SUPPLEMENTARY INFORMATION

Monolithic intercalated PNIPAm/starch hydrogels with very fast and extensive one-way volume and swelling response to Temperature and pH: prospective actuators and drug release systems

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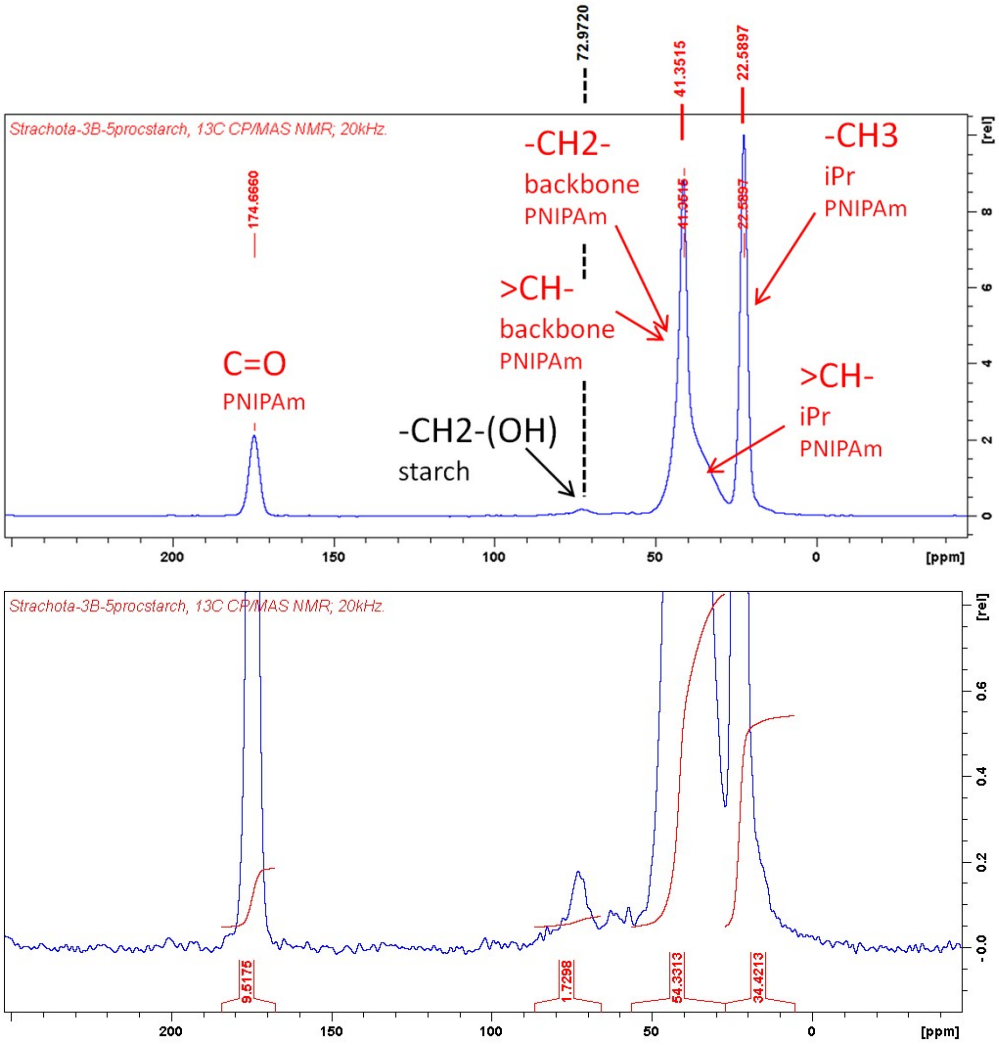
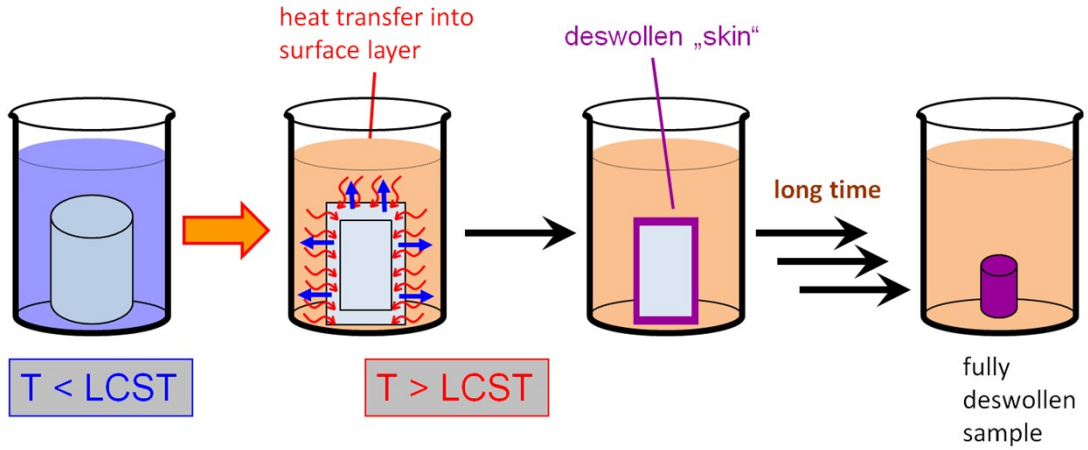
^{13}C-NMR analysis of the gels' composition



SI-Fig. 1: *^{13}C-NMR spectrum (solid state, dried sample) of an exemplary poly(NIPAm-co-sodium methacrylate) gel intercalated by starch (31.2 wt.% in dry gel).*

Slow temperature-induced deswelling and re-swelling

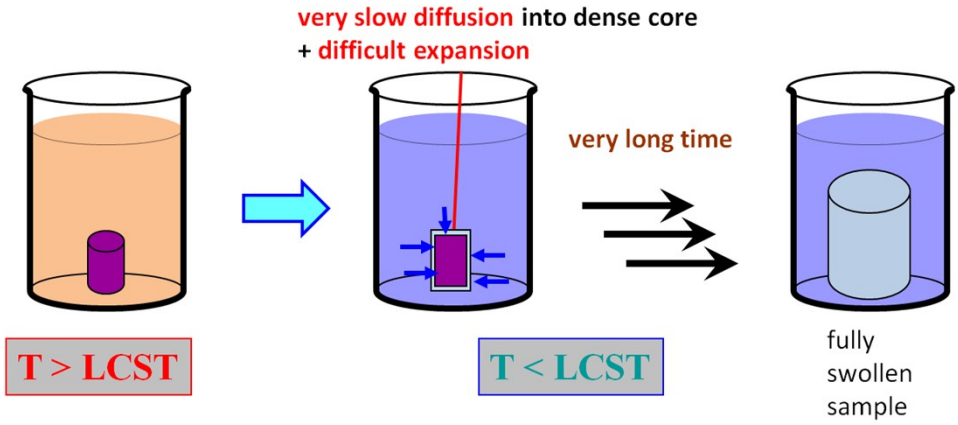
If the **slowly deswelling gels** (with low starch content) are considered, an interesting detail can be noticed, namely that the starch-free reference gel initially, in the first 20 min (see **Fig. 5a** in the paper), deswells faster (in % of releasable water per time unit) than the gel with 8% of starch. In the following 100 min, the slope of the deswelling process of both gels is identical, however. The initial rapid but small deswelling step can be assigned to the deswelling of the surface layer of the monolithic gel. This leads to the formation of a dense deswollen 'skin', which hinders further water diffusion out of the sample and the continuation of the deswelling much more, than the swollen material in the sample's interior (see **SI-Scheme 1**). Such a **'skin effect'** usually occurs in case of monolithic gel pieces and is well-known in the literature (see e.g. [Yoshida, Sakai et al. (1991), citation **53** in the paper]). As the 'Reference' gel displays approximately twice the initial value of the swelling degree than the gel with 8% of starch (see **Fig. 4** in the paper), a more voluminous (ca. twice) surface region of 'Reference' needs to deswell, in order to yield the same dense skin which was formed on the gel filled with 8% of starch.



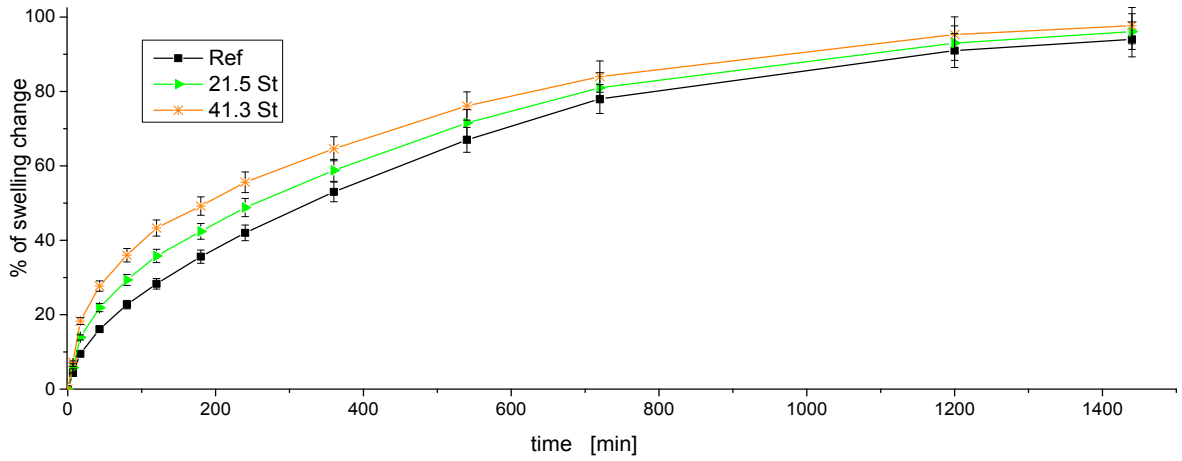
SI-Scheme 1: *Temperature-induced deswelling of a 'normal' sample of monolithic thermo-sensitive hydrogel which displays the so-called 'skin-effect'.*

The **slow re-swelling** of all the studied gels (kinetics shown in **Fig. 5b** in the paper and **SI-Fig. 2**) corresponds with the re-swelling of 'normal' bulk thermo-sensitive gels. In contrast to the deswelling process, there is apparently no mechanism, which would speed-up water uptake (see cold deswollen state in **Scheme 4d** in the paper). In addition to slow water diffusion, the effect of rigid core (see **SI-Scheme 2**) slows down the re-swelling of 'normal' bulk thermo-sensitive gels, similarly like the 'skin effect' slows down their shrinking. Nevertheless, in case of the higher starch loadings (above 21 wt.% in dry gel), it can be observed, that the temperature-induced re-swelling is **slightly accelerated by the increasing**

filler amount (see **Fig. 5b** in the paper and **SI-Fig. 2**). This appears to be an effect of increasing gel heterogeneity (an effect mentioned in the Introduction).

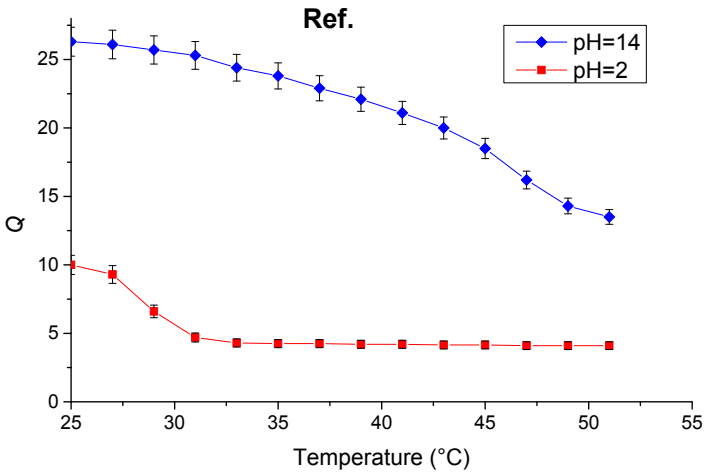


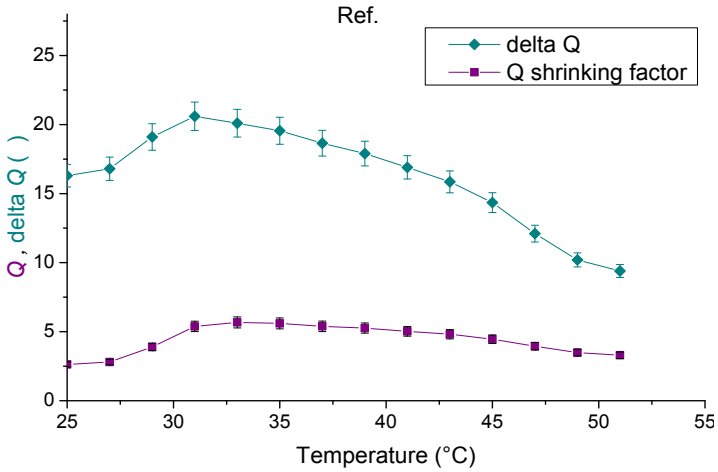
SI-Scheme 2: *Slow re-swelling of 'normal' monolithic hydrogels, affected by the effect of a rigid core.*

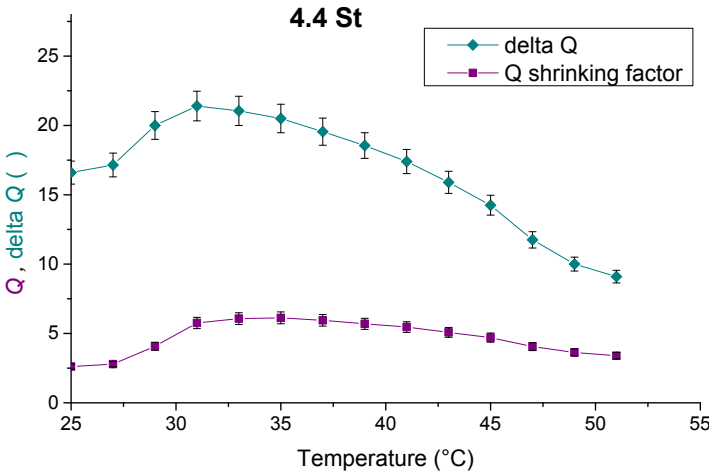


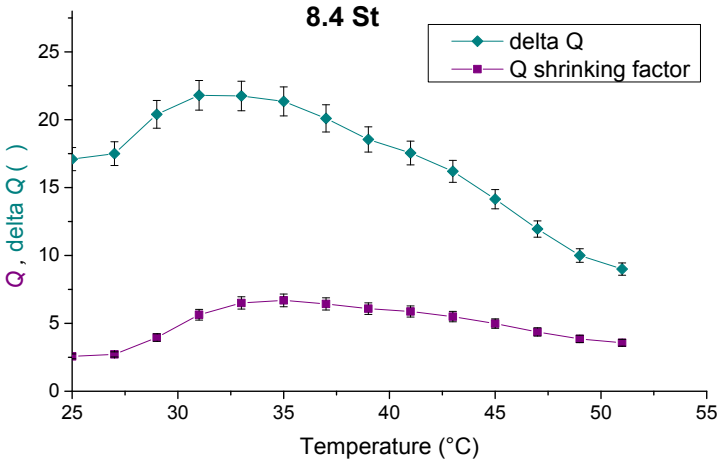
SI-Fig. 2: *Re-swelling kinetics of selected hydrogels at 25 °C after previous deswelling and equilibration (for 2 days) at 50 °C; the curves illustrate the slow rate of response to the temperature jump 50 °C → 25 °C.*

pH: Differences in swelling degrees (*Q*) and corresponding shrinking ratios for the pH jump 14 → 2








8.4 St
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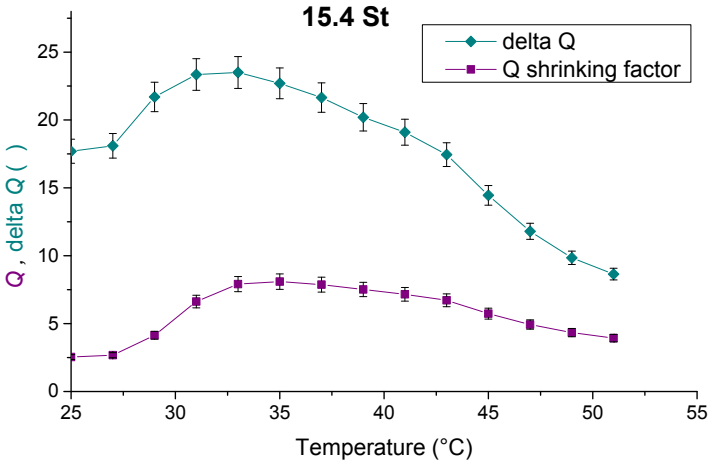
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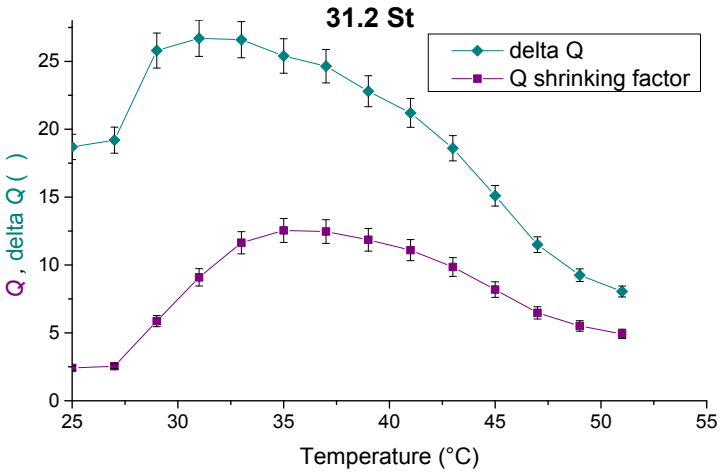
31.2 St
delta Q
Q shrinking factor
Q , delta Q ( )
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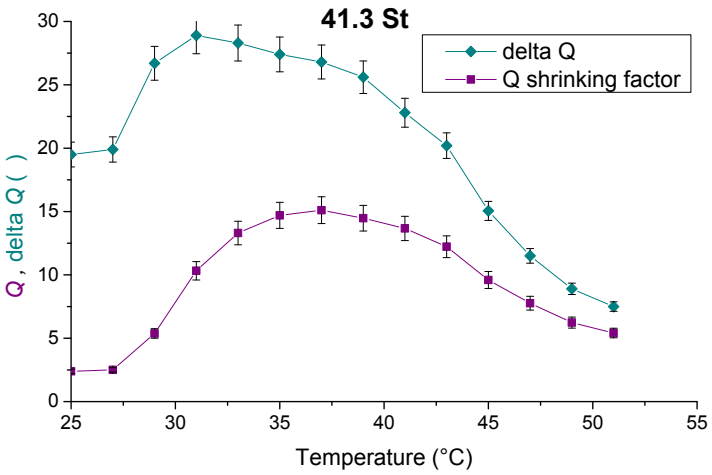
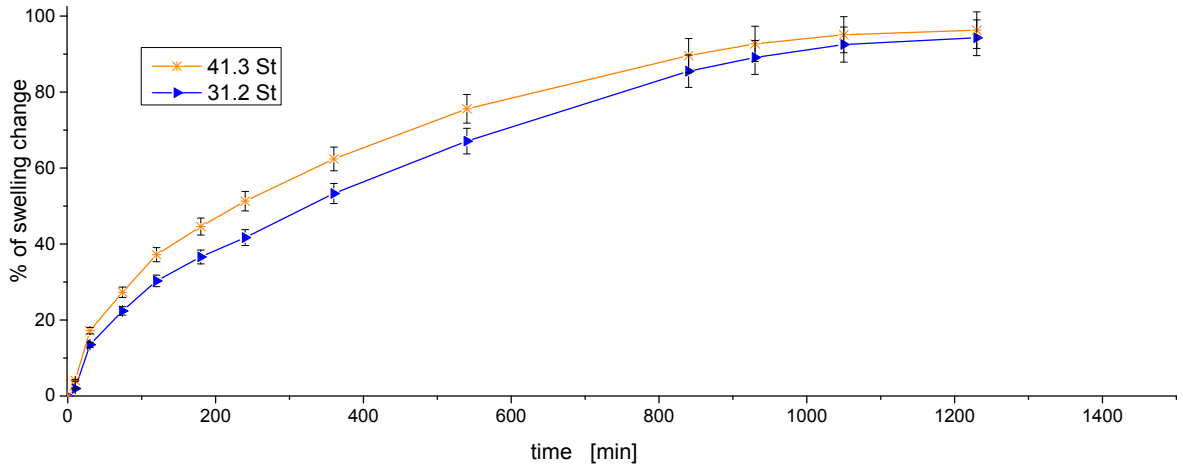


SI-Fig. 3: *Comparison of the temperature-dependent swelling curves at pH = 14 and 2 for the Reference sample (top graph) and Temperature-dependent difference in swelling degree caused by the pH jump 14 → 2, as absolute (ΔQ) value (green curves, top), and as shrinking ratio (= Q_{max}/Q_{min}, violet lines, bottom), for all the studied hydrogels (remaining graphs below).*

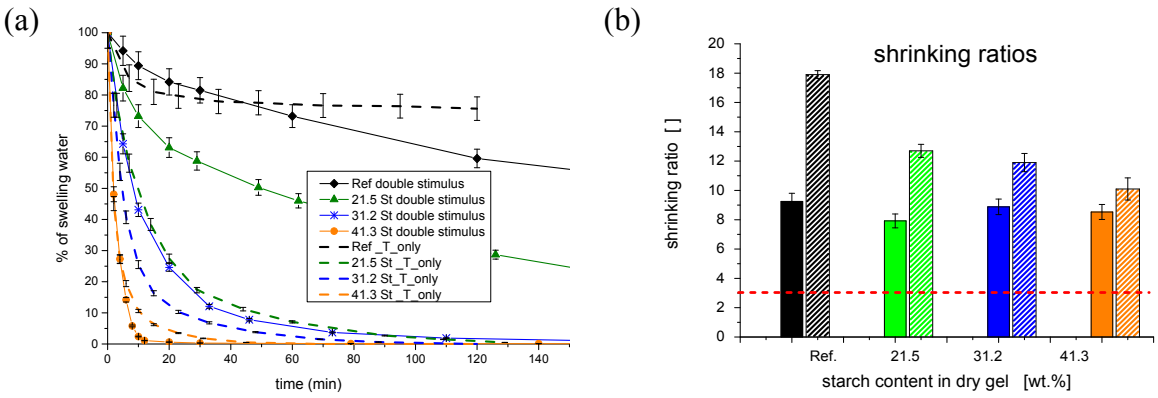
pH-induced (pH = 2 → 14) re-swelling kinetics



SI-Fig. 4: *Re-swelling kinetics of selected hydrogels at pH = 14 after previous deswelling and equilibration (for 2 days) at pH = 2; the curves illustrate the slow rate of response to the pH-jump pH = 2 → 14.*

Comparison of deswelling induced by Temperature alone vs. 'stomach stimulus'

If the doubly stimulated shrinking is compared with the shrinking triggered alone by the further above discussed temperature jump (larger than in the doubly stimulated process, namely 25 → 50°C), a mixed trend can be observed (see **Fig. 13** vs. **Fig. 5a** in the paper; see also **SI-Fig. 5**): Some gels, especially the one containing 21.5% of starch, and to a lesser extent the one with 31.2% shrink faster in case of the 'temperature alone stimulus' (25 → 50°C). On the other hand, in case of the gel with the highest starch content, 41.3%, and of the starch-free reference, the 'stomach stimulus' yields the faster kinetics. The larger shrinking ratios, as well as the larger and faster-propagating temperature stimulus seem to favor the faster response to 'temperature alone', while the synergy of two stimuli favors the faster response to the 'stomach stimulus'.



SI-Fig. 5: *Rate of swelling response to the combined pH- (pure water → pH = 2) and temperature- (25 → 37 °C) stimulus ('stomach stimulus') for selected hydrogel samples in dependence of starch content; the kinetics curves are compared with the ones recorded for the same gels but in response to the 'temperature only stimulus' (25 → 50 °C, dotted lines); (b) amplitudes of the swelling responses expressed as shrinking ratios (Q_{max}/Q_{min}).*

Drug release followed by means of UV/Vis

Drug release kinetics experiments, detailed description

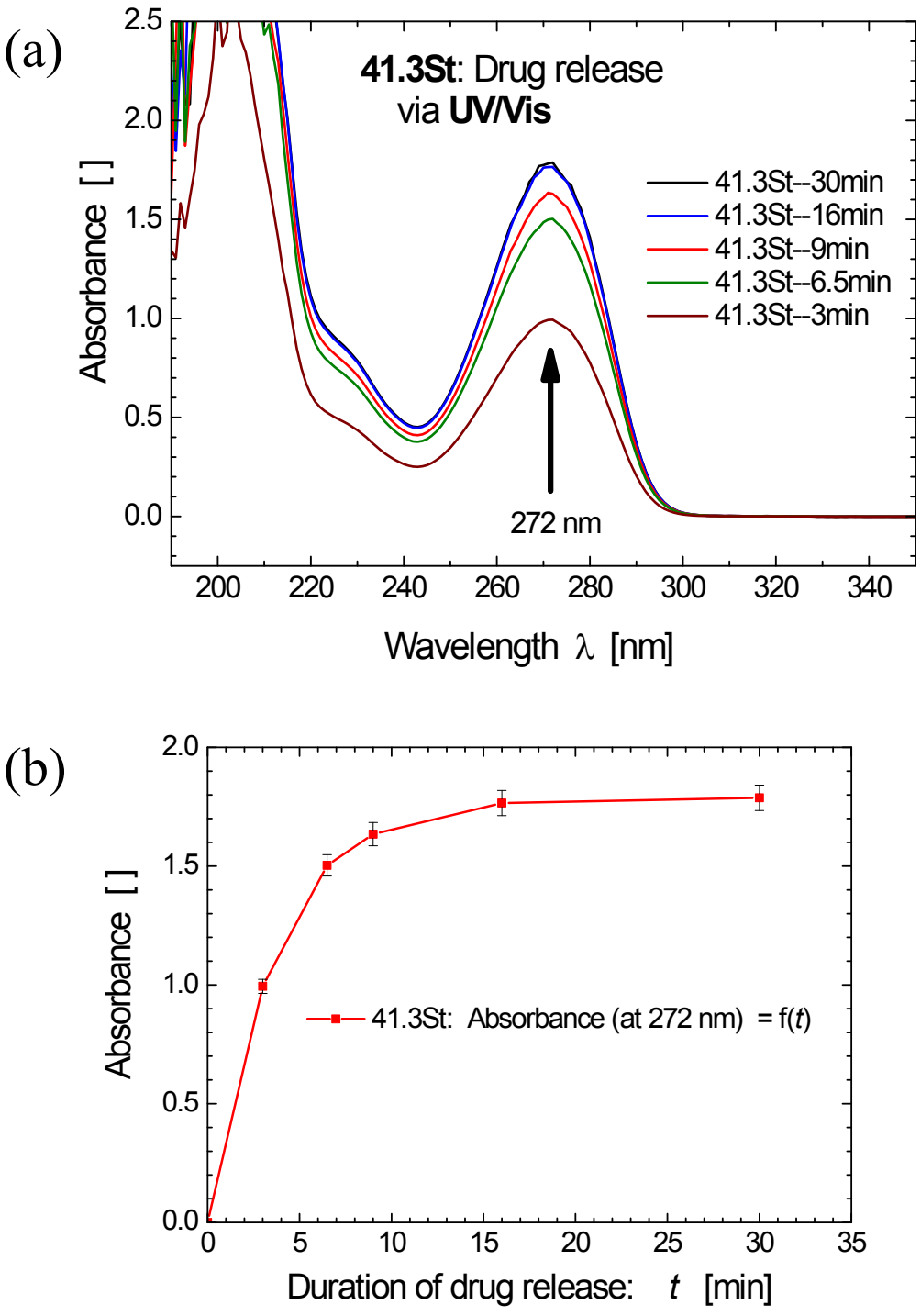
Gels with 31.2 and 41.3 wt.% starch in dry gel were tested.

Each **gel specimen was impregnated** for the drug delivery test as follows: A cylindrical specimen of ca. 1g weight (in the equilibrium swollen state at 25°C) was selected and subjected to deswelling in hot distilled water (50°C) for 24h. Subsequently, the mass of the shrunken specimen was recorded and it was put into a (concentrated) solution of the tested drug to be released, theophylline ($c_{\text{impregnation}}$ = ca. 0.036 mol/L), where the specimen underwent re-swelling (drug-impregnation) for 48h. Thereafter, the re-swollen mass was recorded in order to later calculate the absorbed amount of the drug (and to verify the completeness of re-swelling).

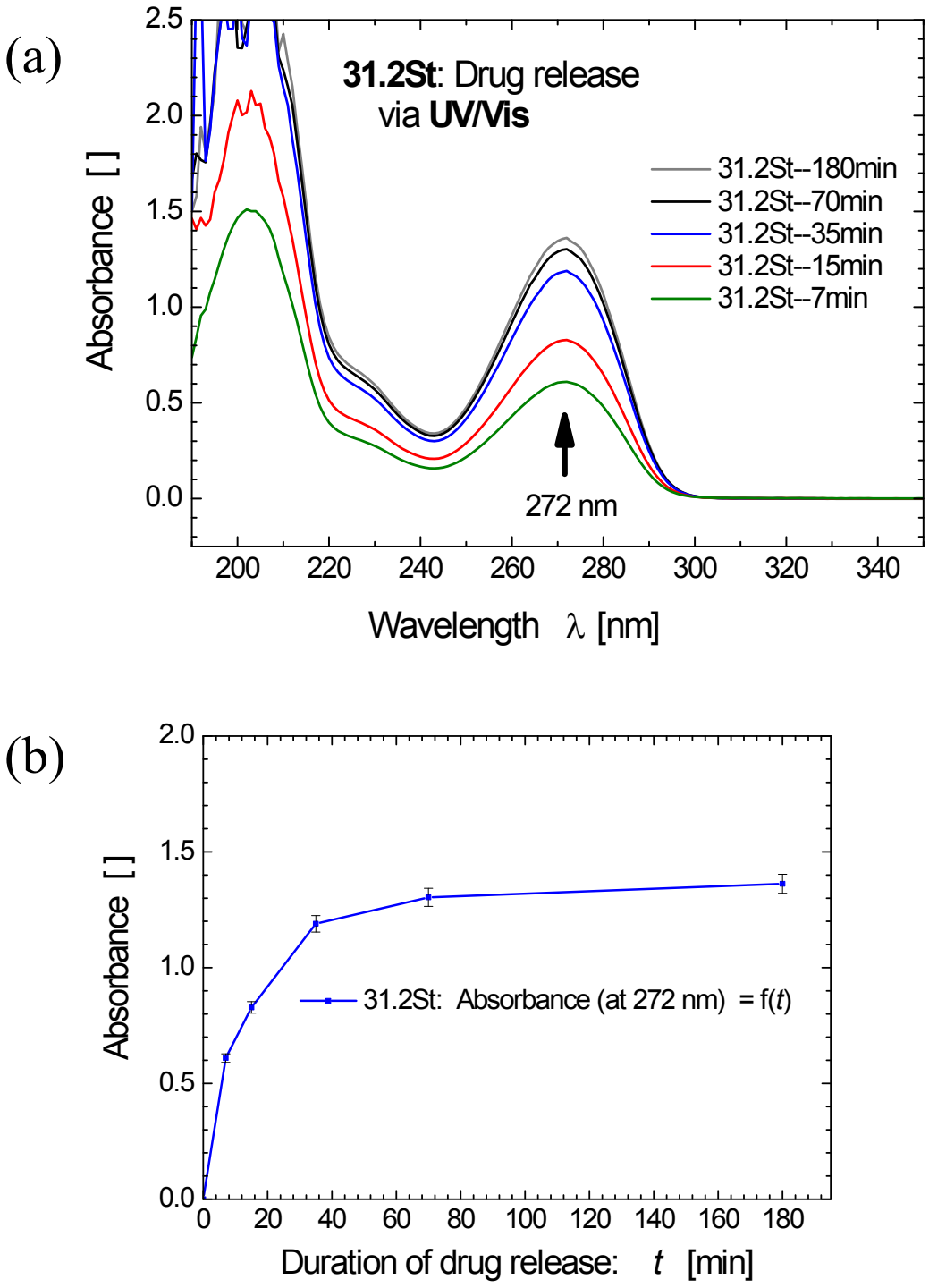
For **measuring the drug-release kinetics**, the drug-impregnated ('loaded') specimen was put into a 'release bath' consisting of H_3PO_4/NaH_2PO_4 buffer (pH = 2) which had a temperature of 37°C, in order to generate the 'stomach stimulus'. The bath volumes for each specimen were chosen (150 and 250 mL were used) in order to achieve final absorbance values (in 1 cm cuvettes), which would not exceed the value of ca. 1.8, in view of the loaded drug amount (whose nearly complete release was expected). Five 3 mL samples were taken after suitable release times (an analogous kinetics like with simple deswelling without drug was expected). The total removed volume of all samples taken from the release bath was then between 10 and 6%.

Concentration evaluation: The absorbance of the solution samples from the 'release bath' was determined using the mentioned "Lambda 35 UV/VIS" spectrometer, and the drug concentrations in them were determined using the Lambert-Beer law ($c = A / (\varepsilon * d)$). The involved bath volumes, the removed sample volumes and the determined drug concentrations made possible the calculation of the time-dependent released chemical amounts of the drug, as well as the total release yield (comparison to the originally loaded amount). The calculation details of the evaluation are given further below (**UV/Vis kinetics data evaluation**).

UV/Vis kinetics spectra



SI-Fig. 6: *(a) Time-dependent UV/Vis spectra of the bath solution (*pH2/37°C*) into which the drug theophylline was released by the gel **41.3St**; marked is the peak used for photometric concentration determination (272 nm); (b) time-dependence of the absorbance at the peak maximum at 272 nm, which was used for photometric concentration determination.*



SI-Fig. 7: *(a) Time-dependent UV/Vis spectra of the bath solution (*pH2/37°C*) into which the drug theophylline was released by the gel* ***31.2St****; marked is the peak used for photometric concentration determination (272 nm); (b) time-dependence of the absorbance at the peak maximum at 272 nm, which was used for photometric concentration determination.*

UV/Vis kinetics data evaluation

Characteristics of samples prior and after impregnation with drug

sample	*m*(deswollen) [g]	*m*(drug-impregnated) [g]	delta(*m*) [g] ≡ delta(*V*) [mL]	delta(*V*) [L]	*c*(impregnating Soln.) [mol/L]	*n*(drug loaded, theoretical) [mol]
41.3St	0.062	0.841	0.779	7.79E-04	3.56E-02	2.77E-05
31.2St	0.071	1.047	0.976	9.76E-04	3.60E-02	3.51E-05

Extinction coefficient (drug = theophylline): ε(272 nm) = 10 328 ±3% $(mol/L)^{-1}$ cm^{-1}

sample: **41.3St** (150 mL bath for drug release; 5 successive samples à 3 mL were taken at given times): time-dependent absorbance and magnitudes calculated from it

t [min]	A [ ]	c [mol/L]	*n*(drug released) * [mol]	drug release in **%** of theory	**%** of deswelling porcess **
0	0	0	0	0	0
3	0.994	9.62E-05	1.44E-05	52.1	56.4
6.5	1.503	1.46E-04	2.17E-05	78.3	84.7
9	1.635	1.58E-04	2.35E-05	84.9	91.9
16	1.765	1.71E-04	2.53E-05	91.4	98.8
30	1.787	1.73E-04	2.56E-05	92.4	100

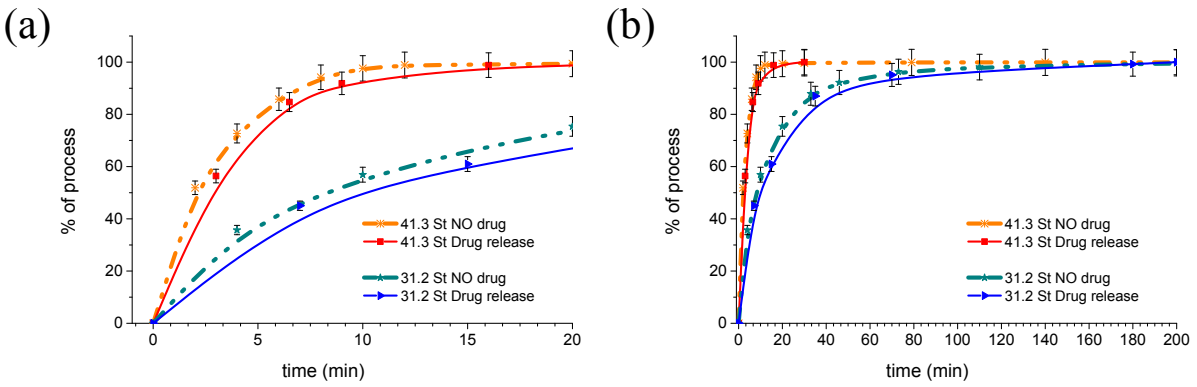
sample: **31.2St** (250 mL bath for drug release; 5 successive samples à 3 mL were taken at given times): time-dependent absorbance and magnitudes calculated from it

t [min]	A [ ]	c [mol/L]	*n*(drug released) * [mol]	drug release in **%** of theory	**%** of deswelling porcess **
0	0	0	0	0	0
7	0.61	5.90E-05	1.48E-05	42.0	45.0
15	0.828	8.02E-05	2.00E-05	57.0	61.0
35	1.189	1.15E-04	2.85E-05	81.2	87.0
70	1.303	1.26E-04	3.12E-05	88.8	95.1
180	1.362	1.32E-04	3.25E-05	92.7	100

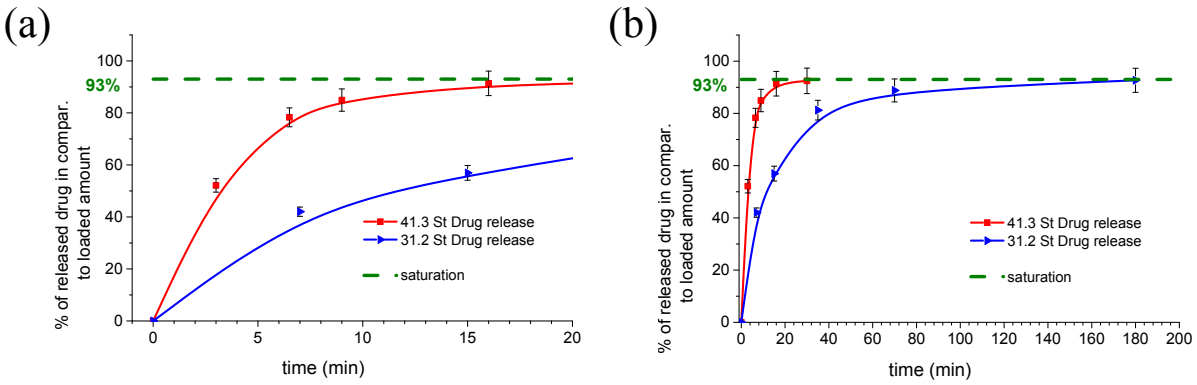
***)** *calculated from measured **Absorbance** values (according to Lambert-Beer: c = A / (ε * d) , where d was the sample thickness in the cuvette), while the amounts removed in previous 3 mL samples were also calculated and added to the actual chemical amount;*

****)** *% of completion of the 'rapid' deswelling accompanied by 'rapid' drug solution expulsion, which causes increase of drug concentration in the test bath; some solvent is retained in the deswollen gel, together with some drug, hence the release yield around 93% of theory; the residual drug amount would be later partly released very slowly via diffusion.*

Drug release kinetics data: final results of evaluation



SI-Fig. 8: *(a) Comparison of process completion in %: simple deswelling (dotted line) vs. drug release (bold line): (a): 20-min-scale, (b): 200-min-scale.*



SI-Fig. 9: *(a) time-dependent drug (theophylline) release from the gels **41.3St** and **31.2St**, expressed in % of the originally loaded drug amount: (a): 20-min-scale, (b): 200-min-scale.*