

Helsinki Drug Research 2008

PMR Pharmaceutical Manufacturing Research

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Purpose of this talk

- Drug manufacturing is high technology
- Pharmaceutical Manufacturing Research gives great possibilities
- Accurate process research results in
 - Molecular-level understanding of pharmaceutical processing
 - General rules
 - Patents
 - Formulations
 - Measuring systems, equipment
 - Computer algorithms
- There are types of modeling
 - 1) statistical models
 - 2) physical models
- Fundamental understanding and controlling of processes

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Content

- Why PMR
- PMR 25 years ago
- Validation
- PAT
- Automation in industry
- Science and understanding
- Hydrogen bonding – van der Waals forces
- Few examples

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Why topic PMR

- PMRC (Pharmaceutical Manufacturing Research Centre)
 - Develops PMR/PAT
 - Mainly non-GMP
 - But only 5 kg GMP, and one 50 kg line
 - Real drug products for clinical trials
 - PPP - model

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PMR 25 years ago

- Tablet compression
- Instrumentation
- LIMS systems in chemical laboratories
- Pharmaceutical process monitoring starts about 30 years ago, data loggers



C64, 1982

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Validation

- How validation started in Finland 1980?
 - Moist heat sterilizers
 - All sterile processes and whole sterile production
 - All types of products
 - All analytical tools
 - Everything?
- “validation ~ research ~ understanding”

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Computer technology

- 1981, IBM 5150
 - 4.77 MHz
 - 16-640 kB
- 2007, MacBook Pro
 - 2.4 GHz Intel Core 2 Duo
 - 2 GB)
- 1 000 000 000



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Mobile phones

- Motorola DynaTAC 1983
- Nokia N95, 2007



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Automation



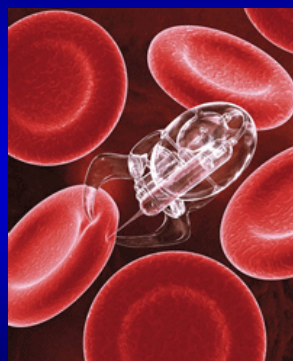
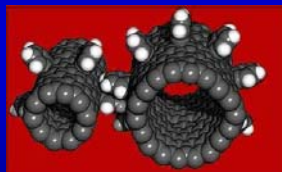
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Robotics



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This will be part of PMR in 2030?



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PAT

- Process understanding.
 - The term *analytical* in PAT is understood very broadly including
 - chemical
 - physical
 - microbiological
 - mathematical
 - risk analysis
- conducted in an integrated manner.

<http://www.fda.gov/cder/OPS/PAT.htm>

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Process understanding

- Accurate and reliable **predictions** reflect process understanding.
- Process understanding is inversely proportional to risk.

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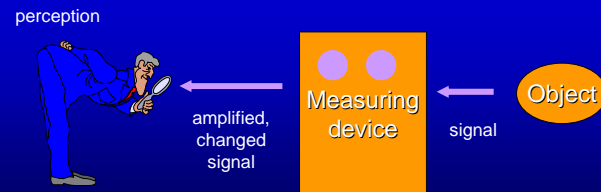
Science and Understanding

- Science is a systematic and solid assembly of universal and reliable facts
- Science is the greatest attempt of the mankind to understand the nature
- **Understanding** is a proper model which can predict the future; no more – no less.

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Measuring and generalization

- Measuring device changes the original signal so that the researcher can get **sense perception**
- Generalization is made on the basis of **earlier personal experiences**



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Data, information, knowledge, understanding

Data and information

- often data is defined as raw facts
- information has meaning (i.e. can inform), while data does not

Knowledge

- information evaluated and organized by the human mind so that it can be used purposefully, e.g., conclusions or explanations (Rousa, 2002).

Understanding

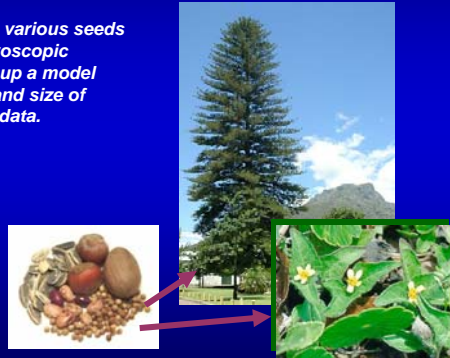
- in physics, understanding is a proper model
- good models can predict the future

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Can we predict the structure of plants?

Suppose, that we measure various seeds by spectroscopic and microscopic techniques and then build up a model which predicts the shape and size of plants on the basis of this data.

This will be quite easy.



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Can we predict the structure of plants?

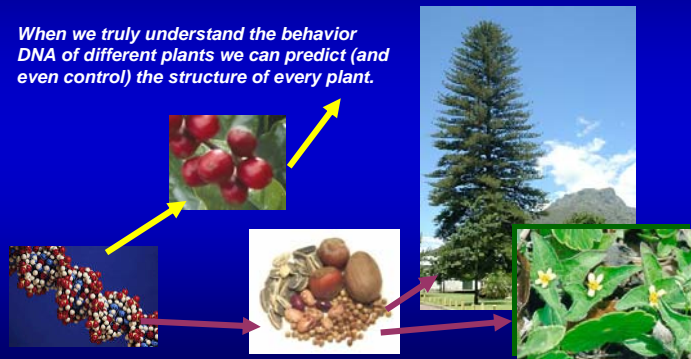
But when we then take a new seed we cannot predict the structure of this new plant (no generalization).



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Can we predict the structure of plants?

When we truly understand the behavior DNA of different plants we can predict (and even control) the structure of every plant.



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Our theories are limited

- This gives great possibilities for experimental scientists
- Theories only give us directions
- Laboratory experiments and hard work can go further than theories

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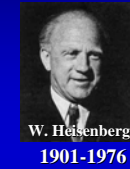
Our theories are limited

- Practical applicability of theories is often limited
- Thermodynamics
 - Deals with averages
 - Old theory, which was developed for steam engines



Our theories are limited

- Quantum mechanics
 - Postulated theory
 - Holistic
 - Maximal information from atoms world
 - Computer based molecular modeling of drugs and crystals
 - simplifications
 - Hellman-Feynman theorem



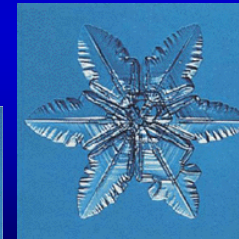
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Our theories are limited

- Two examples:
 - Snow crystals
 - The most studied ELEMENT, carbon
 - One crystal form: fullerene

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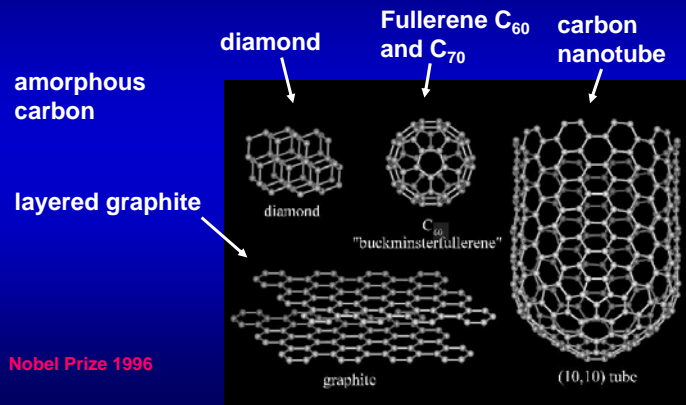
Crystal habit: Snow crystals



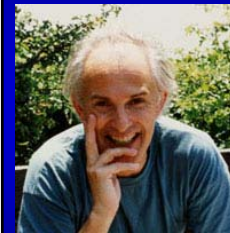
Snow crystals are growing
10 times faster than the
theories suggest

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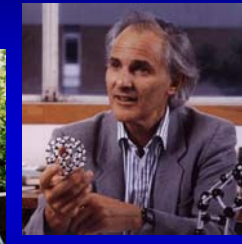
Carbon – the most studied element: polymorphic forms



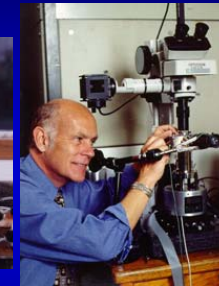
Fullerenes



Robert F. Curl Jr.
1933 -



Sir Harold W. Kroto
1939 -



Richard E. Smalley
1943 - 2005

The Nobel Prize in Chemistry 1996 for their discovery of fullerenes

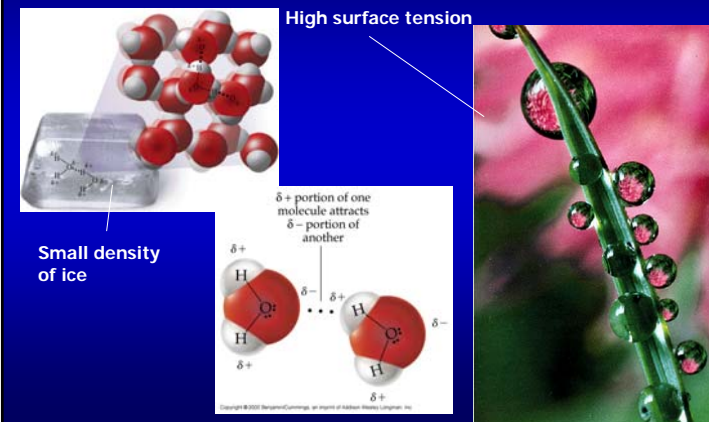
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Challenge for PMR: quantify the two important interactions in pharmaceutical systems

- 1) Hydrogen bonding between molecules
 - theory is complex
- 2) van der Waals interaction between particles
 - theory is well-known

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Hydrogen bonding in water





Hydrogen bonding

Protein backbone

Nobel Laureate in Chemistry 1954
for his research into the nature of the chemical bond and its application to the elucidation of the structure of complex substances

Helix structure is based on the H-bonds

Courtesy of The Archives California Institute of Technology
Linus Pauling
1901-1994

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The Nobel Prize in Physiology or Medicine 1962: DNA

DNA Molecule: Two Views

Rosalind Franklin
1920 - 1958

James Watson
1928 -

Francis Crick
1916 - 2004

Maurice Wilkins
1916 - 2004

for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material

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Hydrogen bonding

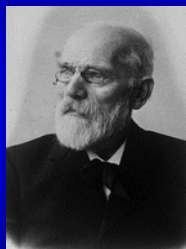
Hydrogen bonding in formulation

- Wetting
- Dissolution
- Disintegration
- If you have in the composition
 - water
 - sugars
 - celluloses

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van der Waals forces

- Keesom (permanent dipoles)
- Debye (induced dipoles)
- London (dispersion effect)
- Short range forces between molecules: r^{-6} field
- attractive
- repulsive



Johannes Diderik van der Waals
1837-1923

The Nobel Prize in Physics 1910

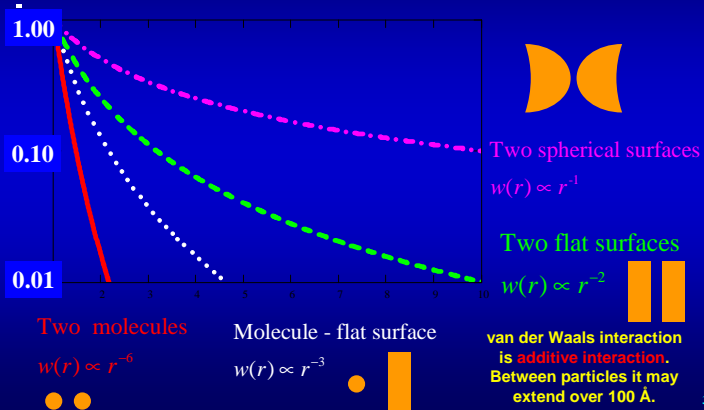
London's dispersion effect between two atoms is

London dispersion interaction energy

$$w(r) = -\frac{3}{4} \frac{\alpha^2 h\nu}{(4\pi\epsilon_0\epsilon_r)^2} \cdot \left(\frac{1}{r^6}\right)$$

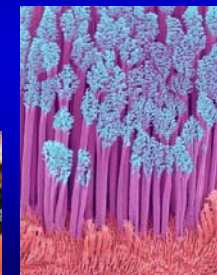
Labels in the diagram: polarizability, ionization energy, electric permittivity, relative permittivity, distance.

van der Waals interaction energy



Ex.: A gecko can hang on a glass surface using only one toe

- The toe pads of geckos and other lizards are covered with fine, keratinous filaments called setae. Each setae branches into about 1000 spatula-shaped tips visible only under a microscope. Molecules in these spatular tips are attracted to molecules in the surface that the gecko is walking on through van der Waals forces



No any suction caps!

Gecko foot/toe hair

Ex.: mathematical and physical models

- **Mathematical model is** always "**STUPID**". Its information content (of the nature) is zero.
 - Describes how my book drops down
- **Physical model** describes and explains the nature. All model parameters in the model have physical meaning.
 - Describes how my book drops down
 - Explains the reason: gravitation
 - Explains also that the same reason (gravitation) held all of us on the floor, explains why the moon is rotating around the earth, it explains tidal waves ...

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We have to develop Pharmaceutical Education

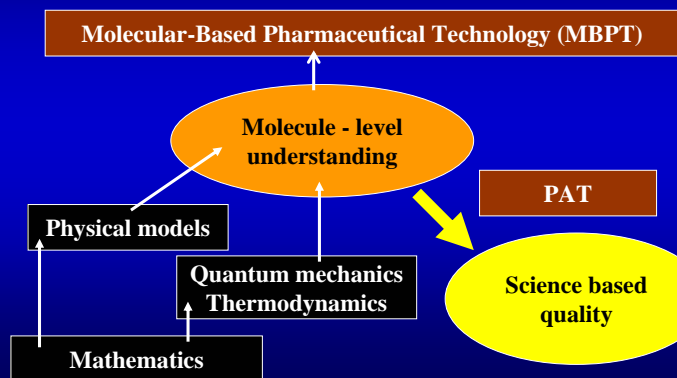
- **Mathematics:** Precise language
- **Physics:** Definition of units and theory of measurements
- **Chemistry:** Science which deals with atoms and molecules
- **Applied Sciences:** Applied sciences exploit basic sciences

The PAT tools can be categorized as:

- 1) Multivariate data acquisition and analysis tools (mat., phys.)
- 2) Modern process analyzers or process analytical chemistry tools (chem., phys.)
- 3) Process and endpoint monitoring and control tools (mat., phys., chem.)
- 4) Continuous improvement and knowledge management tools (mat., phys.)

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What PMR should be



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PMR will be molecular-based understanding of processes



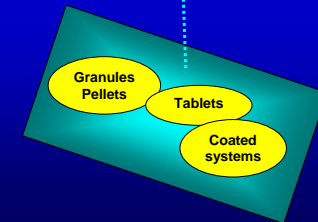
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MOLECULE – CRYSTAL – POWDER – PROCESS – PRODUCT

PMR in tablet manufacture
- how complex?

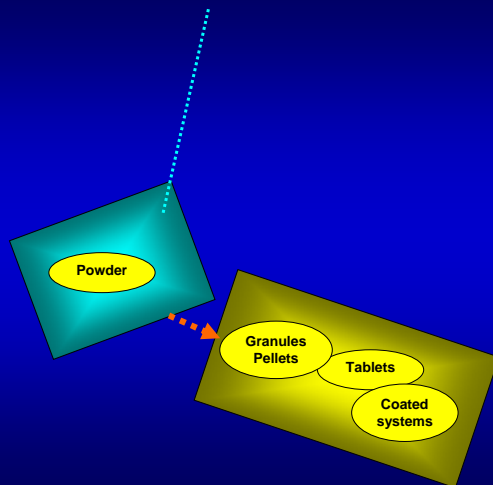
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MOLECULE – CRYSTAL – POWDER – PROCESS – PRODUCT



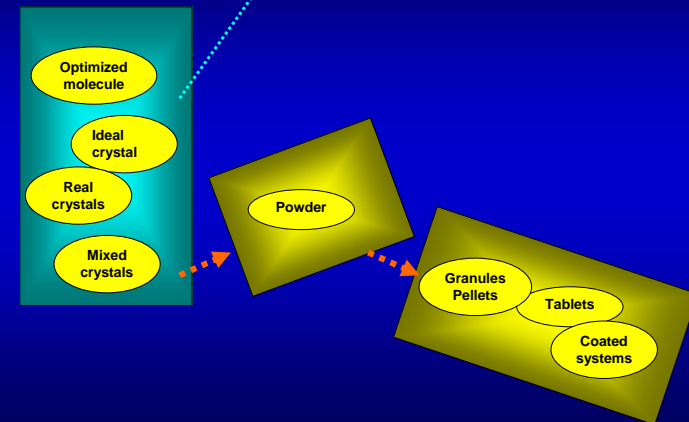
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MOLECULE – CRYSTAL – POWDER – PROCESS – PRODUCT

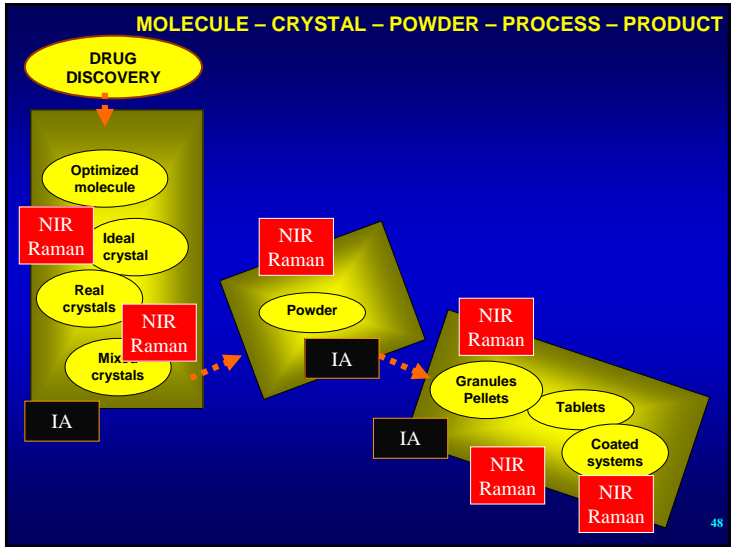
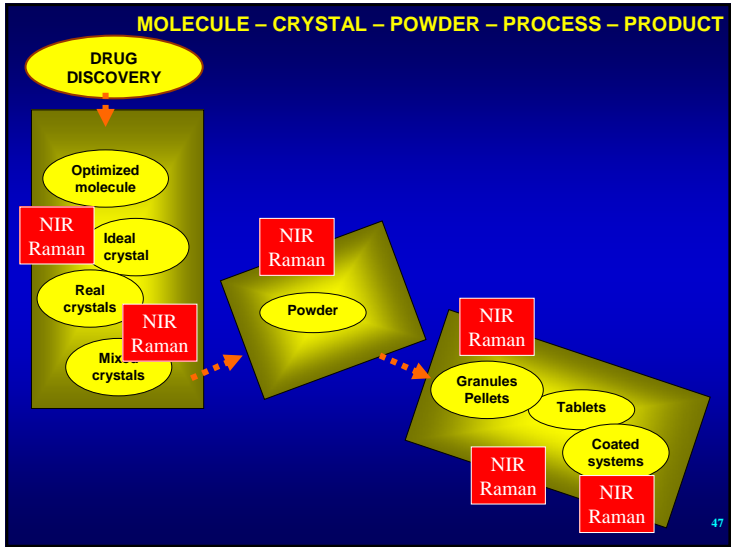
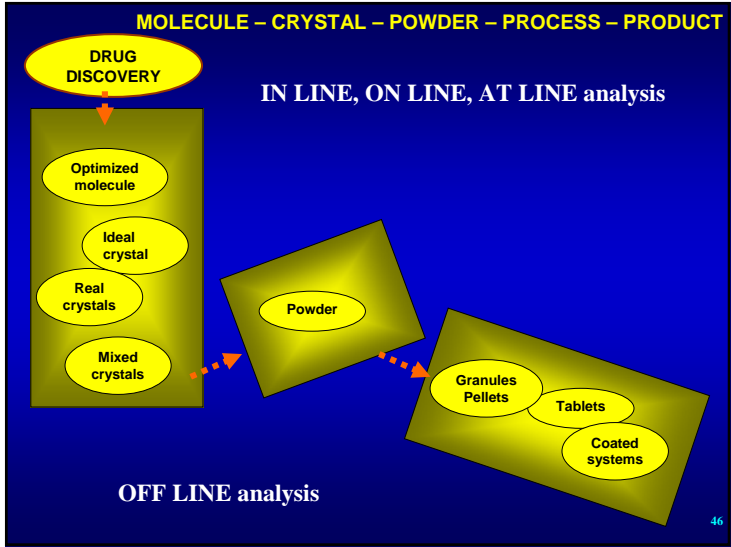
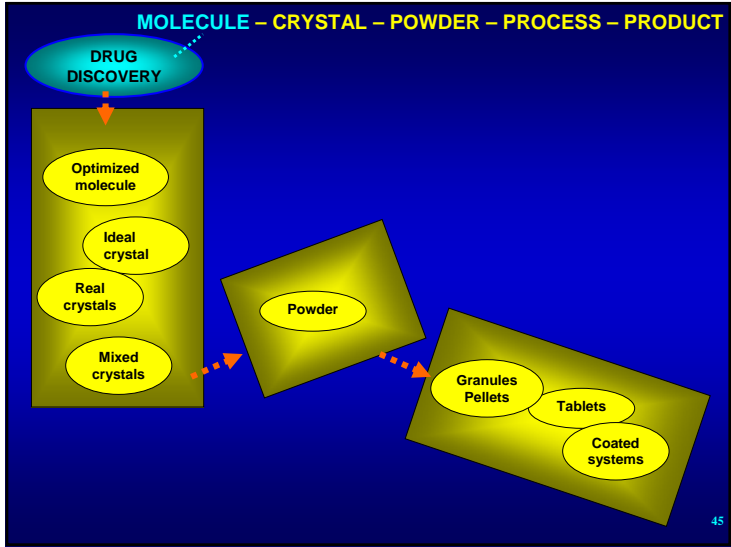


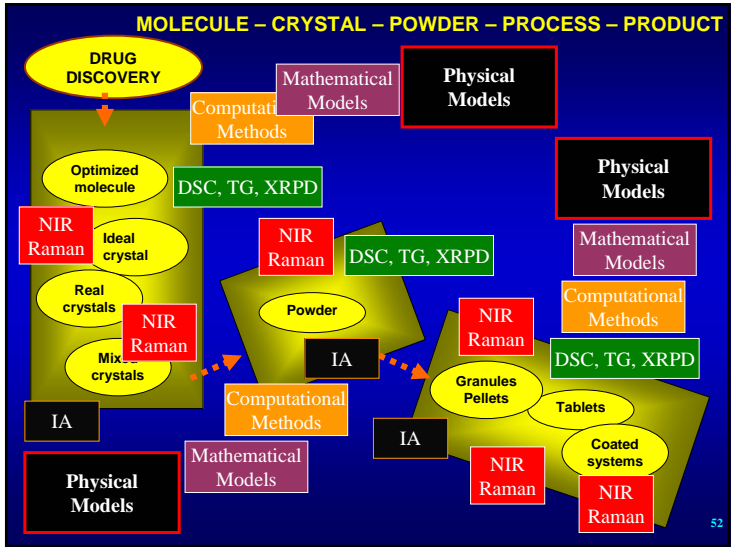
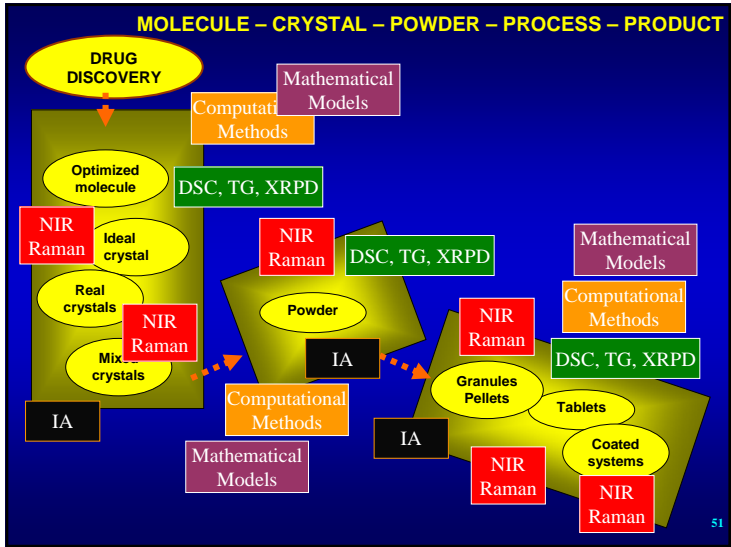
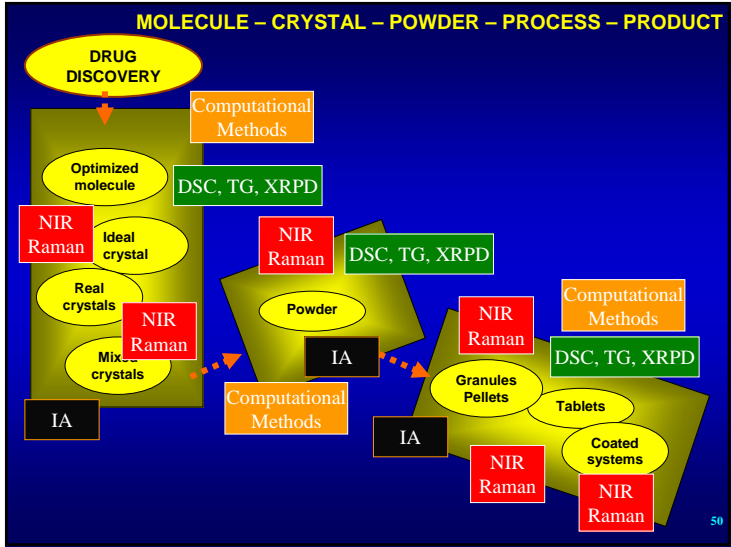
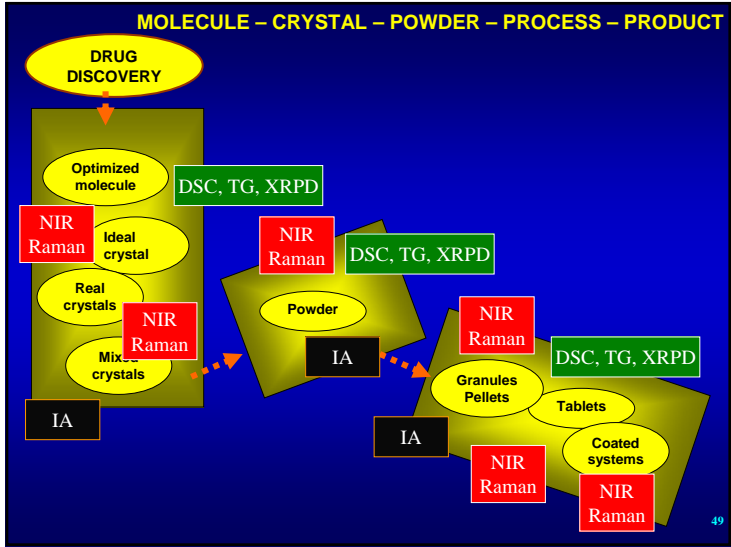
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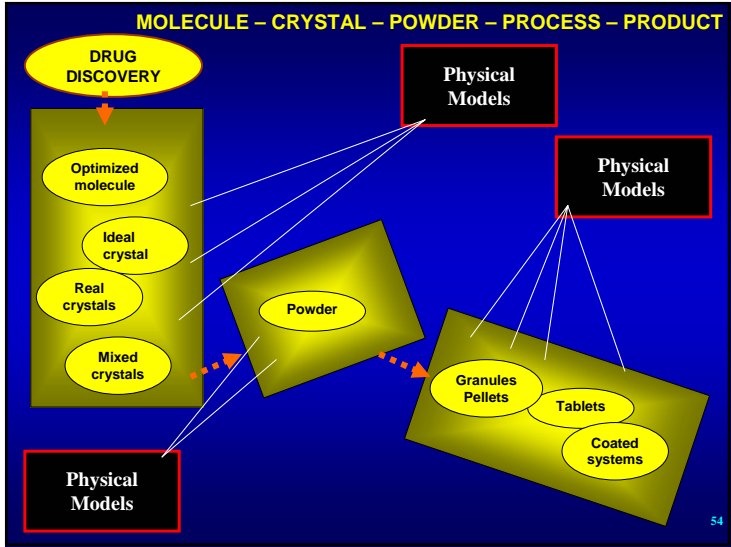
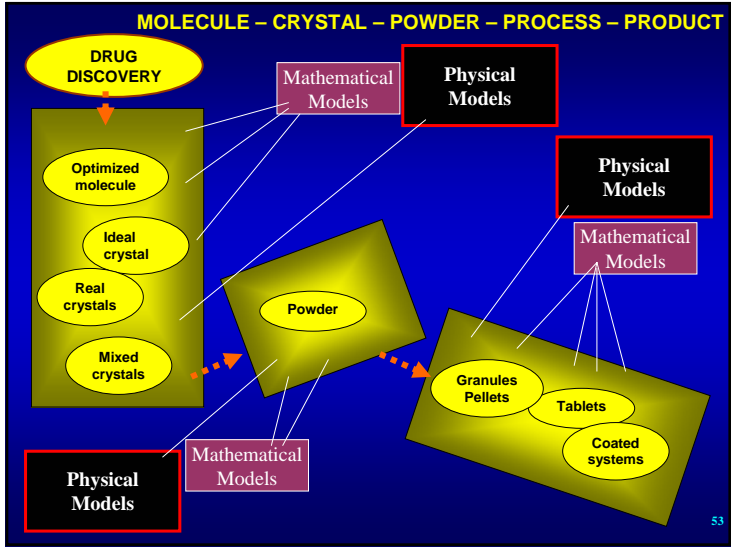
MOLECULE – CRYSTAL – POWDER – PROCESS – PRODUCT



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Few examples of PMR

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Continuous process monitoring

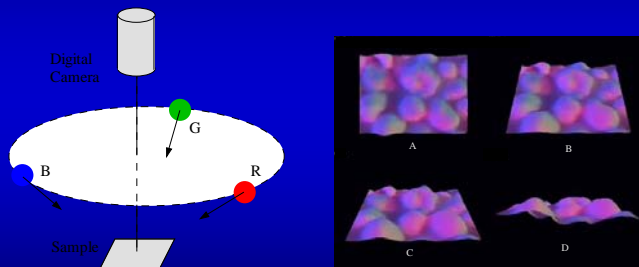
The left photograph shows a complex piece of industrial machinery, likely a tablet press or granulator, with various sensors and components. The right photograph shows a close-up of a large, circular industrial vessel or hopper, possibly used for powder handling or storage, with a sensor or probe inserted into it.

- Particle size, SAY3D, US
- NIR, RAMAN
- Moisture content
- Flow properties

K. Seppälä, T. Närvinen, Orion Pharma

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Image analysis



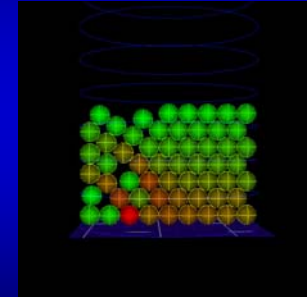
SAY3D K. Seppälä OrionPharma

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Simulation of powder packing

- Powder flow
- Powder packing
- Particle breakage
- Bond formation

- Mechanistic model
Calculations in super computers
- Surface friction
 - Angular momentum
 - Elasticity
 - Particle size

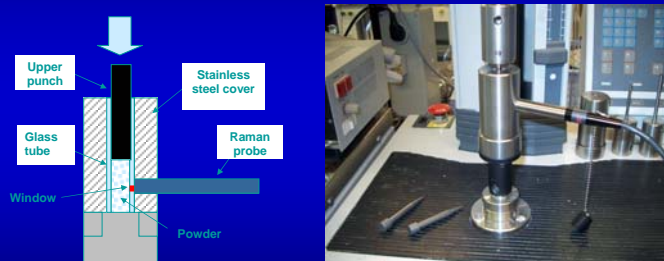


S. Siiriä and J. Yliruusi

Division of Pharmaceutical Technology, University of Helsinki, Finland

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Bond formation monitoring during tablet compression



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Integration in PAT

- Design of experiments
- Selection of process analyzers
- Proper data analysis tools
- Formulation and process development Hand in Hand
- First process optimization in laboratory scale
- Scientific scaling up – only when you know the state of matter
- Continuous quality improvement in production
- **Fundamental understanding of phenomena**

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What PMR should be

PAT

Pactical Analysical
Techniques

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What PMR should be

Molecular-Based Pharmaceutical Technology (MBPT)

Molecule - level
understanding

Physical models

Quantum mechanics
Thermodynamics

Mathematics

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What PMR should be

Molecular-Based Pharmaceutical Technology (MBPT)

Molecule - level
understanding

Physical models

Quantum mechanics
Thermodynamics

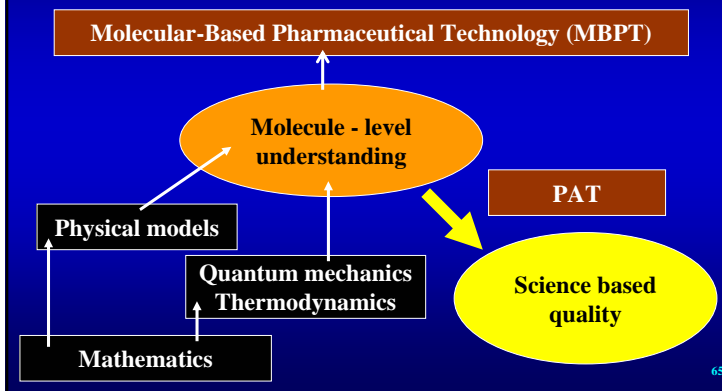
Mathematics

PAT

Pactical Analysical
Techniques

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What PMR should be



PMR - molecular-based understanding of processes

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PMR will be molecular-based understanding of processes



Acknowledgements

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Sari Airaksinen
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Heikki Räikkönen
Satu Virtanen
Simo Siiriä

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Tero Närvänen
Tanja Lipsanen

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