Assessment of microparticle coating quality and functionality

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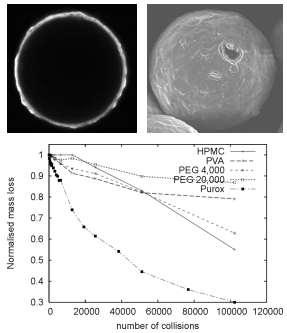
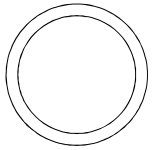
Outline

- Particle coating quality
  - Techniques
  - Case-studies
- Particle coating strength
  - Techniques
  - Case-studies
- Conclusions



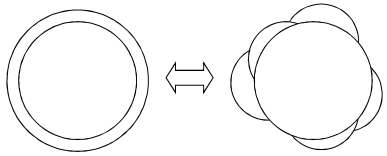
Monitoring of the particle coating process

- **Coating <u>thickness</u> is important !**
  - Too small coating
    - Lack of performance (e.g. protection, controlled release)
  - Too thick coating
    - Delayed liberation of the core
    - Increased coating time, hence cost



Monitoring of the particle coating process

- Coating thickness is important !
- **Coating <u>thickness distribution</u> is at least = important !!!**
  - Overall coating quality
  - Intra- and inter-particle coating variability
  - Presence of coating deficiencies ?



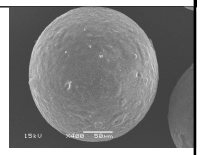
Monitoring of the particle coating process

Tablet coatings

- Procedure
  - Take samples in-process
  - Weighing a known sample size
  - Determine the theoretical amount of coating added
- Cons
  - Identical coatings assumed (inter- & intra-particle)
  - No information about coating uniformity
  - Practical limitations for small particles (100-500 µm)

Monitoring of the particle coating process

Microcapsules



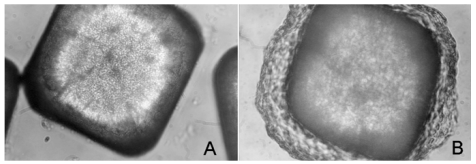
- Procedure
  - Chemical analysis of microcapsules coated with e.g. proteins
  - E.g. Lowry quantitative assay for protein determination

$$w = C_p \cdot \frac{DF_1}{DF_2} \cdot \frac{DF_3}{M_{mc}}$$

- Cons
  - Average value for 20g of microcapsules ~ 1,8 million particles of 200 µm
  - Core particles of same size assumed
  - Conversion to coating thickness: coating particle density is needed
  - No information about coating uniformity

Monitoring of the particle coating process

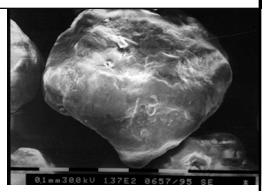
- **Light microscopy**
  - bright field, polarising and fluorescence
  - limited resolution
  - thin sample sections or smears must be prepared → invasive ?
  - +: dynamic experiments, selective staining



Dewettinck, 1997

Monitoring of the particle coating process

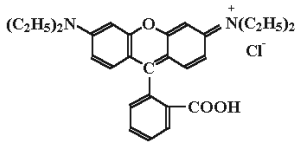
- **Electron microscopy**
  - SEM: surface morphology
  - TEM: inner structure visualisation
  - better resolution than LM (~ x 100)
  - observation of presence of cracks and pores
  - metal coating required (non-conductive samples)
  - tedious preparation steps
    (dehydration, chemical fixation, impregnation with resin)
  - mechanical sectioning required → artefacts ?
  - radiation damage artefacts from the electron beam

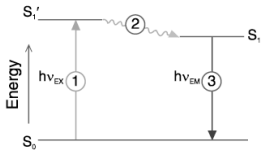


Dewettinck, 1997

Monitoring of the particle coating process

- **Fluorescence microscopy**
  - Use of fluorophores or fluorochromes, e.g. Rhodamine
  - Jablonski diagram
  - better resolution than bright field or polarising LM



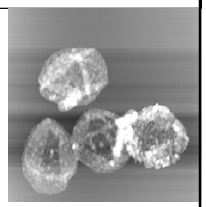


Monitoring of the particle coating process

- **Fluorescence microscopy**
  - +:
    - detection of substances in low concentrations
    - highly selective labelling possible
    - autofluorescent molecules
  - - :
    - emission λ (laser) ~ absorption λ (fluorochrome)
    - thin sample sections remain required
    - tedious invasive preparation remains necessary

Monitoring of the particle coating process

- **Atomic force microscopy**
  - surface roughness scan
  - better resolution than EM
  - non-destructive technique

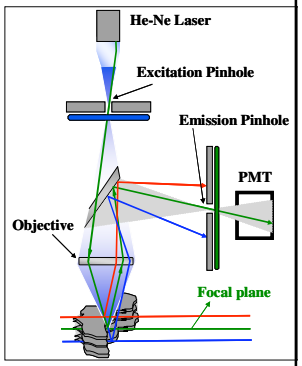


LMN, Parma, 2006

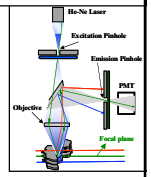
- **Near-infrared spectroscopy**
  - wavelength and intensity of near-IR light absorption
  - rapid, no sample preparation required
  - non-destructive and non-invasive
  - suitable for coatings of rather large thickness

Monitoring of the particle coating process

- **Confocal laser scanning microscopy**
  - bridging conventional LM and EM
  - ! imaging aperture or PINHOLE
  - illumination focus plane
    = detection focus plane
  - only in-focus region information



Monitoring of the particle coating process



- **Advantages**
  - high signal-to-background ratio, superior contrast
  - improved resolution (depth resolution !)
  - exclusion of out-of-focus (fluorescent) light
    → planes of thick samples can be seen separately
  - series of multiple optical slices possible → 3D reconstruction
  - optical slicing → no mechanical sectioning
  - no tedious sample preparation necessary
  - dynamic processes, use of multiple fluorochromes, etc.

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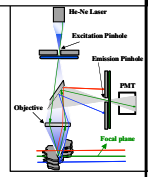
Monitoring of the particle coating process



- **Limitations**
  - lower resolution than e.g. EM and AFM
  - limited axial imaging depth ~ 200 µm
  - spherical aberration
  - fluorochrome laser bleaching
  - compatibility laser - fluorochrome

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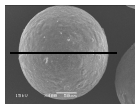
Monitoring of the particle coating process

- **CLSM protocol**
  - Bio-Rad Radiance 2000 CLSM
  - Nikon Eclipse TE300 inverted fluorescence microscope
  - Nikon S Fluor 40x objective
  - He-Ne laser, 543 nm excitation
  - Coating stained with **Rhodamine B**
  - Dispersion of microcapsules in immersion oil
  - Recording of fluorescence at microcapsule equatorial plane



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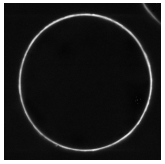
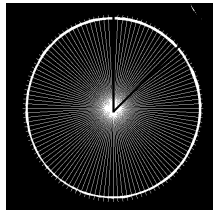
Monitoring of the particle coating process

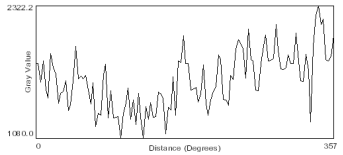
- **CLSM image processing**



Segmentation

Threshold





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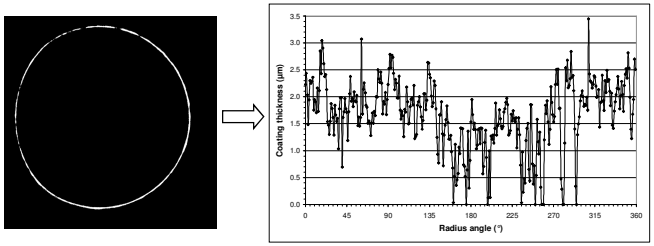
Monitoring of the particle coating process

- **Coating thickness distribution of an INDIVIDUAL microcapsule**



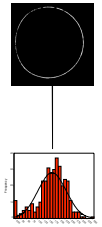
distribution of 360 observations per particle

Monitoring of the particle coating process

- **Coating thickness distribution of an INDIVIDUAL microcapsule**
  - Mean coating thickness µ = 1,66 ± 0,03 µm
  - Coating heterogeneity σ = 0,64 µm
  - Coating quality Q = 2,59

    Q = µ / σ
  - Minimum coating thickness = 0 µm

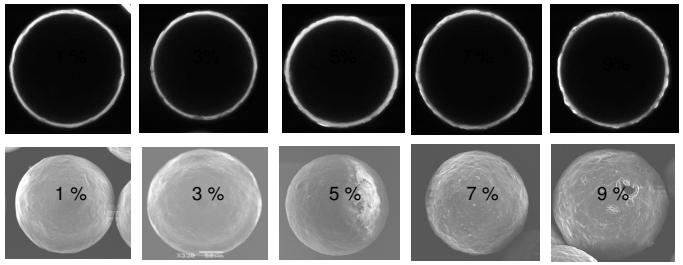
    → % of beads with coating deficiencies in a series of microcapsules



- **Coating thickness distribution of N (e.g., 50) microcapsules**

Case-study: cellulose derivative coatings

- **Methylcellulose coated microcapsules**



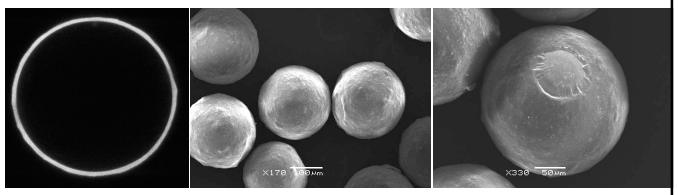
Coating quality Q = Nienaltowska et al., 2009

6,75	6,48	6,03	4,87	4,05

→ % of beads with coating deficiencies: 0 %

Case-study: shellac coatings

- **Shellac coated microcapsules**



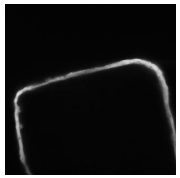
Nienaltowska et al., 2008

Coating quality Q = 7,22

→ % of beads with coating deficiencies: 8 %

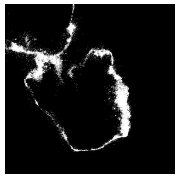
Case-study: non-spherical particles

- **Non-ideal size and/or shape → vector method**



Salt crystal coated with protein

- Coating quality Q = 4,25

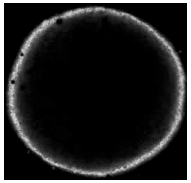


Sucralose coated with sorbitol

- obvious coating inhomogeneity

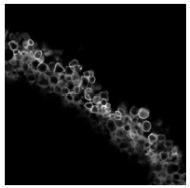
Case-study: dry particle coating

- **Plasticizer visualisation**



Cellulose pellet

- octenyl succinate dextrin of waxy maize
- plasticizer = glycerol



Bilancetti et al., 2009

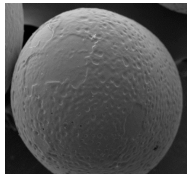
Conclusions

- **CLSM**
  - ideally suitable to QUANTIFY coating thickness & quality
  - study of individual microcapsules
  - generates a coating thickness DISTRIBUTION
  - non-invasive, accurate, quick and simple method
  - dependent on labelling with fluorochromes
  - applicable to particles of all shapes and sizes

Monitoring of the particle coating functionality

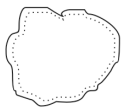
- **Controlled release / protection / …**
  - ~ **performance on-site**
  - Dissolution profile testing
  - Clinical studies

- **Coating strength**
  - ~ **performance during handling**
  - Particle breakage
  - Coating layer fatigue



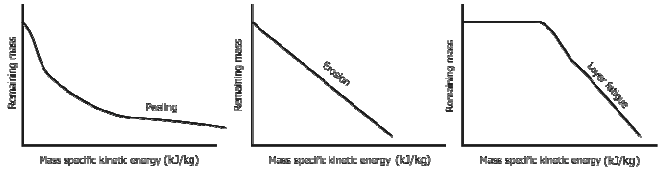
Monitoring of the particle coating strength

- **Particle breakage**

	Normal	Tangential
Low Force Wear	 Attrition	 Abrasion
High force Fracture	 Fragmentation	 Chipping

Monitoring of the particle coating strength

- **Particle breakage – attrition**



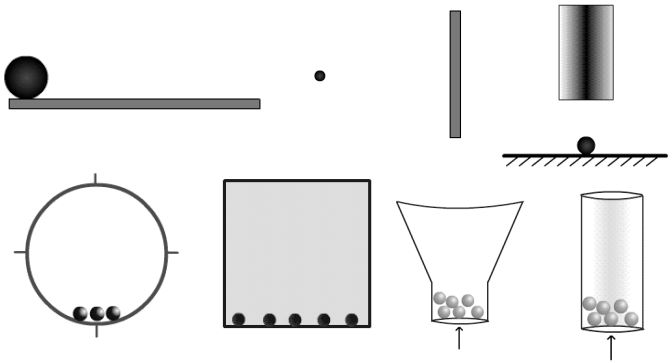
Monitoring of the particle coating strength

Damage ~ magnitude and direction of force
material properties
particle size (distribution)
particle shape
particle porosity
particle surface area
particle surface hardness
number of events

We can not predict damage without a tester… one tester?

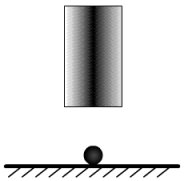
Monitoring of the particle coating strength

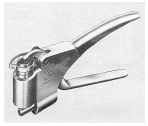
No, different types of testers…

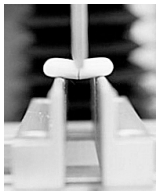


Monitoring of the particle coating strength

- **Compression tests**
  - Feel judgement tests
    - Amount of pressure?
    - Snap
  - Hardness testers
    - Load-deformation curves
    - Breakage force recording
    - Extent of deformation
    - 3-point bend testers
    - + sound and video playback

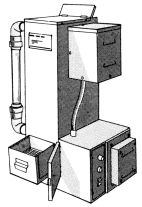






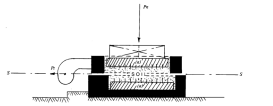
Monitoring of the particle coating strength

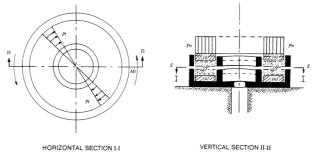
- **Impact tests**
  - Friability index
    - measure = n° of impacts before fracture
  - Free-fall impact testers
    - measure = particle size distribution
  - Drop shatter tests
    - measure = weight of particles smaller than …
  - Jet impingement tests
    - ~ pneumatic conveying
    - recycling



Monitoring of the particle coating strength

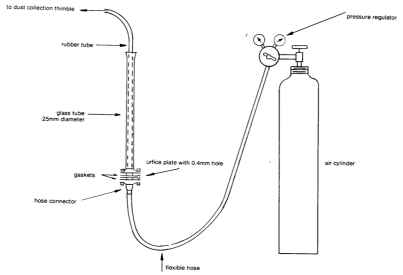
- **Shear tests**
  - Direct shear tests
    - constant stress / strain testing
    - e.g., Jenike shear test
  - Annular shear tests
    - stress ~ radial position

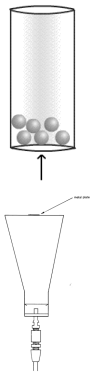




Monitoring of the particle coating strength

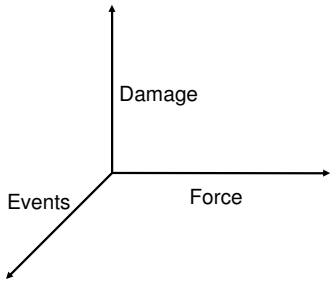
- **Fluid / spout bed tests**





Monitoring of the particle coating strength

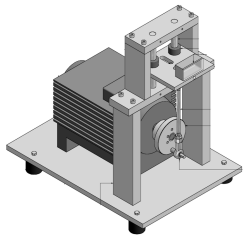
- **The ideal strength tester?**
  - Number of events!
  - Controlled layer fatigue

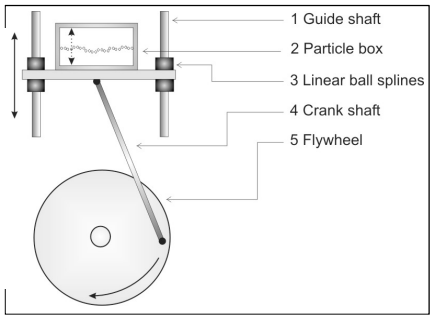


- **Mostly empirical test methods**
- **Well established within one industry, but not general**
- **Each application requires a different tester…**

Monitoring of the particle coating strength

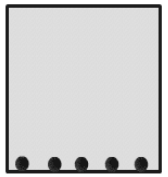
- **TUDelft repeated impact tester**

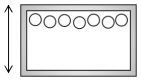




Monitoring of the particle coating strength

- **TUDelft repeated impact tester**
  - What happens inside the box?
    - impact velocities : 0 – 5 m/s
    - 100 – 300 particles tested
    - particle movement = plane
    - only normal velocity
    - intensity = transferred kinetic energy
    - combined with number of events!

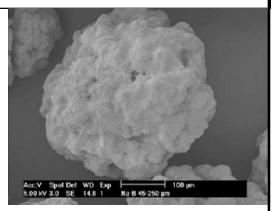


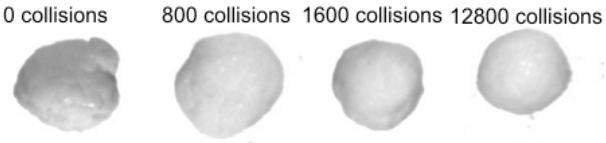


$$E_{kin} = \frac{1}{2} m v_{imp}^2$$

Case-study: attrition of granules

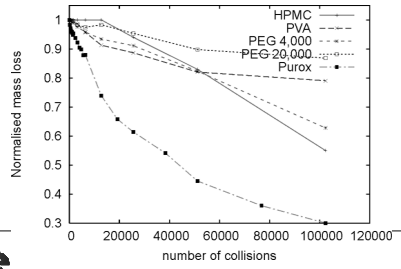
- **Sodium benzoate granules**
  - produced by fluid bed coating
  - 600-900 µm
  - impact of amount of collisions:
    - size reduction
    - rounding-off





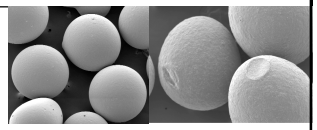
Case-study: attrition of coated particles

- **Sodium benzoate granules**
  - produced by fluid bed coating
  - coated with different materials
    - PEG (2 types), PVA, HPMC
  - mass loss ~ number of collisions:

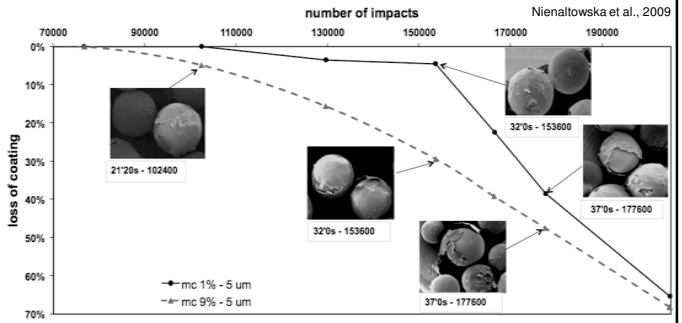


Case-study: attrition of coated particles

- **Cellulose derivatives coatings**
  - MC coatings



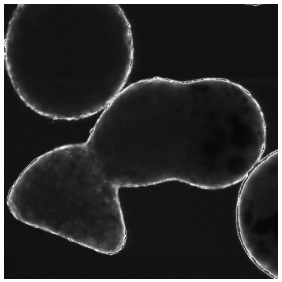
Nienaltowska et al., 2009



Conclusions

- **RIT**
  - **suitable to determine attrition strength and layer fatigue**
  - **promising desktop attrition tester**
- **Attrition strength**
  - **relation to initial surface uniformity**
  - **effect of particle coatings can be studied**
  - **relationship with coating polymer properties**

Questions ?



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