OSeeT

Optical Coherence Technology for the in-line measurement of film-coating

Phyllon
pharmaceutical technology

Optical Coherence Tomography (OCT) for Real-time Evaluation of Pharmaceutical Films and Coatings

OCT Development at RCPE

- Strategic project started in 2012
  - Adaptation of existing technology to the needs of pharmaceutical applications
  - Development of hardware for in-line and off-line analyses
  - Development of first generation of algorithms for in-line data evaluation
- Further development of prototype since 2015
  - Development of GMP compliant systems including documentation
  - Input from big pharma companies
  - Development of algorithms for real-time data evaluation, software and user interface
- Actual status
  - Patent granted
  - System ready for commercialization via Phyllon

Motivation was established procedure

- Low amount of data
- Statistically representative?
- Accuracy?
- No direct measure for thickness
- Time consuming approach
- Lack in methodologies for in-line assessment
- No signals available for active process control
- Missing information on coating homogeneity

Overview of **Analysed Pharmaceuticals**

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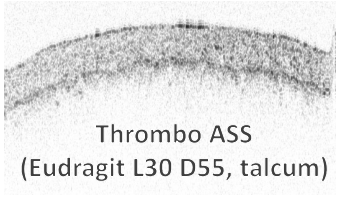
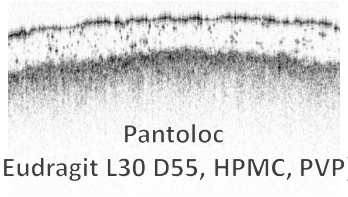
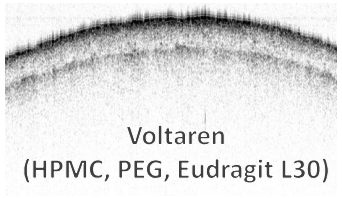
Enteric & controlled release tablets



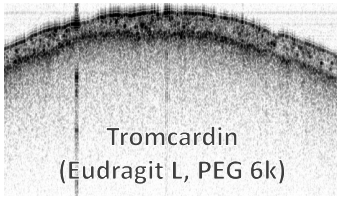
Thrombo ASS
(Eudragit L30 D55, talcum)



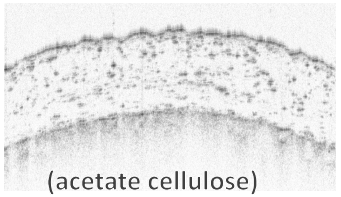
Pantoloc
(Eudragit L30 D55, HPMC, PVP)



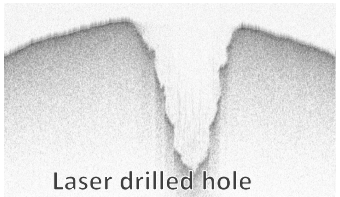
Voltaren
(HPMC, PEG, Eudragit L30)



Tromcardin
(Eudragit L, PEG 6k)

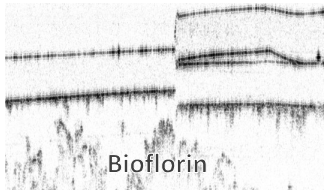


(acetate cellulose)

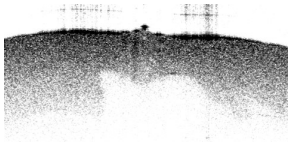


Laser drilled hole

Hard- and soft-gel capsules



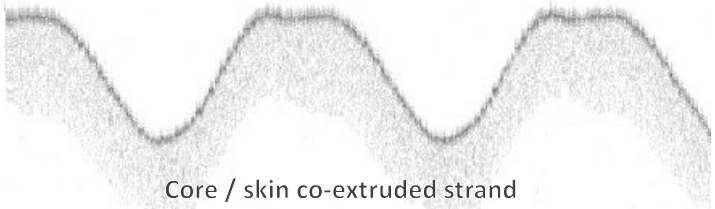
Bioflorin



Convulex

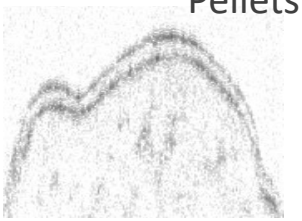
The world of
OCT in Pharma

Co-extrusion

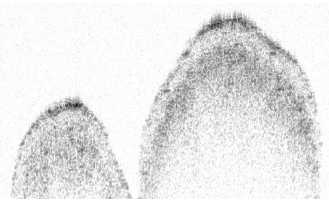


Core / skin co-extruded strand
(EVA, Fe2O3 tracer in skin)

Pellets & beads



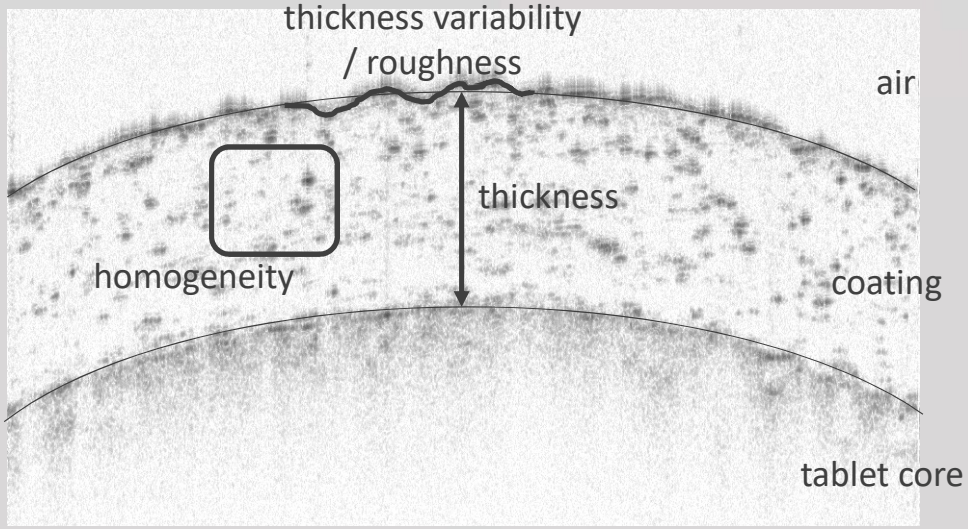
One coating layer



Multilayer coating

Coating Quality Characteristics of Enteric and Controlled Release Tablet Coatings

- Coating layer is of biopharmaceutical importance
- **Thickness**
  - Impact on dissolution time, diffusion kinetics
- **Thickness variability** (between and within tablet)
  - Might directly impact variability in dissolution rate
  - RSD after coating is still significant
- **Surface roughness**
  - Surface affects water uptake
  - Correlation to optical appearance (e.g., scuffing)
- **Homogeneity**
  - The structure within the coating
  - Agglomerate of excipients, air bubbles, …
  - Potential link to dissolution variability

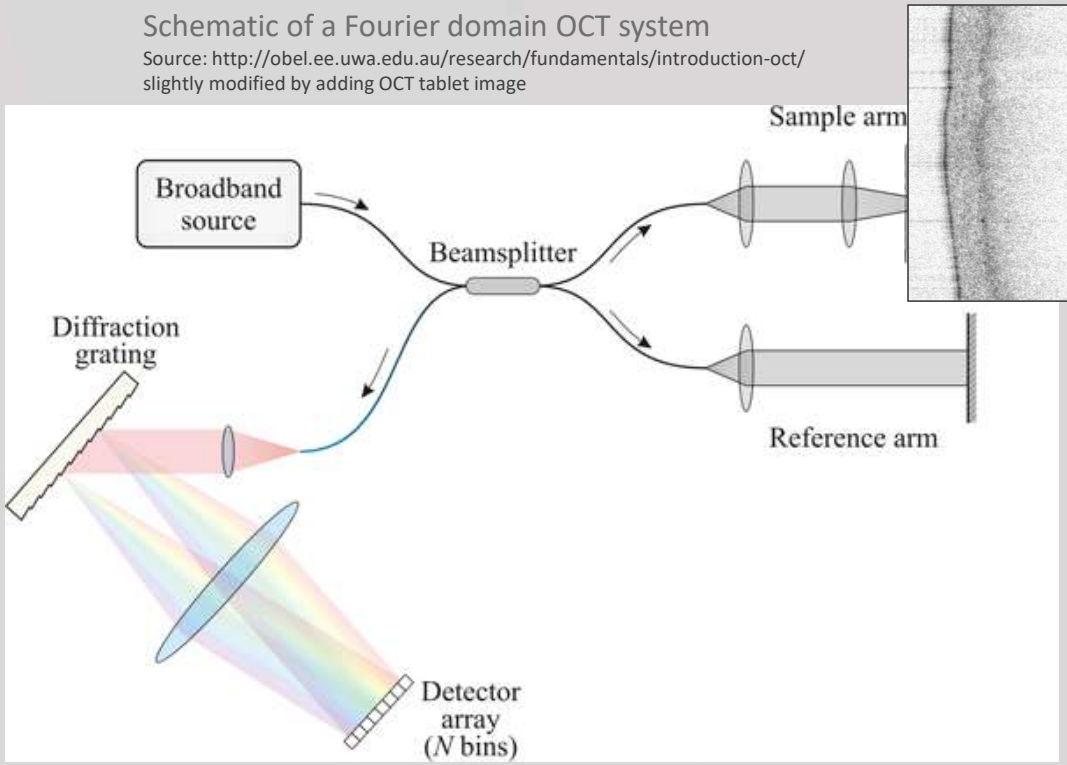


Better understanding of coating quality
brings significant benefit in formulation and process development

Interferometry: The Technology behind OCT

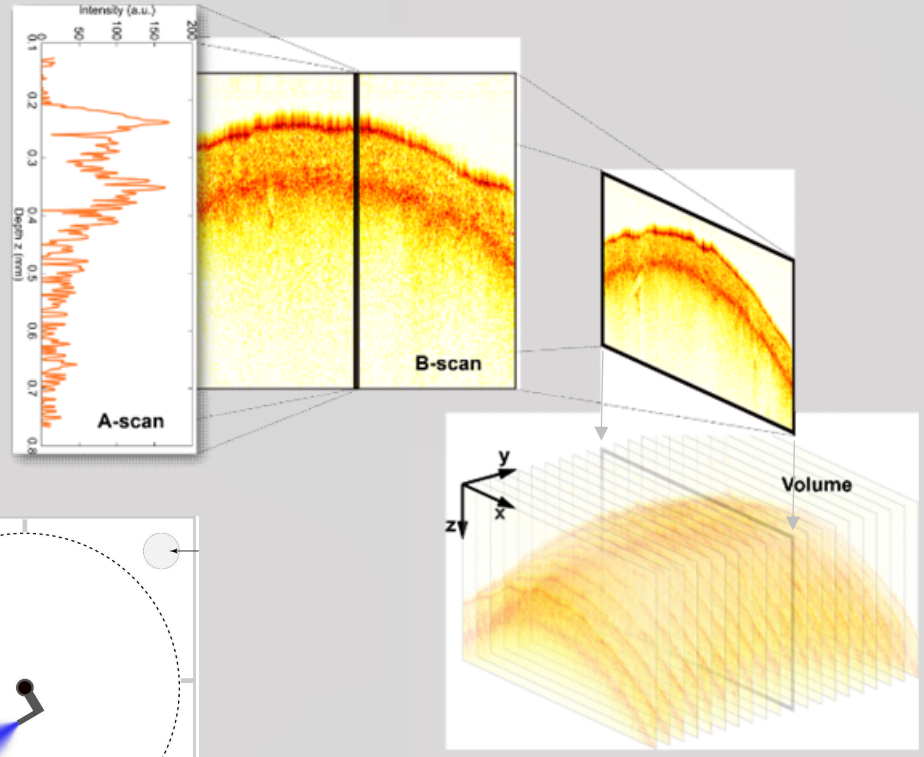
- OCT is based on (coherence gated) interferometry
  - 75nm bandwidth at 830nm center wavelength
  - Defines the **axial (=depth) resolution – 5µm**
- Light is split in reference and probe path
- Optics of sample arm focus light and define **lateral (=surface) resolution – 14µm** in focus
- Interference of light reflected back from both paths
- Spectrometer (grating, CCD line scan camera)
- Depth-information is generated from interference by Fourier-transformation (FFT)
- Depth scan measurement rate: **100kHz**
- **Direct thickness measurement** (optical path length)

Schematic of a Fourier domain OCT system
Source: http://obel.ee.uwa.edu.au/research/fundamentals/introduction-oct/
slightly modified by adding OCT tablet image

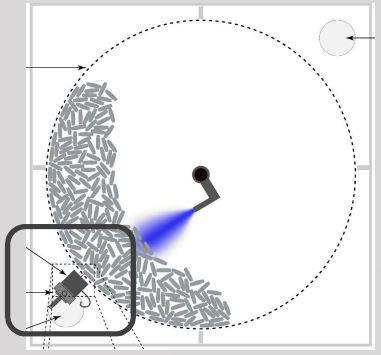


The “ABC of OCT” - Nomenclature

- Each interferogram → one depth reading (“**A-scan**”, 1D)
  A-scan rate: 100kHz max.
- Multiple A-scans → cross-sectional image (“**B-scan**”, 2D)
  Demands moving of objects or scanning sensor beam
- Multiple B-scans → full **OCT volume** (“C-scan”, 3D)
  Raster-scanning of probe with sensor beam



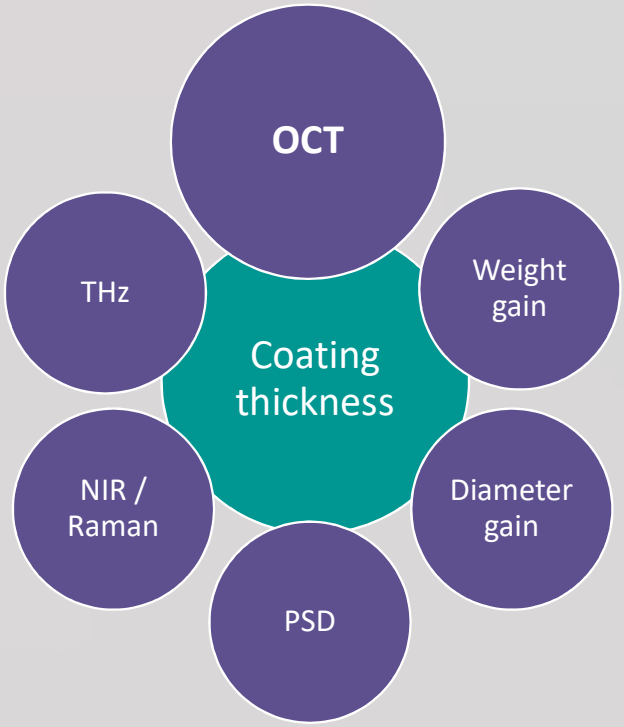
OSeeT pharma 1D is based on B-scans,
by moving objects relative to the OCT sensor
(e.g. tablets in a pan coater)



Implementation
in a pan coater

Why **OCT**

for in-line measurement of coatings



- Direct measurement of coating thickness & quality
  - No chemometric modelling → low Total Cost of Ownership
  - No indirect monitoring of growth via D50 shift of particle size
- Statistically relevant; hundreds of samples evaluated per minute
- Wealth of information
  - Mean coating thickness over whole run
  - Coating variability between particles
  - Homogeneity and roughness of coating
- Ease of use; intuitive software requiring no special scientific training

End-point control of an industrial pan coating process

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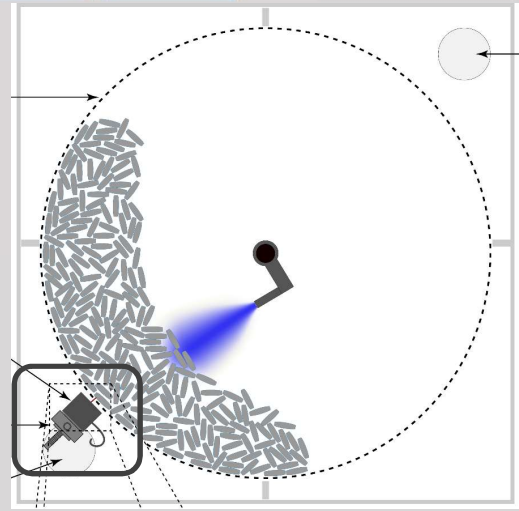
Materials & Methods

- Coater: Glatt GCC 150
- Materials
  - Placebo oval shaped cores: 11.6 x 6.1 x 4.6 mm
  - 50kg batch
  - Coating: Kollicoat IR, PVA-PEG copolymer, 15% aqueous solution
- Common reference methods
  - Weight gain of 100 tablets, corrected for residual moisture via LoD
  - Sprayed coating solution
- OCT based end-point detection at 50µm; manual stop of coating
- Aim for Glatt: Test data quality and in-line capability of OCT



Performed Experiments and Results

- Run 1a-d: **Replicates** with identical process parameters
- Run 2: **Higher spray gun to bed distance**
  - Lead to spray drying
    → higher total amount sprayed (kg)
  - Same weight gain, also for lower efficiency
- Run 3: **Larger cores**
  - Core dimensions: 18.5 x 9 x 6.5 mm
  - Less total surface area
    → lower total amount sprayed (kg)
  - Higher area per tablet
    → higher weight gain (mg)
- Run 4: **Lower PVA concentration**
  - 10% instead of 15% in aqueous solution

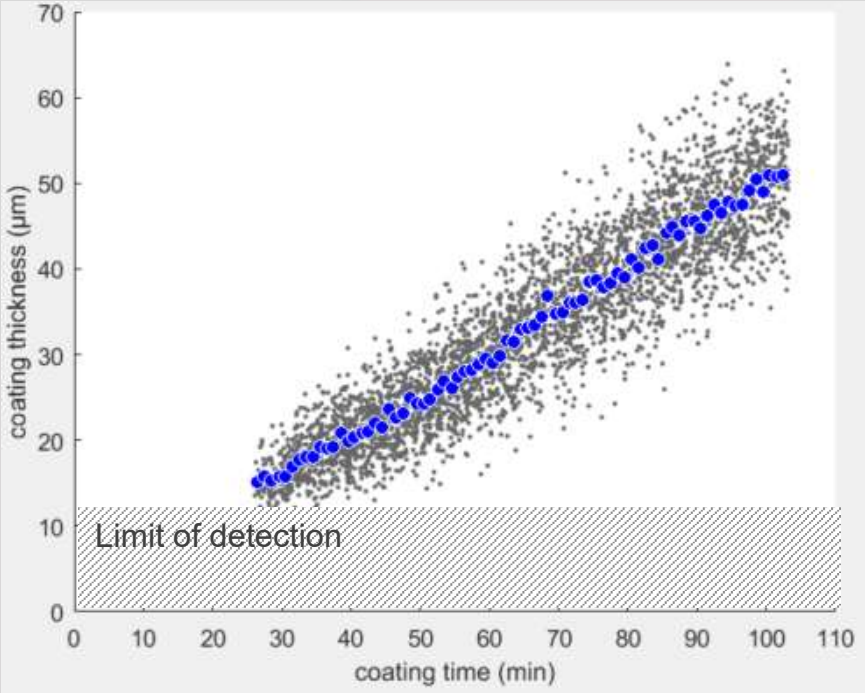
Glatt Test runs

	Run 1a	Run 1b	Run 1c	Run 1d	Run 2	Run3
Tablet core [mg]	256.6	256.6	256.6	256.6	256.6	782.0
Gun to bed distance [mm]	200				300	200
Total spray amount [kg]	13.9	14.6	13.9	14.3	15.7	11.4
Weight gain [mg]	10.9	11.0	10.9	11.4	11.4	28.2
Weight gain [%]	4.2	4.3	4.2	4.4	4.4	3.6
Film thickness [µm]	50					
Efficiency, moisture corrected	98%	96%	98%	97%	91%	98%

OCT Coating Trajectory of Run 1a

End-Point Results			
Mean Thickness:	**50.67 µm**	Mean Roughness:	4.82 µm (± 20.94 %)
Target Thickness:	150 µm	Mean Homogeneity:	48.43 % (± 18.55 %)
Batch Variation:	**±5.66 µm**	# Datapoints:	3467
Relative Batch Variation:	±11.18 %	Elapsed Coating Time:	01:17:12
End-Point Time Frame:	00:01:00		

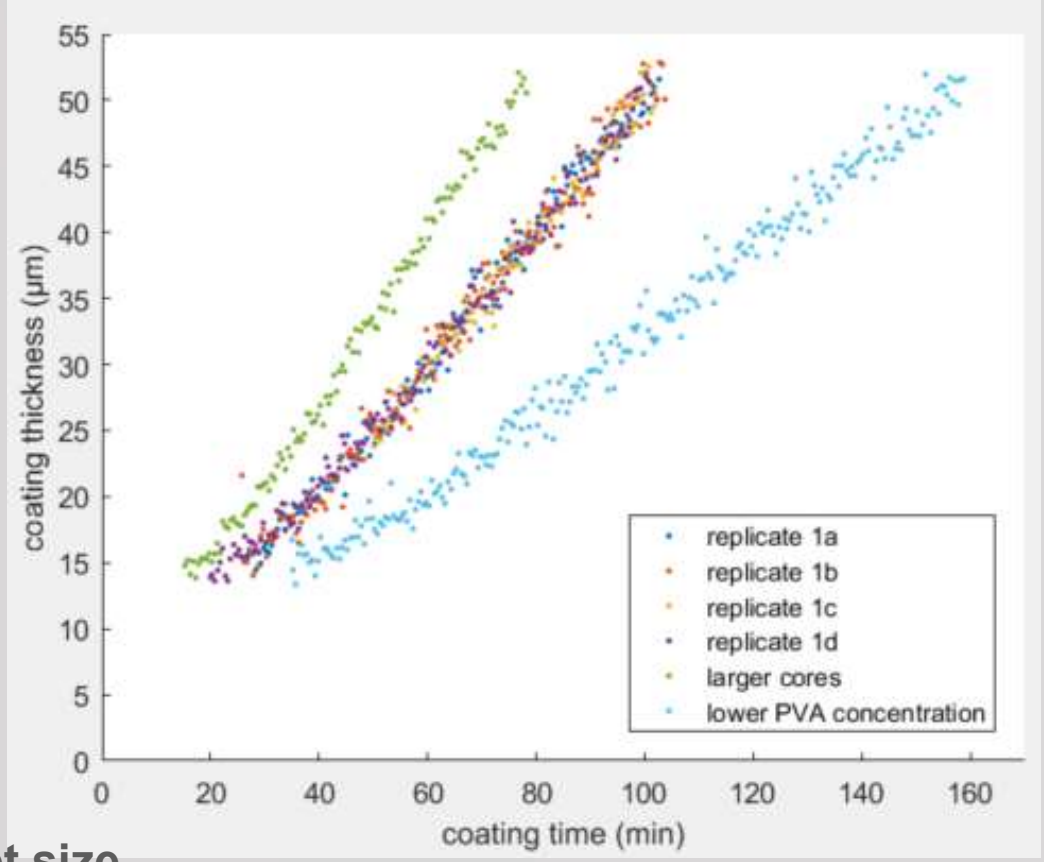
- Dark gray: Each point is a single tablet
- Blue: Mean of all tablets within 60 seconds
- Statistics for end-point are calculated on an adjustable time frame of 60 seconds
- Observed variation (RSD of ~11%) for single tablets at the coating end-point is common



Comparison of Coating Runs

- Replicate 1a-d:
  - Very good repeatability
    → stable coating process
- Run 3: Larger cores
  - Less total surface area
    → faster coating process
- Run 4: Lower PVA concentration
  - 10% instead of 15% in aqueous solution
    → 50% longer coating time

- **Reliable end-point detection via OCT, despite variations in efficiency, concentration or tablet size**



OCT based surrogate model for dissolution

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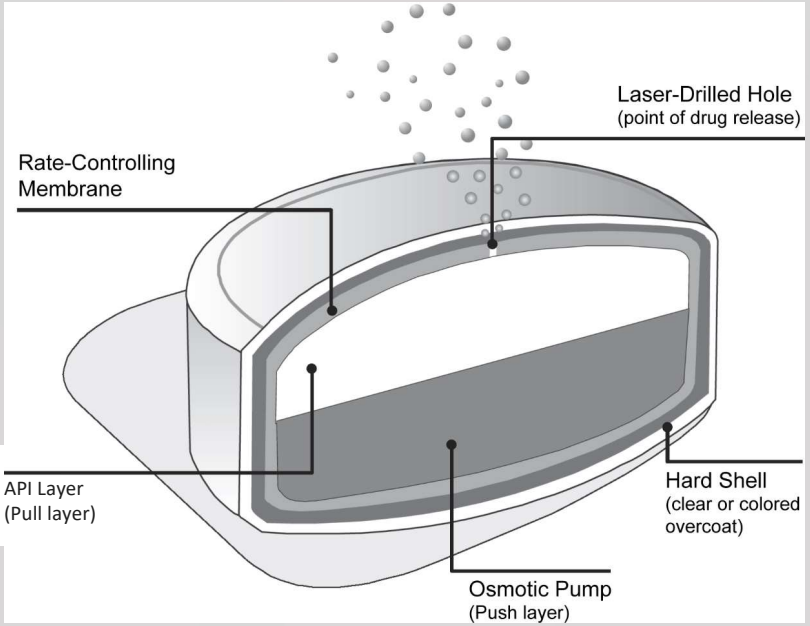
Osmotic Push/Pull Tablets (OROS) for Controlled Release

- First order release
  - Constant release rate over extended periods (>10 hours)
- Semi-permeable membrane
  - Permeable to water, but impermeable to drug solution
  - Commonly cellulose acetate (good water permeability)
  - Adjustable permeability by e.g. plasticizers
- Swell-able polymer as push layer
- Drug solution will be pushed through orifice
- **Aim of the study:**
  Understand impact of coating on drug release rate to develop surrogate model for dissolution



Slightly modified from source: Providing Constant Analgesia with OROS Hydromorphone, S. Gupta, S. Gayatri, Journal of Pain and Symptom Management, vol. 33 (2), 19-24, 2007

Materials & Methods

Coating Process of OROS Tablets

- 4 semi-perforated pan coaters (Freund-Vector)
  - Solvent coating
  - Differences in design and spray gun configuration
  - Lead to different efficiencies and OCT coating quality parameters
- Sampling
  - Drawn at t = 0, 50, 60, 70, 80, 90, 100, 104% coating progress
  - Sample size per time point: 300 tablets
- At-line OCT to measure samples
- Dissolution test over 16 hours

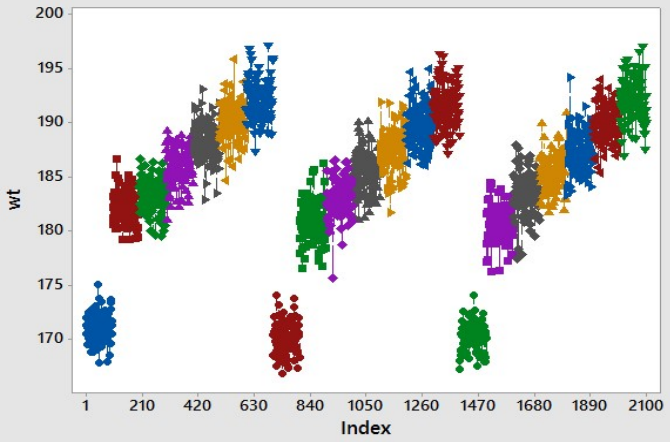
At-line sampling device with integrated OCT probe

Classical Methods to Measure Coating Progress

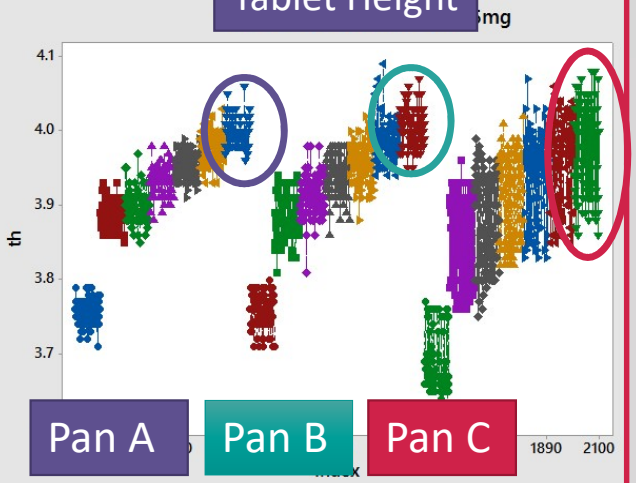
- Classical methods:
  - Weight-, height- and diameter-gain
  - Observed variation is due to coating AND method
- Large variations in dissolved API despite similar readings

	Dissolved API (%)		
Dissolution time	**4 hours**	**8 hours**	**16 hours**
Pan A - 100%	25.3%	63.5%	106.2%
Pan B – 100%	14.9%	48.1%	103.7%
Pan C – 100%	13.1%	40.9%	95.0%

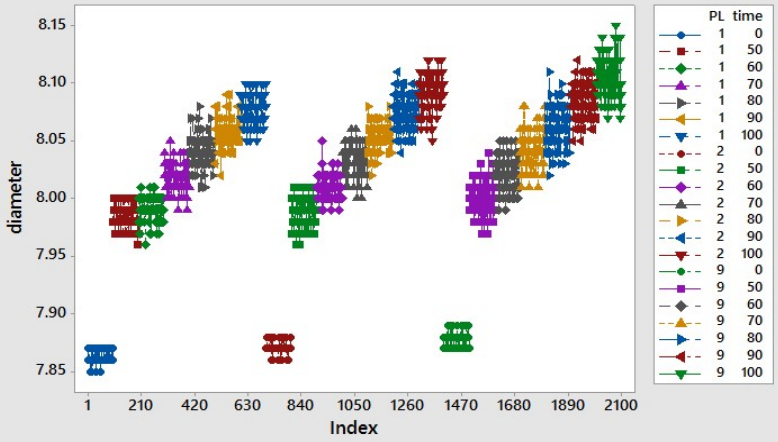
Tablet Weight



Tablet Height



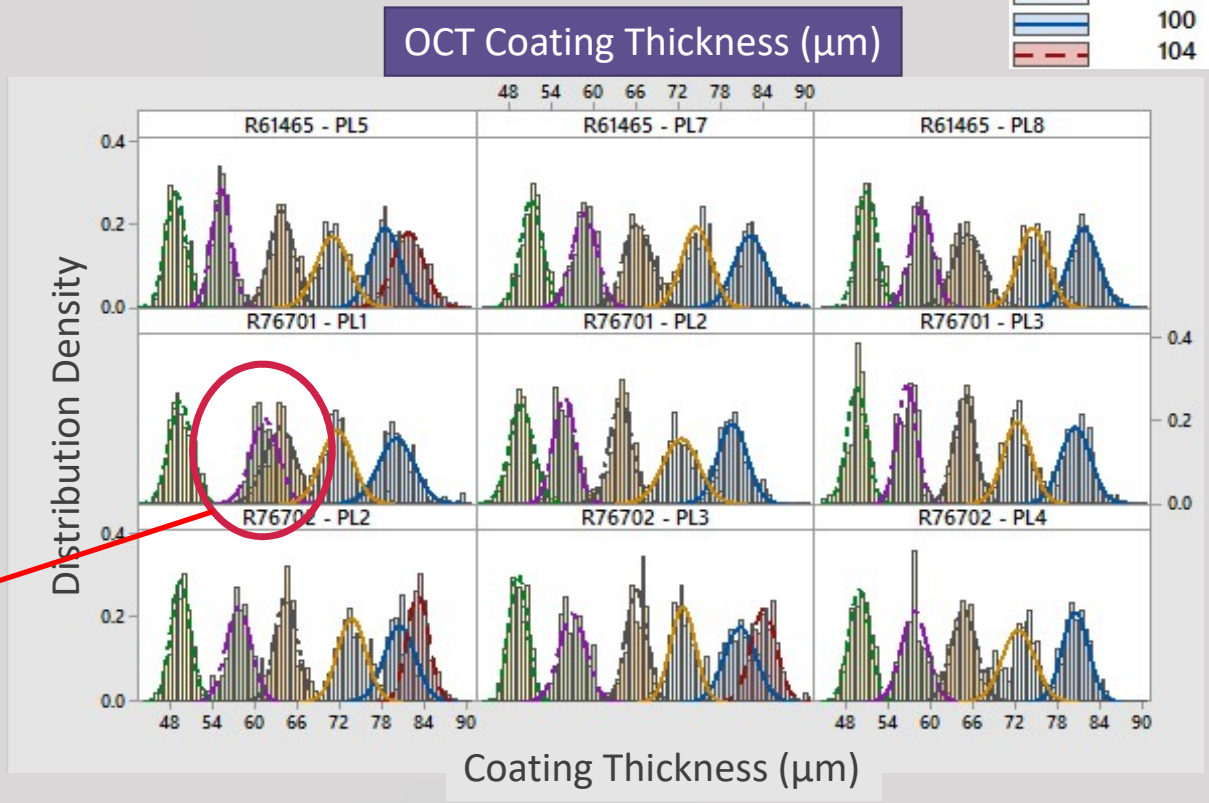
Tablet Diameter



OCT to Measure Coating Thickness

- OCT measures coating thickness distribution for each sample
- Gaussian like distribution
- Human error in timing of sample drawing was detected

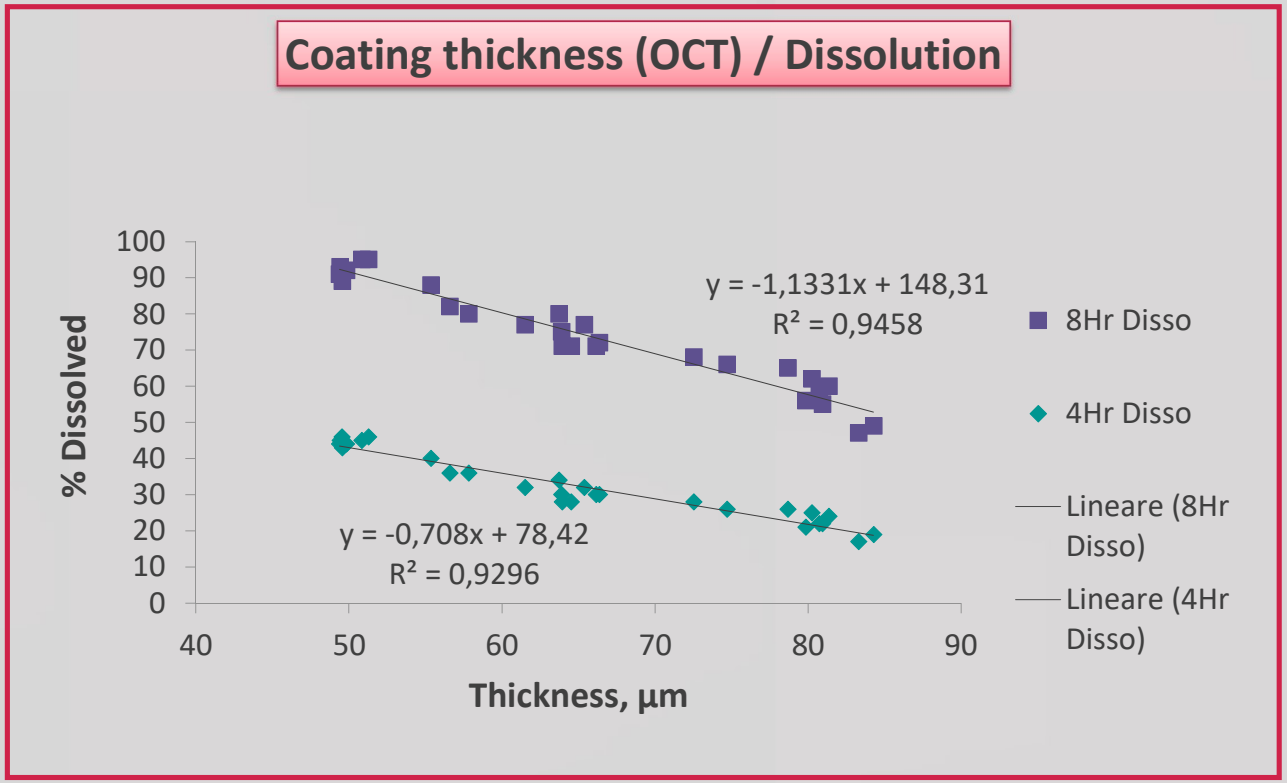
Samples	Thickness (µm)	4 Hr Disso (API %)	8 Hr Disso (API %)
PL7-60%	51.28	46	96
PL7-80%	66.35	30	73
PL1-60%	49.54	46	91
PL1-70%	**61.51**	**32**	**77**
PL1-80%	**63.72**	**33**	**79**



Correlation of OCT Data to Dissolution

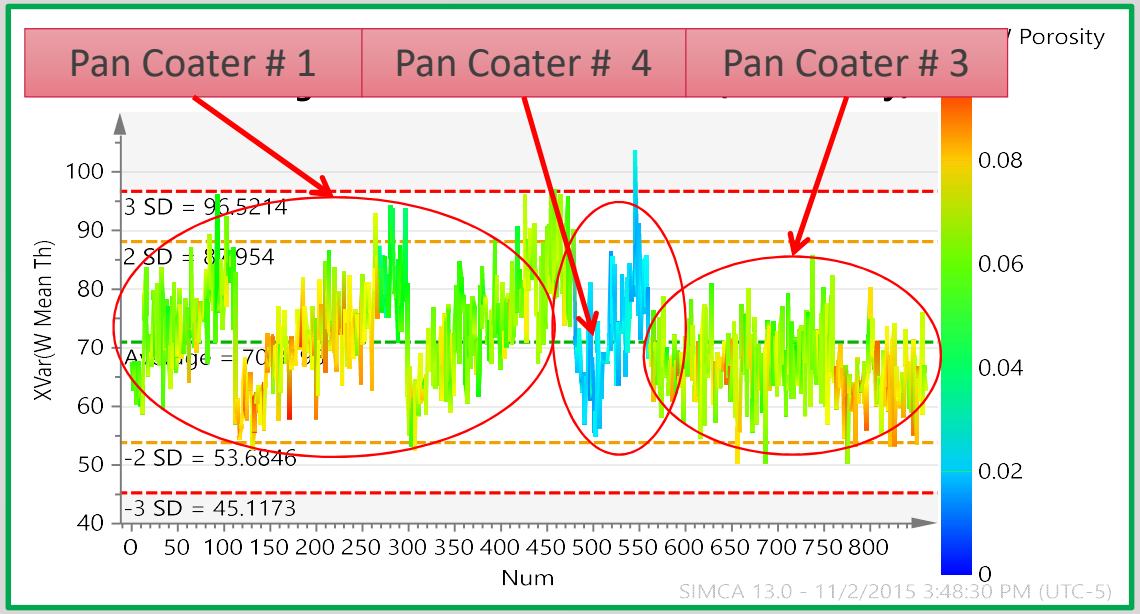
- Linear relation between OCT measured coating thickness and dissolution rate observed
- OCT shows better correlation than current weight gain method

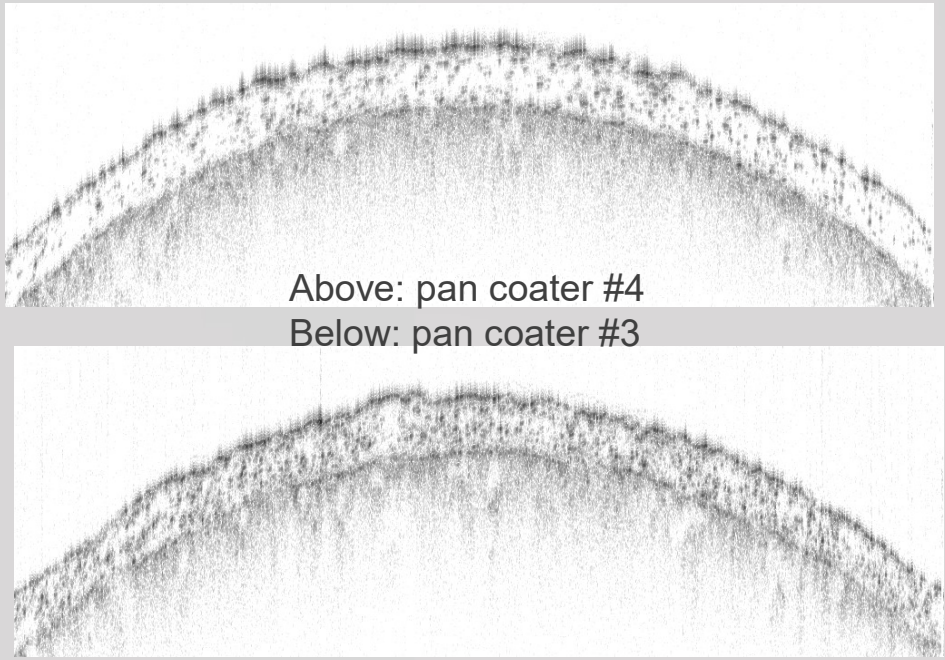
	OCT –R^2	WT Gain–R^2
4 Hrs Disso	0.93	0.86
8 Hrs Disso	0.95	0.90



Not Only Coating Thickness Matters

- Tablets of pan coater #4 showed higher coating homogeneity
- OCT images show that visually





Above: pan coater #4
Below: pan coater #3

Wrap-Up

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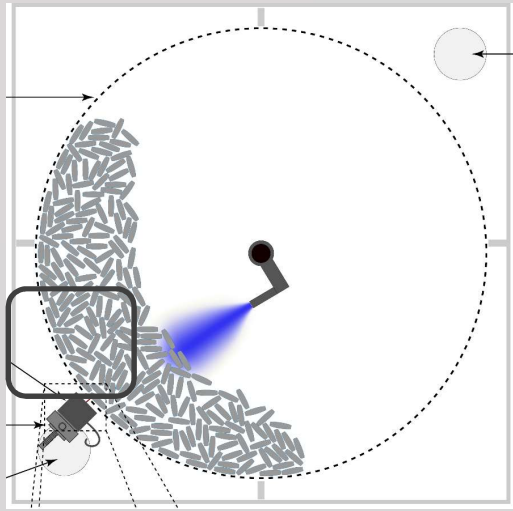
Wrap-Up

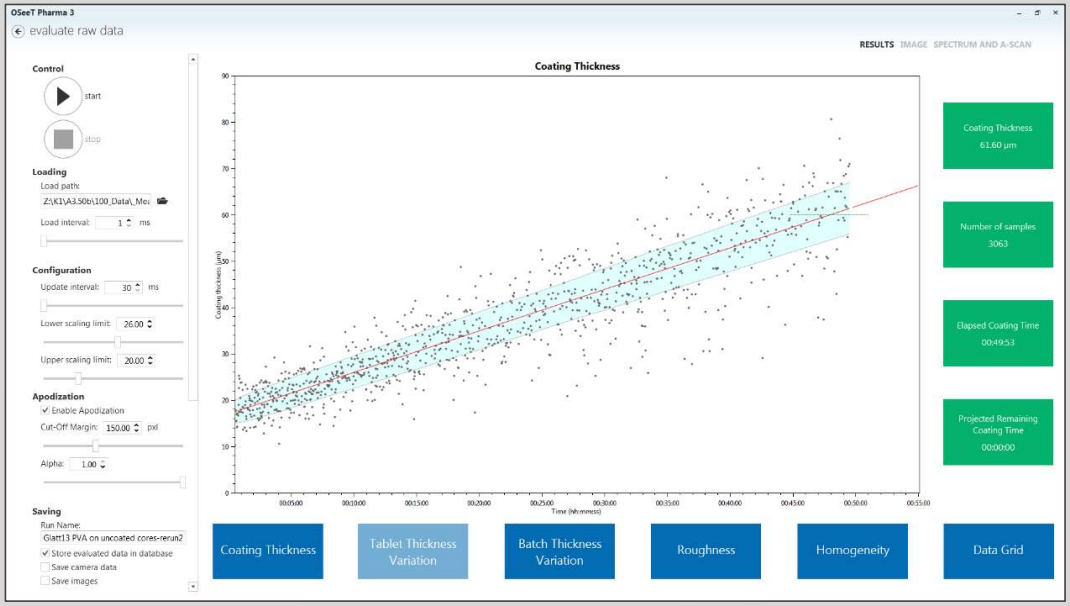
In-line Monitoring of a Pan Coating Process

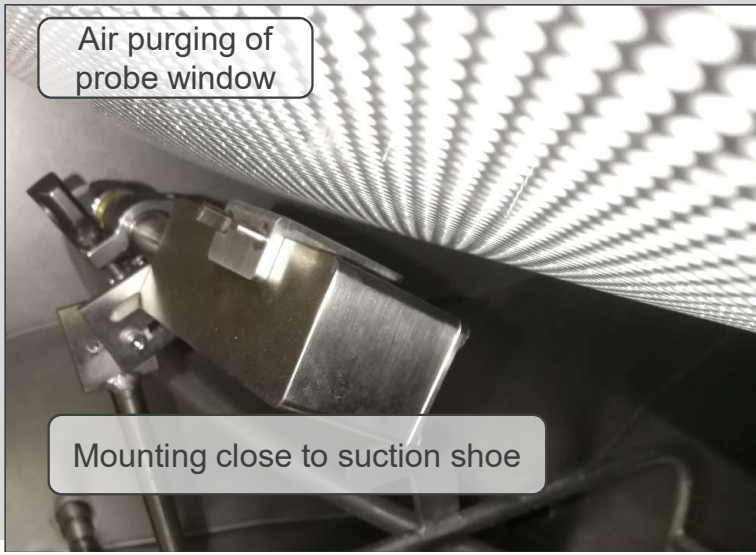
Process development: fast coating quality and thickness analysis during DoE studies

Scale-up: compare coating quality (e.g. scuffing) and thickness between scales

Manufacturing: end-point independent of spray efficiency or process variations

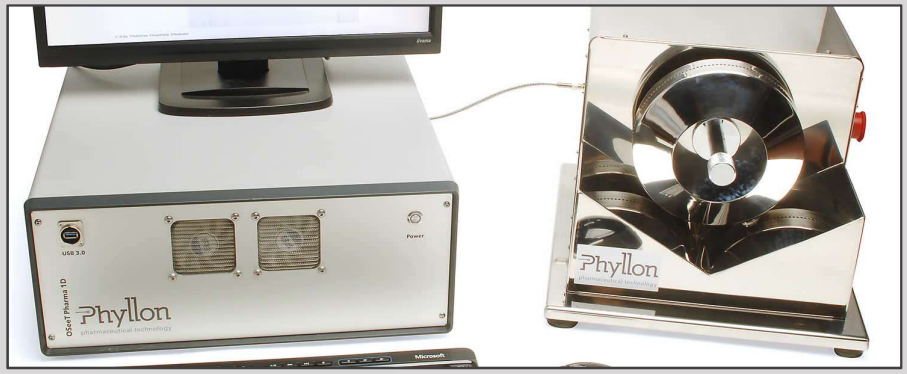






OSeeT pharma 1D: Industrial Ready OCT System

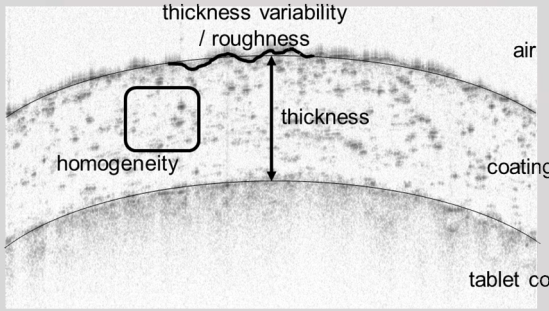
- **In-line configuration**
  - Hygienic design, rugged, air purging
  - ATEX, IP66 certification
  - Real-time monitoring of coating process
- **At-line configuration**
  - Sampling device (miniature drum) for mixing of sample
  - Fast analysis of representative number of tablets, at-line in manufacturing area
- A strong collaboration
  - RCPE holds patent is developing technology
  - Phyllon is manufacturer and distributor



Wrap-Up

OCT for Pharmaceutical Films and Coatings

- OCT is a **calibration free** method
  - No chemometric modelling needed - only refractive index
- Mean **coating thickness** over whole run
- Inter- and intra-particle **coating variability**
- **Coating quality: homogeneity** and **roughness**

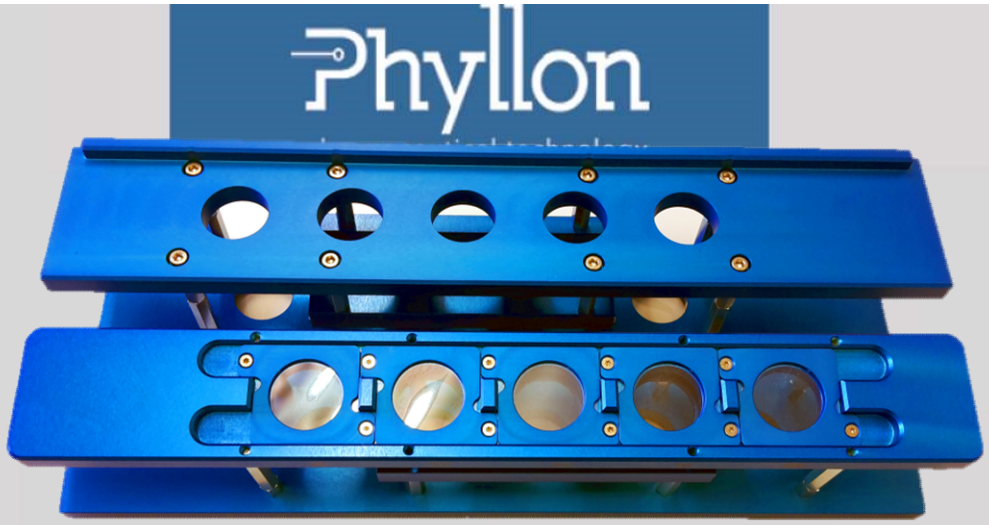


OCT brings the quality and confidence
of labor intensive and manual methods (e.g. diameter or weight gain)
to a real-time in-line method with additional insights in coating quality

Wrap-Up

Reference Target for OQ

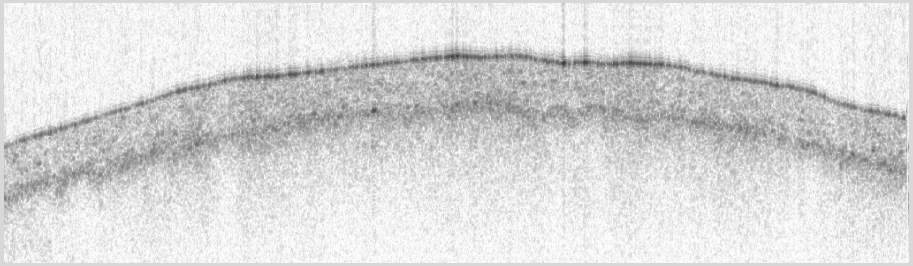
- Verify accuracy and linearity (operational qualification) by sliding probe over reference target
- Software support via reference wizard
- Foils with defined thicknesses
  - 19, 36, 50, 75, 100, 125, 190 µm
- Foils characterised via
  - OCT
  - THz
  - µCT
  - Caliper
- Paper on reference target in preparation



Feasibility Study

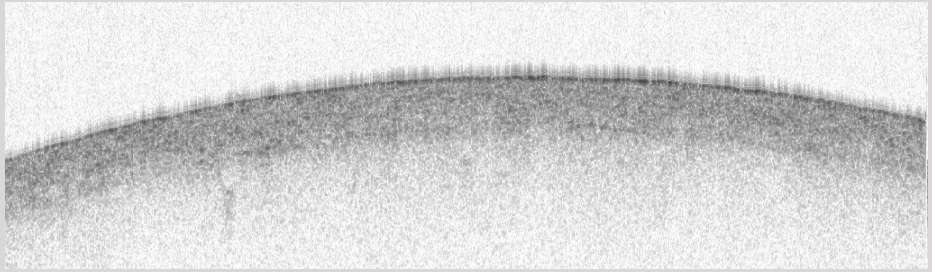
Differentiating Coating Quality with OCT

Good coating process



- Lower scattering in coating indicating a uniform coating layer
- Coating-Core interface clearly visible

Sub-optimal process



- Highly scattering coating layer likely caused by incomplete film forming or poorly dispersed talc
- Less ballistic photons reach coating-core interface, resulting in poorer contrast

- EUDRAGIT® L30 D-55 does not show curing
- Thus, process conditions for coating must be well chosen
- **Coating quality differences can be determined with OCT**

Monitoring of a Fluid Bed Coating Process

- Emulation of a Wurster coater fluid bed process
- Up to 250rpm = ~2m/s circumferential speed
- Pellets: Cellets 1000, 40µm coating
- Probe can measure through glass of fluid bed coater
- From 1 mm to 25 mm thickness
- Tests in industrial Wurster coaters lab and production scale (MiniGlatt and Glatt GPCG30 with 18” tube)

Pellets with a velocity of ~2m/s (typical for Wurster coaters)

Pellets on rotating disc

Fluid Bed OCT Probe

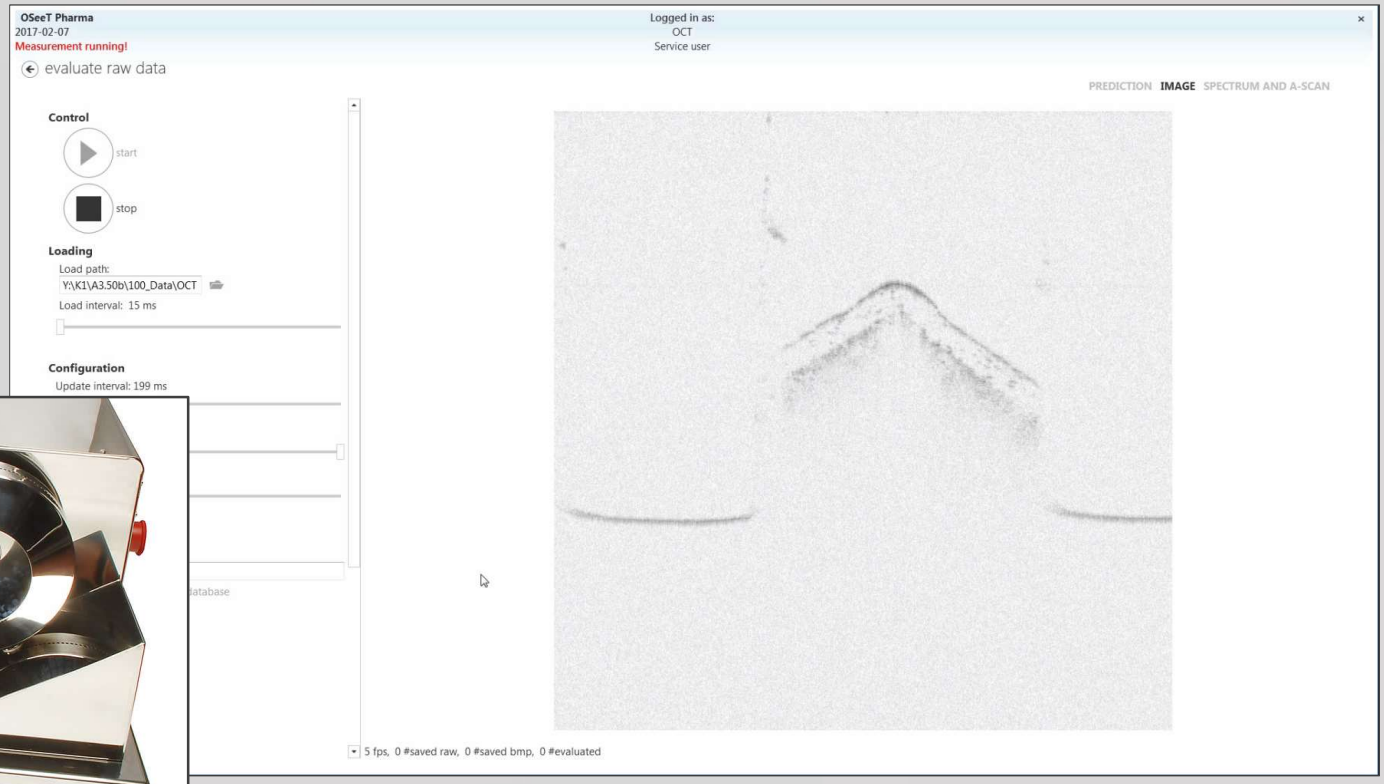
Glass window (hidden)

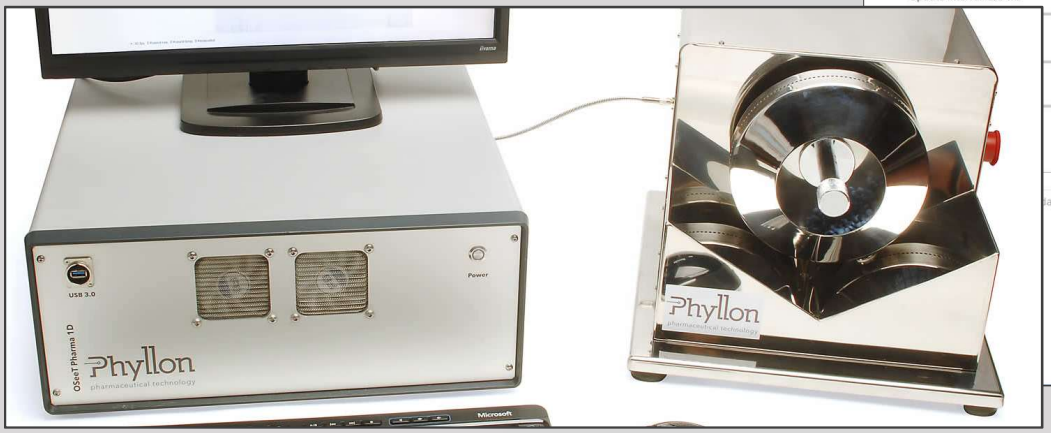
Suggested OCT probe location

Example image of Wurster coater

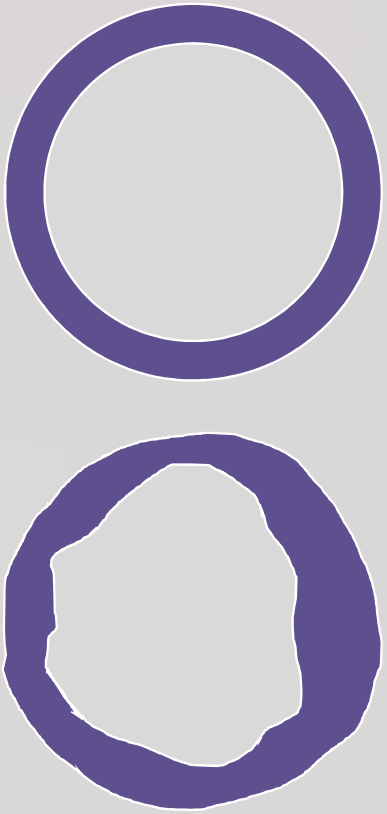
At-line Sampling Device for In-Process Control

- Miniaturised drum-set up tailored to mimic large scale pan coater
- Fast analysis of representative number of tablets at-line in manufacturing area
- Confirm coating end-point, independent of process variations
- Support in process development





Co-extrusion of Core-Skin Reservoir System

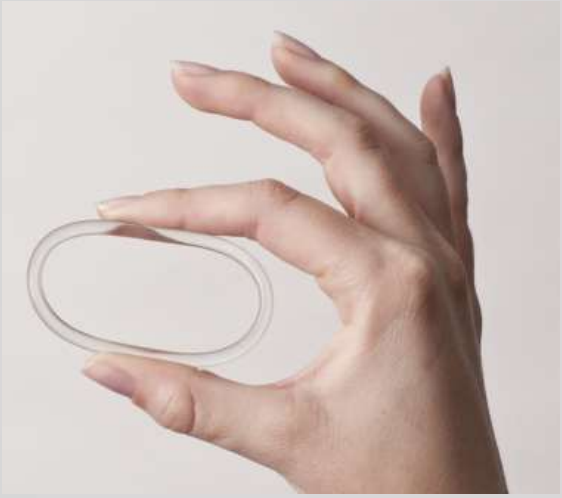


Desired (“the good”) co-extruded strand

- Spherical core and skin
- Identical center point
- Resulting in homogenous skin thickness

Real (“the ugly”) co-extruded strand

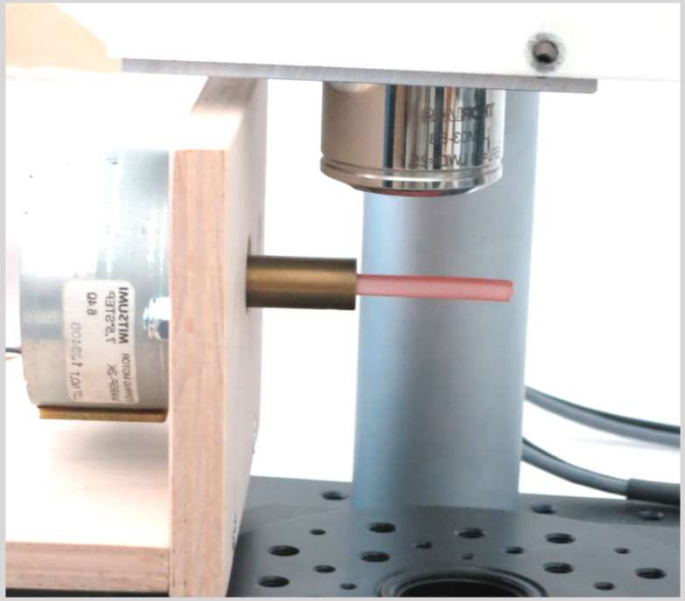
- Rough core and/or skin
- Variations in skin thickness

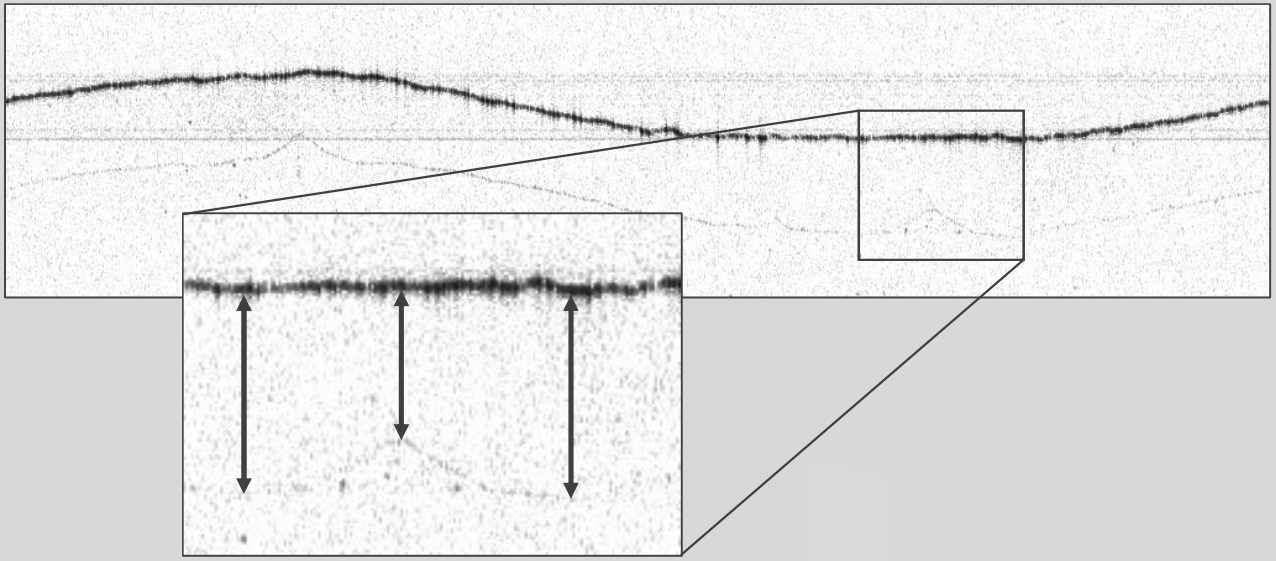


source: ourmomentoftruth.com

Co-extrusion product:
NuvaRing for birth control

Co-extrusion of Core-Skin Reservoir System



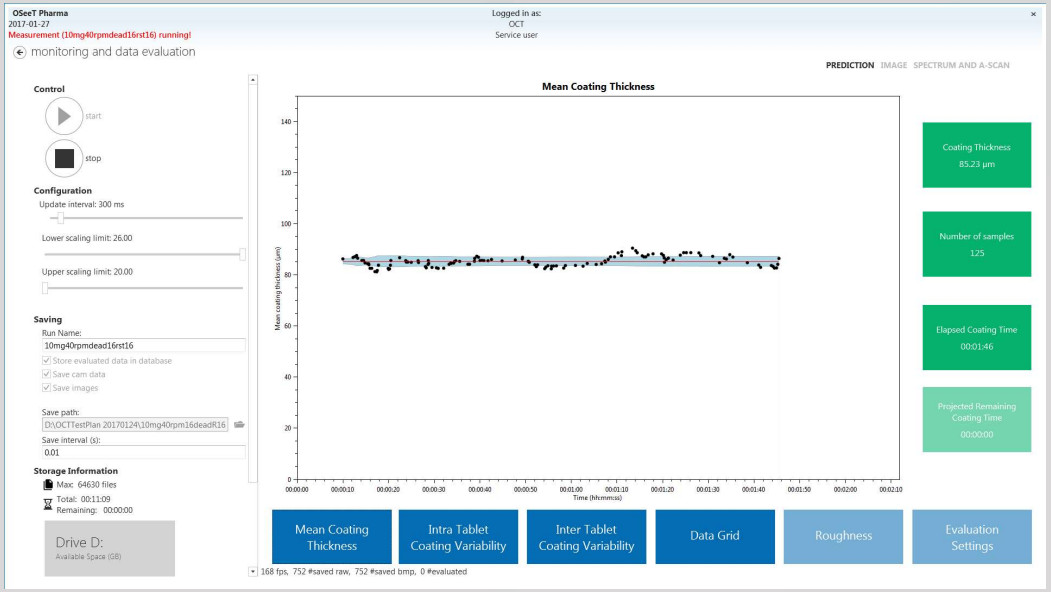


- Rotation of strand with stepper motor
- Map of circumference with 3D OCT head

- Skin of co-extrusion product over entire circumference
- Skins thickness variations can be seen
- Two thin regions: Melt fronts merge
- OCT to support co-extrusion process development

OCT System Commercialisation

- Strategic project started in 2012
  - Hardware for in-line and off-line analyses
  - 1st gen. algorithms for in-line data evaluation
- Further development of prototype since 2015
  - Algorithms and UI for **real-time data evaluation**
  - Collaboration with **large industry partners** for near-line sampling
  - **GMP, CE and ATEX compliant** equipment
  - **Patent granted** for in-line pharmaceutical applications
  - Technology commercialised via **licensing agreement with Phyllon GmbH**



OCT Software for in-line / at-line analysis

OCT 1D GMP Pan Coater Probe