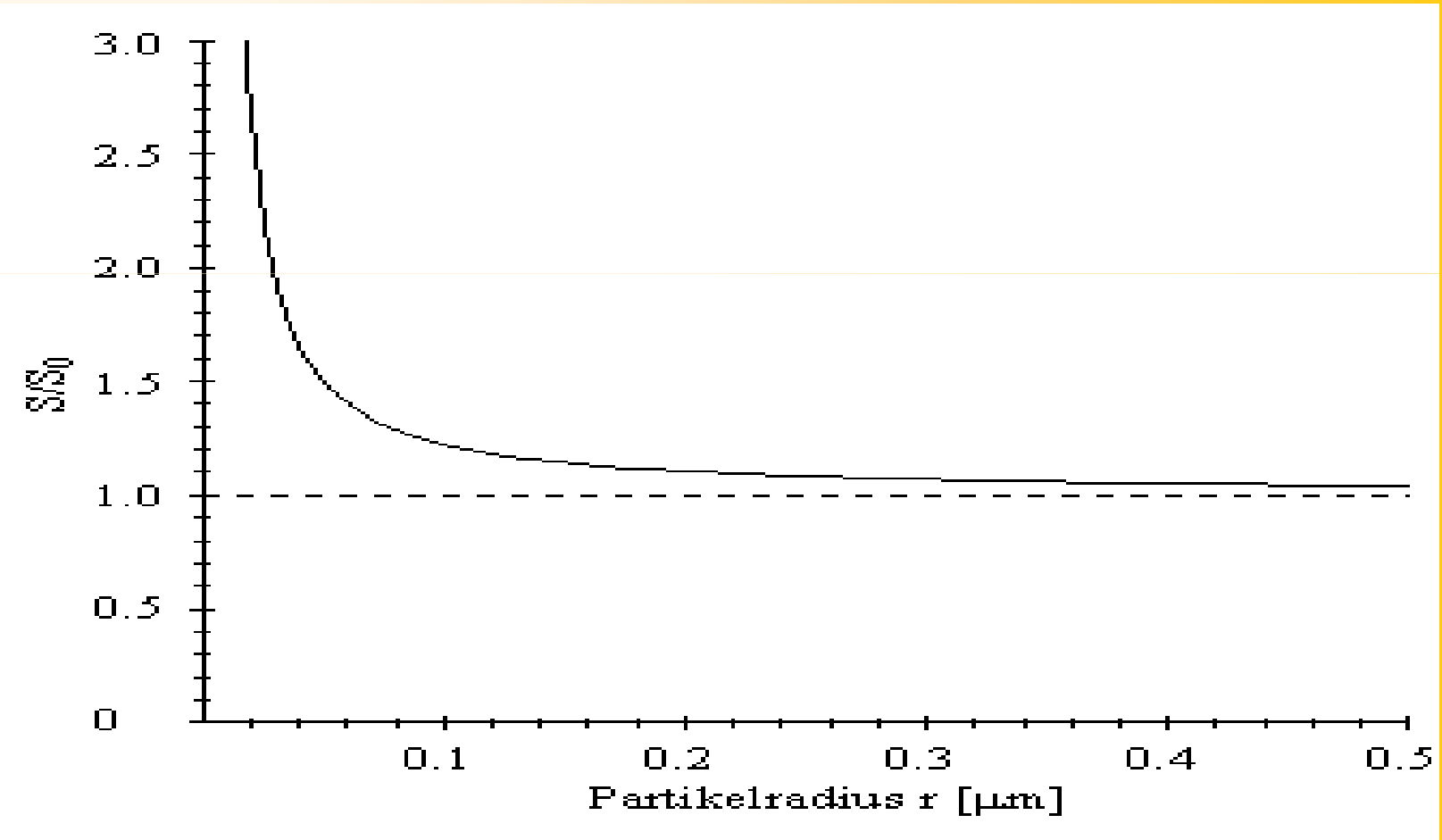
- Advantages:

→ideal for the preparation of nanocomposite pellets for low water soluble drugs to enhance bioavailability of the drug.

→ideal for the formulation of temperature and structure sensitive drugs such as Biologicals i.e. Pharmaproteins such as Interferons, Insulin.

# ***Solubility S*** *of a fine particle*

with radius r < 0.1 µm compared to the Solubility S0 of a large particle with r > 1 µm



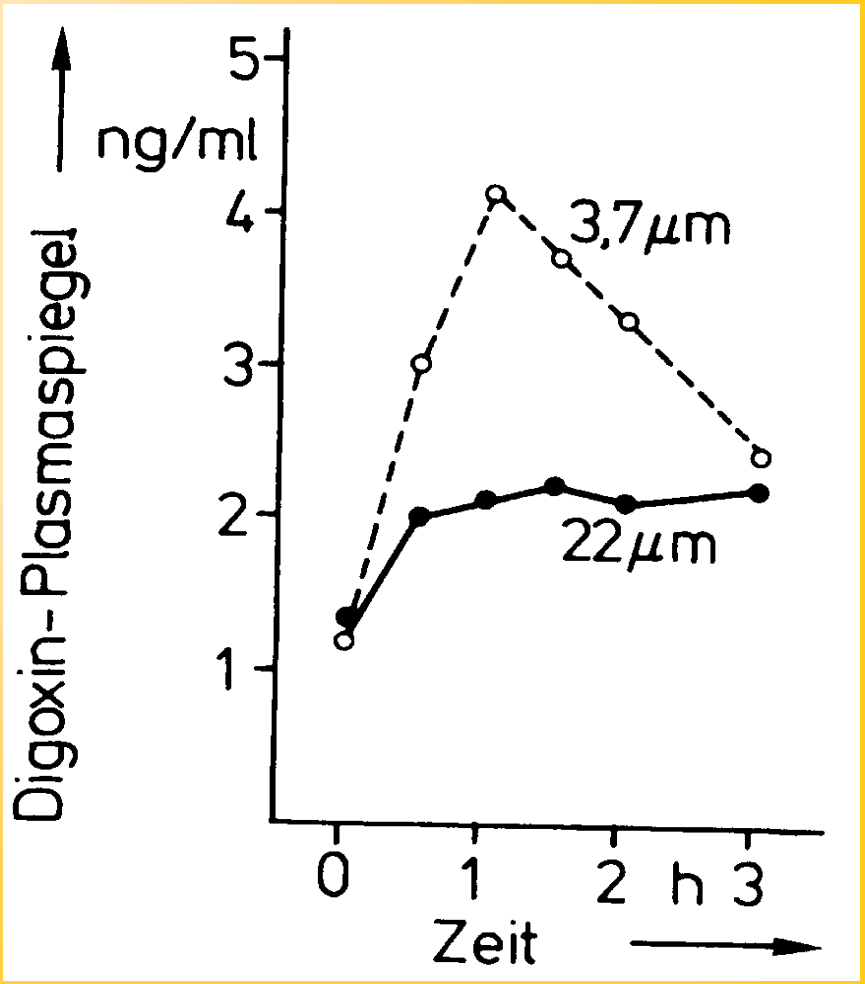
# The Bioavailability of a drug

- The Bioavailability of a drug depends on the size of the drug particles, the solubility and the dissolution rate
- Plasma level of the drug Digoxin as a function of the particle size:

  cmax (3.7 μm) = 4 ng/ml

  cmax ((22 μm ) = 2 ng/ml

  – T.R.D. Shaw, J.E. Careless, Eur.J.Clin.Pharmacol.**7**,269 (1974)



# Solid Solutions/Nanocomposites

- Enhancement of Bioavailability as a function of specific surface Griseofulvin.

**First Nanocomposite!**

(produced as a melt of drug in PEG)

Nature, (1962)
Vol.193, No.4815

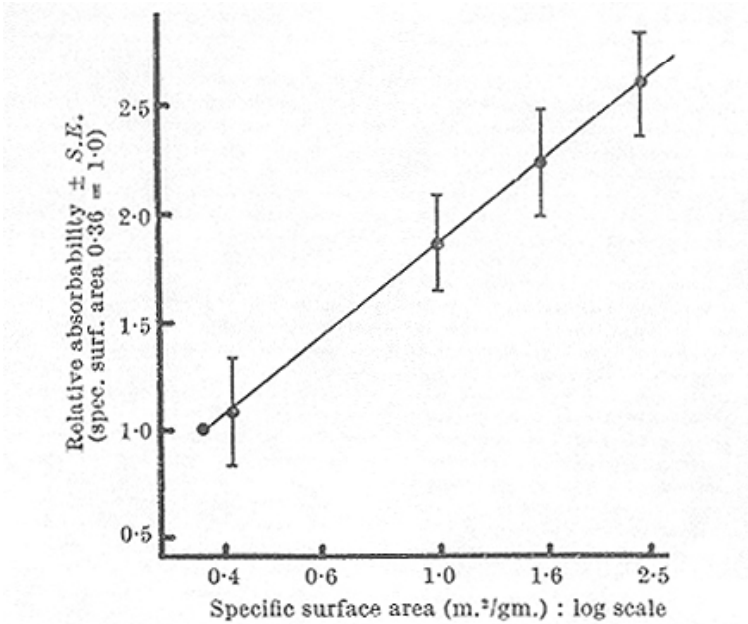



Fig. 1. Regression of relative absorbability of griseofulvin on log specific surface area

# Atmospheric Spray Freeze Drying as an Alternative

- Advantages:

→The result is a highly porous free flowing powder (pellets) with instant solublitiy properties.

→The high porosity of the pellets ( up to 85% ) and the nanostructured internal surface is ideal for the formulation of novel drug delivery systems for the lung.

# Atmospheric Spray Freeze Drying as an Alternative

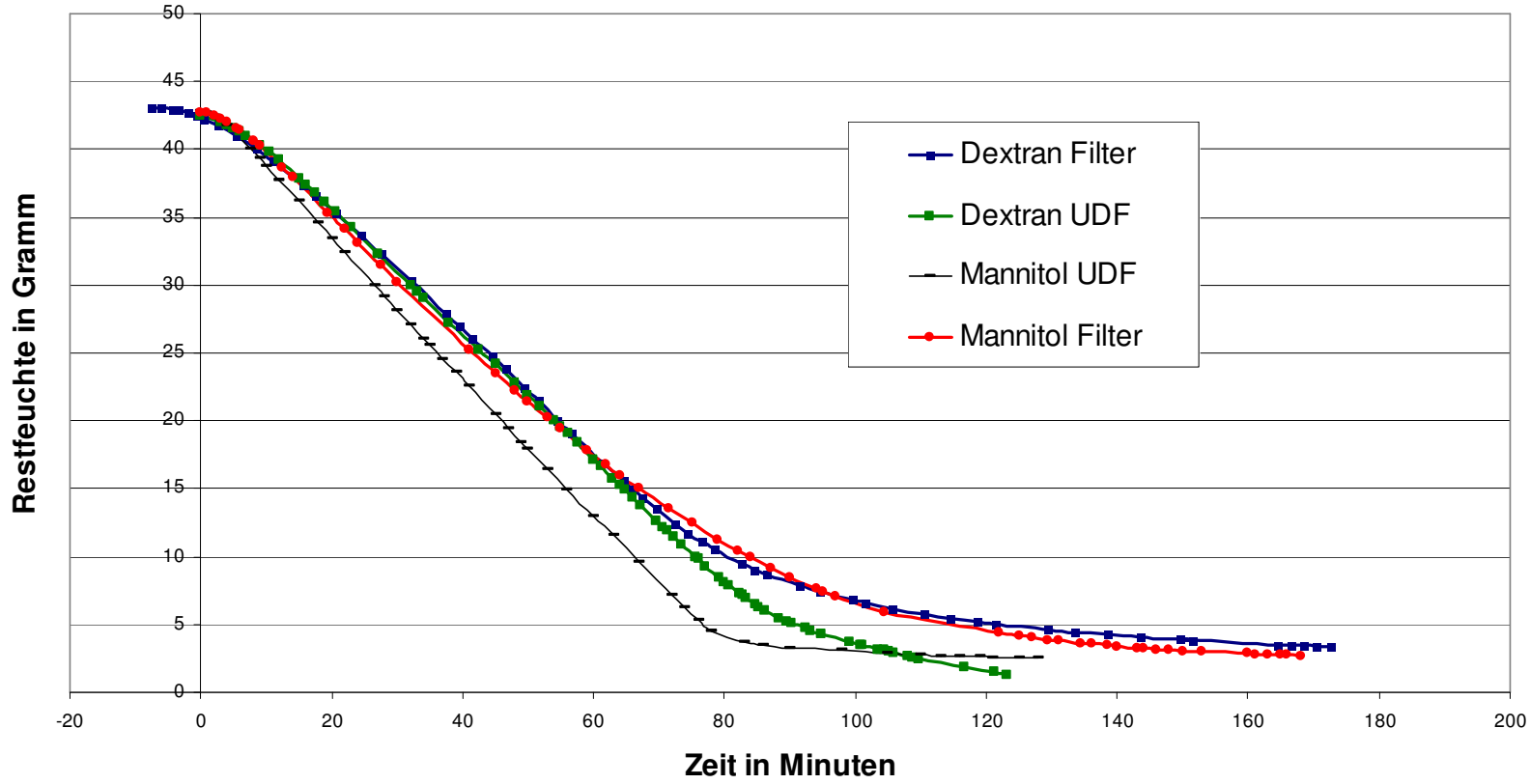
- Advantages:

→The highly porous pellet can be easily crushed in a powder inhaler for pulmonal administration.

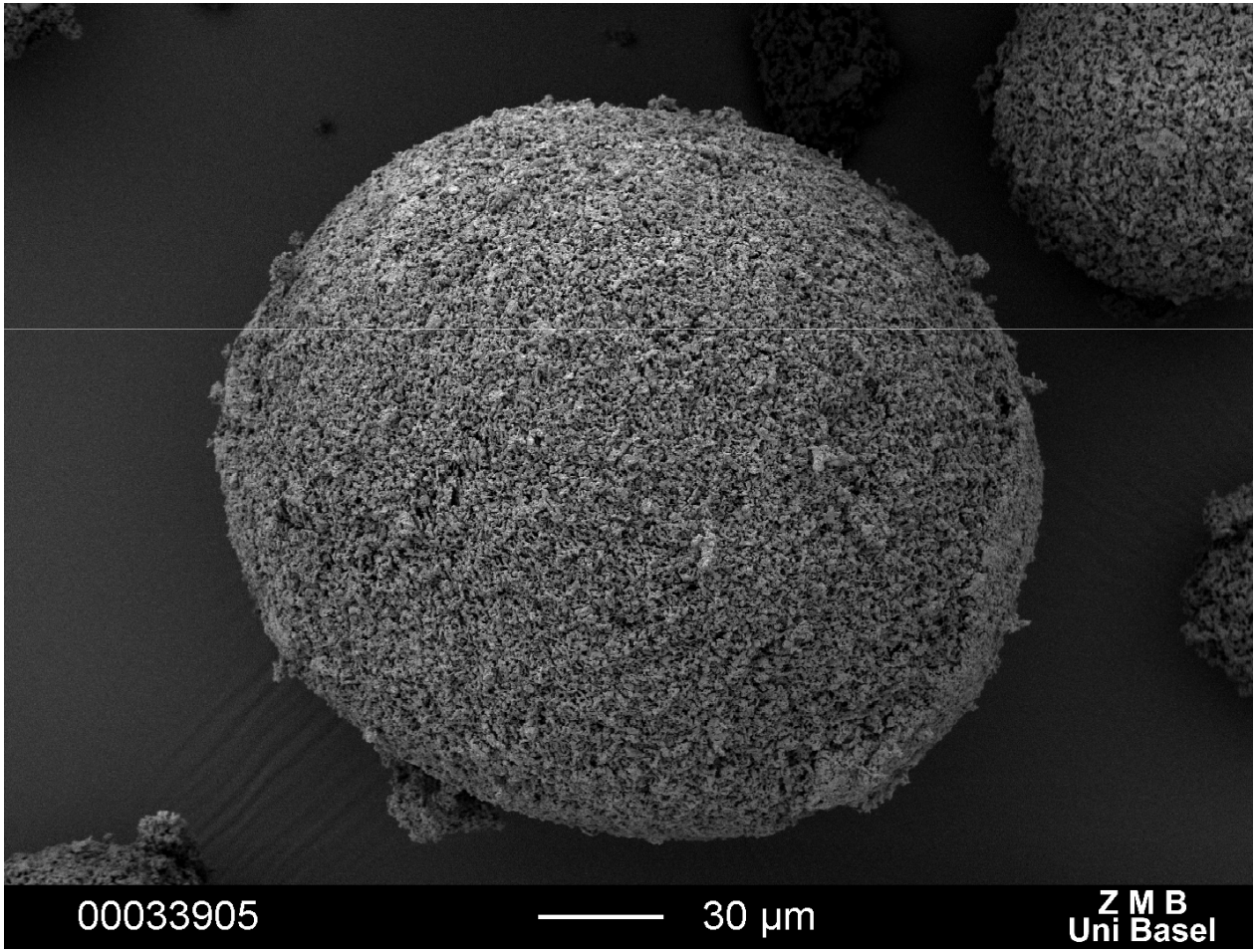
→The genlte production of organic nanostructured micrometer sized pellets unique (patents pending).

# Atmospheric Spray Freeze Drying as an Alternative

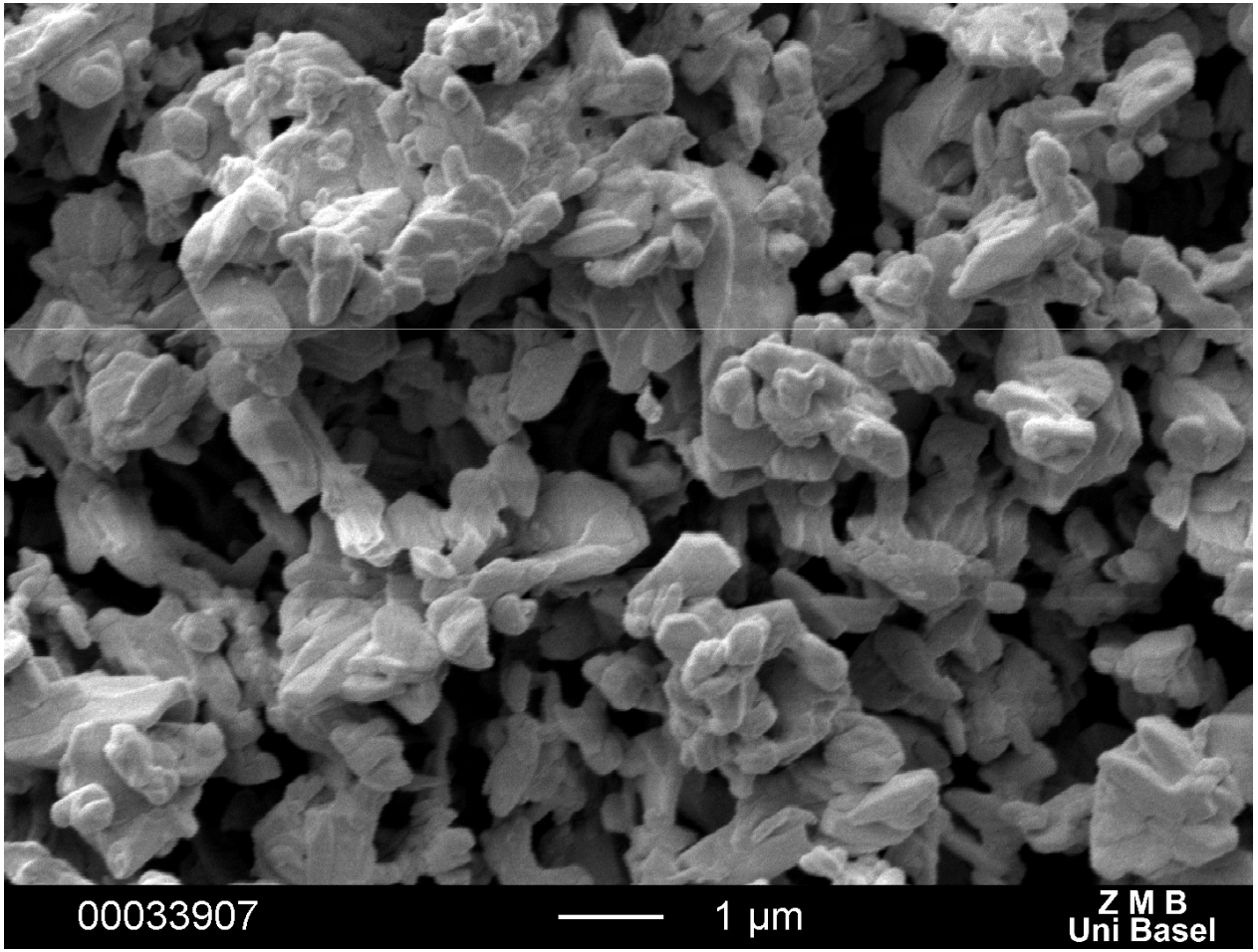
- Fast Drying Kinetics (Time in Minutes !)



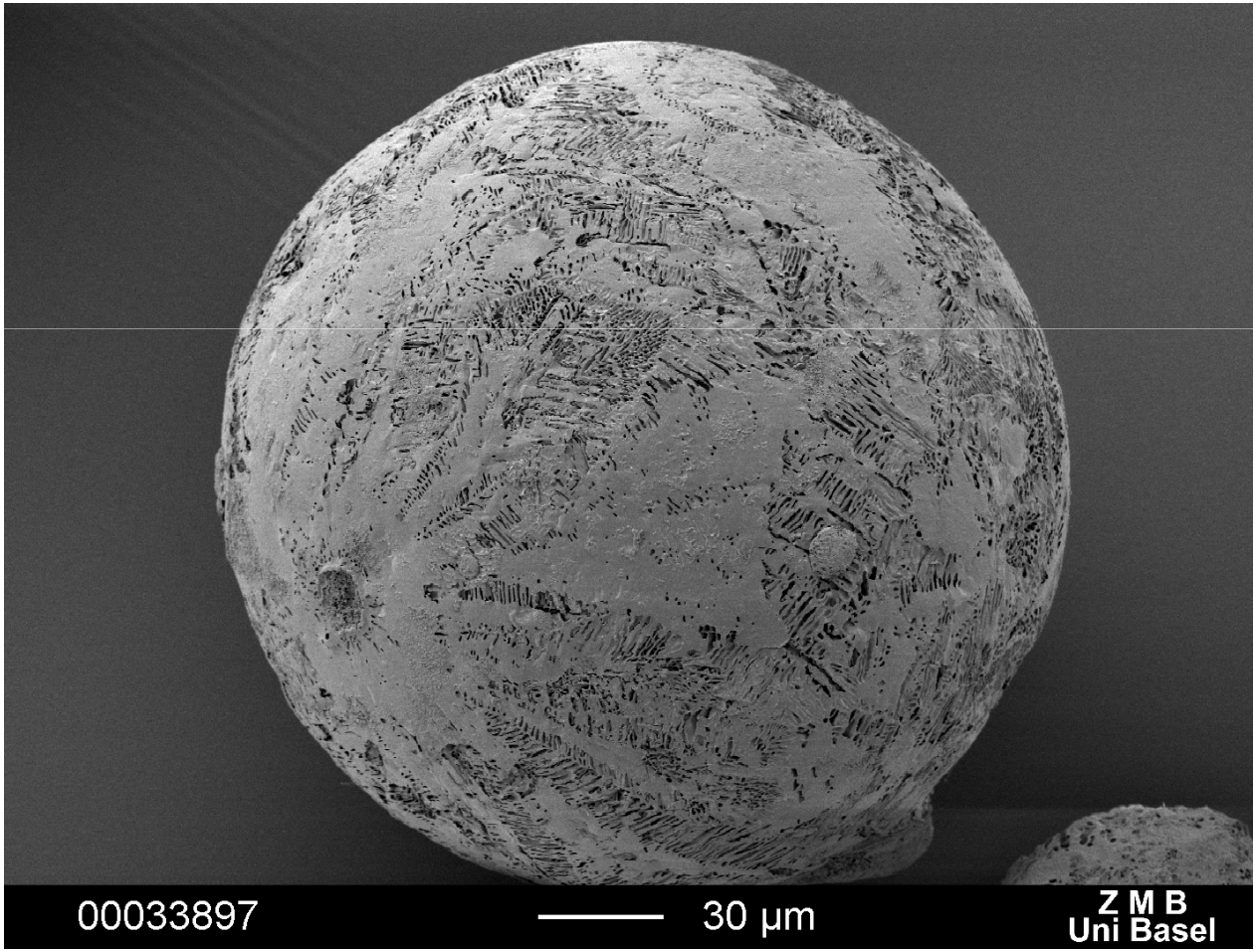
# Nanocomposite Mannitol (1)



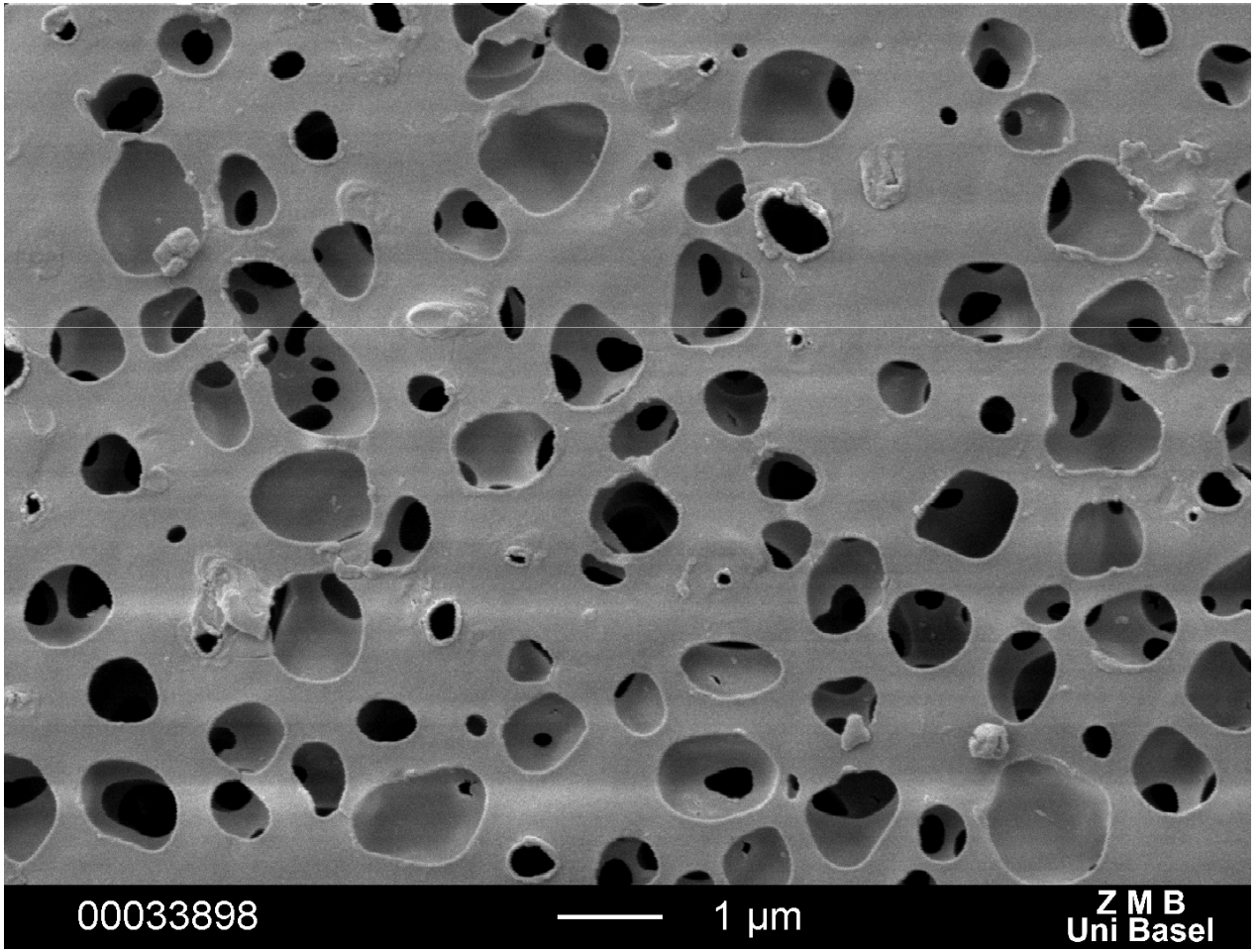
# Nanocomposite Mannitol (2)



# Nanocomposite Dextran (1)



# Nanocomposite Dextran (2)



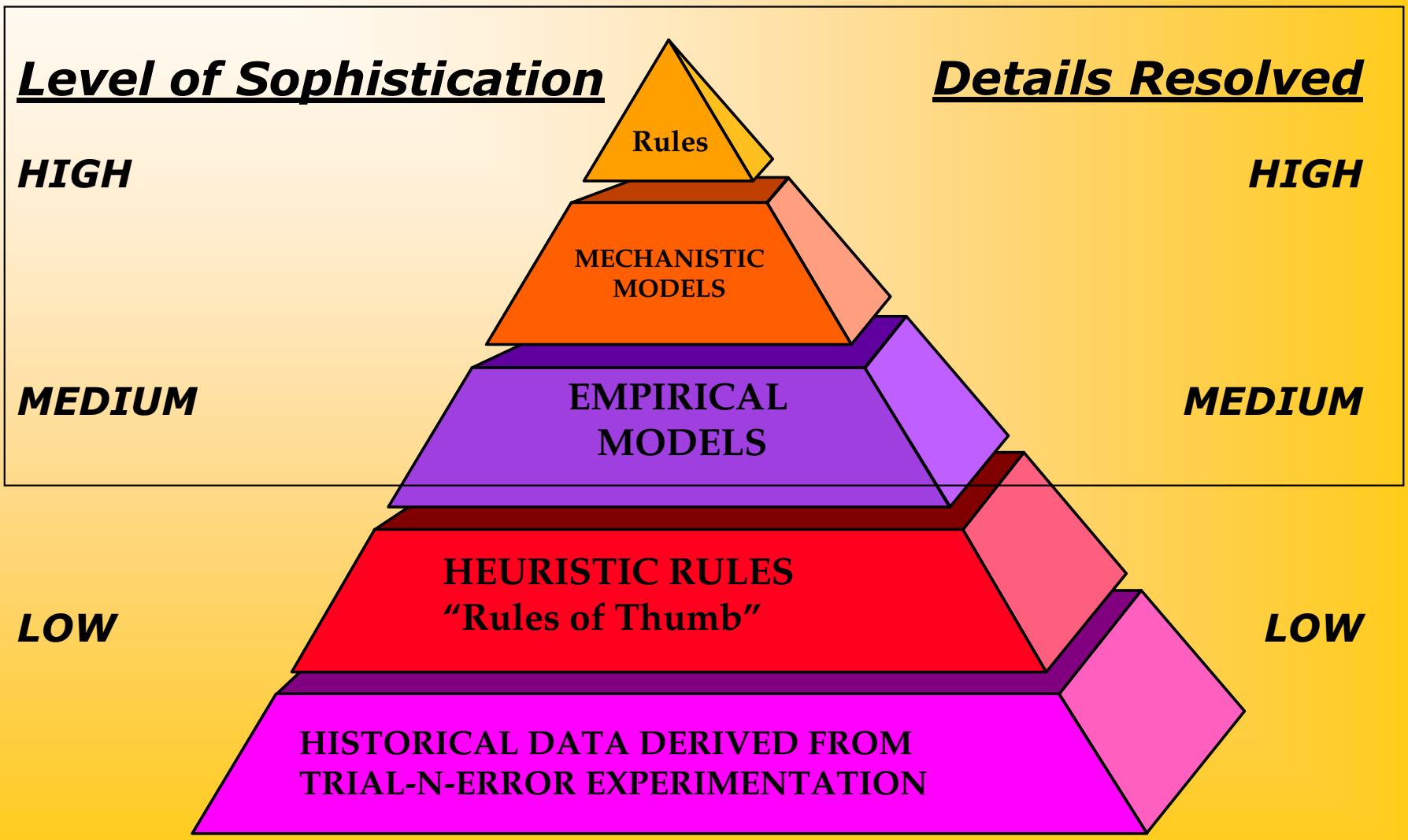
# Atmospheric Spray Freeze Drying as an Alternative

- Other Advantages:

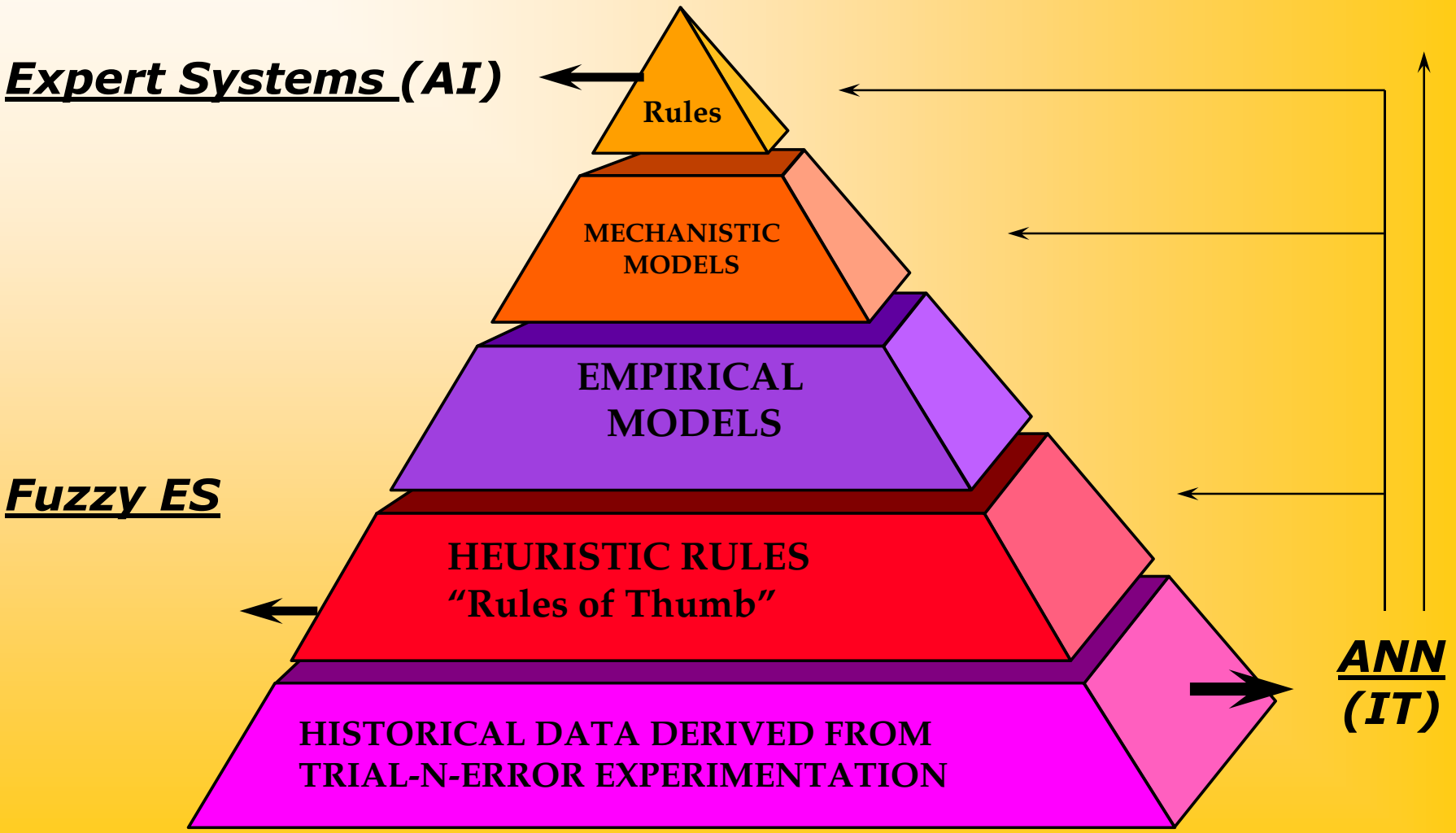
→Due to the drying at atmospheric pressure volatile components such as flavourings of Nescafé Gold is kept back!

→Due to the vacuum in classical freeze drying volatile components are lost and need to be recovered separately (by condensation)!

# Product Development Knowledge



# Artificial Intelligence AI & Information Technology IT can Improve the Utility of Historical Data



# Hypothesis (Hussain,1989):

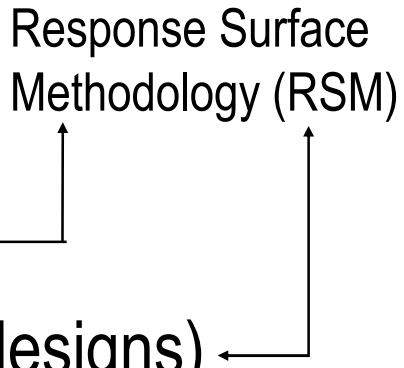
**“ANN Based Computer Aided Formulation Design”**

- Many Challenges
  - Very complex systems
  - Subjective descriptions of excipient “functionality”
  - Historic process controls that do not necessarily control critical attributes of in-process materials
  - Subjective equipment similarity descriptions
- Initial focus on
  - Comparison to RSM
  - Tool for improving technical and marketing support functions of an excipient supplier: Klucel Net © (Aqualon)
  - Formulation and marketing tool for a propriety formulation technology: TIMERx

# Comparison with other methods

**used for process optimization**

- classical experimental design
- empirical models, overfitting
- factorial design (statistical designs)
- central composite design (higher order designs)
- simplex design
- application of percolation theory
- the black box model (convolution/deconvolution model)
- true physical (mechanistic) models…

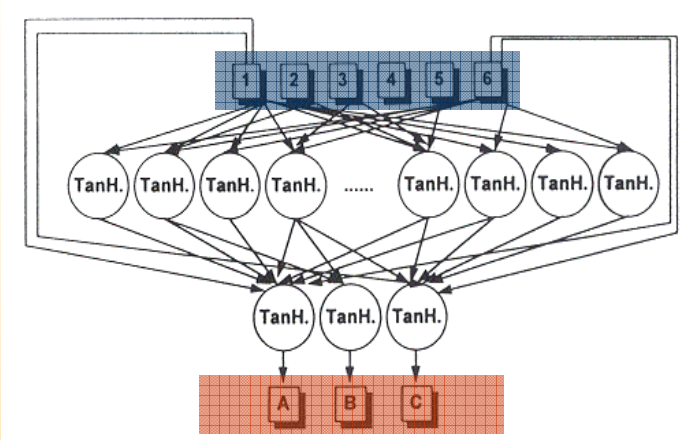


# An example

- Tablet compression study using two Artificial Neuron Networks
  and the RSM-technique

**The Generalized Feed Forward Multilayer Perceptron (GFF-MLP)**

# GFF-MLP simplified




**The input layer consists of 6 PEs, which correspond to 4 compression variables (matrix filling speed, precompression force, compression force, rotation speed) the formulation and the batch.**

Not used for prediction

**The output layer consists of three results, i.e.**

**A: the hardness of the tablet**

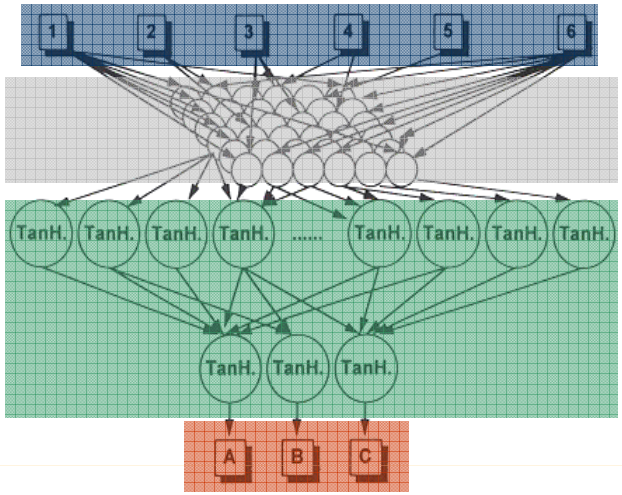
**B: % drug diss. after 15min. and**

**C: $t_{50\%}$ (time, when 50% of drug dissolved)**

**Transfer function tanh (z) is used.**

**Between input and output layer → hidden layer with 11 Processing Elements (PEs) - direct connections between in- and output layers.**

# Self organizing feature map (SOFM) - MLP




**The hybrid network consists of a SOFM (Kohonen network) combined with a normal MLP**

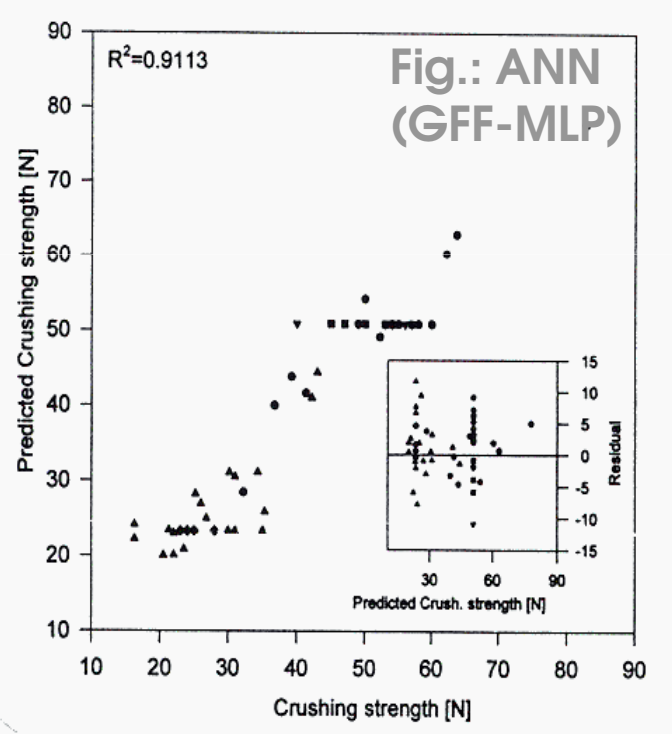
**The input layer** is identical to the input layer of the GFF-MLP.
The following Kohonen Layer (SOFM) consists of 6x6 Processing Elements (PE) and the hidden layer of 11 PEs of the subsequent „MLP“.

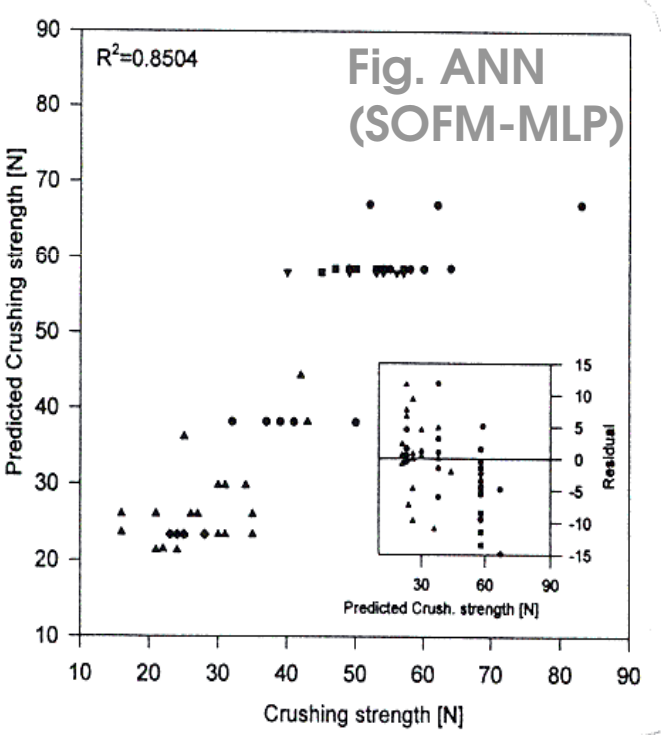
**The output layer** is identical to the GFF-MLP network.

**The resulting output** of the SOFM is then used as a new input to the MLP.
The factor „Batch“ was used as a further variable.

# Results$_1$ of the 2 networks

and of the RSM – technique




Hardness (Crushing strength) values and dissolution rate data

# Results$_2$ of the 2 networks

## and of the RSM - technique

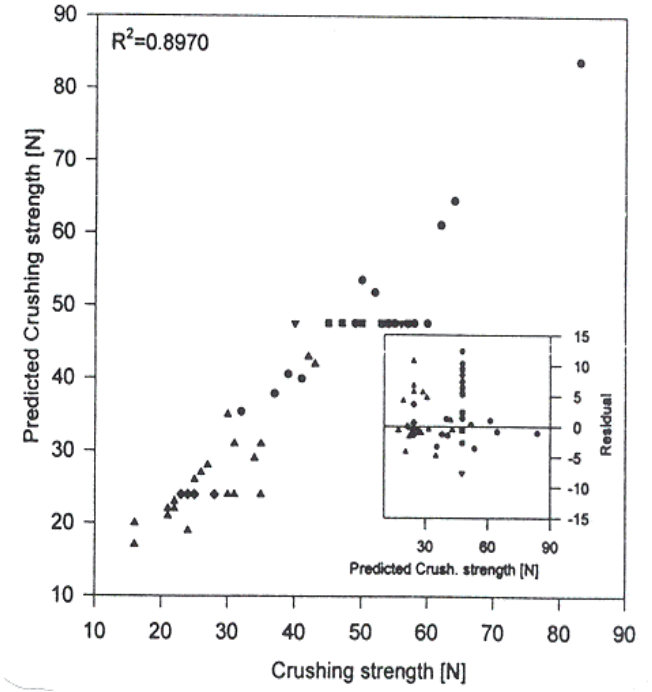



Fig.: RSM - technique

*Percentage of Drug Dissolved After 15 min (%)*
*R-Square Results for the Tablet Compression Study*

| | GFF-MLP | SOFM-MLP | RSM |
|---|---|---|---|
| $R^2$ without factor "Batch" | 0.2589 | 0.1040 | 0.1366 |
| $R^2$ with factor "Batch" | 0.8809 | 0.8775 | 0.8679 |

*Time to 50% Drug Dissolution (min)*
*R-Square Results for the Tablet Compression Study*

| | GFF-MLP | SOFM-MLP | RSM |
|---|---|---|---|
| $R^2$ without factor "Batch" | 0.3411 | 0.2942 | 0.2739 |
| $R^2$ with factor "Batch" | 0.8709 | 0.8536 | 0.8449 |

Fig. $R_2$ - Results „Dissolution Rate“

# Results$_3$ of the 2 networks

**and of the RSM - technique**

**Dissolution rate data**

- The factor „batch“ can not be used for prediction purposes! BUT...
- The factor „batch“ can be used in the case of unknown, hidden factors, → to be analysed in a subsequent, separate study!

# Results$_4$ of the 2 networks

**and of the RSM - technique**

**Dissolution rate data**

- No miracles can be expected from ANN or other evaluation/modelling techniques if the experimental data are not sufficient to explain the behaviour of a system!

# First Principles

**Remark:** 80% of marketed products are solid dosage forms.

- Pharmaceutical Powder Technology is still an art and needs to be transferred to a science*

* Pharmaceutical Powder Technology - From Art to Science: The Challenge of FDA's PAT Initiative

# First Principles

- Science of Powder Technology „Particuology“ term coined by the Chinese Society of Particuology.

- See journal:
  China Particuology; Editor Mooson Kwauk;
  Science Press, Beijing; ISBN 1672-2515

# First Principles

- The situation in Powder Technology may be compared to the situation of chemistry in the early 19th century.
- The economic drive of the chemical industry did boost chemical research and science leading to the rigorous scientific framework of „Physical Chemistry“ in the 20$^{th}$ century.

# From Art to Science

- Physical Pharmacy is a good starting point but does not yet represent a rigorous scientific framework like „physical chemistry“.
- An important problem is the fact that the science of powder technology is still in the state of infancy.

# From Art to Science

- The underlying concept of the rigorous scientific framework of „Physical Chemistry“ is based on Statistical Thermodynamics with the definition of a molar Volume $V_m$ consisting of $N_A$ molecules.

- $N_A$ = Avogadro number
  = $6.0221367 * 10^{23}$ mol-1

# First Principles

- In order to achieve a rigorous scientific framework in Powder Technology a multidisciplinary, joint effort is necessary and different approaches have to be explored.

# First Principles

As an example the following **„roadmap“** could be helpful for further explorations.

- It is possible to „translate“ the laws of the rigorous framework of Physical Chemistry into the area of Pharmaceutical Powder Technology?

# First Principles

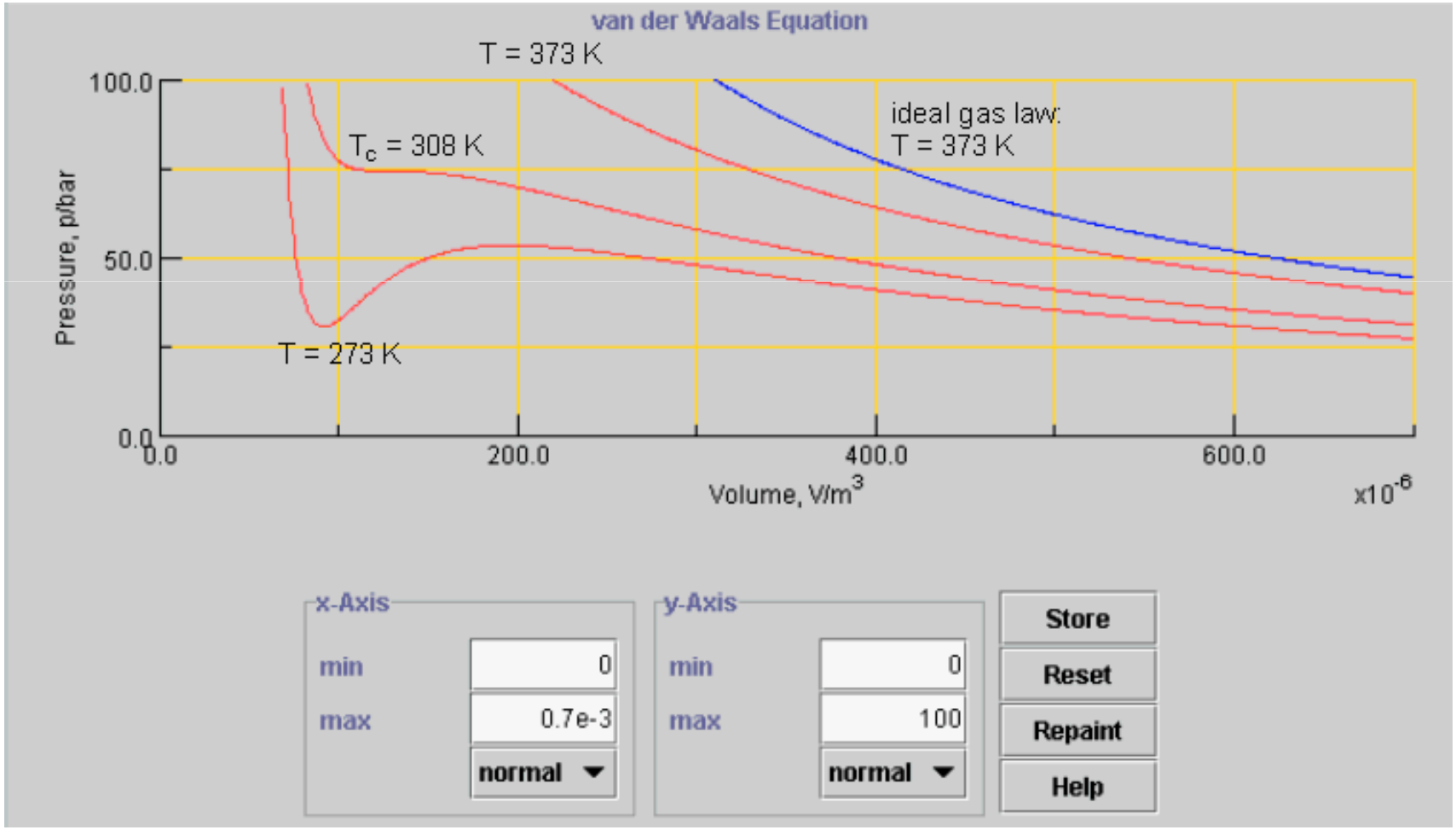
**What are the boundary conditions:**

- Is an „atomistic“ view of powder particles reasonable, e.g. by the fact, that there is a lower limit of the particle size e.g. obtained by a micronization process.
- Is it a prerequisite that the number N of „atomistic“ powder particles is very high, i.e. close to $N_A$?

# First Principles: Case study 1

- Can the van der Waal‘s Equation be used in case of the compaction of powder?
- In case of a tablet with $N < N_A$ powder particles, which e.g. undergo brittle fracture during the compaction process.

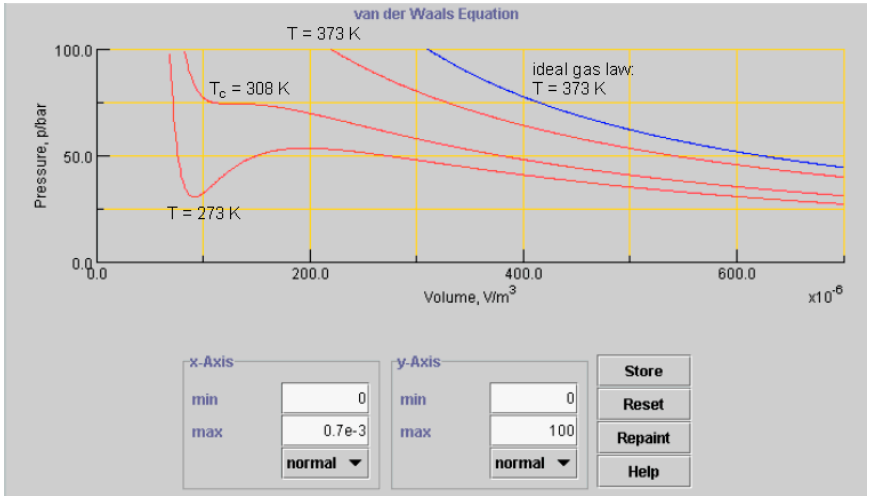
# Van der Waal‘s Equation



# Van der Waal‘s Equation

- CD:

  H. Burkhart,
  S. Rizzotti,
  M. Lanz and
  H. Leuenberger;

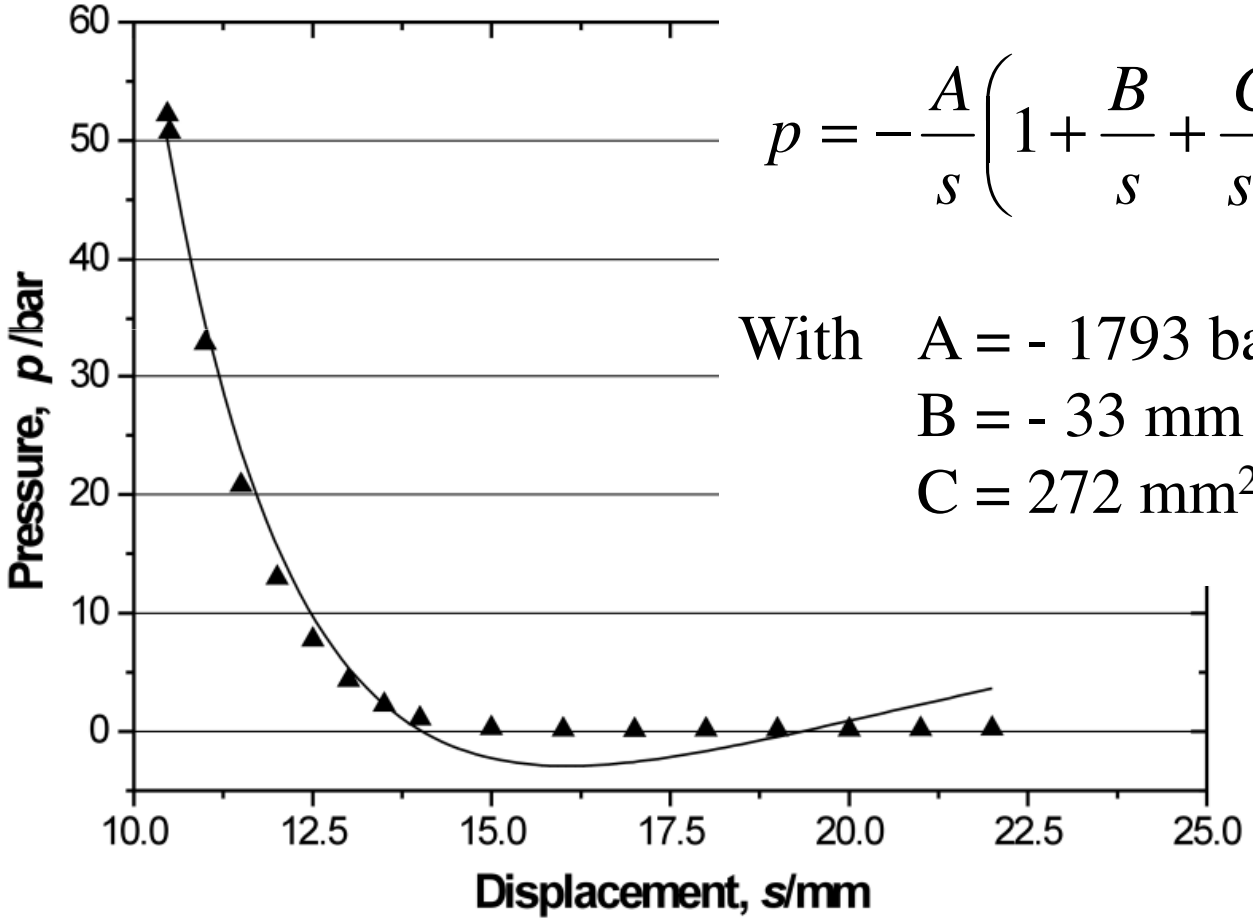



LivingFormulae and PhysPharm: A Tool for Science Education and its Application.

$$p = \frac{RT}{V}\left(1 + \frac{B(T)}{V} + \frac{C(T)}{V^2} + \ldots\right)$$

Virial Equation

# The compaction of a powder

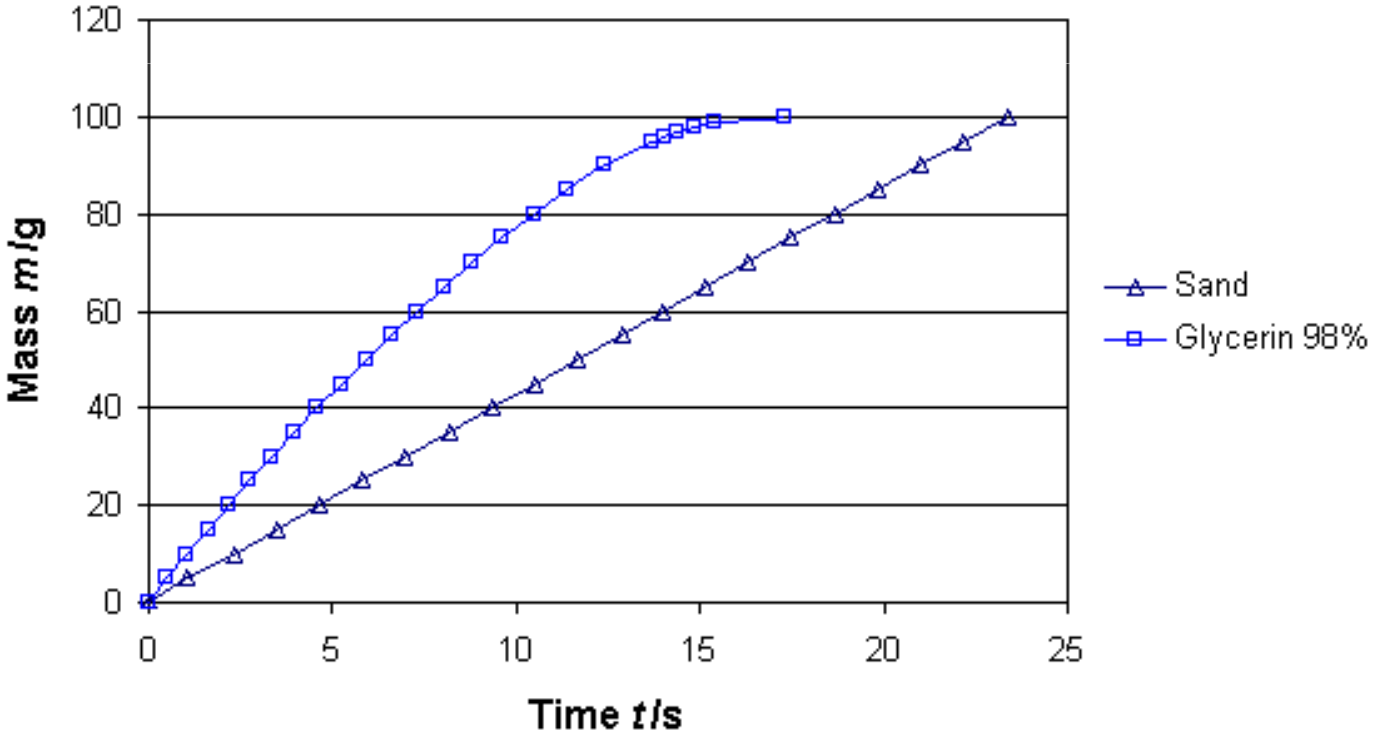



$$p = -\frac{A}{s}\left(1 + \frac{B}{s} + \frac{C}{s^2} + \ldots\right)$$

With A = - 1793 bar
B = - 33 mm
C = 272 mm$^2$

# First Principles: Case study 2

- Discharge kinetics from a hopper: difference between a liquid and a powder



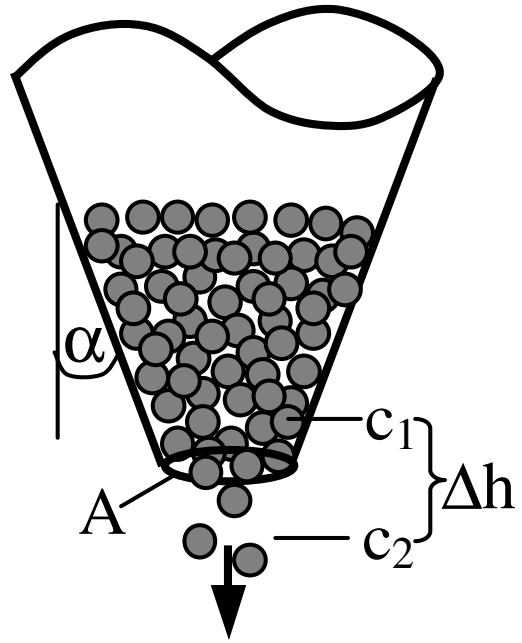
# First Principles: Case study 2

- The flow of powder discharged from a hopper can be modelled with Fick‘s First Law (under sink conditions): →

$$\frac{dm}{dt} = \frac{D \cdot A \cdot dc}{dh} \approx \frac{D \cdot A \cdot (c_1 - c_2)}{\Delta h}$$

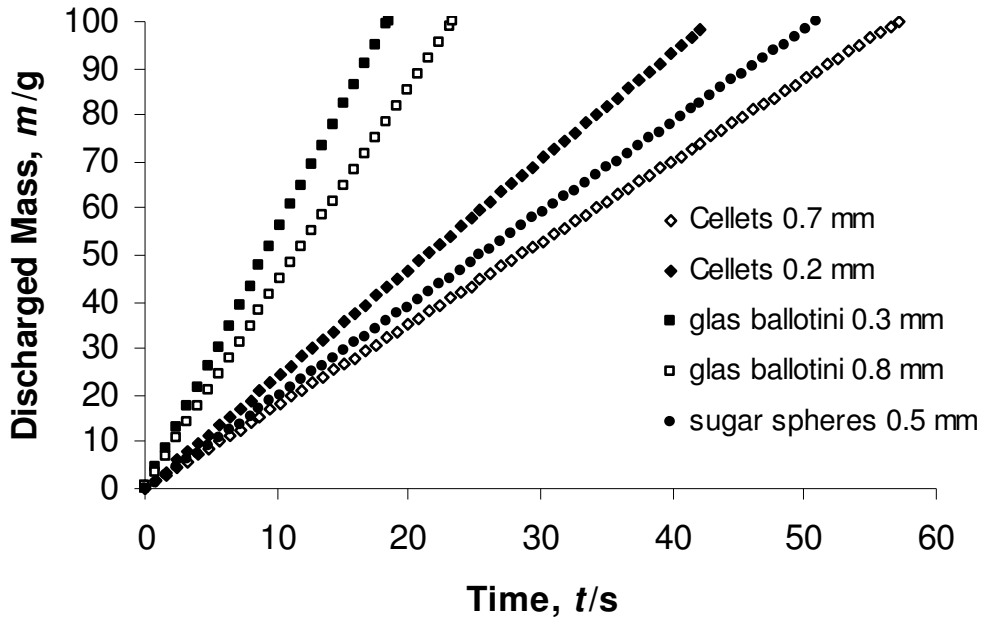
# First Principles: Case study 2

- Flow of particles out of a hopper
  - A: area of the orifice with a diameter d = 5mm
  - α: half center angle = 17°
  - $c_1$: particle concentration in the hopper;
  - $c_2$: particle concentration out of the hopper ⇨~0



# First Principles: Case study 2

- Flow of Cellets® (Pellets made of microcrystal-line cellulose), glass ballotini and sugar spheres with different diameters out of a hopper with an orifice diameter of 5mm.



# First Principles: The impact of Nanoscience

- Comparison with Nanoscience:
  - Nanoparticles have special properties due to the low number of atoms in a nanoparticle (= agglomerate of atoms) $N << N_A$ (Avogadro)
  - Powder particles have special properties as the particle consists of $N << N_A$ „atomistic“ particles.

# First Principles: Conclusion

- Conclusion to achieve a rigorous scientific framework of Powder Technology

  - **A joint effort of Pharmacists, pharmaceutical Engineers, chem. Engineers, physical Chemists and Nanoscientists is necessary.**
  - **A research initiative like the Nanoinitiative is desirable to achieve the goals in a reasonable time.**

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# Thank you for your attention

Hans Leuenberger

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