



Dissolution monitoring of hydrophilic matrix tablets by using Frequency information of Ultrasound Echo

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10th June 2008, HDR Helsinki
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Acoustics

- Sound: *mechanical longitudinal waves propagating via medium*
- Ultrasound: *Sound with frequency > 20 kHz, usable range usually 100 kHz - 50 MHz*
- Interface reflection intensity from interface between 1 & 2:

$$I = I_0 \left(\frac{Z_1 - Z_2}{Z_1 + Z_2} \right)^2$$

Z_i is the acoustic impedance of medium i

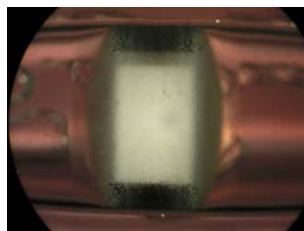


Image courtesy of imagnis.com

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Oral Drug Dosage: Hydrophilic Matrix Tablets

- Quite easy and popular form of dosage
- Tablets are compacted from hydrophilic polymer powder mixture including active pharmaceutical ingredient (API)
- Tablets start swelling during contact with water
- API is released with eroding gel in digestion chain



4mm

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Tests:

- Standard (US Pharmacopoeia):
 - Chemical Assay with Dissolution tank (Sotax, etc.)



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Tests:

- Eroding front movement by ultrasound echo (Konrad et. al. 1998)
 - Strong gel-water interface reflection
 - Core-gel interface impossible to detect

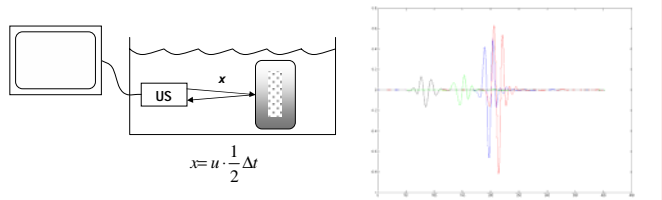


Figure: US echo in different time points (0, 30, 120 and 240 minutes)

Tests:

- Swelling front detection with Ultrasonic window setup
 - Sample fixed into plastic tube, "US window" with proper acoustic impedance
 - 2D-geometry: dissolution medium can penetrate only from tube ends
 - Dry core can be detected

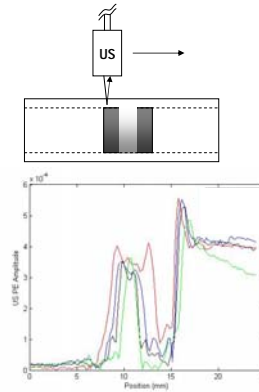


Figure: US echo in different time points (red: 0, blue: 60, black: 120 and green: 240 minutes)

Tests:

- Frequency analysis of pulsed US Echo

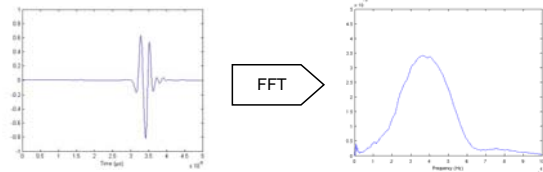


Figure: US PE from single point.

Figure: US PE frequency response.

Samples:

- Three formulation of two common polymer matrices (donated by AstraZeneca):
 - Hydroxypropyl Methyl Cellulose (HPMC)
 - HPMC Metolose 60 SH4000 Shin Etsu
 - Polyethylene Oxide
 - 2 million WSR N60K (PEO1)
 - 0.1 million WSR N10 DOW (PEO2)
- Tablet compaction w/ Puuman PCS-1
 - flat faced, dia. 10 mm, 300 mg
 - sinusoidal upper and lower punch profile



Setup:

- UltraPAC-system (Physical Acoustics Corp., NJ, USA).
 - A/D-board (PAC-AD-500)
 - manipulator for 3D measurements
 - Panametrics V307, 5 Mhz focused
 - Custom-made Labview software
 - Pulsed Echo Measurements
- Degassed Phosphorus Buffered Solution
 - US Pharmacopoeia pH = 6.8



Figure: UltraPAC System located in Biophysics of Bone and Cartilage Lab in BioMater Centre of University of Kuopio.

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Setup:

- Six tablets in a row
 - Line scan with 0.3 mm steps in every timepoint until 4 h
- Gel thickness references by visual determination

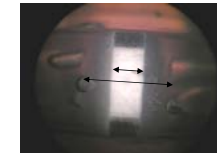
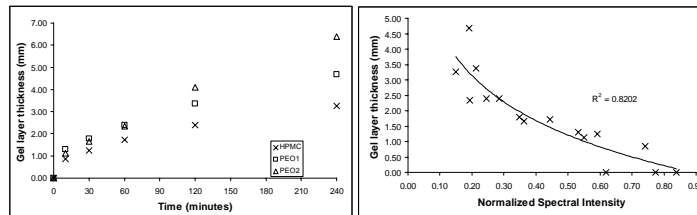


Figure: Visual gel thickness determination.
 $x_{gel} = (x_{total} - x_{core})/2$

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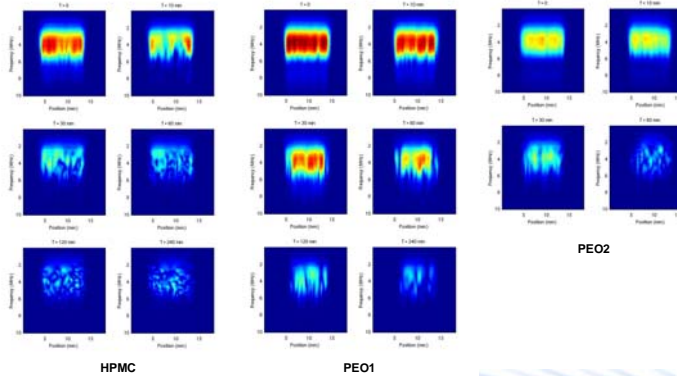
Results: Gel Layer thickness



Figures: Visually determined gel layer thickness as a function of time (left) and normalized spectral intensity (right).

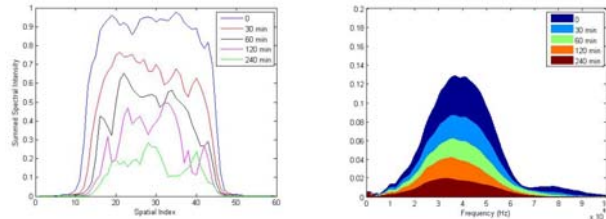
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Results: Frequency Response vs. time



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Results: Frequency Response



Figures: Normalized spectral intensity of HPMC tablet in timepoints (left) and frequency response of measured from the center point of the tablet (right).

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Conclusions

- Ultrasound measurements can provide useful information of (tablet) dissolution process
- The method can make difference between different polymer types
- The feasibility of the method (in dissolution processes) should be further inspected

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Acknowledgements

Susanna Abrahmsen-Alami, AstraZeneca R&D Lund, Sweden
M. Sc. Marko Kuosmanen
M. Sc. Jarkko Leskinen
Ph. D. Mikko Hakulinen
Prof. Jarkko Ketolainen
Prof. Reijo Lappalainen

THANK YOU!

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