Compaction Simulation Forum
CONNECTING SCIENTISTS AND COMPRESSION TECHNOLOGY

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Controlling the lag-time and release kinetics of press-coated tablets using process parameters and tablet geometry

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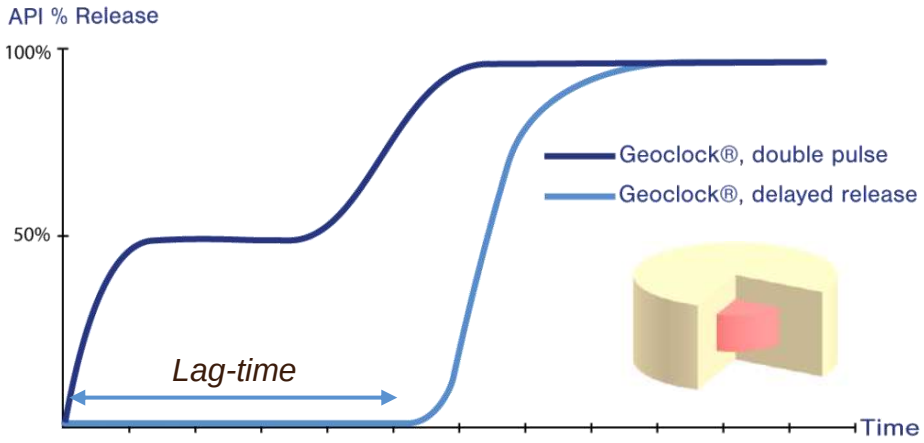
Introduction : Press-coated tablets

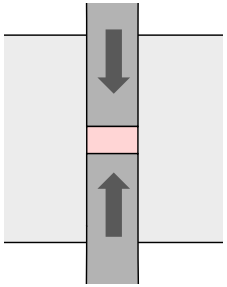
- Core / shell structure
- API usually in the core
- **Delay** before the release of the API.



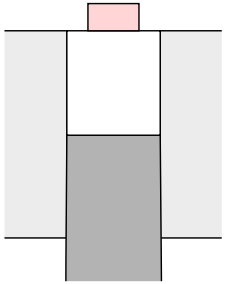
- This delay (called **lag-time**) is very **important to control** to meet the therapeutic goal
- High added value in the controlled release and chronotherapeutics fields, e.g. to treat diseases with night symptoms

Introduction : Press-coated tablets

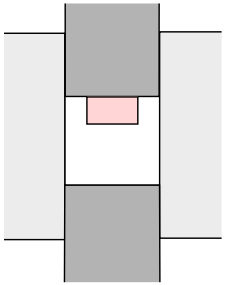
Steps of the press-coating process:



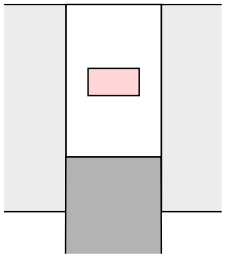
1 - **Core compression** (on a separate machine)



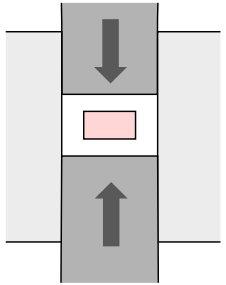
2 - **First powder filling** and deposit of the core on powder bed



3 - **Tamping** of the core in the powder bed



4 - **Second filling** above the core



5 - **Coating compression**

➡ **How can the parameters of this process influence the release attributes of the tablets ?**

Methods – Compression of the press-coated tablets

Core tablet

- Contains a dose of API: Prednisone
- Mostly soluble formulation
- Compression: **Ø5 mm** bevel-edged punches

  $P_{compression}$: **360 MPa**

  Mass : **60 mg**

	Concentration (w/w)
Prednisone	8 %
Lactose monohydrate	65%
Povidone	7 %
Sodium croscarmellose	18 %
Colloidal silica	0,5 %
Magnesium stearate	1,0 %
Red iron oxyde	0,5 %

Coating-compression

- Powder without active ingredient
- Mostly insoluble formulation

	Concentration (w/w)
Calcium phosphate	50 %
Glyceryl Behenate	40 %
Povidone	8 %
Colloidal silica	0,5 %
Magnesium stearate	1,0 %
Yellow iron oxyde	0,5 %

Methods – Compression of the press-coated tablets

Compaction simulator

- **Styl'One Evo**, Medelpharm
- Punches motion is numerically controlled
- Possibility to reproduce the different steps of coating-compression

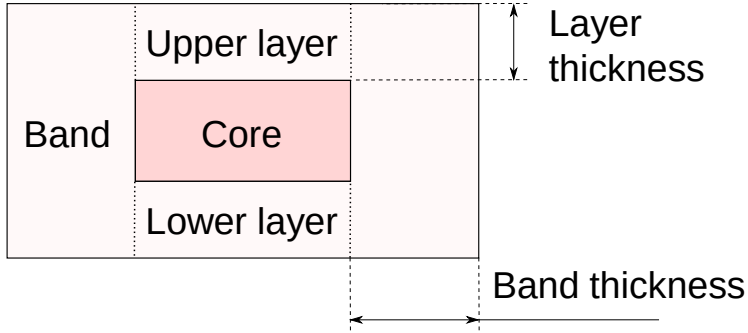
Methods – Compression of the press-coated tablets

Variable parameters of the coating-compression

Layer thickness: controlled with the two powder fillings

Band thickness: determined by the diameters of the core and shell

Pressure applied for the coating-compression: compression force divided by the punch surface



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Methods – Compression of the press-coated tablets

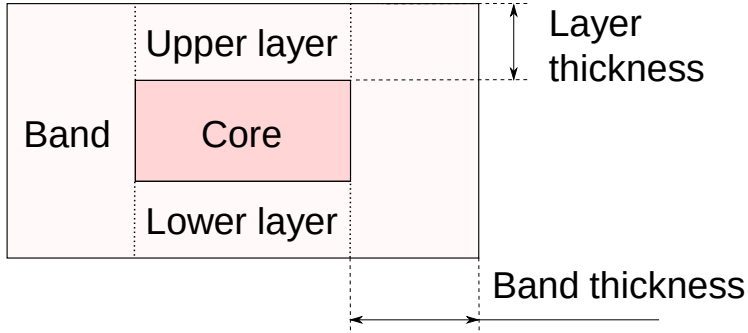
Chosen levels for the experiments

Layer thickness:
0.6 mm, 1.1 mm, 1.5 mm and 2.0 mm

Band thickness:
1.5 mm, 2.5 mm and 3.1 mm

(core Ø5 mm // shell Ø8 mm, Ø10 mm and Ø11.28 mm)

Compression pressure:
25 MPa, 50 MPa, 75 MPa



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Methods – Dissolution test and analysis

Dissolution test for the press-coated tablets

Apparatus: Sotax AT7

Dissolution medium: purified water, 37°C

Stirring: standard paddle,100 rpm

Three tablets per parameters set

Objective

Determine **when** and **how** the shell opens during the dissolution test, according to the compression parameters.

Methods

Visual observation

Camera set in front of the dissolution tester
(1 picture per minute)

- **Lag-time**: first minute where the shell is opened and exposes the core to the medium
- Observation of the opening mode

Drug release analysis

2 mL samples, taken every 5 min during the shell opening

UV spectrophotometry at 244 nm

- Percentage of dissolved API at every sampling time

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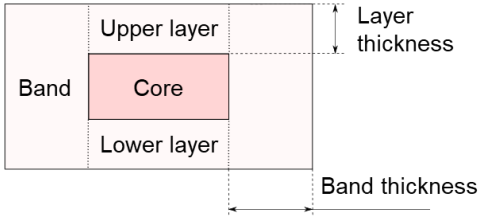
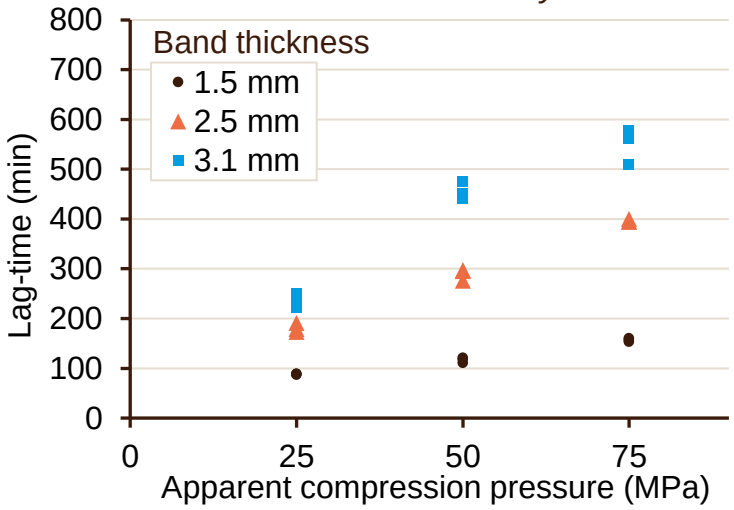
Results – Lag-time

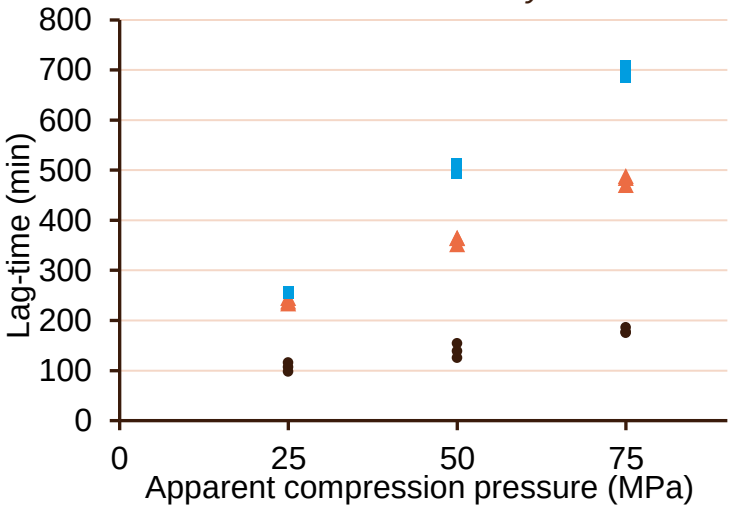


Influence of the band thickness on the lag-time

With 1.1 mm layer thickness



With 2.0 mm layer thickness



➡ The lag-time increases with pressure, but **also with band thickness**

➡ Similar results for every layer thickness

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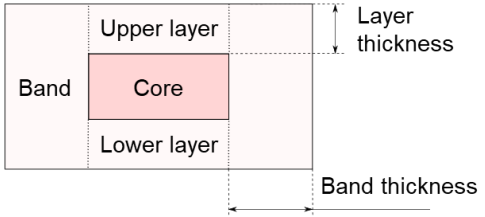
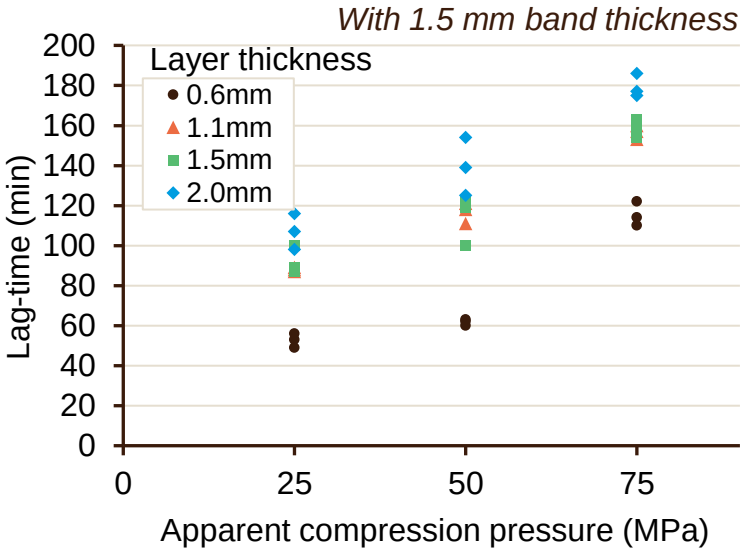
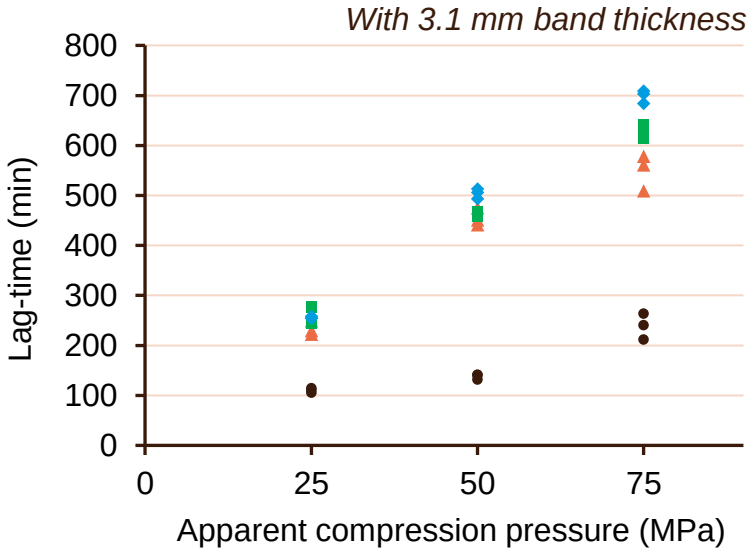
Results – Lag-time



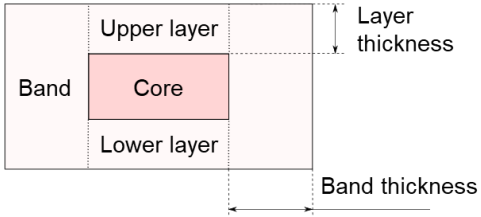
Influence of the layer thickness on the lag-time



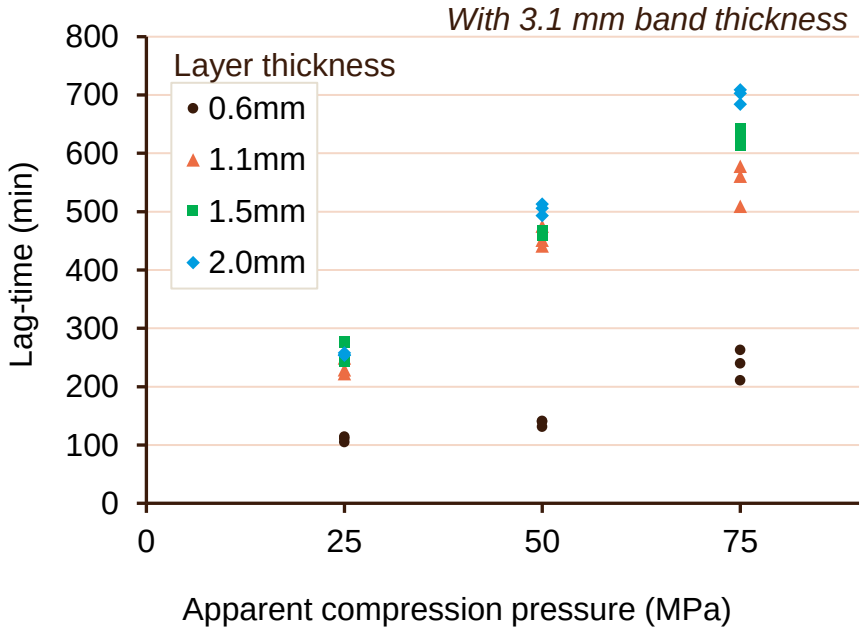


➡ Similar pattern for every band thickness

Results – Lag-time



Influence of the layer thickness on the lag-time



- Increase of the layer thickness : high impact on the lag time **from a low to a medium thickness**
  - On this range, the layer thickness is a **lever to modify the lag-time**
- Much less impact on the lag-time **from a medium to a high layer thickness**.
  - On this range, the layer thickness has a **low influence** on the lag-time and can be chosen for other reasons

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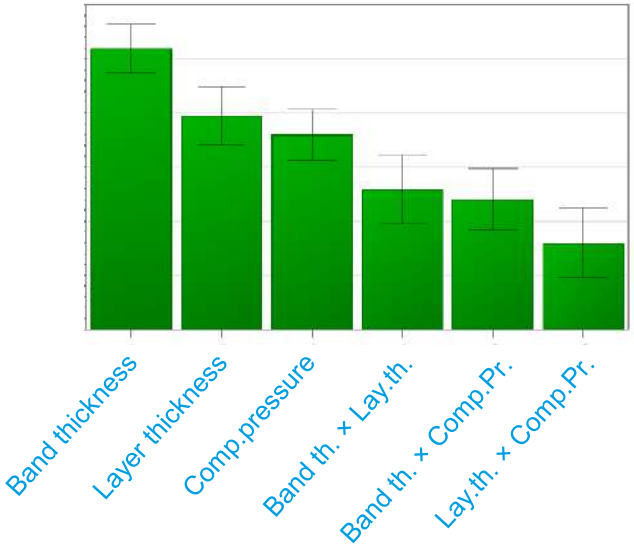
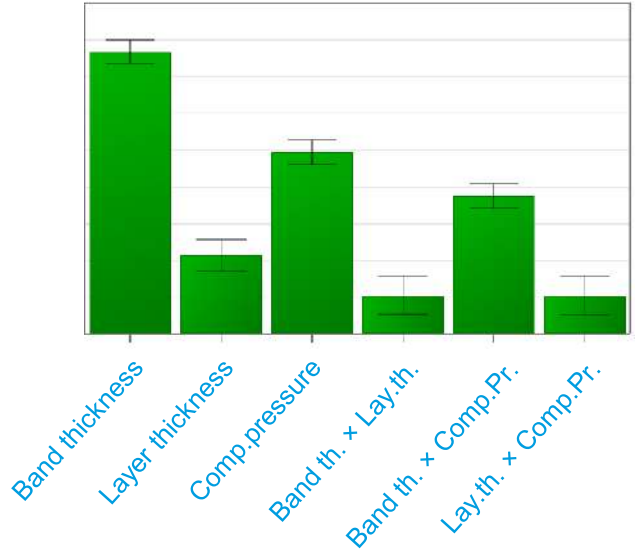
Results – Lag-time

Relative influence of the different parameters in a linear model



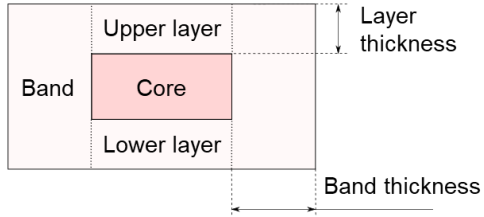
➡ **High sensitivity of the lag-time to the band thickness**

Same analysis, without the data at 0.6 mm layer thickness

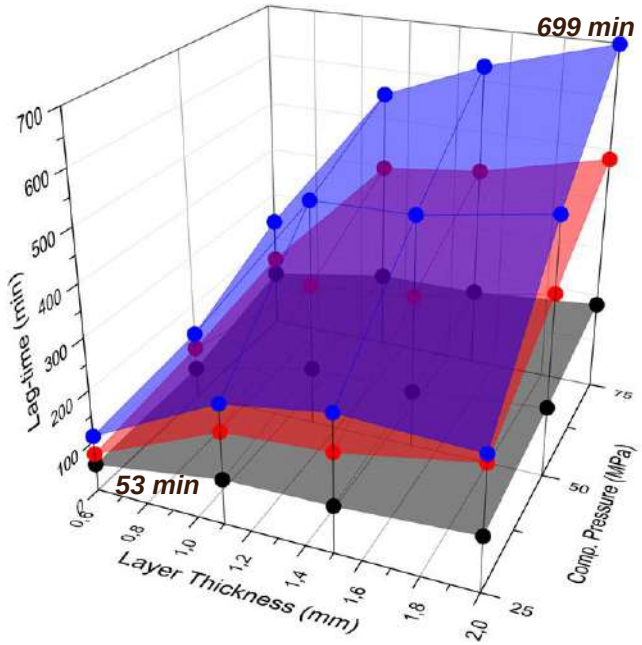


➡ **Confirms that the influence of the layer thickness is not linear**

Discussion – Lag-time



Summary of the tablets' lag-times



Band thickness

- 1,5 mm
- 2,5 mm
- 3,1 mm

With modification of the compression pressure, band thickness and layer thickness:

➡ **Controlled lag-time from 1 h to 11 h**

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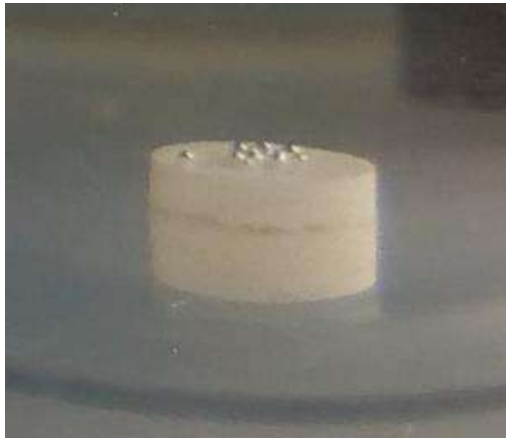
Discussion – Lag-time

Why do the geometrical parameters influence the lag-time ?

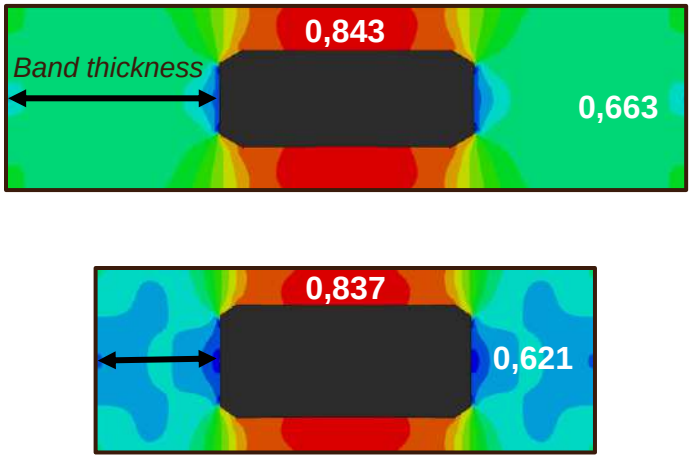


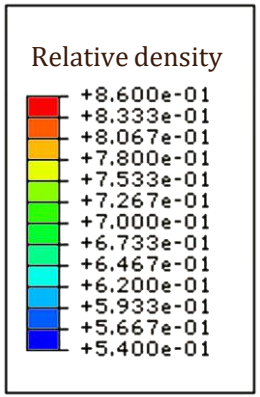
- The crack always initiates in the band of the tablet
- The lag-time might be linked with the properties in this zone

Discussion – Lag-time

Reminder : Increase of band thickness → Increase of lag-time

➡ Previous work: influence of the process parameters on the press-coated tablets structure





Picart et al. 2021, International journal of pharmaceutics, 596

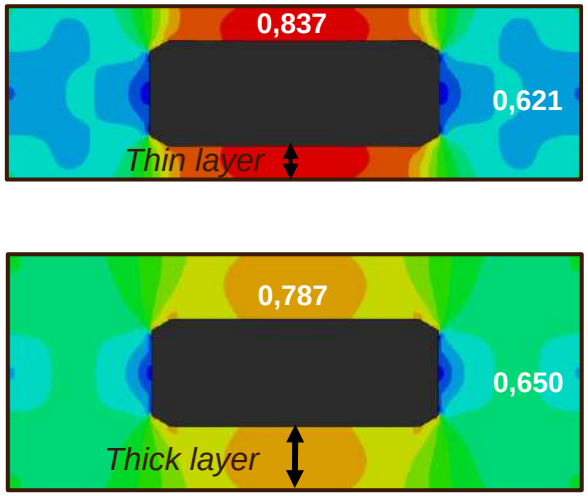
➡ **High band thickness**: promotes a high band density

➡ Resistance to the crack propagation

➡ Additional effect: distance of crack propagation

Discussion – Lag-time

Reminder : Increase of layer thickness → Increase of lag-time



➡ **High band thickness: also** promotes a high band density

Modification of the compression pressure, band thickness and layer thickness

⬇

Modification the density in the band zone of the shell

⬇

Modification of the lag-time

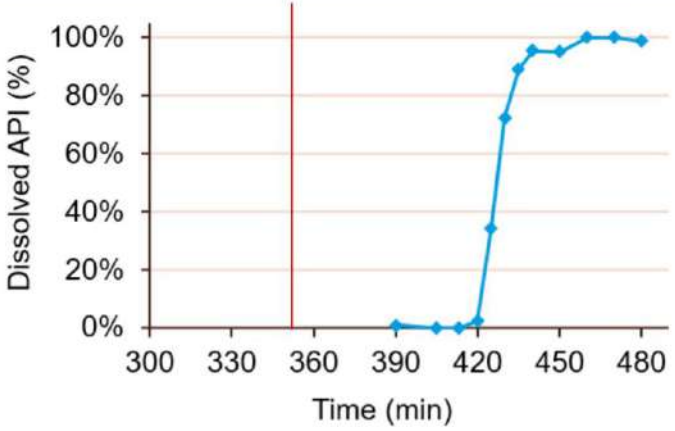
Results – Opening modes and release kinetics

Two main observed opening modes

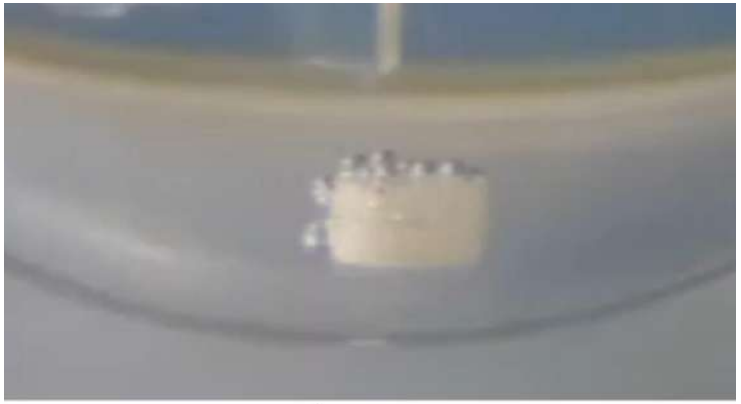
➡ Layer opening

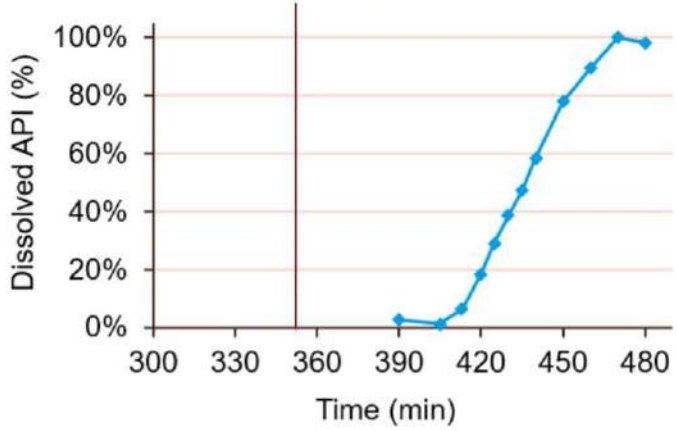
➡ Band opening

Layer opening



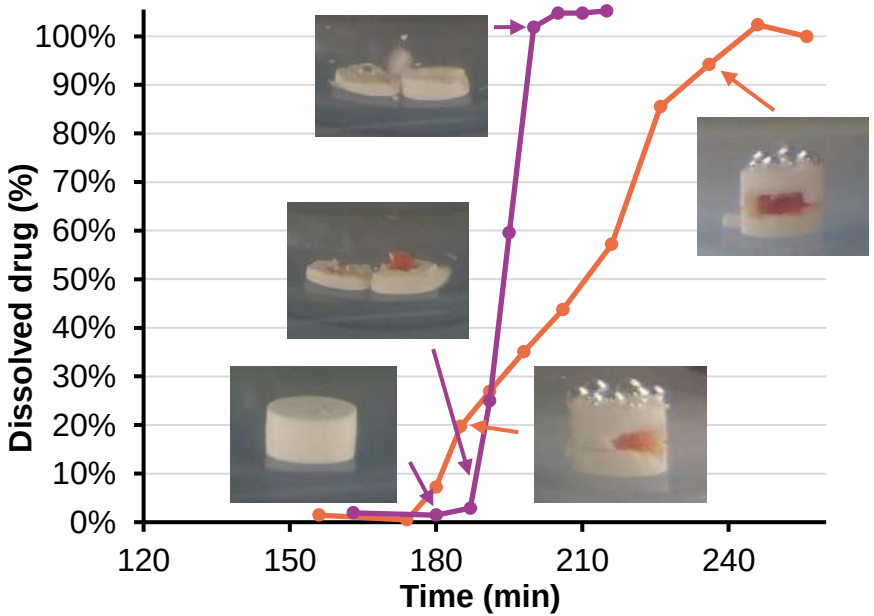
Band opening





Results – Opening modes and release kinetics

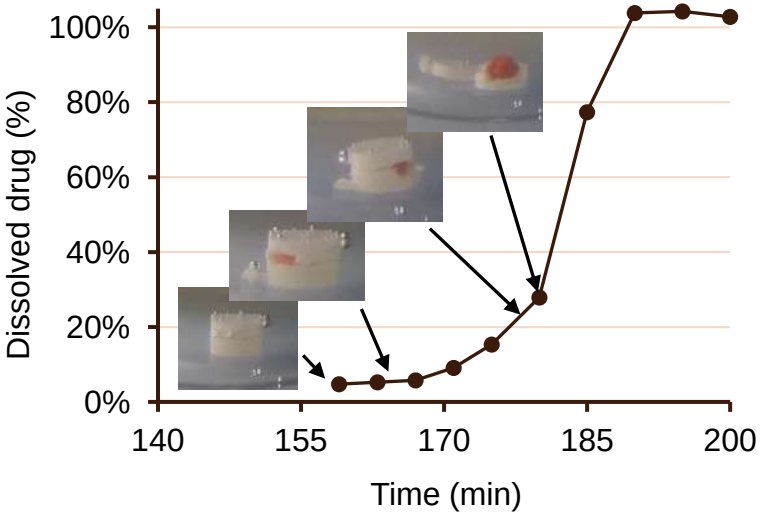
Release kinetics related to the opening modes

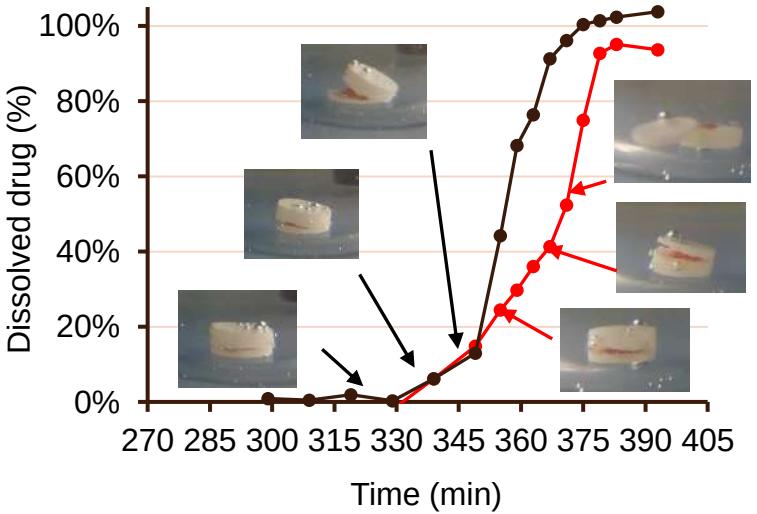


- API release perfectly synchronized with the visual opening
- A **layer opening** results in a **fast** release (less than 15 minutes)
- A **band opening** results in a **slow** release (up to 60 minutes)

Results – Opening modes and release kinetics

Hybrid opening modes





➡ Band opening followed by a layer detachment

➡ Partial layer opening followed by a layer detachment

➡ **Immediate switch** from a **slow release** to a **fast release** when the layer detaches.

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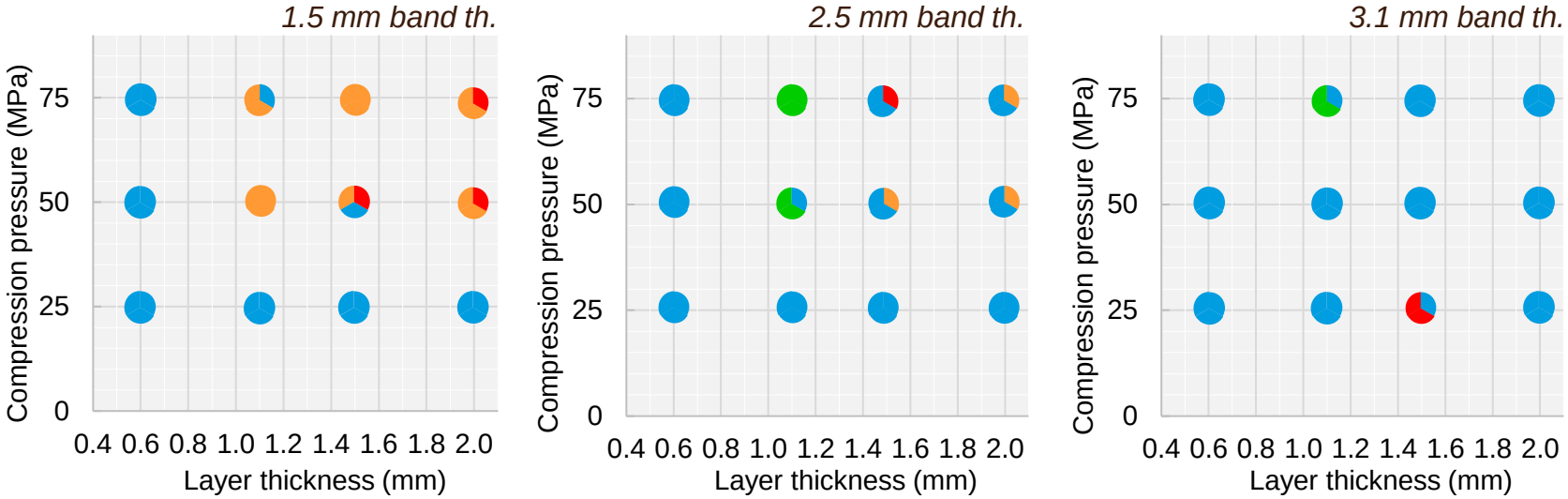
Results – Opening modes and release kinetics



- Layer opening
- Hybrid opening : slow layer detachment
- Hybrid opening: band followed by layer
- Persistent band opening

➡ There can be a variability in the opening mode, even with the same parameters

➡ To promote a fast **layer opening**: avoid the high pressures combined with a high layer thickness

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Conclusions

- **Process parameters** like layer thickness, shell diameter and compression pressure have a strong **influence on the lag-time and opening mode** of the press-coated tablets

- A wide range of **lag-time (1h to 11h)** is reachable without changing neither the shell nor the core formulations, by increasing the compression pressure, layer thickness or shell diameter.

- The dissolution kinetics of the press-coated tablet core are directly dependent on the opening mode: layer opening or band opening. It highlights **the interest of the visual observation** in addition to the drug release data.

- **Geometrical parameters and compression pressure** should be considered as critical parameters during the design and development of a press-coated tablet to play on the **drug release attributes**.

Many thanks for your attention !

And thank you to

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for welcoming this presentation !

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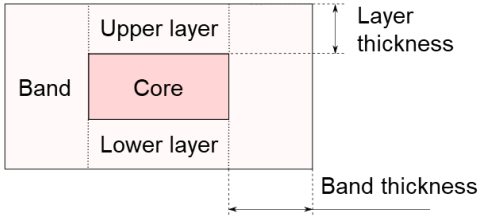
Results – Lag-time



Influence of the band thickness on the lag-time

Ratio between the lag-time at 75 MPa and the lag-time at 25 MPa

Band thickness	Layer thickness			
	0,6 mm	1,1 mm	1,5 mm	2 mm
1,5 mm	*2,17*	*1,78*	*1,72*	*1,67*
2,5 mm	*2,02*	*2,19*	*2,18*	*2,01*
3,1 mm	*2,16*	*2,36*	*2,37*	*2,74*

- The relative increase of the lag-time with compression pressure is higher with a high band thickness
- **High sensitivity of the lag-time to the band thickness**

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