M1332

EFFECT OF HYDROPHOBIC INCLUSIONS ON HPMC SWELLING KINETICS STUDIED BY MAGNETIC RESONANCE IMAGING COMBINED WITH MATHEMATICAL MODELING

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UCT PRAGUE

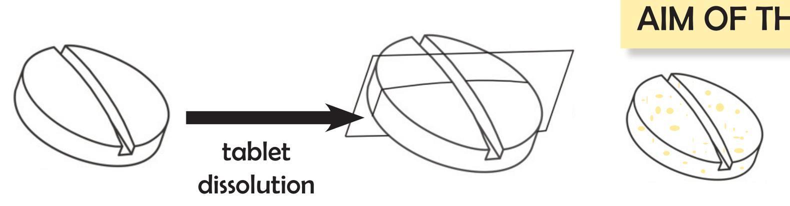
ZENTIVA A SANOFI COMPANY

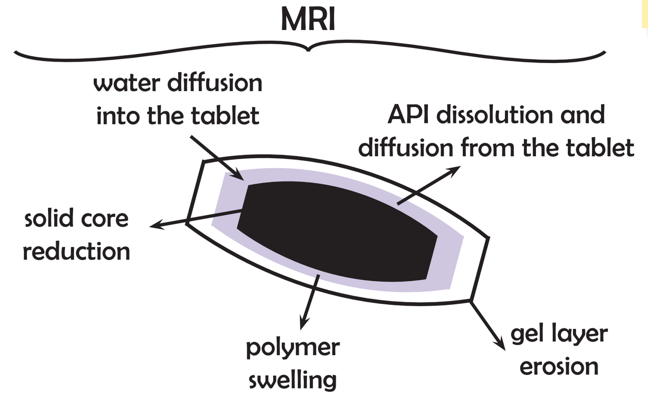
PURPOSE

MATRIX COMPOSITION
additives
polymer
API
TECHNOLOGICAL PARAMETERS

DISSOLUTION PROFILE of API

IMAGING METHODS
ATR-FTIR imaging
UV imaging
MRI

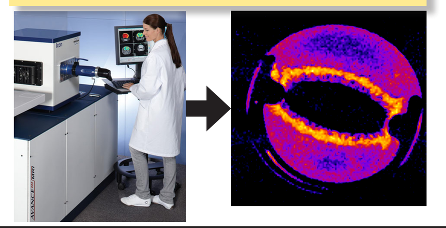




MEDICINE

vs.

OUR RESEARCH



Will the presence of hydrophobic inclusions slow down or speed up the drug release?

AIM OF THE STUDY

- To evaluate the effect of hydrophobic inclusions (carnauba wax) on the hydration, swelling and erosion kinetics of HPMC matrix tablets using MRI and mathematical modeling.

MATHEMATICAL MODEL / PHYSICAL EXPERIMENT

virtual tablet with particular structure → simulation of dissolution with parametric study → set of parameters → SIMULATION → simulated kinetics of gel layer creation

set of tablets with particular structure → DISSOLUTION → measured kinetics of gel layer creation

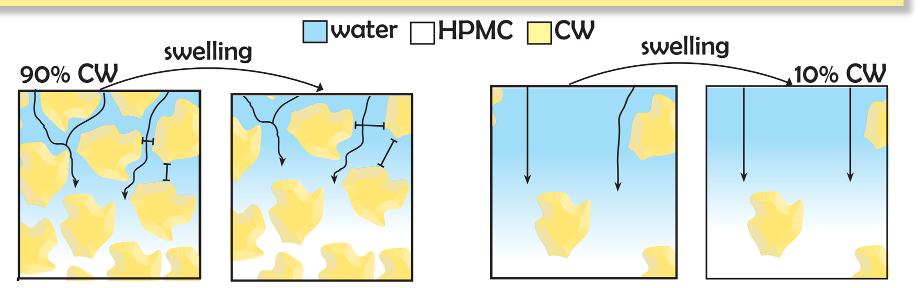
METHODS

CHEMICALS

hypromellose - HPMC (Methocel K100M, Dow Chemicals, USA), carnauba wax - CW (Mach Chemicals s.r.o., Czech Republic), and Levetiracetam (Zentiva k.s., Czech Republic), which was chosen as a model, highly water-soluble API.

TABLET COMPOSITION

The amount of substances in tablet (%)	HPMC K100M	CW	The amount of substances in tablet (%)	HPMC K100M	CW	LA
CW90	10	90	CW80_LA	10	80	10
CW70	30	70	CW65_LA	25	65	10
CW50	50	50	CW45_LA	45	45	10
CW30	70	30	CW25_LA	65	25	10
CW10	90	10	CW10_LA	80	10	10



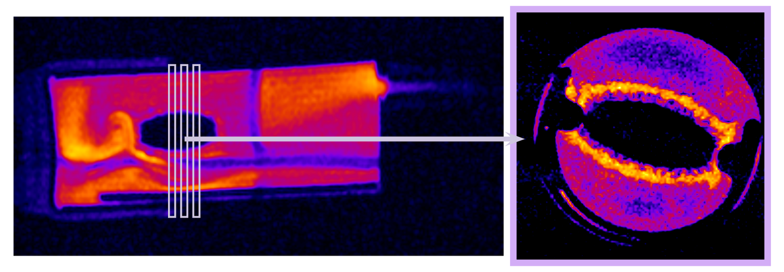
TABLET PREPARATION

homogenization (homogenizer TURBULA type T2C, WaB Company, Switzerland)
direct compression (excentric tablet press STYL´ONE, IMA s.p.a., Italy)
final shape: lenticular
final size: 10 mm

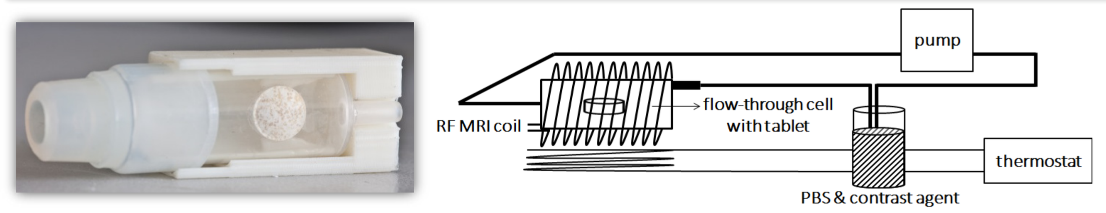
MRI SETTINGS

MSME (Multi-Slice-Multi-Echo)

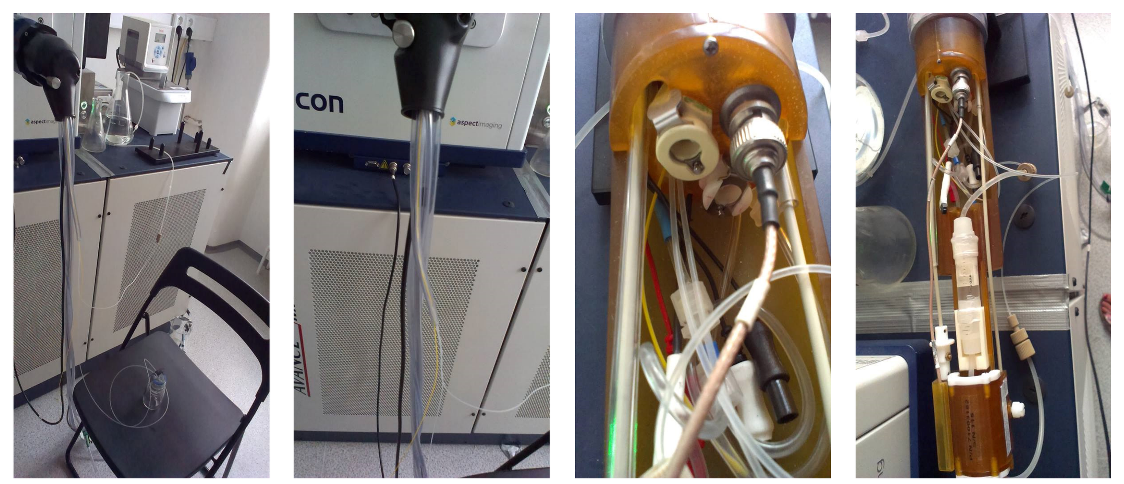
repetition time:	2000 ms
number of averages:	2
field of view:	(1.8 x 1.8) cm
number of axial slices:	3
slice thickness:	1 mm
echotime:	18 ms
matrix size:	128 x 128 pixels
bandwidth:	2000 Hz



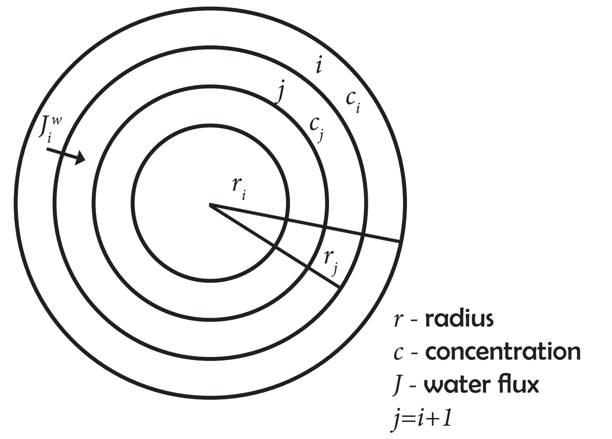
EXPERIMENTAL SETTING



MRI ADJUSTMENTS



MATHEMATICAL MODEL



r - radius
c - concentration
J - water flux
$j=i+1$

- simplified 2D cylindrical geometry of tablet
- finite volume discretisation
- numerical analysis by Runge-kutta method

Mass balance equations:

$$\frac{dm_i^w}{dt} = J_j^w A_j - J_i^w A_i \qquad \frac{dm_i^p}{dt} = 0 \qquad \frac{dm_i^c}{dt} = 0$$

Mass transport:

$$J_i^w = -D_{ij}^w \frac{c_j^w - c_i^w}{r_j - r_i}$$

Volume additivity:

$$V_i = V_i^w + V_i^p + V_i^c = \frac{m_i^w}{\rho^w} + \frac{m_i^p}{\rho^p} + \frac{m_i^p}{\rho^p}$$

The local effective diffusion coefficient of water in the polymer matrix (power law form):

$$D_{ij}^w = \min\left(\varepsilon_i, \varepsilon_j\right)^\alpha \left[D_{\min}^w + \left(D_{\max}^w - D_{\min}^w\right) \min\left(\frac{c_i^w}{\rho_i^w}, \frac{c_j^w}{\rho_j^w}\right)^\beta \right]$$

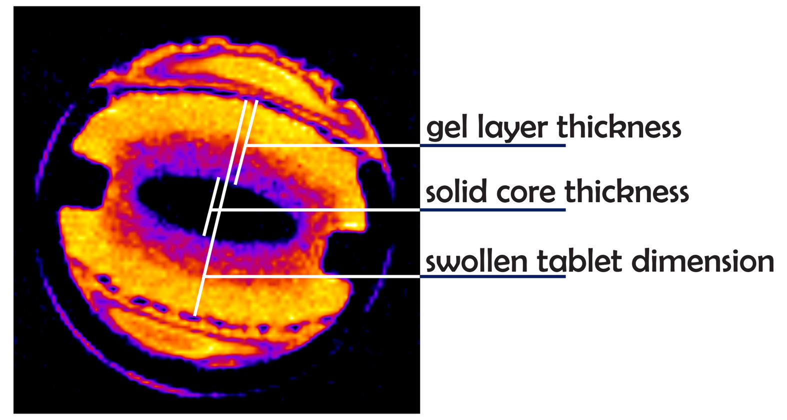
Initial and boundary conditions:

$$m_i^w(t=0) = 0 \quad \forall \iota$$
$$m_i^p(t=0) = \left(1-\phi^c\right)\rho^p \pi \left(r_i^2 - r_j^2\right)\Delta z \quad \forall \iota$$
$$m_i^c(t=0) = \phi^c \rho^c \pi \left(r_i^2 - r_j^2\right)\Delta z \quad \forall \iota$$
$$J_j^w = 0 \qquad c_N^w = \rho^w$$

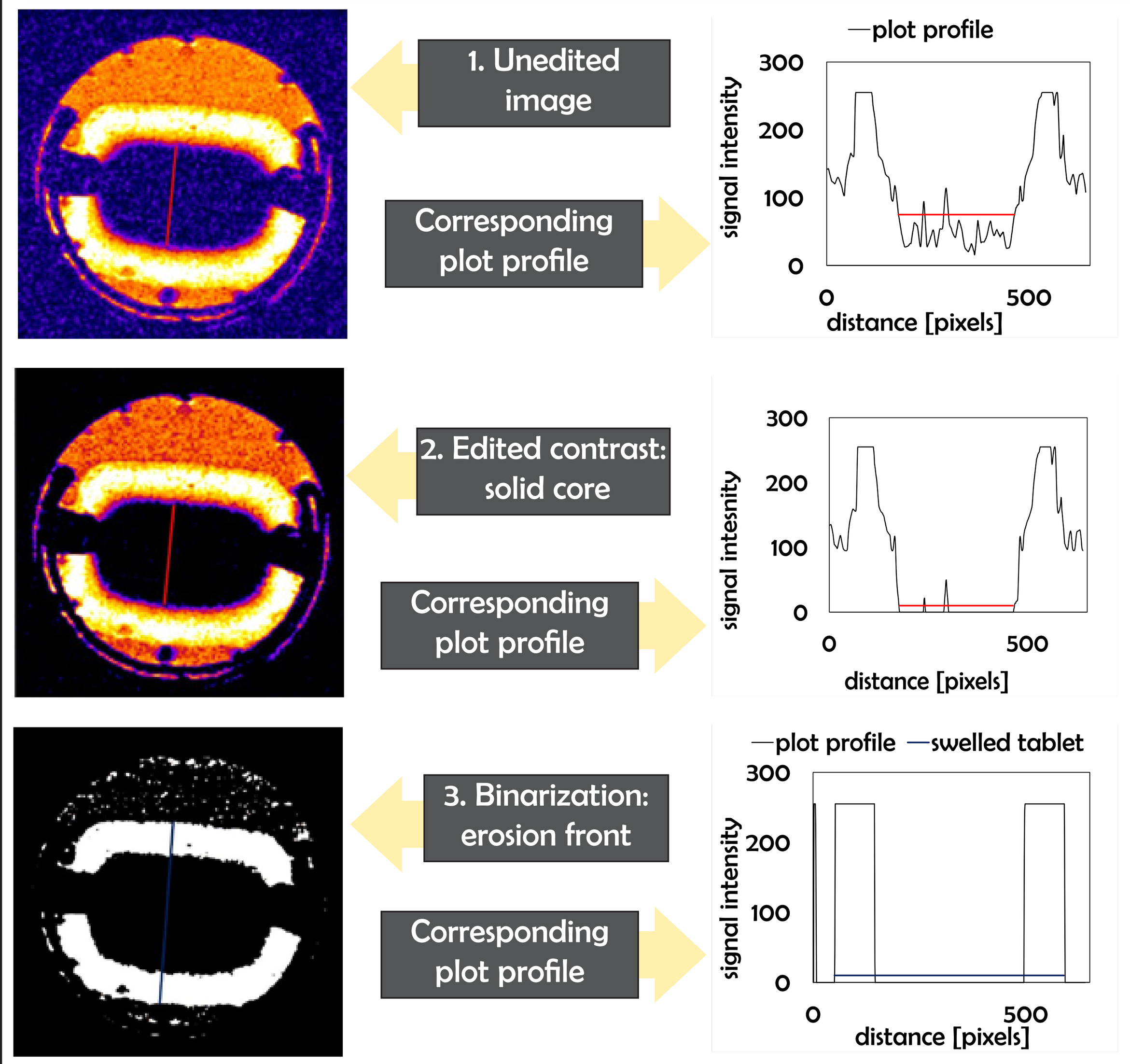
RESULTS

IMAGE EVALUATION

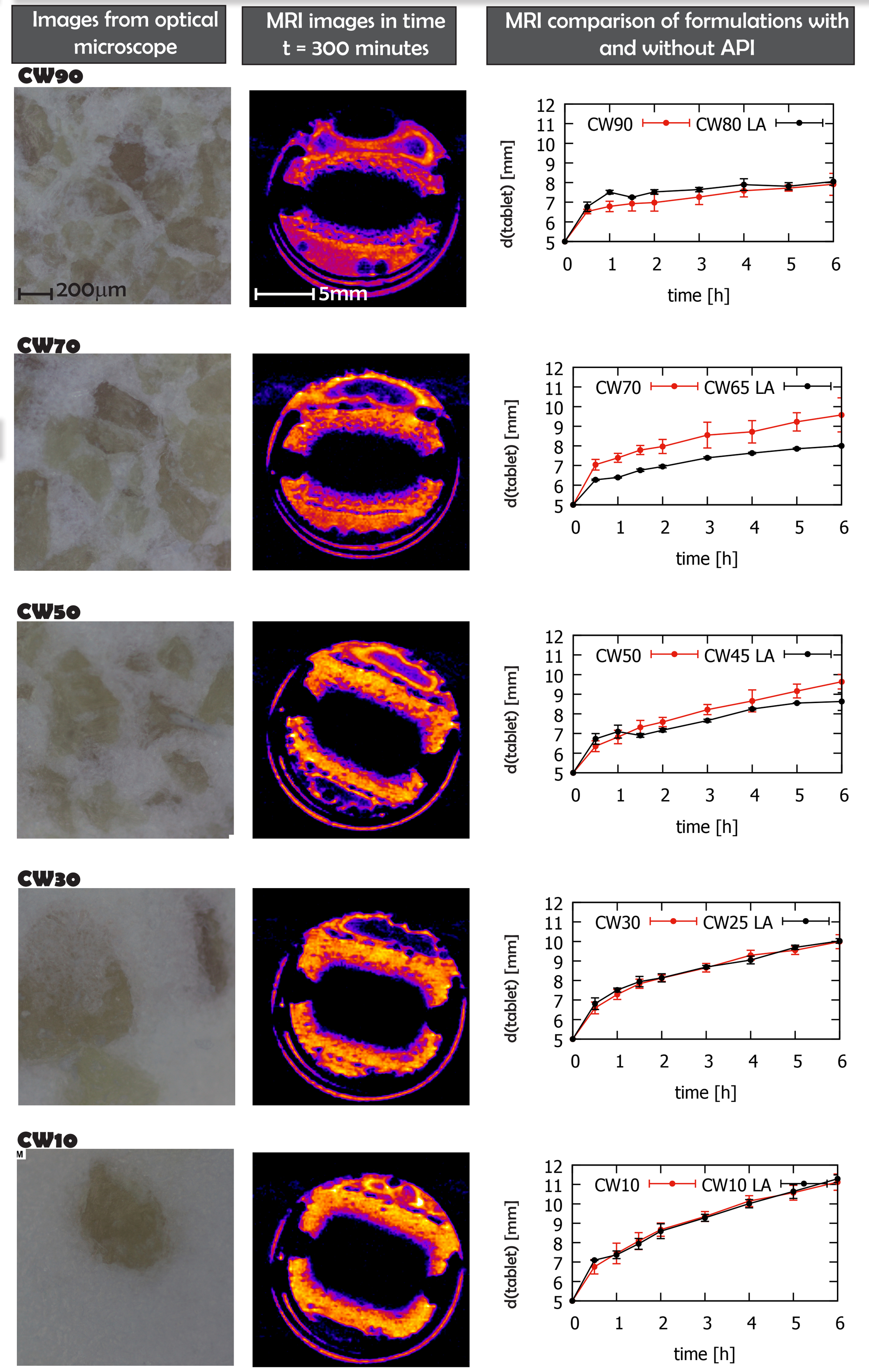
- ImageJ
- Brightness and contrast adjustment
- Binarization
- Plot profile export to MS Excel
- Determination of given parameters
- Statistics



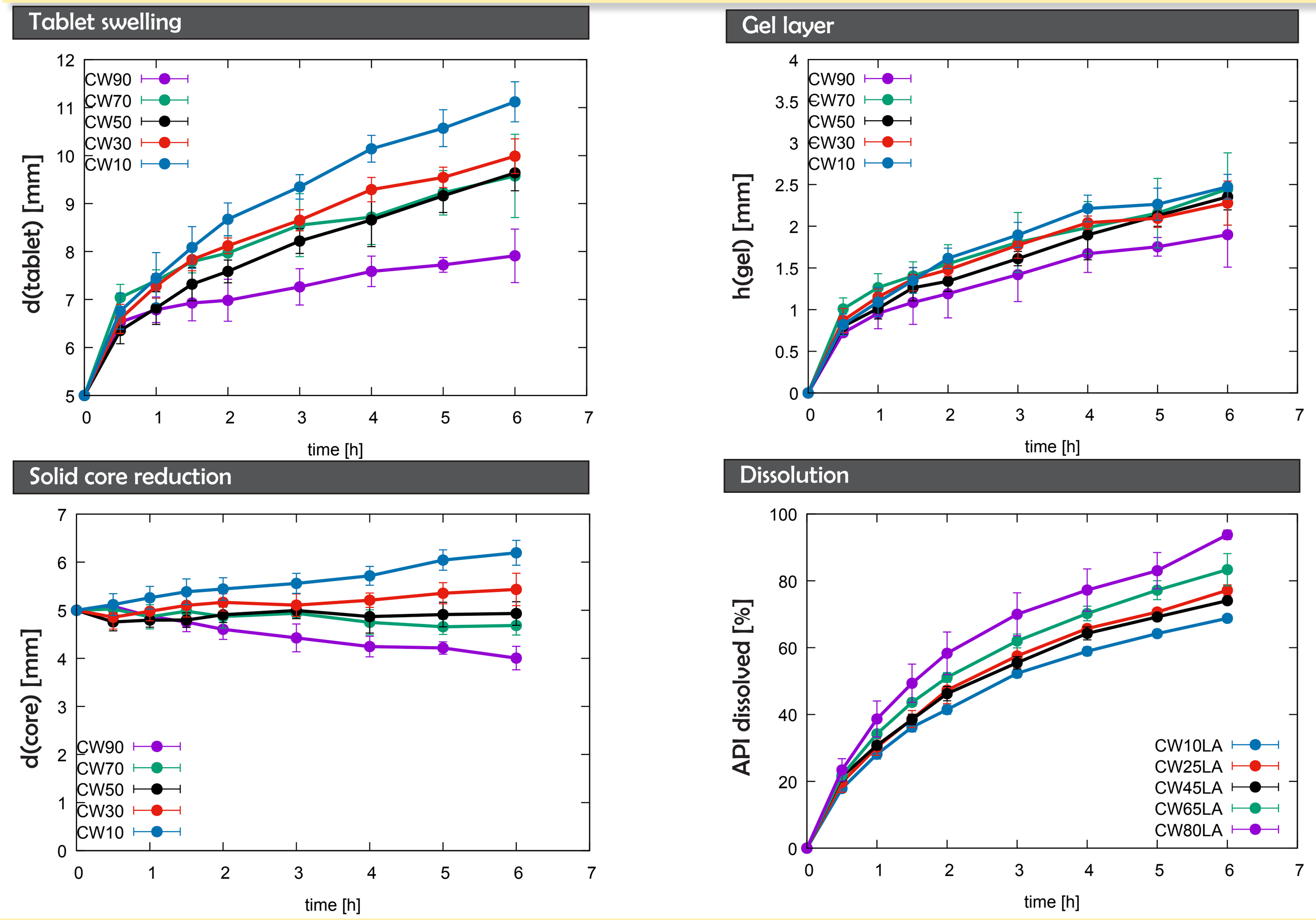
DATA PROCESSING



RESULTS FOR FORMULATIONS CW90 - CW10



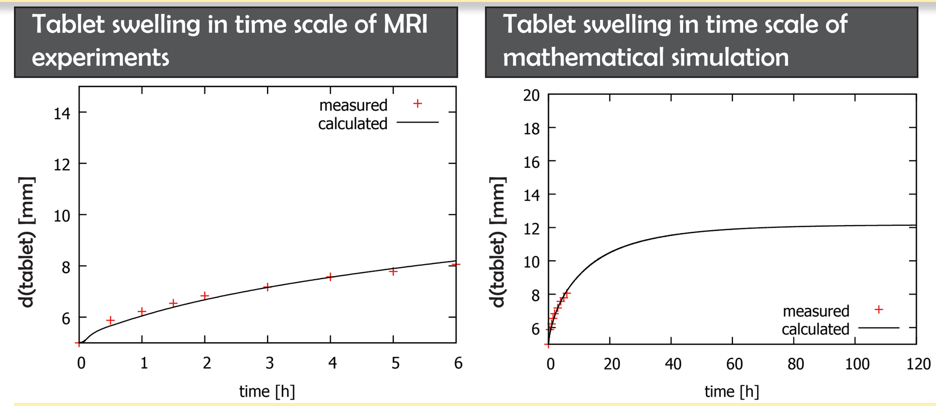
MRI RESULTS IN PLOTS



SIMULATION RESULTS FOR CW10

Parameters - fixed:	physical logical	
polymer density [g/mm³]	ρ_p	1.326E-3
water density [g/mm³]	ρ_w	1.000E-3
CW density [g/mm³]	ρ_{cw}	0.970E-3
tablet radius [mm]	r_o	5.0
tablet thickness [mm]	h	1.0
mass fraction of CW	w_{cw}	0.1 – 0.9
polymer dissolution coefficient [mm/s]	k_{dis}	3E-5
power law exponent	α	1

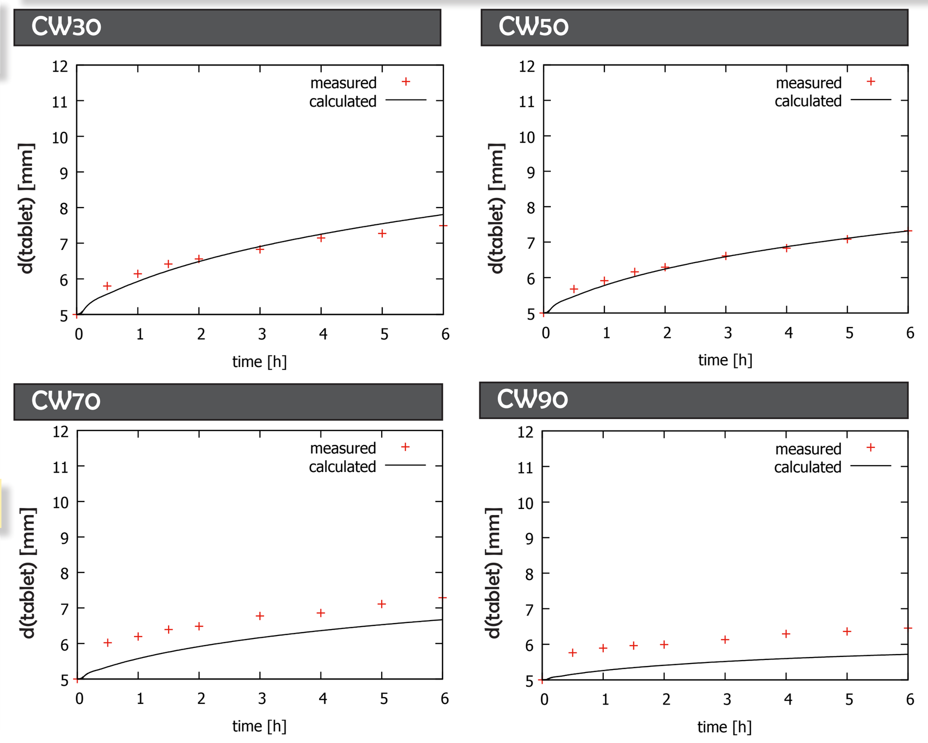
- variable:	diffusivity characteristics mass transfer characteristics	
concentration of polymer in dissolution medium [g/mm³]	c_p(bulk)	0
maximum diffusion coefficient [mm²/s]	D_w(max)	2E-3
disentanglement threshold	φ_d	0.98
mass transfer coefficient [mm/s]	k_w	3E-3
water fraction in polymer	φ*	0.8 - 0.98
exponent	β	0.5 - 3
minimum diffusion coefficient [mm²/s]	D_w(min)	2E-6 2E-4



FINEST FIT PARAMETERS

mass transfer coefficient [mm/s]	k_w	5E-3
water fraction in polymer	φ*	0.85
exponent	β	2
minimum diffusion coefficient [mm²/s]	D_w(min)	2E-5

SIMULATION FOR CW30; CW50; CW70; CW90



CONCLUSION

- The addition of hydrophobic additive in hydrophilic swelling matrix has significant effect on the swelling kinetics.
- Expected effect of decreasing the rate of water ingress to the matrix was displaced by our results, where the presence of CW caused faster API liberation and core reduction.
- Dissolution tests suggest the faster water ingress into the formulations with higher content of carnauba wax.
- Mathematical modeling turned out to be the useful supplement to the experimental results, it confirmed the theory of different water ingress mechanisms in formulations with the higher content of carnauba wax.
- Overall, this study provides interesting and valuable data for our research which is supposed to offer an effective tool for sustained release formulation design.

Acknowledgements:

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