Understanding the Science behind Coating Technology

The Heidelberg PAT Conference 2008

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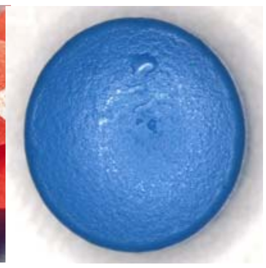
Tablet film coating

- Purposes of coating – cosmetic and therapeutic.
- Coating defects - blisters, peeling, variations in film coating thickness and density.
- Unpredictable dosing rate, dose dumping – life threatening





www.benoliel.com/graphics/Coating.jpg

Photographs courtesy of Colorcon®

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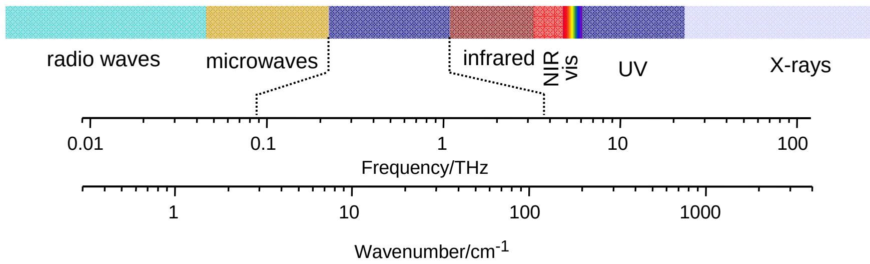
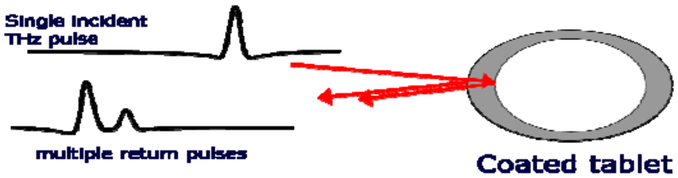
EUROPEAN COMPLIANCE ACADEMY

Terahertz radiation

2 cm^{-1} – 120 cm^{-1}, 60 GHz – 3.6 THz, 5 mm – 83 µm





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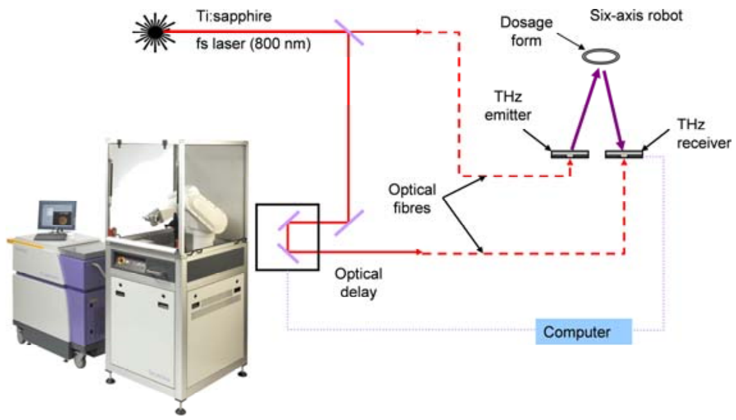
Terahertz Pulsed Imaging

Non-destructive coating analysis.
Fully automated process.



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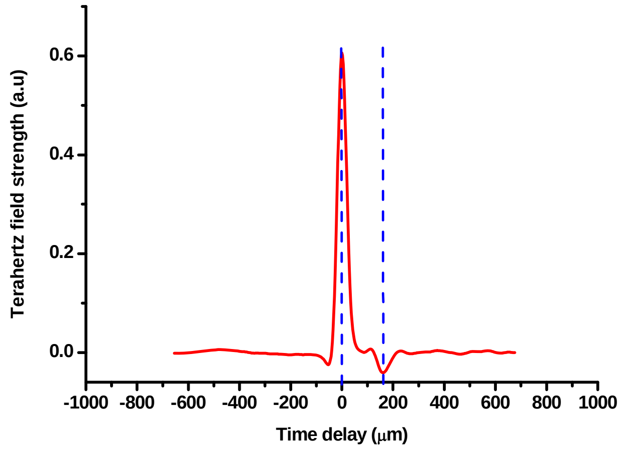
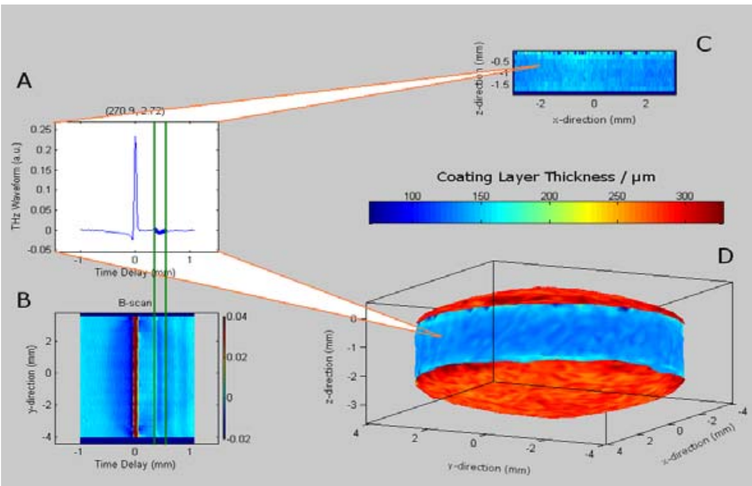
Terahertz parameter

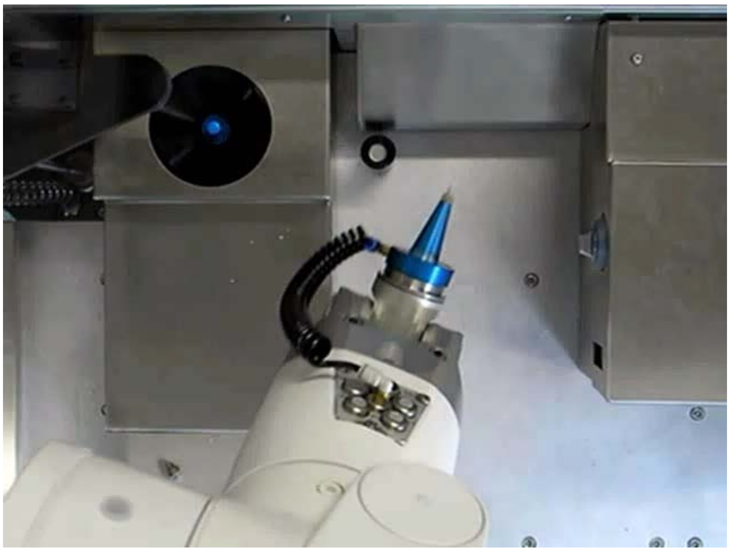
Coating thickness = 160 µm



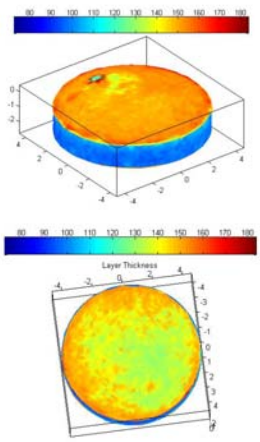
Terahertz 2D images and 3D models



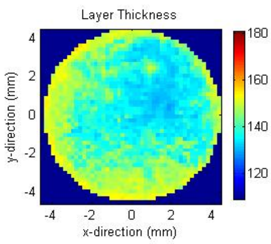
L. Ho, *et al*. EJPB., *In Press*. DOI: 10.1016/j.ejpb.2008.06.023 6

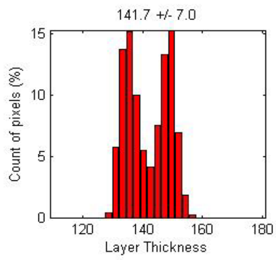


Intra-tablet variability



- Bimodal distribution.
- One side of the tablet was 10 µm thicker than the other.
- The coating around the central band was 33% thinner than that on the tablet surfaces.





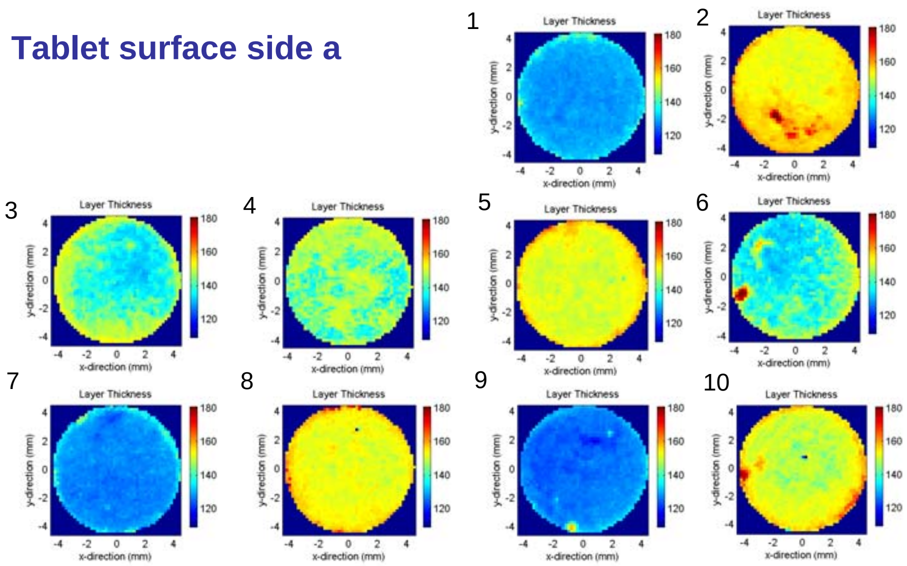
L. Ho, *et al. J. Controlled Rel.*,119 (2007); 253-26

Inter- tablet variability - 7%

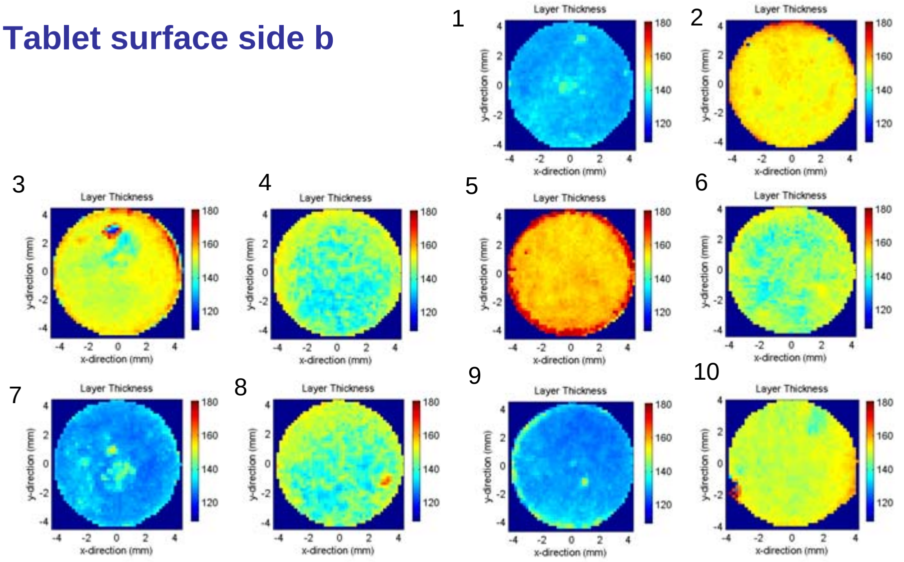
Sample	Microscopy layer thickness (µm)	TPI layer thickness (µm)
S1	139	130
S3	149	149
S4	144	143
S5	160	155
S6	137	143
S7	142	130
S8	150	150
S9	134	128
S10	151	152
Average	145	142
T Test **(p value)**	0.17	

L. Ho, *et al. J. Controlled Rel.*, 119 (2007); 253-26

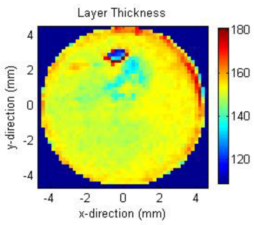
Tablet surface side a

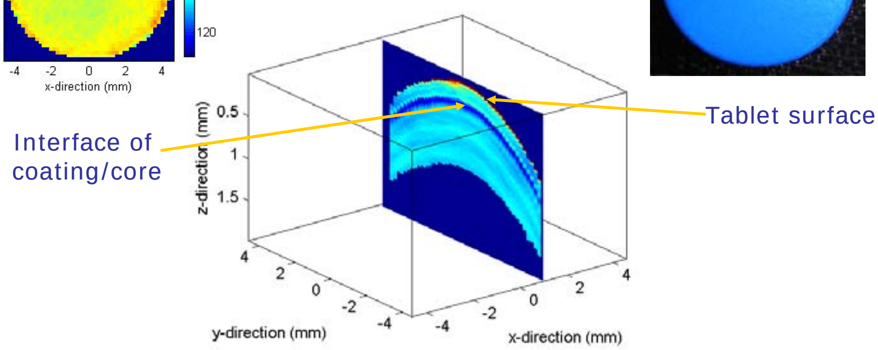


Tablet surface side b



Coating defects - craters and blisters





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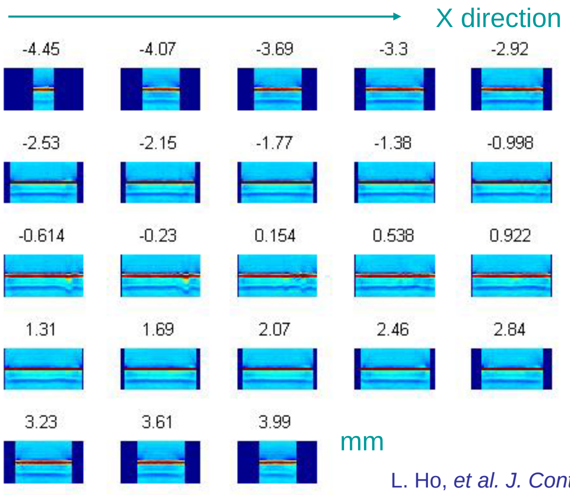
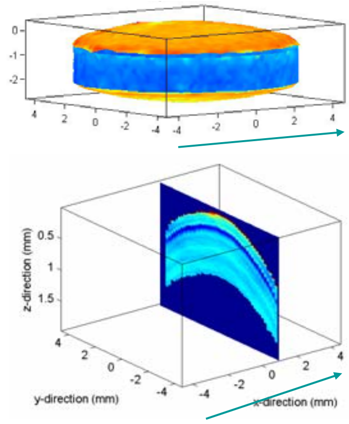
Coating defects - craters and blisters





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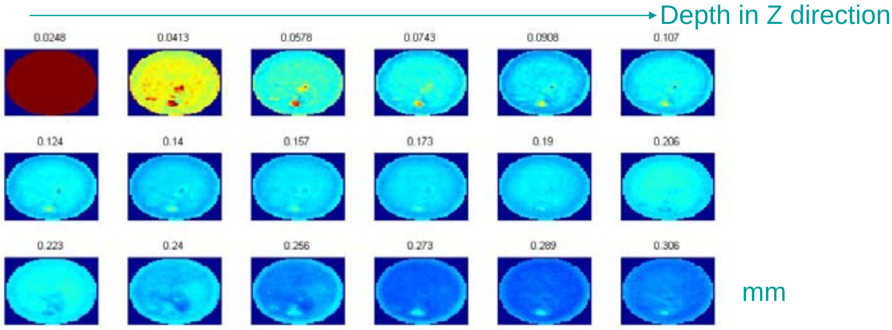
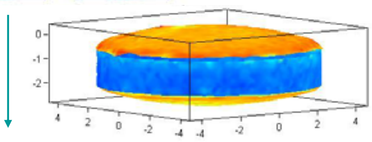
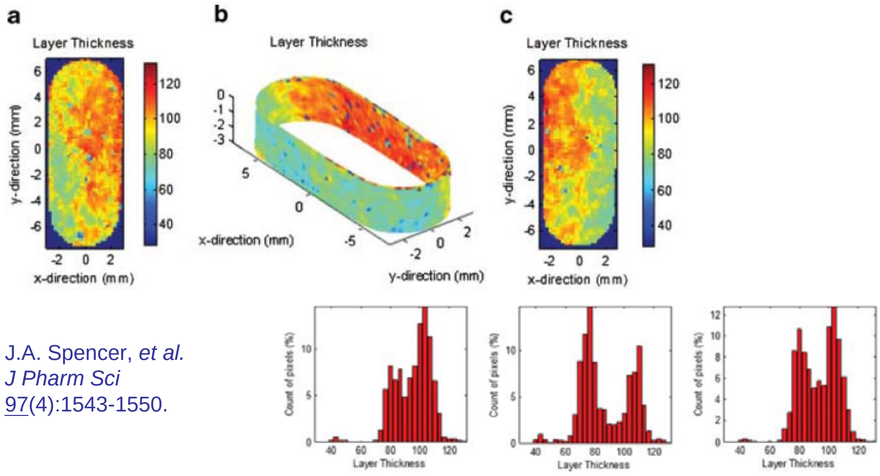
Coating defects - craters and blisters





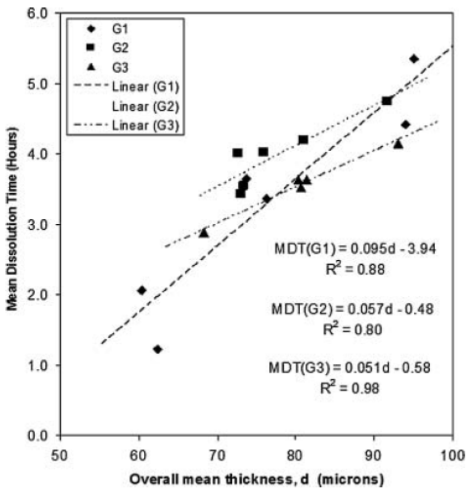
L. Ho, *et al. J. Controlled Rel.*,119 (2007); 253-26

FDA study - coating thickness variation



J.A. Spencer, *et al.*
J Pharm Sci
97(4):1543-1550.

FDA study - coating thickness and dissolution



J.A. Spencer, *et al.*
J Pharm Sci
97(4):1543-1550.

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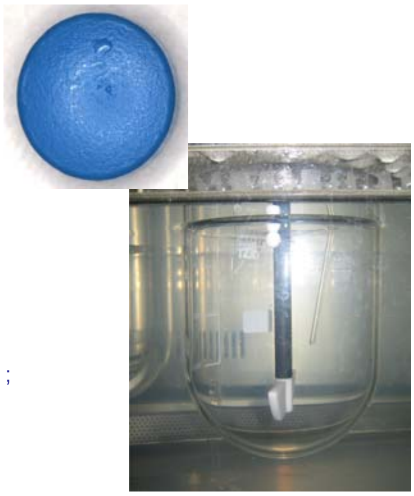
Traditional coating quality parameters

- Weight gain – non-specific
- The amount of coating formulation/ polymer applied – non-specific
- Dissolution – end stage



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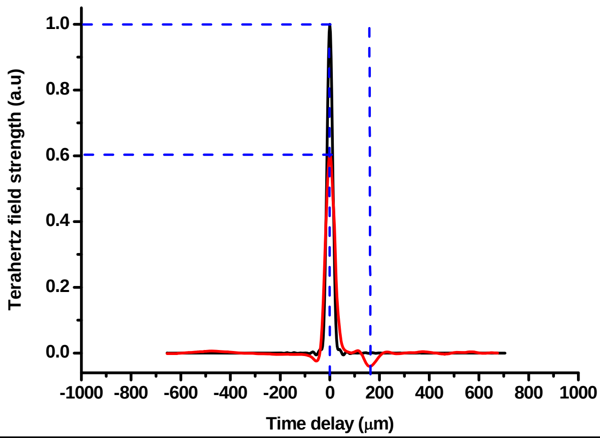
Terahertz parameters

Terahertz Electric Field Peak Strength (TEFPS) = 60%



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Sustained-release tablets

Diprophyllin	10%
Kollidon VA 64	5%
Magnesiumstearate	0.5%
Flowlac 100	84.5%

	aqueous	solid
Kollicoat SR 30 D	50%	67.8%
Kollicoat IR	6%	27.11%
Polysorbat 80	0.075%	0.34%
Glycerolmonostearat	0.30%	1.36%
Triethylcitrat	0.75%	3.39%
Deionised water ad	100%	

Production of lab and pilot scale tablets

- Lab scale

Batch size = 4 kg (2 batches)
Coater = BFC 5
(D x L = 316 mm x 356 mm)

- Pilot scale

Batch size = 20 kg (2 batches)
Coater = BFC 25
(D x L = 546 mm x 630 mm)

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Coating quality parameters

- Weight gain
- Dissolution model independent parameters:
  - MDT
  - Dissolution rate constant
  - $t_{20\%}$, $t_{50\%}$, $t_{80\%}$
- Terahertz parameters:
  - Coating layer thickness
  - Terahertz electric field peak strength (TEFPS)

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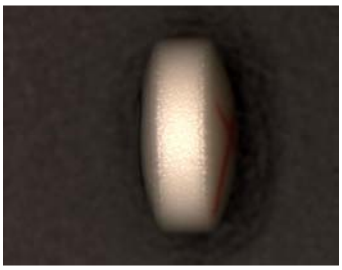
Weight gain

- Transparent tracer tablets
- 100 / batch
- Weighed prior and after coating



- 10 samples of similar weight gain (~42mg) were selected from each batch

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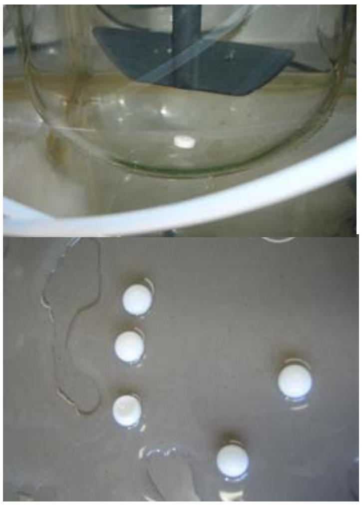
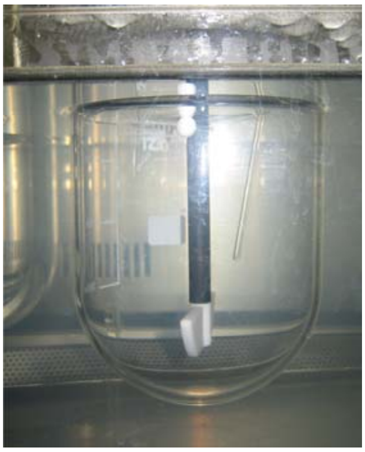
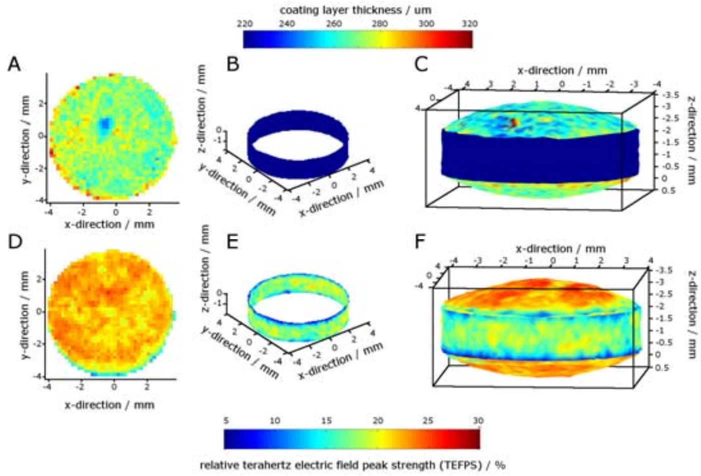
Dissolution





Coating thickness and TEFPS



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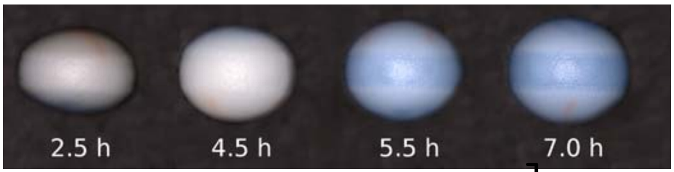
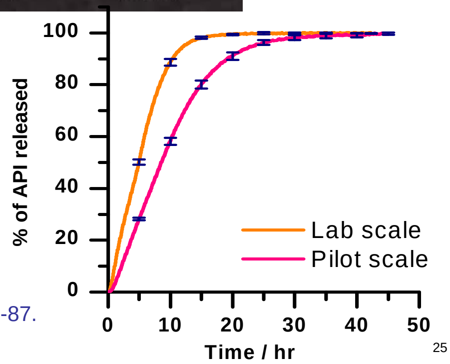
Discrimination between pilot and lab scales





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Discrimination between pilot and lab scales
Dissolution vs weight gain

	MDT (hr)	T20% (hr)	T1/2 (hr)	T80% (hr)	Dissolution release constant	Weight gain (mg)
PBI Mean	9.7	3.5	8.6	15	1.29	42.5
PBII Mean	9.8	3.6	8.4	15	1.23	42.6
LBI Mean	5.4	1.9	4.8	8.0	2.30	42.8
LBII Mean	5.4	1.9	5.0	8.4	2.26	42.5
PBI & LBI						
SD	2.2	0.87	1.9	3.6	0.52	0.490
RSD %	29	32	28	31	29	1.15
T test	2.0E-20	5.4E-20	5.1E-21	6.4E-17	1.0E-17	0.185
PBI & LBII						
SD	2.2	0.86	1.8	3.4	0.50	0.738
RSD %	29	32	27	29	28	1.74
T test	1.01E-20	1.57E-21	7.15E-22	1.05E-18	3.09E-20	0.930
PBII & LBI						
SD	2.3	0.91	1.8	3.5	0.55	0.387
RSD	30	33	28	30	31	0.906
T test	3.36E-16	6.20E-20	1.61E-20	1.47E-15	5.89E-18	0.247
PBII & LBII						
SD	2.2	54	1.8	3.3	0.53	0.686
RSD	29	33	27	28	30	1.61
T test	1.36E-15	2.84E-21	2.70E-21	1.03E-16	2.87E-20	0.707

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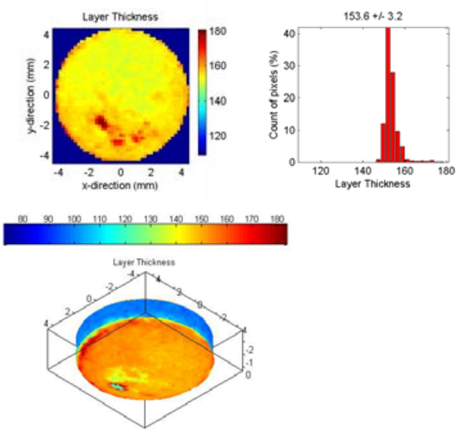
Discrimination between pilot and lab scales

Terahertz vs weight gain



	Weight gain (mg)	TEFPS (%)	Coating layer thickenss (um)
PBI Mean	42.5	20.9	190
PBII Mean	42.6	20.7	188
LBI Mean	42.8	19.4	200
LBII Mean	42.5	19.5	202
PBI & LBI			
SD	0.490	0.815	6.02
RSD %	1.15	4.05	3.09
T test	0.185	9.0E-08	4.1E-08
PBI & LBII			
SD	0.738	0.769	7.10
RSD %	1.74	3.81	3.63
T test	0.930	3.21E-07	5.08E-07
PBII & LBI			
SD	0.387	0.744	6.72
RSD	0.906	3.70	3.47
T test	0.247	5.37E-08	1.02E-10
PBII & LBII			
SD	0.686	0.698	7.80
RSD	1.61	3.46	4.00
T test	0.707	2.24E-07	1.28E-08

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Correlations – early indications

	MDT	T20%	T1/2	T80%	Dissolution release constant	Weight gain	TEFPS	Coating layer thicknes
MDT	1.00	0.99	0.99	0.99	-0.98	-0.29	0.89	-0.95
T20%	0.99	1.00	1.00	0.99	-1.00	-0.24	0.89	-0.93
T1/2	0.99	1.00	1.00	1.00	-0.99	-0.27	0.90	-0.94
T80%	0.99	0.99	1.00	1.00	-0.99	-0.26	0.89	-0.93
Dissoluton release constant	-0.98	-1.00	-0.99	-0.99	1.00	0.24	-0.90	0.93

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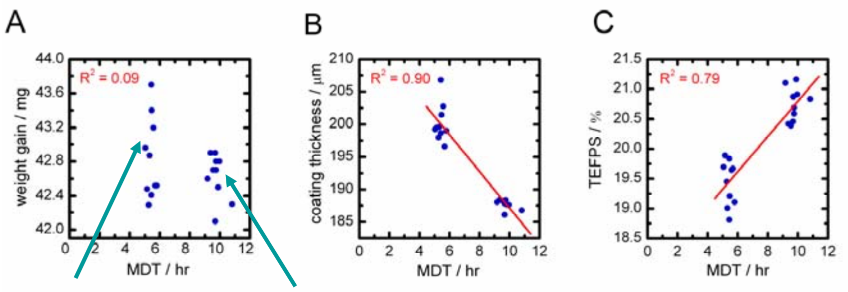
Correlations – early indications



Lab-scale

Pilot-scale

The thicker the coating layer, the faster the dissolution rate and the shorter the dissolution process???? (Lab scale)

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Contributing factor - TEFPS and density

- TEFPS is sensitive to refractive index changes

$$R = (n_s - n_{air}) / (n_s + n_{air})$$

- Refractive index variations:
  - Chemical properties: coating formulation, volume etc.
  - Physical properties: surface roughness, density.

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Contributing factor - TEFPS and density

- Pilot scale:
  - Higher TEFPS → higher RI → higher density → slower dissolution rate → longer MDT???

	MDT (hr)	T20% (hr)	T1/2 (hr)	T80% (hr)	Dissolution release constant (mg/hr)	Weight gain (mg)	TEFPS (%)	Coating layer thickenss (um)
PBI Mean	9.7	3.5	8.6	15	1.29	42.5	20.9	190
PBII Mean	9.8	3.6	8.4	15	1.23	42.6	20.7	188
LBI Mean	5.4	1.9	4.8	8.0	2.30	42.8	19.4	200
LBII Mean	5.4	1.9	5.0	8.4	2.26	42.5	19.5	202

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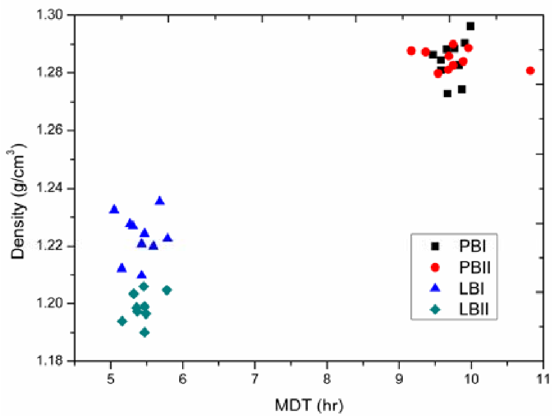
Contributing factor - coating layer thickness and density



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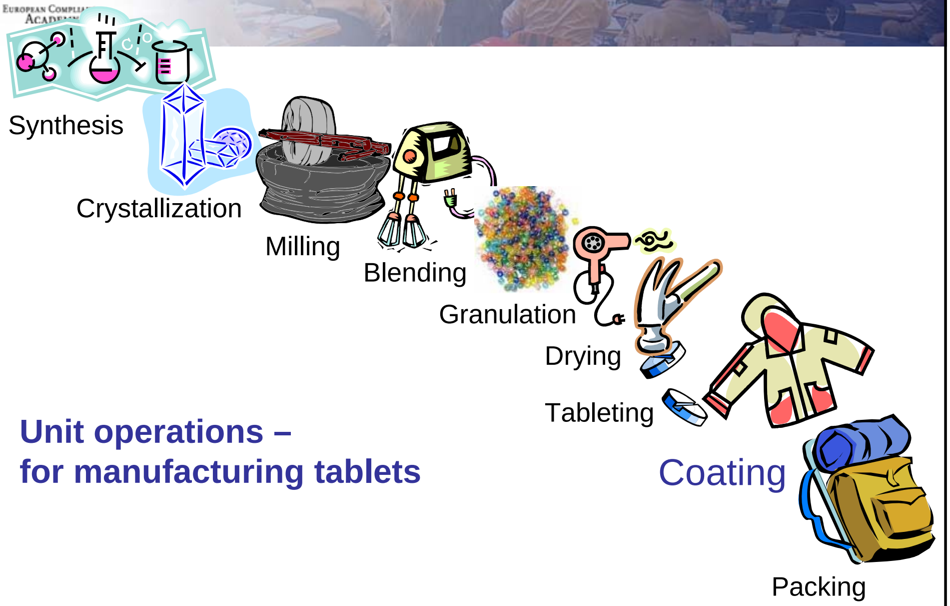
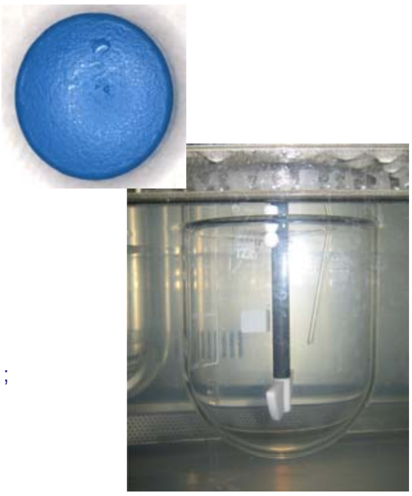


Unit operations –
for manufacturing tablets

Traditional coating quality parameters

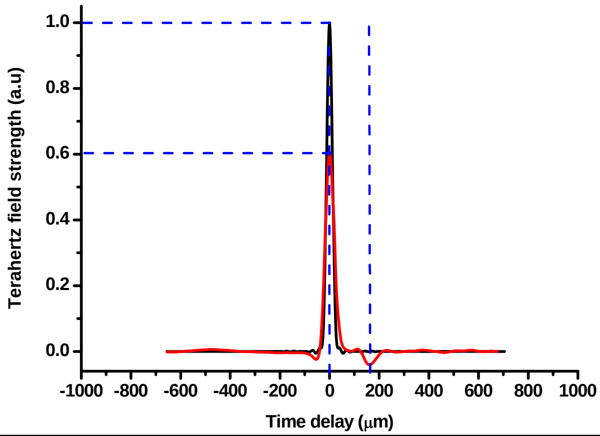
- Weight gain – non-specific
- The amount of coating formulation/ polymer applied – non-specific
- Dissolution – end stage



L. Ho, *et al. J. Controlled Rel.*,119 (2007) 253-26 ;
L. Ho, *et al. J. Controlled Rel.*, 127 (2008) 79-87.

Terahertz parameters

Coating thickness = 160 µm
Terahertz Electric Field Peak Strength (TEFPS) = 60%



Lab and pilot-scale tablets

- Lab-scale

Batch size = 4 kg
Coater = BFC 5
(D x L = 316 mm x 356 mm)

10 samples taken from 10% increments of the amount of polymer applied (7.0, 8.7, 10.5, 12.2, 14.0, 15.7 and 17.5 mg/cm^2).

- Pilot-scale

Batch size = 20 kg
Coater = BFC 25
(D x L = 546 mm x 630 mm)

10 samples taken from 10% increments of the amount of polymer applied (7.3, 9.1, 10.9, 12.7, 14.5, and 18.2 mg/cm^2).

L. Ho, *et al*. EJPB., *In Press*. DOI: 10.1016/j.ejpb.2008.06.023

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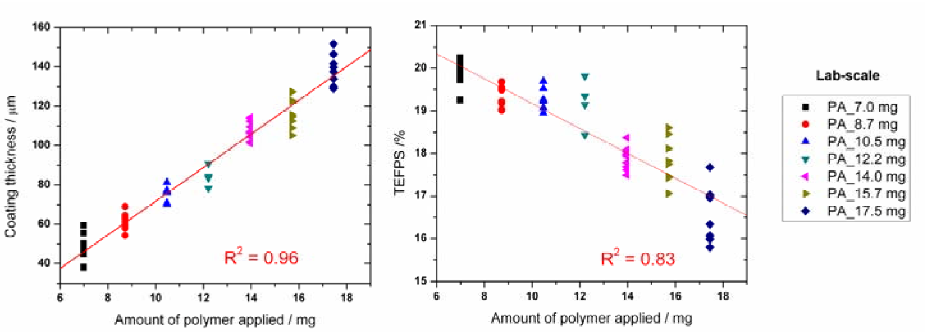
Terahertz parameters and the amount of sustained-release polymer applied



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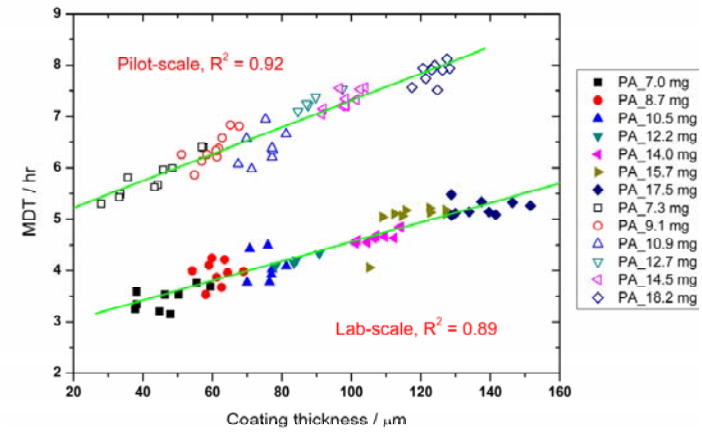
Amount of polymer applied (mg/cm²)	Increment	Average film coating thickness (µm)	Increment	Average TEFPS (%)	Reduction
7.0		46		19.9	
	10%		12%		3.0%
8.7		62		19.4	
	10%		10%		0.6%
10.5		76		19.3	
	10%		10%		2.4%
12.2		90		18.9	
	10%		13%		6.0%
14.0		108		17.9	
	10%		7%		0%
15.7		117		17.9	
	10%		15%		7.8%
17.5		138		16.6	

L. Ho, *et al*. EJPB., *In Press*. DOI: 10.1016/j.ejpb.2008.06.023

Monitoring film coating unit operation



L. Ho, *et al*. EJPB., *In Press*. DOI: 10.1016/j.ejpb.2008.06.023 39

Monitoring film coating unit operation

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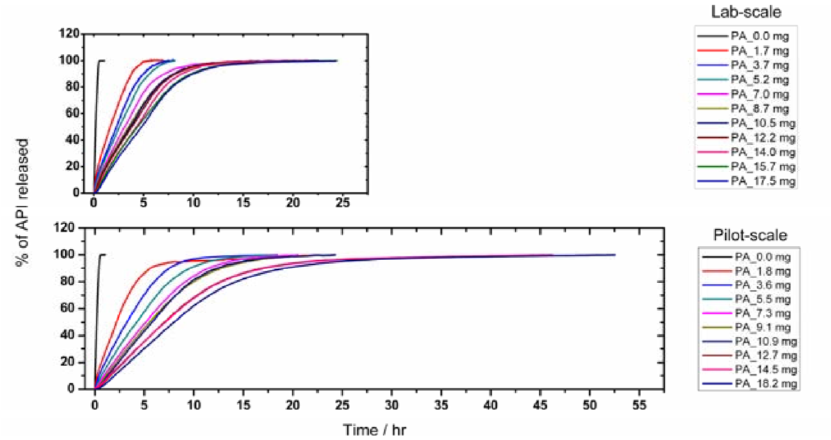
Assessing film coating process scale-up



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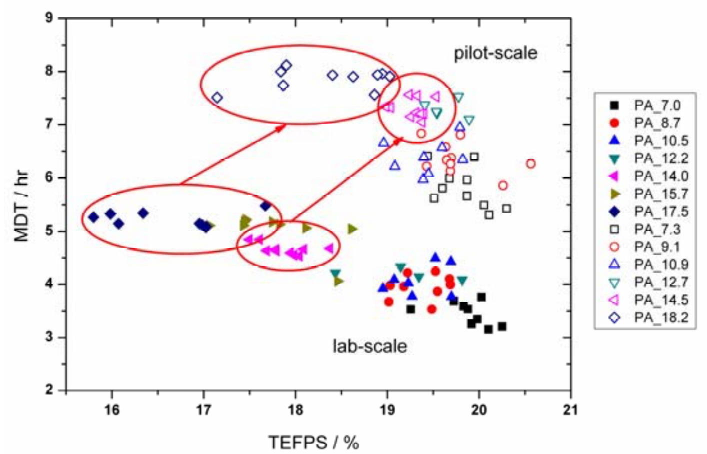

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Contributing factor - TEFPS and density

- TEFPS is sensitive to refractive index changes:

$$R = (n_s - n_{air}) / (n_s + n_{air})$$

- Refractive index variations:
  - Chemical properties: coating formulation, volume etc.
  - Physical properties: surface roughness, density.
- Higher TEFPS → higher RI → higher density → slower dissolution rate→ longer MDT

Batches	TEFPS / %	MDT / hr
Pilot-scale	18.28	8.12
Lab-scale	16.65	5.48

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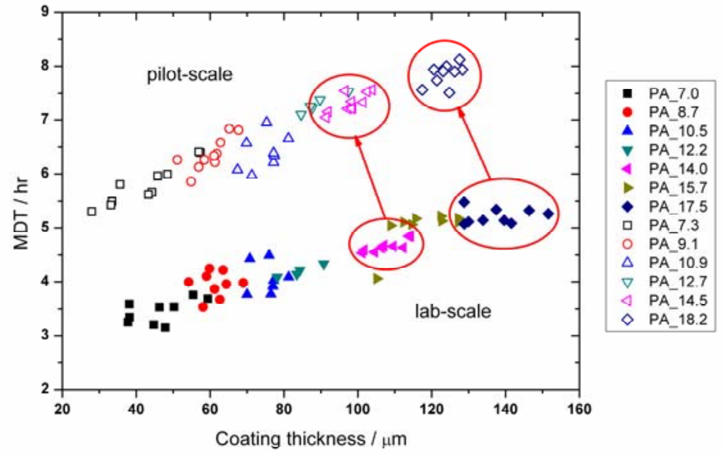
Assessing film coating process scale-up



L. Ho, *et al*. EJPB., *In Press*. DOI: 10.1016/j.ejpb.2008.06.023

Detecting film coating weak spots

- Optimal coating conditions – same transit time, exposure through the spray zone.
- In practice – difficult to achieve.
- Consequences – defects and weak spots.
- Functional coating – modified-release profile may be compromised and limited by the weak spots.

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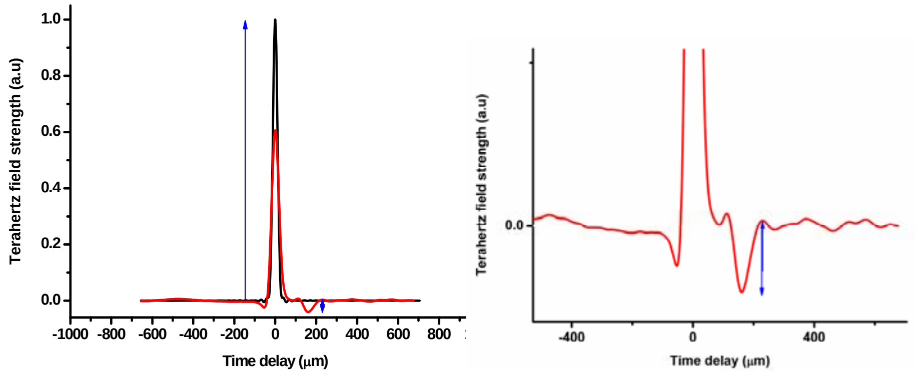
Terahertz parameters

Coating thickness = 160 µm
Terahertz Electric Field Peak Strength (TEFPS) = 60%
Terahertz Interface Index (TII) = 4%



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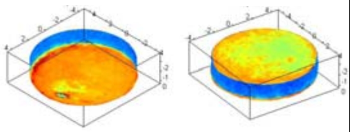
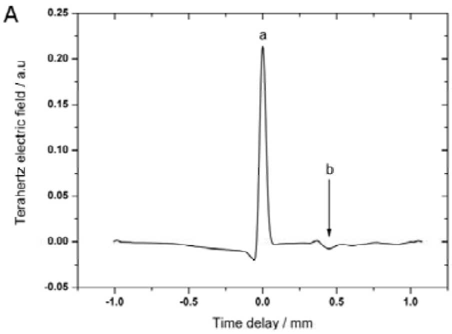
Terahertz time domain waveforms

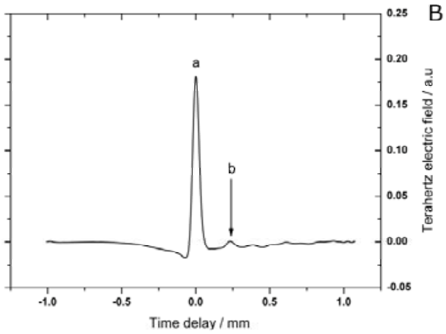
Central Band – weakest area of film coating???



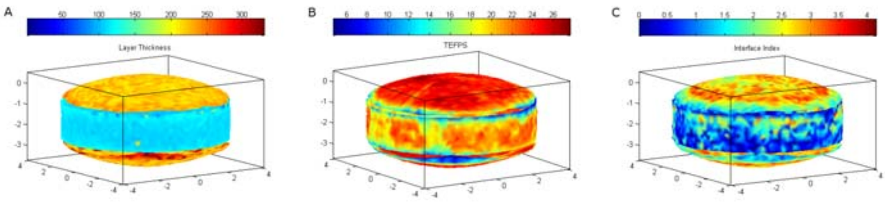
Top/bottom surface

Central Band





Terahertz parameters



- Coating thickness – top/bottom (110 – 261 µm) > central band (46 – 137 µm).
- TEFPS – top/bottom (20.9 – 23.8%) > central band (16.6 – 19.9%)
- TII – top/bottom (2.81 – 3.68%) > central band (0.92 – 1.72%)

Central band - thinner coating, higher density, higher surface roughness?

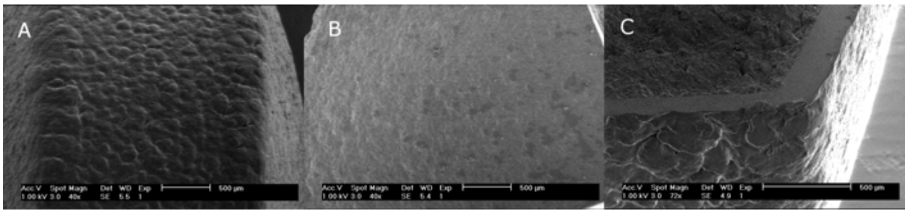
TEFPS is sensitive to refractive index changes:

$$R = (n_s - n_{air}) / (n_s + n_{air})$$

Refractive index variations:

Chemical properties: coating formulation, volume etc.

Physical properties: density, surface roughness.



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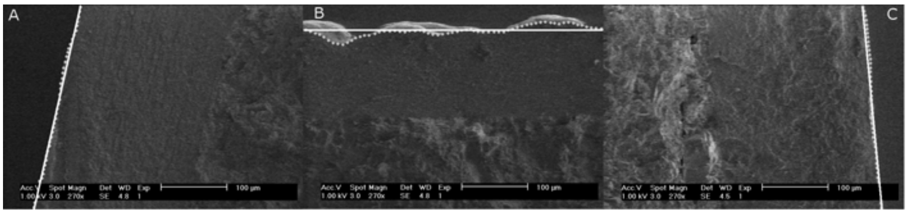
SEM – surface roughness



- Central band R_a = 1.09
- Top/bottom surfaces R_a = 1.02
- Central band is 7% rougher.

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Dissolution

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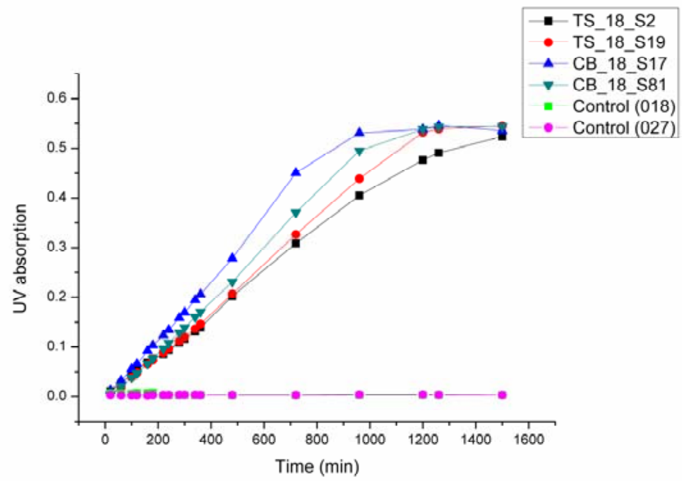
Dissolution



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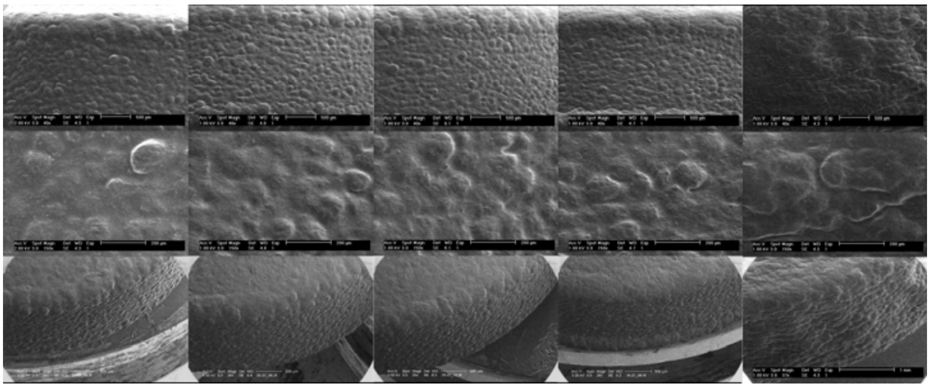
Dissolution



5 seconds → 2 hours

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Conclusions

- TPI affords non-destructive testing.
- Knowledge on coating weak spots, thickness, density, roughness, variability, reproducibility and distribution.
- Terahertz parameters – can monitor and refine the coating unit operation and the scale-up procedure.
- TPI is used for process understanding and optimisation of the product design space.

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