HOST-GUEST INTERACTIONS IN POLY(N-ISOPROPYLACRYLAMIDE) GEL. A THERMOANALYTICAL APPROACH

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Abstract

Responsive hydrogels are one of the most frequently proposed vehicles for targeted and controlled drug delivery. Interaction between the transported drug and the three-dimensional polymer network could compromise the kinetics and the efficiency of delivery in thermoresponsive polymers. Poly(N-isopropylacrylamide) (PNIPA) gel was equilibrated with excess 500 mM aqueous solutions of three model drug molecules, phenol, ibuprofen and dopamine. These molecules affect the swelling properties of PNIPA in different ways. After determining the drug uptake and drying to constant mass the loaded samples were studied with simultaneous thermal analysis (STA). The difference in thermal response is interpreted in terms of the different typical molecular interactions in these systems under confined conditions. For phenol and dopamine the water – phenol and dopamine – dopamine interactions, respectively, are stronger than that between the guest and polymer. For ibuprofen – PNIPA the synergy in the thermal decomposition may stem from a strong polymer – ibuprofen relation.

Keywords temperature sensitive polymers, poly(N-isopropylacrylamide) gel, host-guest interactions, dopamine, ibuprofen, phenol

1. Introduction

One of the vehicles most frequently considered for targeted and controlled delivery of chemically or medically active species is responsive hydrogels. Such systems are generally triggered by external physical stimuli (temperature, mechanical effect, electromagnetic radiation, electric or magnetic field) or chemical stimuli (solvent conditions: dissolved species, composition, pH, ionic strength). For biomedical applications temperature is a stimulus commonly applied for regulating drug release on account of its physiological relevance. Poly(*N*-isopropylacrylamide) (PNIPA) has a lower critical solution temperature (LCST) around 34 °C in pure water, i.e., close to the temperature of the human body. That is the reason why most thermoresponsive delivery systems are based on PNIPA hydrogels [1]. PNIPA gels can be used as pulsing drug release systems, where on-off drug release can be triggered by stepwise temperature change [2].

The interaction between the drug to be delivered and the three dimensional polymer network is of crucial importance for the rate and efficiency of the drug delivery. The release should not be inhibited by specific interactions between the guest molecule and the polymer, and understanding the nature of such interactions is therefore of great importance. However, in spite of intensive studies on PNIPA gels during the past decades, these interactions are not fully exploited.

The properties of PNIPA gels are affected by the synthesis conditions (composition of the monomer solution, temperature, reaction time, etc.). The key parameter however is the cross-link density defining the overall distance between the cross-link points. The glass transition temperature (T_g) of PNIPA polymers varies between 126-141 °C, based on the molar mass and tacticity [3]. According to Sousa et al., for dry PNIPA gels obtained from *N*-isopropylacrylamide (NIPA) with *N,N'*-methylenebisacrylamide (BA) crosslinker (nominal molar ratio NIPA/BA 135) the value of T_g is 135 °C. In DSC measurements (at heating rate 20 °C min^{-1}) they found that decomposition started at 388 °C and the corresponding peak displayed a maximum at 431 °C. Thermogravimetric studies on the same gel showed a 10 % loss of mass at about 100 °C due to the residual water and a more substantial mass loss (85 %) at 400 °C [4].

The influence of various incorporated small molecules on the swelling behaviour of the PNIPA hydrogels has been the focus of our research group for a decade [5-10]. Swelling and DSC investigations have shown that certain organic molecules present in the swelling medium may significantly reduce the temperature of the volume phase transition (VPT), and

that the shift depends on their concentration. At a particular guest molecule concentration, deswelling as abrupt as that in water at 34°C may occur already at room temperature, in which the concentration is characteristic of the dissolved molecule (critical concentration) [5-9]. Some molecules have only a slight effect or no affect at all [10].

Based on our previous experience, three molecules affecting the swelling properties in different ways were selected for thermoanalytical studies. These three molecules, which are of environmental and/or biomedical relevance, are phenol, ibuprofen and dopamine.

Phenol is a pollutant generated in industrial processes such as paper manufacturing, and in the production of dyes, resins, plastics, pharmaceuticals, etc. It is a toxic molecule that accumulates in the environment. Phenol is frequently used as a model for various drug molecules with substituted aromatic rings, such as tyrosine [11]. PNIPA exhibits a concentration dependent response in the presence of phenols. [6-7] Binding of phenol to PNIPA is mediated by hydrogen bonding between the amide group of the NIPA chain and the hydroxyl group of the phenol molecule [11]. The associative behaviour between phenol and PNIPA was also proved by small-angle neutron scattering (SANS) and solid state NMR techniques [5,8]. Based on these interactions, PNIPA is a potential candidate as a phenol sensor or actuator.

Ibuprofen (2-(4-isobutylphenyl)-propionic acid) is a hydrophobic non-steroidal anti-inflammatory drug. It is usually commercialized as (*R,S*)-(±)-ibuprofen sodium salt. The *S* enantiomer of ibuprofen is the active agent. The *R* enantiomer can be partially converted into (*S*)-(+)-ibuprofen in humans. Racemic ibuprofen displays polymorphism. The gamma form (where *R* and *S* enantiomers are crystallized into segregated particles containing either pure *R* or pure *S* enantiomer) is thermodynamically stable. Its alfa and beta forms, where *R* and *S* enantiomers crystallize in a joint lattice, are metastable. Controlled release experiments with various polymers revealed that the more hydrophobic the gel matrix is the stronger is the interaction between ibuprofen and the gel. [12-16] Ibuprofen interacts with PNIPA via hydrogen bonding when its carboxylic group binds either to the carbonyl oxygen or to the nitrogen atoms of the polymer chain in aqueous solution [15].

Dopamine (4-(2-aminoethyl)benzene-1,2-diol) is a neurotransmitter present in the brain and the nervous system. Abnormal levels of dopamine may result in Parkinson's disease and mental disorders [17]. In PNIPA gels it has a solvent quality improving effect and slightly increases the VPT temperature. However, no phase transition occurs even at internal concentrations as high as 1M [10]. Previous studies including two-dimensional ^{1}H solid-state

NMR combined with rotation and multiple-pulse spectroscopy (CRAMPS) techniques showed no association with the polymer chains [9].

The aim of the study reported here was to obtain deeper insight into the interactions between these guest molecules and the polymer gel host by studying the thermal behaviour of the drug loaded polymer in the dry state.

2. Materials and methods

2.1. Materials

N-isopropylacrylamide (NIPA) (99%) and *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TEMED) (99%) were purchased from Fluka, *N,N'*-methylenebisacrylamide (BA) (99%), ammonium persulphate (APS) (99%), sodium salt of ibuprofen (≥98%) and dopamine hydrochloride (98%) from Sigma-Aldrich, and phenol (analytical grade) from Merck. All chemicals were used without further purification. Selected properties of the guest molecules are summarized in Table 1.

2.2. Synthesis of the polymer gel

PNIPA gel films with thickness of 3 mm were synthesised by mixing 18.75 mL of a 1 M aqueous solution of NIPA and 1.225 mL of a 0.1 M solution of BA with 4.9 mL of water and 0.25 μL TEMED. Finally, 125 μL of ammonium persulfate (APS) was added to the mixture, and polymerization took place at 20 °C for 24 hrs. This yielded gels having a molar ratio of [NIPA]/[BA] equal to 150. The gels were dialyzed in doubly distilled water and cut into disks of 7 and 17 mm, then dried and stored above concentrated sulphuric acid.

2.3. Swelling measurements

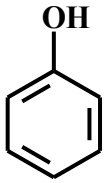
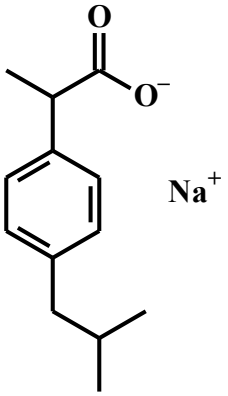
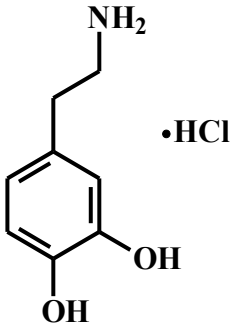
For swelling measurements dry disks were equilibrated with excess aqueous phenol, dopamine and ibuprofen solutions of different initial concentrations (0- 500 mM) for 1 week at 20.0 ± 0.2 °C. The ratio of dry gel/liquid was 0.012. The swelling degree at equilibrium was characterised as $100 \times m/m_0$, where m and m_0 are the mass of the swollen and the initial dry gel sample, respectively.

The aromatic guest uptake was determined as

$$n_a = (c_0V_0 - c_eV_e)/m_0 \quad (1)$$

where n_a is the amount of guest molecules in the gel (mmol $g_{dry\ gel}^{-1}$), c_0 and V_0 are the concentration and volume of the aromatic molecule in the initial liquid phase, and c_e and V_e are the same in the free liquid in equilibrium.

Table1 Selected properties of the guest molecules*

	Phenol	Ibuprofen sodium		Dopamine hydrochloride
Structure				
Molar mass	94.11	228.26		189.64
Melting	Melting: T = 40.89 °C ΔH_{fus} = 11.51 kJ mol^{-1} [18] Sublimation: T = - 43 - 40 °C ΔH_{sub} = 65.3-69.7 kJ mol^{-1} [19]	β**	T = 190 °C [13,20-21]	T = 241 °C (decomposition) [22]
		γ	T = 200 °C ΔH_{fus} = 10.8 kJ mol^{-1} [13,20-21]	
Boiling	T = 181.87 °C ΔH_{vap} = 45.69 kJ mol^{-1} [18]			

*T = temperature of the process; ΔH = enthalpy; subscripts fus = fusion, sub = sublimation, vap = vaporization; ** α→β transition occurs at 120 °C [20].

2.4. Thermal methods

Simultaneous thermal analysis (STA) was carried out on an STA6000 instrument (PerkinElmer) in high purity (99.9995%) nitrogen with the flow rate 20 mL min^{-1}. Samples

equilibrated in 500 mM solutions were used for the thermal studies. The loaded gels were air-dried, ground in an agate mortar and stored over silica gel. Samples of about 10 mg were incubated at 30 °C for 5 minutes then heated from 30 to 650 °C with a scanning rate of 10 °C min^{-1}. The thermogravimetric (TG), and differential thermal analysis (DTA) curves were recorded. The position of the peaks of the DTG and DTA curves was characterized by the temperature of their maximum. All the heat effects deduced from DTA are endothermic. The pure guest molecules were also stored over silica prior to the thermal measurement.

3. Results and discussion

3.1. Equilibrium swelling properties in aqueous solutions

The three aromatic molecules have different effects on the swelling behaviour of the PNIPA gel (Fig.1). In aqueous phenol solutions a limited reduction in swelling occurs up to 52 mM, at which an abrupt change occurs already at 20 °C. Above this concentration the phenol loaded system exhibits only limited swelling [6-7]. Ibuprofen causes only a minor depletion that is proportional to its concentration in the swelling medium in the wide concentration range of the experiments, while dopamine shows no detectable influence at all up to 500 mM.

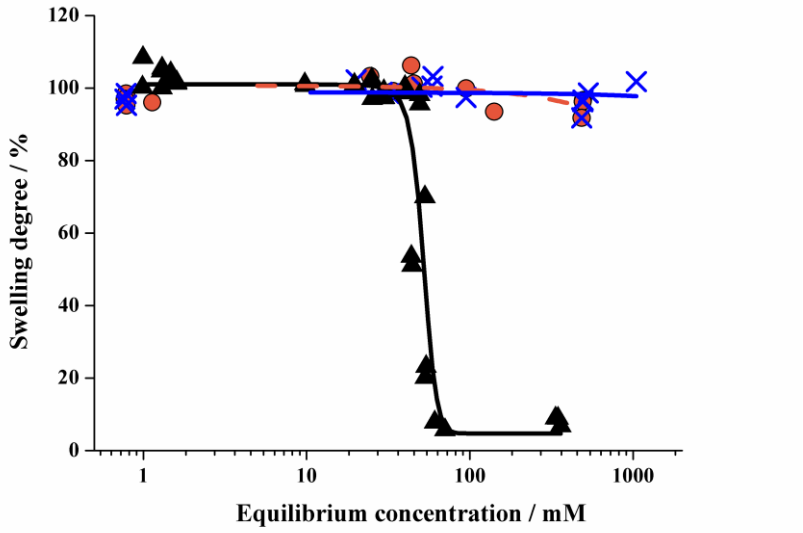


Fig.1 Equilibrium swelling degree of PNIPA hydrogel in different swelling media at 20 °C. Phenol: ▲, ibuprofen: ●, dopamine: ✖

The dry samples prepared for the thermal studies have very different appearances. The phenol loaded samples are elastic and transparent, and their diameter shrinks to ca 5 mm. The diameter of gel disks equilibrated in ibuprofen is ca 15 mm. Their surface is decorated with

mat white ibuprofen crystals. Dopamine loaded samples have even larger diameter (ca 20 mm) than the one swollen in pure water. Their surface is shiny dark brown, as dopamine darkens, even in dark bottles, during the equilibration period. Table 2 compares the uptake and the composition of the guest loaded samples.

Table 2 Equilibrium swelling degree and aromatic uptake of PNIPA samples after equilibrating for a week at 20 °C in 500 mM solution

Guest molecule	Swelling ratio /%*	Uptake** / $\frac{mmol_{guest}}{g_{dry\ gel}}$	Sample composition**		
			$\frac{Guest}{monomer}$ molar ratio	w/w%	
				Guest	Monomer
Phenol	2	2.2	0.25	17.1	82.9
Ibuprofen sodium	24	14.2	1.61	76.3	23.7
Dopamine.HCl	28	15.1	1.71	74.1	25.9

*100×m/m_0 (m and m_0 are the mass of the swollen and the initial dry gel sample, respectively); ** based on uptake measurement (Eq.1)

According to material balance calculations the dried phenol and dopamine loaded samples retain ca 24% and 5% water, respectively.

3.2. Thermal analysis of the pure components

3.2.1. Pure PNIPA gel

Fig. 2 shows the thermal response of the dry PNIPA gel. It is noteworthy that even after a week-long storage in a desiccator some water is still retained. The degradation occurs in a single step and is preceded by 3.4 % water loss around 100 °C. The glass transition at ca 130 °C is hardly observable on the DTA curve (Fig.2). These are in a good agreement with reference data [3-4]. The decomposition in the range 330-430 °C results in 94.9 % mass loss. The corresponding DTG and DTA peaks appear at 415.5 and 414.5 °C, respectively. The latter is preceded by a small heat effect (14.8 J g_{sample}^{-1}) at 329 °C, verifying the asymmetric DTG peak. The enthalpy change is 478.0 J g_{sample}^{-1}. Considering the water content, the estimated enthalpy of the decomposition is ΔH = 56.0 kJ $mol_{monomer}^{-1}$ for the water-free gel. The residue at 650 °C is 1.7 %.

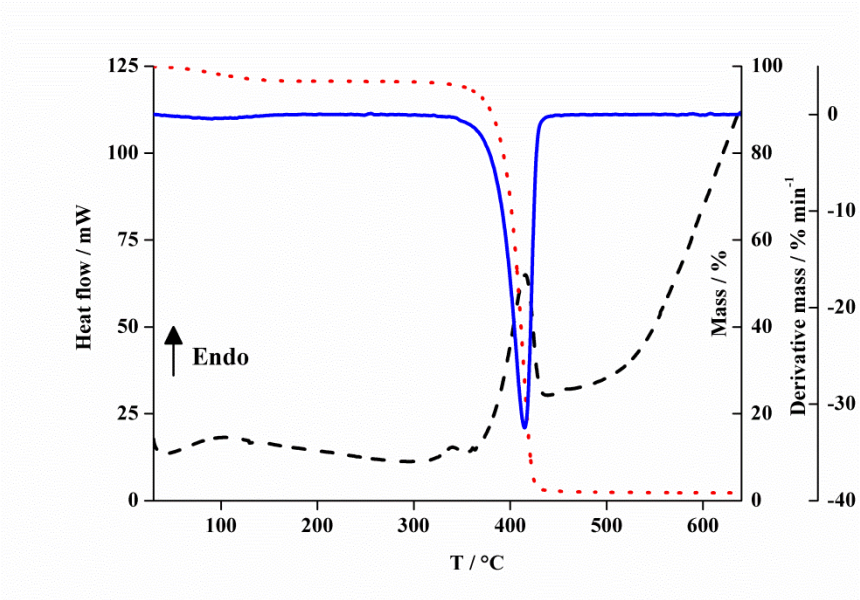


Fig.2 TG, DTG and DTA responses of pure PNIPA in N_2 flow. TG: dotted line, DTG: solid line, DTA: dashed line

3.2.2. Phenol

In the response of the pure phenol no separate water loss can be distinguished (Fig.3). The DTA peak at 43 °C is due to the phenol melting. Its sharpness and the corresponding enthalpy (9.4 kJ mol^{-1}) reveal the lack of sublimation [18]. The TG curve has a single step in the 50-140 °C interval, as the phenol slowly and completely evaporates in the nitrogen flow (mass loss100%). The corresponding DTA and DTG peaks at 137 °C and at 136 °C, respectively, appear below the normal boiling point (182 °C) [18], due to the dynamic conditions. The molar heat from the second peak (54.9 kJ mol^{-1}) overestimates the heat of evaporation [18] owing to the high volatility of phenol.

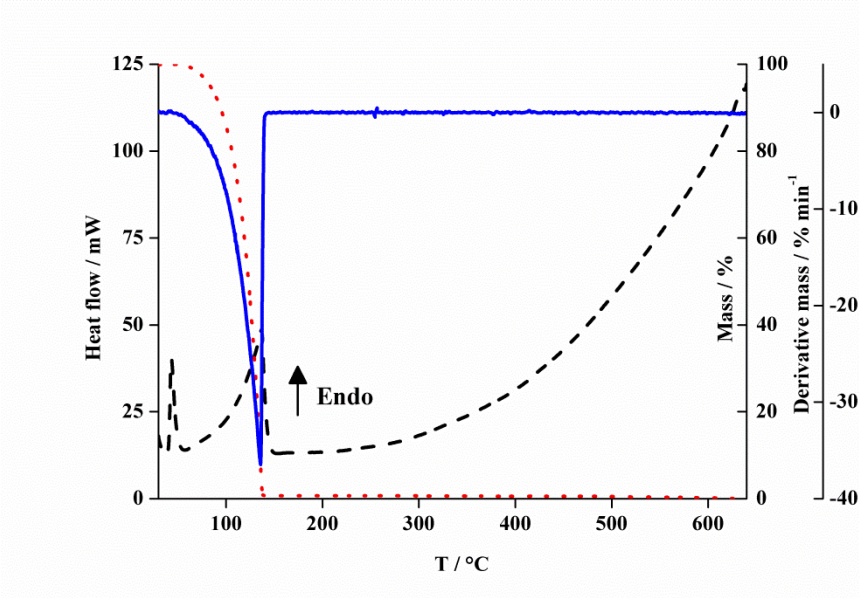


Fig.3 TG, DTG and DTA responses of the pure phenol in N_2 flow. TG: dotted line, DTG: solid line, DTA: dashed line

3.2.3. Ibuprofen sodium

Pure ibuprofen sodium was examined in racemate form containing both *S* and *R* enantiomers (Fig.4). The TG curve shows an initial water loss of 2.8 % below 100 °C. The 198 °C peak in the DTA response is related to the melting of the gamma form of ibuprofen sodium [20-21]. The corresponding enthalpy (ΔH = 68.4 J g_{sample}^{-1} = 16.1 kJ $mol_{dry\ ibuprofen}^{-1}$) however significantly exceeds the reference value (Table 2). The heat effect associated with the decomposition at 465 °C is ΔH = 360.4 J g_{sample}^{-1} = 84.8 kJ $mol_{dry\ ibuprofen}^{-1}$. Finally, 25.7 % residue remained.

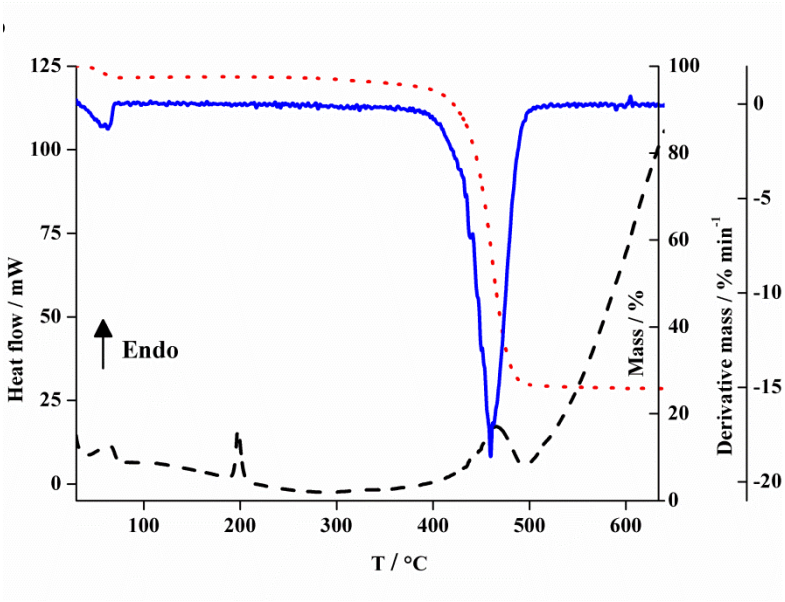


Fig.4 TG, DTG and DTA responses of pure ibuprofen sodium in N_2 flow. TG: dotted line, DTG: solid line, DTA: dashed line

3.2.4. Dopamine hydrochloride

The TG curve of dopamine hydrochloride, in compliance with the literature [31], exhibits a wide and complex step in the 220-500 °C interval (Fig.5). The total mass loss is 77.2 %, leaving 22.8 % residue, very close to reference data [23]. The melting point is detected in the DTA response at 244.7 °C with a corresponding enthalpy of 193.7 J g^{-1} (36.8 kJ mol^{-1}). Earlier DSC studies on dopamine hydrochloride showed a sharp peak with a maximum 240 °C [24]. The DTG response confirms that dopamine starts to decompose already at its melting point. The sharp peak assigned to the decomposition appears at 327 °C in the DTG curve with a corresponding heat of 450 J g^{-1} (85.5 kJ mol^{-1}). A well separable 353 J g^{-1} (66.9 kJ mol^{-1}) heat pertains to the tail of the DTG curve. The total heat of decomposition can be estimated as 155.4 kJ/mol.

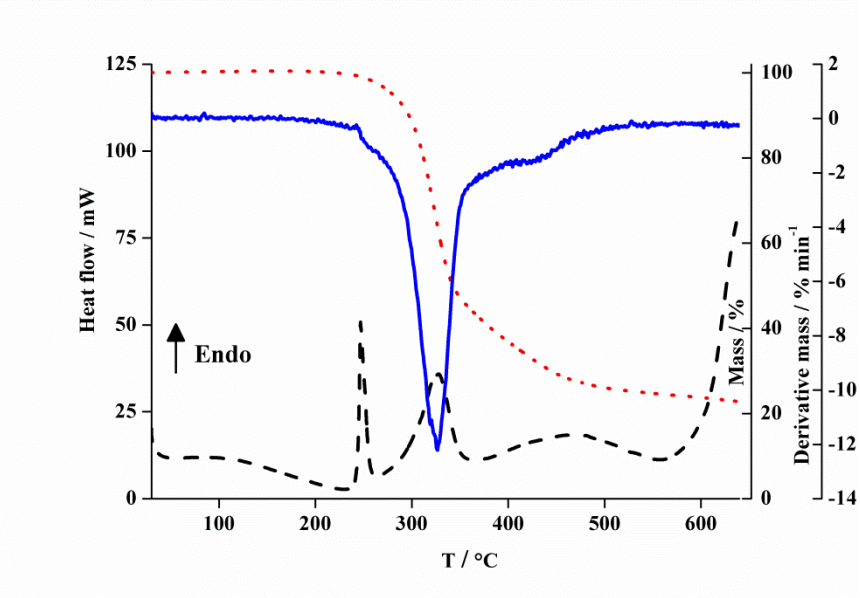


Fig.5 TG, DTG and DTA responses of pure dopamine hydrochloride in N_2 flow. TG: dotted line, DTG: solid line, DTA: dashed line

3.3. Guest molecule - PNIPA systems

3.3.1. Phenol-PNIPA

PNIPA is in the collapsed state in 500 mM phenol solution, i.e., this sample was prepared above LCST conditions. Instead of the freely moving organic chains, the polymer forms thick hydrophobic walls (ca 10 nm) [25]. The liquid phase retained is limited, although the swelling degree is still 8.2 (Fig.1). The small molecules withheld are distributed both in the hydrophobic region of the walls and in the cavities of about a hundred nanometers [26]. Independent investigations revealed that close to the phase transition state a direct interaction develops between the phenol and the polymer chains as well [5,11].

From the comparison of Figs. 2, 3 and 6, the thermal response of the complex system cannot be derived as a simple proportional combination of the corresponding phenol and PNIPA gel curves. The melting peak of the phenol disappears completely. The T_g of the PNIPA is not recognisable, but, in the temperature range 325-430 °C the shape of the DTA curve is very similar to that of the pure PNIPA, except for a downward temperature shift. The characteristic features are shown in Table 3 and the DTG responses are compared in Fig.7. The mass loss in the first wide step in the TG curve (60 – 280 °C) significantly exceeds the phenol content (Table 2). According to Fig.3 PNIPA itself starts to degrade only at higher temperature, and therefore it may not contribute to this effect. Mass balance of the loaded sample indicates about 24 % water even in the sample dried till constant mass, which also

contributes to the elasticity observed on the macroscopic sample. Therefore this step may stem from the slow discharge of phenol and strongly bound water molecules. The secondary interactions ~~existing~~ among these components are overcome at this elevated temperature. Interaction between the phenol, water and the PNIPA gel [8] may explain the prolonged release of the phenol. The decomposition occurs at 382 °C. The interaction between the small molecule and the polymer chain may weaken the polymer – polymer attraction when the loaded gel is drying and the less ordered structure causes this depression in the decomposition temperature. The high surface area of the remaining polymer [26] may also contribute to the higher thermal sensitivity. The PNIPA content of this sample (63 % from the mass balance and Table 2) yields for the estimate of the heat of degradation: 552 J g_{NIPA}^{-1} = 62 kJ $mol_{monomer}^{-1}$. This is in relatively good agreement with the values obtained for pure PNIPA gel in Section 3.2.1.

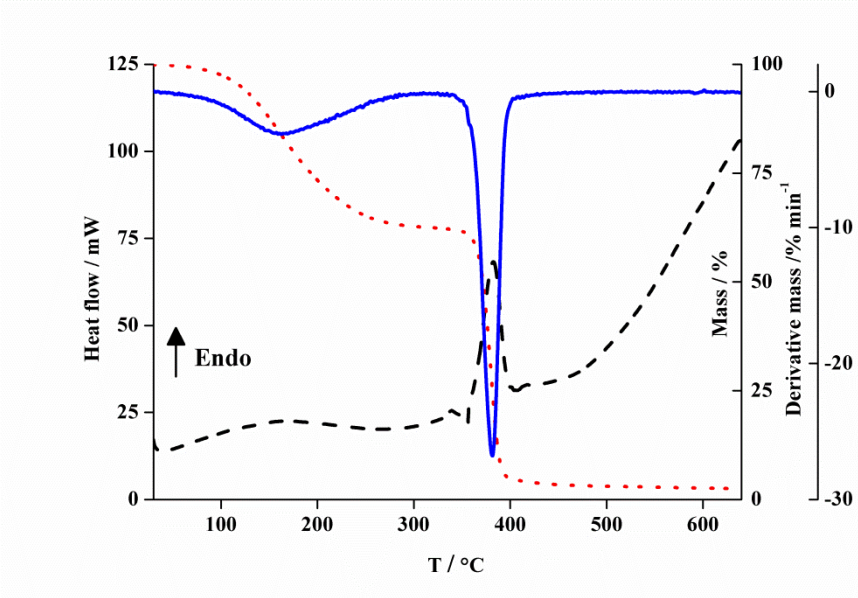


Fig.6 STA response of the phenol loaded PNIPA gel in N_2 flow. TG: dotted line, DTG: solid line, DTA: dashed line

Table 3 Characteristic features of the phenol loaded PNIPA gel

Characteristics	Peak position (from DTG)	
	153.3 °C	381.7 °C
Δm / %	37.3	59.4
ΔH / J g_{sample}^{-1}	234.5	347.5

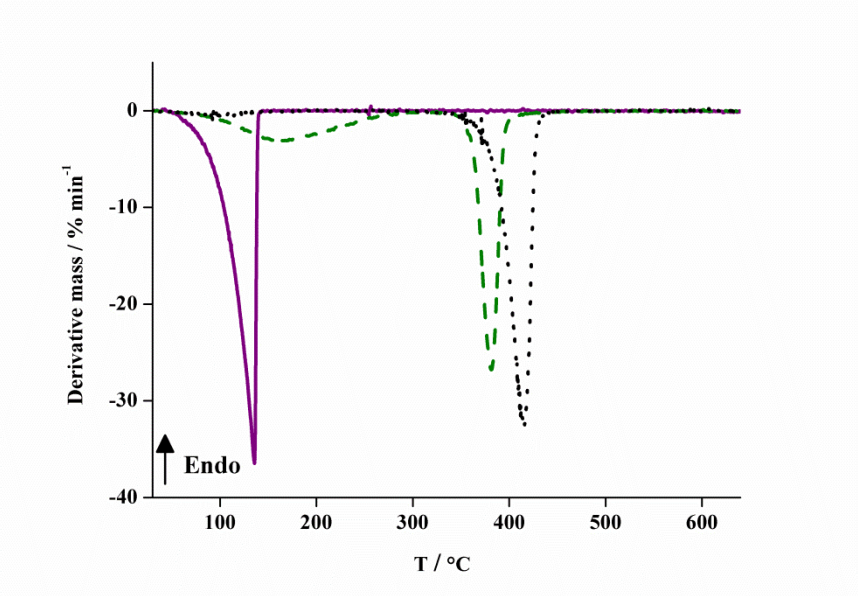


Fig.7 Comparison of the DTG response of PNIPA equilibrated in 500 mM phenol solution to the pure systems in N_2 flow. Pure PNIPA: dotted line, phenol: solid line, phenol loaded PNIPA: dashed line.

3.3.2. Ibuprofen sodium - PNIPA

PNIPA was highly swollen in 500 mM ibuprofen solution during the sample preparation. In the TG response of the ibuprofen loaded polymer a dehydration peak (mass loss 9.0 %) ending at around 145 °C was observed (Fig.8). As only a limited amount of water was retained both by pure ibuprofen and pure PNIPA, the enhanced attraction of water can be attributed to the composite system. According to the DTA curve, the hardly detectable melting point of ibuprofen is shifted to ca 184 °C, and above 300 °C a sharp degradation appears with an elongated tail ending at 500 °C (total mass loss 81.1 %). The total heat effect accompanying the dominant DTG peak is 419.2 J g_{sample}^{-1}. The DTA curve reveals that this process is complex: the degradation of ibuprofen and the polymer overlap, providing the corresponding sharp DTG peak at 357 °C. Only a flat DTG peak remains from the intense degradation peak of the free ibuprofen (Fig.9). The sharp DTA peak at 357 °C confirms that in the loaded system the degradation is shifted to a substantially lower temperature than in the free components. The presence of the ibuprofen makes the dry loaded gel less ordered and thus more sensitive to temperature. The deviation is almost 60 °C for both the DTA and DTG signals, i.e., the degradation of ibuprofen is also promoted by the decomposition of the polymer. The total residual mass at 650 °C (8.3 %) is much less than expected from the

individual pure signals, corroborating such synergy. It suggests that at least part of the ibuprofen is strongly attracted to the polymer chains.

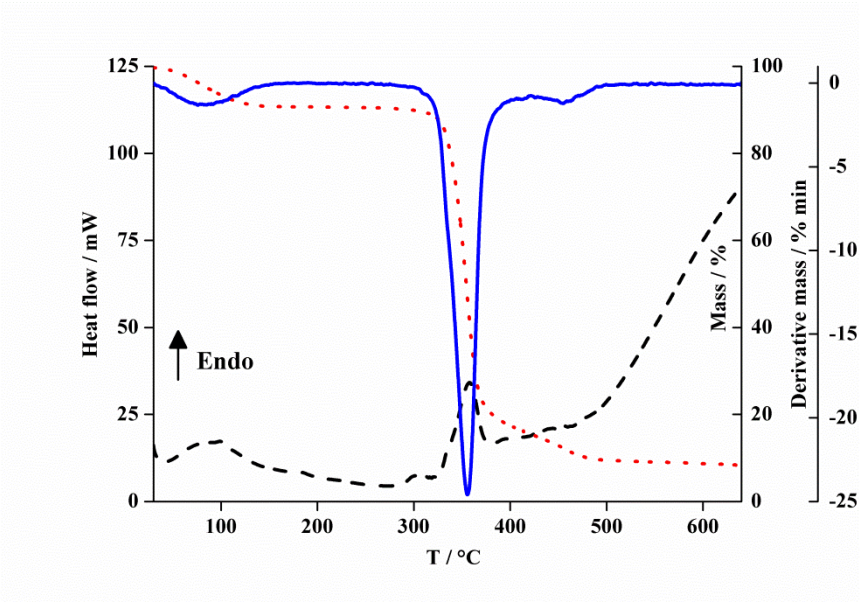


Fig.8 STA response of the ibuprofen loaded PNIPA gel in N_2 flow. TG: dotted line, DTG: solid line, DTA: dashed line

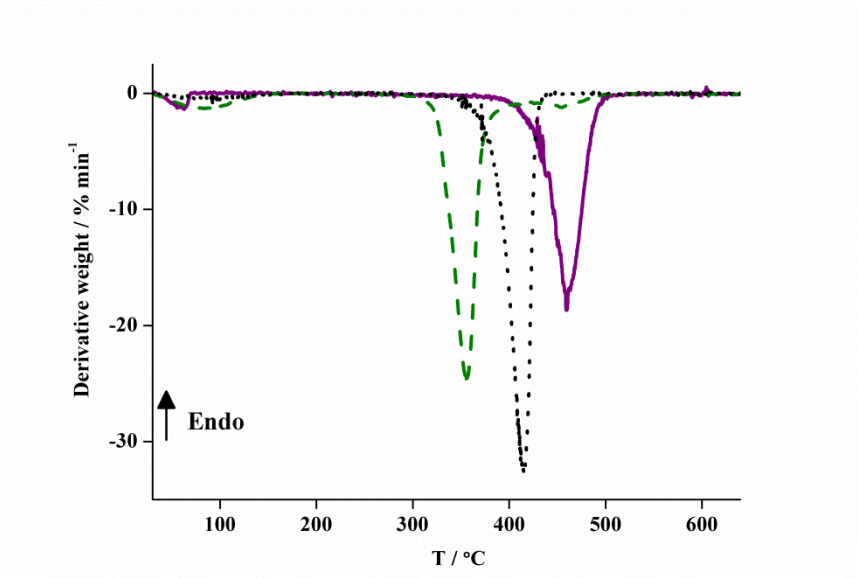


Fig.9 Comparison of the DTG response of PNIPA equilibrated in 500 mM ibuprofen solution to the pure systems in N_2 flow. Pure PNIPA: dotted line, ibuprofen sodium: solid line, ibuprofen loaded PNIPA: dashed line

3.3.3. Dopamine hydrochloride - PNIPA

The characteristic regions belonging to the two components can be straightforwardly identified in the response curves of the dopamine loaded PNIPA (Fig.10). Practically no shift

in the peak positions is observed (Fig.11). The residue at 650 °C (ca 21 %) also confirms the practically independent decomposition of PNIPA and dopamine. The melting peak of the dopamine can be clearly recognised at 224.8 °C on the DTA curve with ΔH = 80.0 J g_{sample}^{-1} corresponding to ca 21 kJ $mol_{dopamine}^{-1}$. This value is about 60 % of that obtained for pure dopamine (Section 3.2.4.). It is possible that the rest of the dopamine interacts preferentially with other dopamine molecules and only a limited amount contributes to this peak [27]. Although the degradation of the polymer matrix and the guest molecule give signals that are very close, they can be clearly distinguished: the 313.9 °C part of the double DTG peak belongs to dopamine, while that at 405.4 °C corresponds mainly to PNIPA. Due to the extended degradation of dopamine (Fig. 5) only the enthalpy corresponding to the 313.9 °C peak was estimated. The obtained 81 kJ $mol_{dopamine}^{-1}$ shows a good agreement with the respective signal in the pure dopamine curve (Fig. 5).

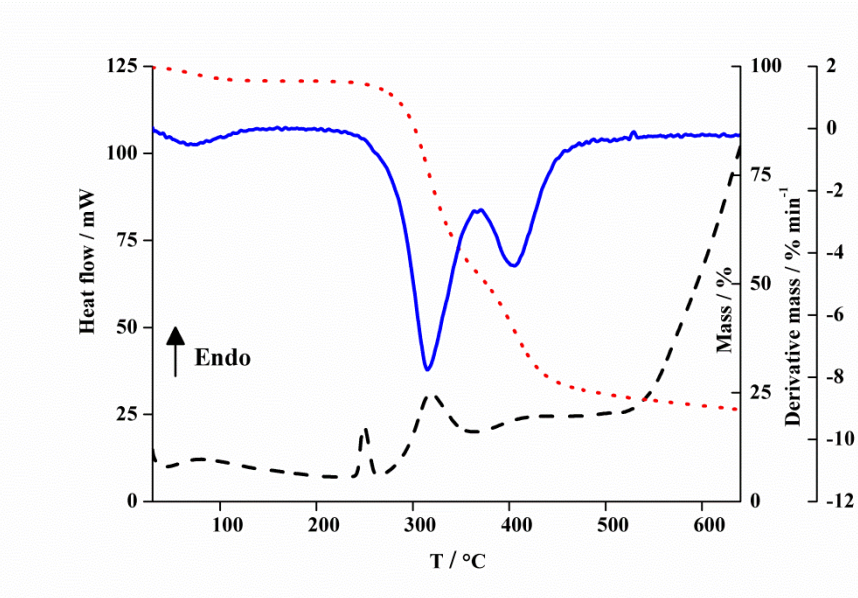


Fig.10 STA response of the dopamine loaded PNIPA gel in N_2 flow. TG: dotted line, DTG: solid line, DTA: dashed line

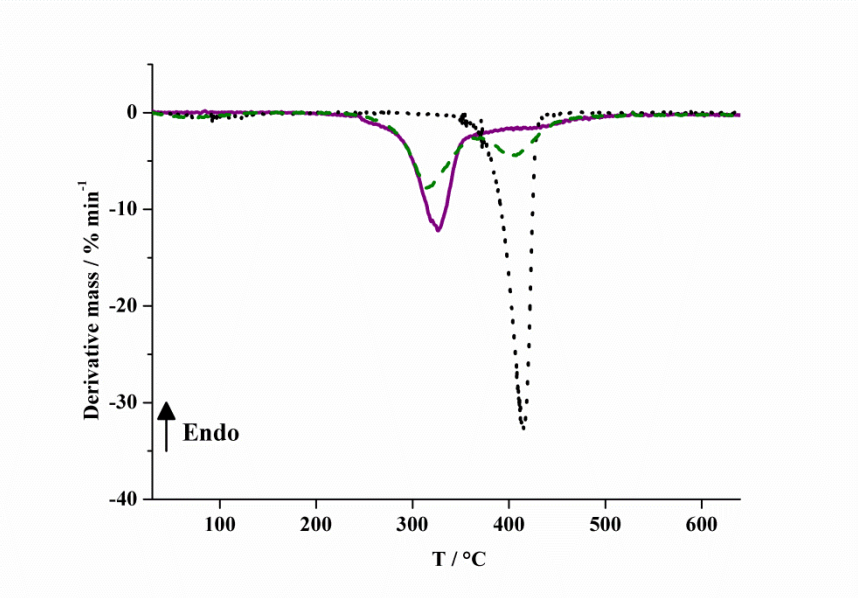


Fig.11 Comparison of the DTG response of PNIPA equilibrated in 500 mM dopamine solution to the pure systems in N_2 flow. Pure PNIPA: dotted line, dopamine hydrochloride: solid line, dopamine loaded PNIPA: dashed line

3.4. Discussion

Due to the delicate hydrophobic/hydrophilic balance of PNIPA, any interaction that influences this balance directly or indirectly may result in a shift in the phase transition temperature. In spite of the wide range of studies aiming the subject, no simple relationship was found between the response of PNIPA and the structure of the interacting small molecule [5, 7-12, 30-36]. The three probe molecules investigated here have very different influence not only on the swelling properties of PNIPA hydrogel but also on its thermal response when confined in the dry gel. Phenol only slightly reduces the decomposition temperature of the gel, but the elongated collective release of phenol and water confirms that the interaction between PNIPA and phenol might be mediated by the retained water molecules. Nevertheless, the strength of interaction between the water and the phenol seems to be stronger than that between phenol and PNIPA. The degradation peak of the polymer decreases by more than 30 °C. A possible explanation is that the surface area of the porous gel remaining after the "evaporation" of water and phenol is larger. It is very probable that no phenol remains in the gel at higher temperatures. This can be concluded from the comparison of the corresponding residues at 650 °C. Phenol adsorbed on porous carbon is withheld on the surface and its pyrolyzed form increases the mass of the residual carbon considerably even above 900 °C [28]. No such effect was observed here.

Ibuprofen, although its effect in swollen state is very moderate, modifies the PNIPA signal the most. Instead of detecting responses in the mixed system around the temperatures characteristic to the individual components, the degradation DTG peaks of both the polymer and ibuprofen "disappear" and a single peak appears at significantly lower temperature. The shift is 60 °C for the polymer and exceeds 100 °C for the probe molecule. The reduced amount of residue at 650 °C corroborates that all these observations may be related to a strong interaction that survives even elevated temperatures. Independent measurements are needed to confirm this hypothesis.

Unlike ibuprofen, dopamine behaves as is expected from the swollen state behaviour. Dopamine and PNIPA degrade practically independently based on the thermal observations. The shifts of the peaks can be more attributed to the slightly modified shape of the signal than any interaction. The reduced area of the melting peak implies that part of the dopamine forms dimers or oligomers. The strong relation between the guest molecules may hinder their interaction with the polymer [29].

4. Conclusions

The influence of the three probe molecules selected for these studies is different not only on the swelling properties of the PNIPA hydrogel but also on its thermal responses on the dry loaded gel. Dopamine has practically no influence either in the swollen or the dry state. Most probably the strong guest - guest interaction prevents the interaction with the polymer even in confined conditions. Although phenol has a strong effect on the swelling properties of PNIPA in aqueous medium, in dry state its effect on the thermal properties is moderate. The remaining water and phenol are released simultaneously at relatively low temperature, which is high enough (> 200 °C) to indicate a strong phenol - water interaction. The limited degradation in the decomposition temperature of the gel may be explained by its porosity. The ibuprofen - gel interactions may explain the striking difference between the behaviour of ibuprofen in aqueous and dry conditions.

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