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Calculations of the magnitude of responsivities in pH-, temperature- and ion- responsive hydrogels

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A R T I C L E I N F O

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A B S T R A C T

Stimuli-responsive hydrogels (SRHs) were prepared by thermal free radical redox polymerization in the aqueous solution of N-isopropyl acrylamide (NIPAAm), acrylamide (AAm) with any weak organic acid (such as propenoic acid, cis-butenedioic acid, crotonic acid, methacrylic acid, methylfumaric acid, itaconic acid, aconitic acid in the presence of N,N′-methylene bisacrylamide. DSC thermograms were taken to find the transition zone parameters of SRHs. Swelling studies were carried out to determine the effects of stimuli such as temperature, pH, and ionic strength on the swelling-shrinkage behavior of SRHs and to calculate the magnitude of the stimuli. A sigmoidal equation was used to calculate the parameters such as transition point, the magnitude of the stimulus, minimum and maximum swelling, the amplitude of the transition zone, etc. of the temperature or pH transition zones of SRHs, while the exponential decay equation was used to calculate the parameters of the swelling-ionic strength relationship of the same gels. With the idea that SRHs can be used as a biomaterial, swelling values of SRHs at the pH values of the body fluids at 37 °C were calculated with the help of these sigmoidal equation parameters. Similarly, swelling values of SRHs in hypertonic, isotonic, and hypotonic saline solutions were determined with the help of these exponential decay equation parameters.

In conclusion, calculating the responsivity magnitude with the sigmoidal equation or exponential decay equation approach can be a useful tool for chemists, chemical engineers, bioengineers, biomedicine, biomaterials, polymer, and plastic scientists to find the transition zone parameters of stimuli-responsive hydrogels.

1. Introduction

Water-loving 3-D cross-linked polymeric structures can be defined as hydrogels [1–3]. Hydrogels that respond to external stimuli are called stimuli-responsive hydrogels. Physical stimuli (mechanical stress, electric field, magnetic field, ultrasound, light, temperature, ultraviolet), chemical stimuli (electrochemical, pH, ionic strength, redox potential, hydrogen peroxide), and biological stimuli (enzymes, receptors, biomolecules, antigens, ligands, other biochemical agents) are external stimuli [1–4].

While hydrophobic monomers (i.e. N-isopropyl acrylamide, N-isopropylmethacrylamide, N-cyclopropylacrylamide, vinyl methylether, 2-(dimethylamino)ethyl methacrylate, N-methylacrylamide, N, N-dimethyl acrylamide, N-tertbutylacrylamide, vinyl caprolactame, 2-isopropy-2-oxazoline) can provide temperature responsivity of hydrogels, ionizable acidic monomers (i.e. acrylic acid, methacrylic acid, vinylphosphonic acid, 4-vinyl-benzyl phosphonic acid vinylsulfonic acid, 4-sytyrenesulfonic acid, 2-acrylamido-2-methylpropanesulfonic acid, aspartic acid, histidine, vinylphenyl boronic acid), basic monomers (i.e. dimethyl amino ethyl methacrylate, diethyl amino ethyl methacrylate, acryoylmorpholine, vinyl pyrrolidone, vinyl imidazole, 4-vinyl pyridine, N-acryloyl-N′-alkenyl piperazin) and some natural polymers (i.e. alginate, hyaluronic acid, carboxymethyl cellulose, chitosan) can provide pH and ion responsivity of hydrogels [1].

Hydrogels sensitive to stimuli are generally used in areas such as environment, agriculture, biomedicine, pharmacy, medicine, bioengineering. On the other hand, since the coil to globule transition temperature of temperature-responsive hydrogels is close to the physiological temperature, suitable biomaterials are preferred in use. These responsive hydrogels can also be used in biosensing, controlled drug release, tissue repair, artificial muscle construction, microvalve construction, and microfluidity controls. In addition to these uses, it is

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seen that hydrogels are used in the production of materials used in daily life such as baby diapers, irrigation, and smart windows [5–13].

As shown in Fig. 1, in temperature-responsive gels, a coil-to-globule transition occurs and the hydrogel shrinks when the environment temperature is increased above a limit. Increasing hydrophobic interaction and decreasing hydrogen bonds lead to such a transition. The temperature value at this coil-to-globule (or hydrophilic to hydrophobic) transition is defined as the LCST (lower critical solution temperature). At temperatures less than the LCST value, the harmonious interaction of the hydrogel with water rises, thus giving the hydrogel a higher swelling. The reason for the high swelling is that the water molecules form stronger hydrogen bonds with the hydrophilic groups in the hydrogel. [14–16].

Hydrogels with acidic or basic ionizable pendant groups swell (positive response) or shrink (negative response) with the effect of changing environmental pH. Depending on the change in pH of the surrounding solution, ionizable pendant groups that accept or donate protons form an invariant electric charge (positive/negative charge) in the hydrogel. These electrostatic forces repel each other, diffusion of water into the hydrogel is facilitated, and swelling occurs. The acidic groups of a hydrogel with acidic pendant group(s) cannot be anionized at small pHs. However, at higher pHs, the acidic groups in the hydrogel anionize, resulting in negative charges. The hydrogel becomes rich in anions. One of these anions repels the other. Thus, water penetration into the hydrogel is facilitated and the swelling of the gel increases considerably with increasing pH. Hydrogels with basic pendant groups are protonated at small pHs. One of these positive charges repels the other. Thus swelling of the hydrogel is observed with the initiation of water diffusion into the hydrogel. After a certain pH value, the pendant cationic groups in the hydrogel become uncharged by donating protons. In this case, the gels begin to shrink. This critical pH value at the swelling-contraction transition is defined as the IP (inflection point) [14–16].

In addition to the LCST and IP values found for temperature- and pH-stimuli, knowing the range of transition zone (amplitude), height (responsivity), slope values (steepness or flatness), and the sign of slope (positive or negative direction) in the transition zone is very important in determining the end-use location of SRHs. Since these are important parameters, it is very important to calculate these parameters.

The range of the transition zone, namely the amplitude, can be quite narrow for stimuli-responsive monomers, slightly wider for polymers, and quite wide for gels. The height of the transition zone, that is, the responsiveness, is the difference between the minimum and maximum swelling values and shows the magnitude of the SRH's response to stimuli. A high responsiveness value of an SRH indicates that SRH is very sensitive to stimuli. If the slope value of the transition zone is large, it indicates that the transition takes place in a narrow range. The positive direction of the slope (the slope has a positive value) is an indication that the stimulus increases the swelling.

From 1970 to the present, the number of publications in SCI, in which hydrogel is mentioned, is around 73,000. Only 8% (7920) of these articles are about stimuli-responsive or smart or intelligent hydrogels (Fig. 2). This low number of publications of stimuli-responsive hydrogels indicates that they are still in their infancy compared to hydrogels [17]. Only 827 of the publications on hydrogels (1% of hydrogel publications and 10% of stimuli-responsive hydrogel publications) mention LSCT. However, there are no publications on the calculation of parameters (i.e., the magnitude of responsiveness to stimuli and transition point) with appropriate equations in the use of these stimuli-responsive hydrogels as possible biomaterials.

In our previous work, mono-, di- or tri-protic carboxylic acids were incorporated to impart pH- and ion- responsivity to temperature-responsive N-isopropyl acrylamide/acrylamide hydrogels. The produced hydrogels were responsive to both temperature, pH, and ion. Our general focus of interest is AAm-based hydrogels [18–21]. Therefore, in this study, we report the method of calculating the transition zone parameters of hydrogels we produced with acidic co-monomers containing carboxyl pendant groups as well as NIPAAm and AAm (Fig. 3).

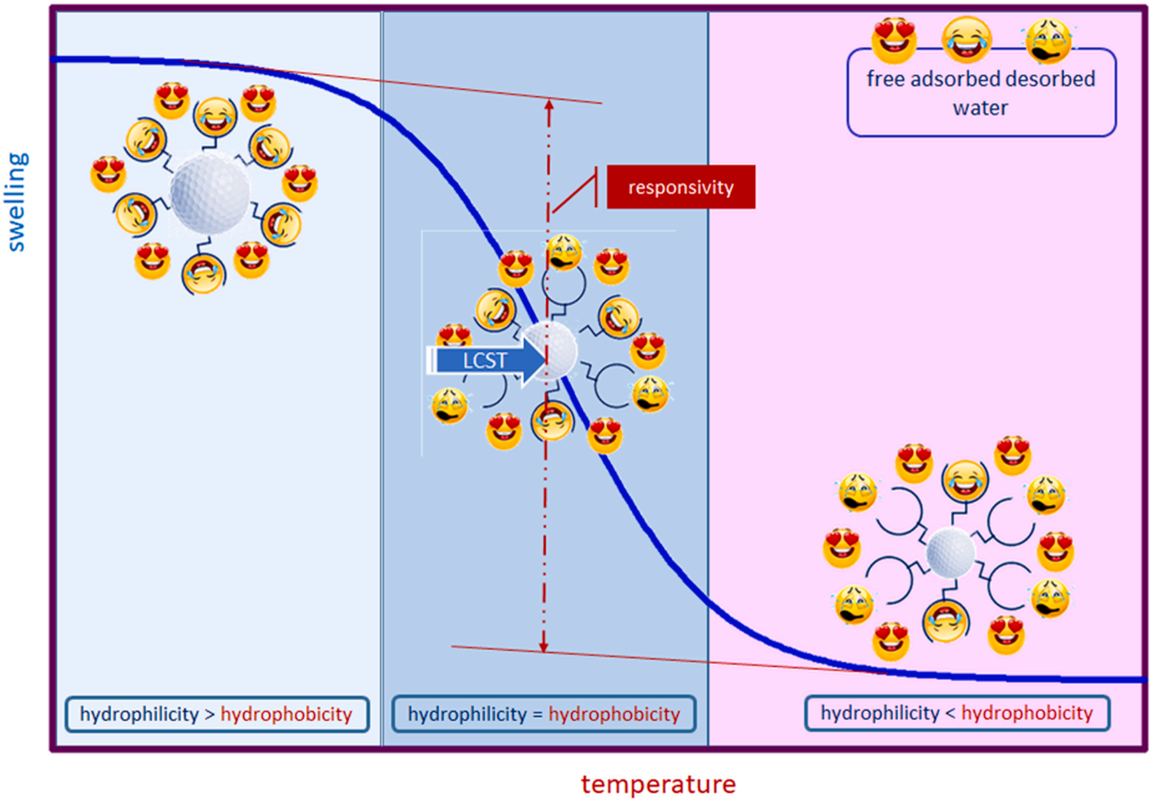


Fig. 1. An illustration of the hydrophilic to hydrophobic transition in temperature-responsive hydrogels.

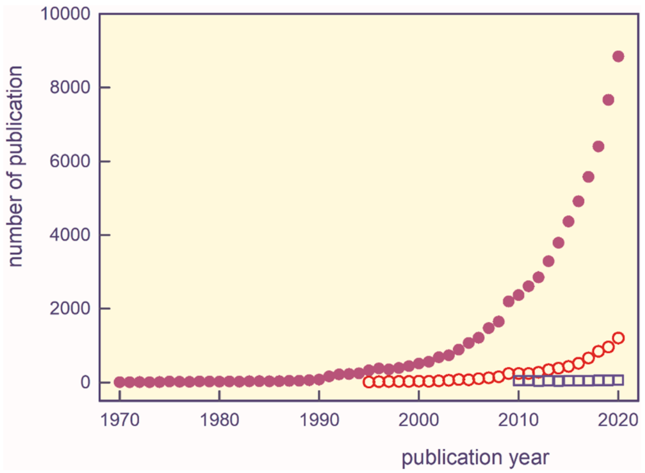


Fig. 2. Evolution of published research articles about hydrogel (●), stimuli-responsive hydrogel (○), and LCST (■).

The goal of this research is to calculate the parameters of the transition zone formed by the effect of stimuli (such as pH, ion- and temperature) in N-isopropyl acrylamide/acrylamide-based hydrogels prepared using acidic co-monomers with carboxyl group. To compare the influences of the calculated stimulating parameters, co-monomers with chemical structures similar to acrylic acid were chosen. Here, a detailed analysis of calculating the transition point, magnitude of responsivity, and transition intervals of stimuli-sensitive hydrogels with appropriate equations is given.

Knowing the physical properties of stimuli-responsive hydrogels related to molecular heterogeneity in detail is a very important criterion in temperature, pH, and ion sensitive biomaterial applications.

2. Experimental methods

2.1. Chemicals

The monomers, crosslinker and co-monomers used are presented in Table 1 along with their manufacturers. AMPS; ammonium persulfate (Merck Schuchardt, Hohenbrunn, Germany) as redox initiator, and TEMED; N, N, N′, N′-tetramethylethylenediamine (Sigma, St. Louis, MO, USA) as catalyst were used as received. All chemicals were analytical grade.

2.2. Production of hydrogels

The production and characterization of hydrogels prepared by dissolving NIPAAm, AAm monomers, and carboxylic acid co-monomer (such as P, B, C, M, F, I, A) in water in the presence of N-Bis and adding APS and TEMED were described in detail in our previous publications [22–25].

DSC thermal analyzer (Shimadzu-50 model) was used to find the LCST values of the hydrogels. 10 mg of hydrogel was heated from 15 °C to 60 °C at a heating rate of 10 °C min^{-1} and a flow rate of 25 mL min^{-1} nitrogen gas.

The equilibrium swelling values of SRHs (S, g g_{SH}^{-1}) were determined from the following equation [26] by measuring the masses of hydrogels unswollen/swollen in different aqueous media.

$$S = \frac{m_f - m_i}{m_i} \qquad (1)$$

where m_f and m_i are the initial mass and equilibrium mass of the swelling or shrinking of SRH, respectively.

Hydrogels were swollen to swelling equilibrium under the following conditions for temperature, pH, and ion sensitivity of SRHs;.

i. In HCl (pH=3) or NaOH (pH 8) solution whose ionic strength is fixed with 0.05 M NaCl, at temperatures between 10 and 60 °C;
ii. In HCl or NaOH solutions with a pH ranging from 2 to 9, at 25 or 37 °C;
iii. At 25 °C in the solutions of $NaNO_3$ or NaCl, or $CaCl_2$ at concentrations in the range of 0.05–1.0 M.

To calculate the responsivity of SRHs, a software was used and calculated values were produced automatically with SE (standard error) and r^2 (correlation coefficients).

3. Results and discussion

While the transition zone parameters of stimuli-responsive monomers or polymers can be found by DSC, turbidimetry, UV NMR, and FTIR methods [27–34], these parameters of the hydrogels can be found by DSC and swelling methods.

3.1. Determination of LCST and magnitude of responsivity by DSC analysis

Transition zone parameters such as T_i (initial temperature in °C), T_f (final temperature in °C), LCST (lower critical solution temperature in °C), E (energy in J g^{-1}), R_{DSC} (temperature responsivity in W g^{-1}), C_{DSC} (heat capacity in J g^{-1} $^{o}C^{-1}$), and ΔT (the temperature ranges of the transition zone in °C) which are automatically determined by the evaluation of DSC thermograms of SRHs in Fig. 4 are presented in Table 2.

The transition point (LCST) value found from the peak value [28] in DSC thermograms taken between 15 and 45 °C (Fig. 5) was found to be very close to 32 °C in SRH-O, as in its polymer [3].

At the same time, the LCST values of SRH-P, SRH-M, and SRH-I were found to be close to physiological temperature, while transition point values of other SRHs are in the range of 26–32 °C. These differences between the LCST values of SRHs may be due to steric effects arising from the chemical structure of the structural repeating unit of the polymer, and intra-molecular and inter-molecular interactions. The

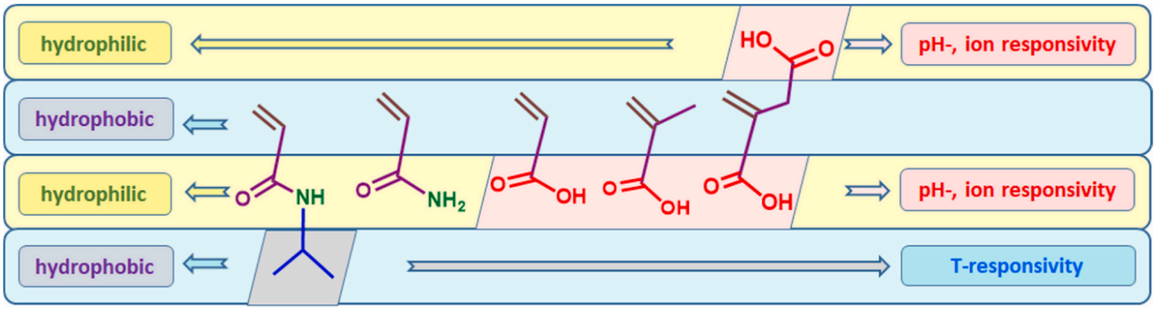
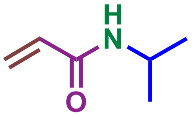
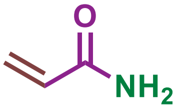
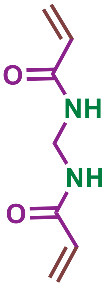
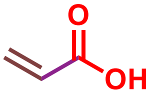
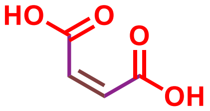
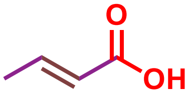
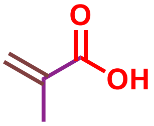
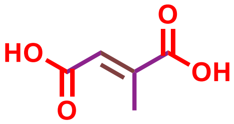
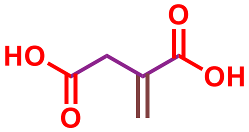
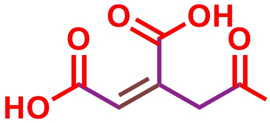


Fig. 3. Structures of NIPAAm, AAm and some acidic co-monomers used in SRHs showing hydrophilicity-hydrophobicity and responsivity.

Table 1
The chemicals used and manufacturers.

chemicals	abbreviation	illustration	manufacturer
N-isopropylacrylamide *(2-propenamide N-(1-methylethyl)-)*	NIPAAm		Aldrich, Milwaukee, WI, USA
acrylamide *(2-propenamide)*	AAm		Merck KGaA, Darmstadt, Germany
N, N′-methylenebisacrylamide *(bisacrylamide)*	N-Bis		Merck Schuchardt, Hohenbrunn, Germany
propenoic acid (*acrylic acid, vinyl formic acid,* *acroleic acid*)	P		Merck KGaA, Darmstadt, Germany
cis-butenedioic acid (maleic acid, *toxilic acid,* *maleinic acid*)	B		Sigma, St. Louis, USA
crotonic acid *(trans-2-butenoic acid,* *3-methacrylic acid)*	C		Sigma, St. Louis, USA
methacrylic acid *(propenoic acid 2-methyl,* *methyl acrylic acid)*	M		Merck KGaA, Darmstadt, Germany
methylfumaric acid *(citraconic acid, mesaconic acid, methylmaleic acid)*	F		Aldrich, Milwaukee, USA
itaconic acid *(methylenesuccinic acid,* *propylene dicarboxylic acid)*	I		Sigma, St. Louis, USA
aconitic acid *(achilleic acid, acinitic acid, citridic acid, carboxyglutaconic acid, equisetic acid,* *pyrocitric acid)*	A		Aldrich, Milwaukee, USA

change in the magnitude of responsivity and energy values from hydrogel to hydrogel may also be due to the same reason.

Considering that SRHs will be used as a potential biomaterial, these gels will interact with various body fluids in the body. Finding the transition zone parameters by swelling/shrinking as a result of different physical and chemical effects will be closer to reality than the parameters found from DSC.

3.2. *Determination of magnitude of responsivity and transition points by swelling*

The pH-, temperature-, and ion- responsivities of SRHs were determined by measuring the fluid held by the hydrogel [24].

3.2.1. *Determination of magnitude of responsivity and IP by swelling*

Among the ionizable gels, cationic ones exhibit negative pH sensitivity and anionic ones exhibit positive pH sensitivity [2]. Graphs were drawn for the responsibility of environmental pH on the swelling of SRHs in the pH= 2–9 range at 25 °C (environmental temperature) and 37 °C (physiological temperature) and I = 0.05 M, and some of them are shown in Figs. 5, 6.

In the plots drawn for SRH-O, the relationship between pH and swelling is in the form of a linear line, while in the graphs of all other hydrogels, these relationships are in the form of sigmoidal curves. The sigmoidal 4-parameter relationship [22], adapted by Saraydın's approach, was arranged as follows to calculate the parameters of the transition zone in pH-sensitive-swelling of SRHs;

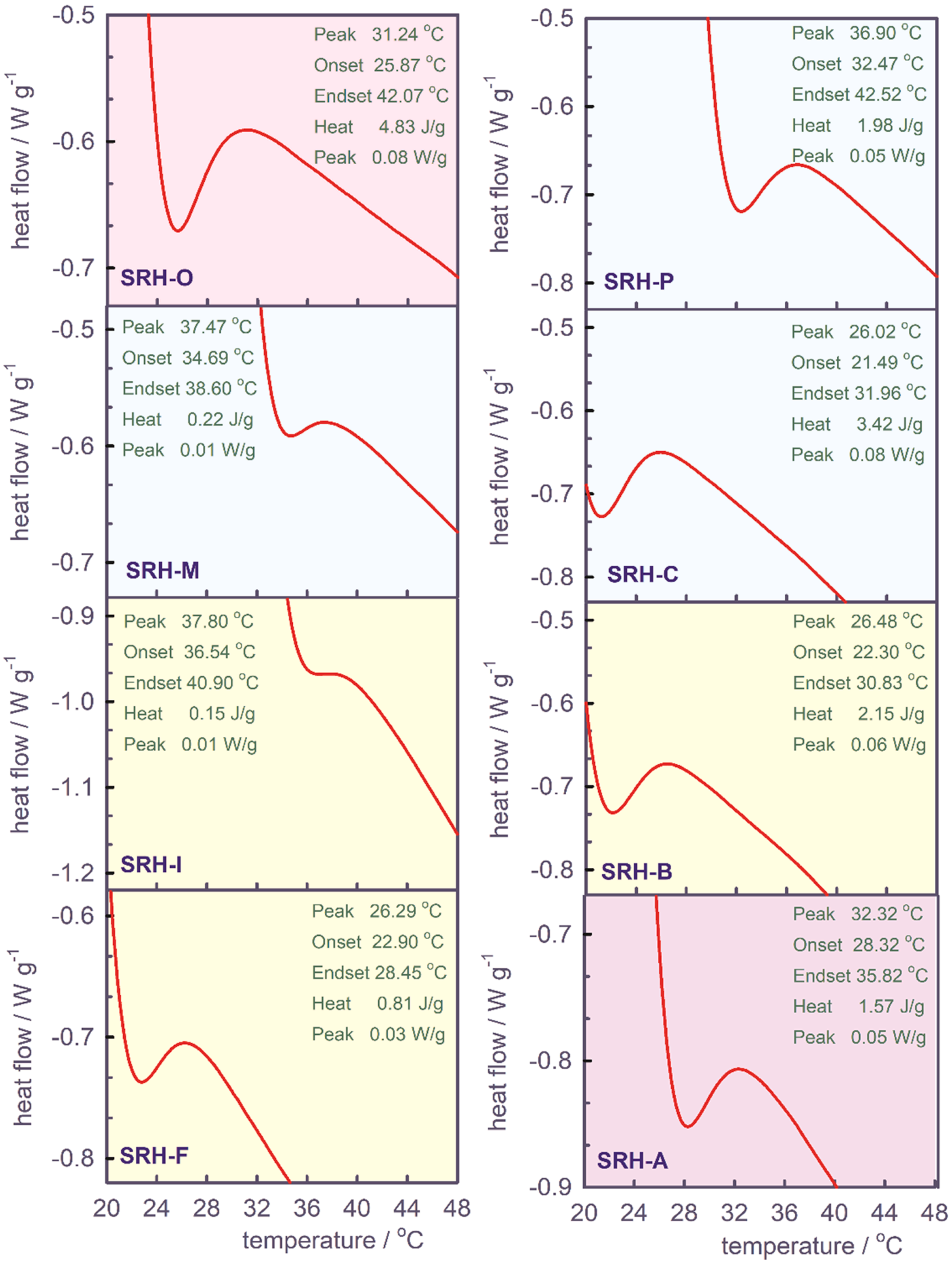


Fig. 4. DSC thermograms of the SRHs.

$$S = S_o + \frac{\alpha}{1 + e^{-\left(\frac{pH - IP}{\beta}\right)}} \tag{2}$$

where S_o (g $g_{SRH}{}^{-1}$) is the minimum swelling value and S_{max} (g $g_{SRH}{}^{-1}$) is the maximum swelling value (asymptotic values of the function). α (g $g_{SRH}{}^{-1}$) is the magnitude of the responsivity of the hydrogel, that is, the change in the swelling value of the stimulus, that is, it is equal to the difference $S_o - S_{max}$. β is the slope factor that defines the steepness of the curve, and a small β indicates a narrow transition zone, while a large one indicates a wide transition zone. The sign of β (- or +) determines the direction (negative or positive) of the responsivities. The IP value gives the inflection point of the network.

All graphs have r^2 (correlation coefficients) values of 0.995 or greater. These r^2 values specify that the adapted equation can be used to calculate the responsivity parameters of SRHs.

Table 2
Transition zone parameters of the SRHs from DSC thermograms.

SRH	T_i /°C	T_f /°C	LCST /°C	E / J g^{-1}	R_{DSC} / W g^{-1}	C_{DSC} / J g^{-1} °C^{-1}	ΔT/ °C
SRH-O	25.7	42.6	31.24	4.83	0.08	0.48	16.9
SRH-P	32.4	42.4	36.90	1.98	0.05	0.30	10.0
SRH-B	22.2	32.1	26.48	2.15	0.06	0.36	9.9
SRH-C	21.3	33.3	26.02	3.42	0.08	0.48	12.0
SRH-M	34.7	39.9	37.47	0.22	0.01	0.06	5.2
SRH-F	22.8	29.5	26.29	0.81	0.03	0.18	6.7
SRH-I	37.0	41.0	37.80	0.15	0.01	0.06	4.0
SRH-A	28.2	37.3	32.32	1.57	0.05	0.30	9.1

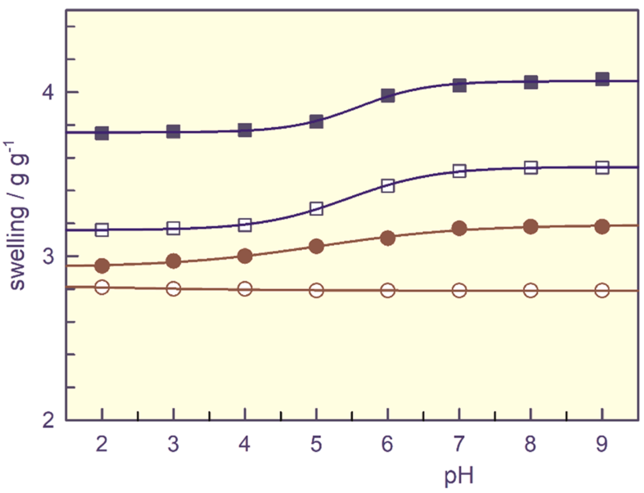


Fig. 5. pH-responsive swelling of some SRHs at 25 °C, ○; SRH-O, ■; SRH-C, □; SRH-F, ●; SRH-A, and – ; model fit.

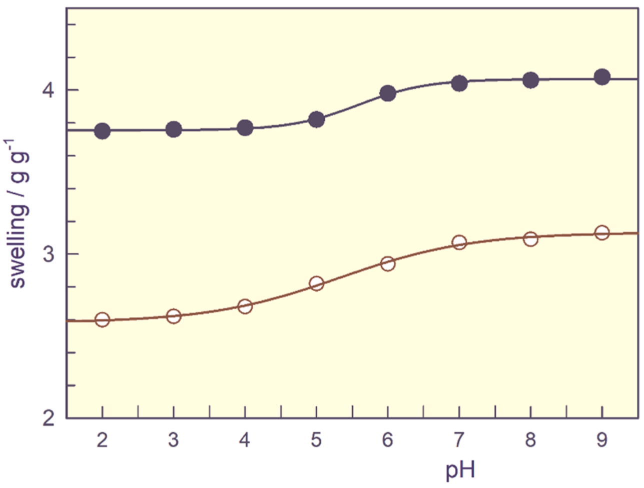


Fig. 6. pH-responsive swelling of SRH-C, ●; 25 °C, ○; 37 °C, and – ; model fit.

Table 3a, 3b, and 3c present S_o, α, IP, and β with SE and r^2 found from Eq. (2). Also in the presented table, maximum swelling, swelling at IP value (S_{IP}), the transition interval (pH_{tr}), the initial (pH_i), and the finish (pH_f) pH values of the transition zone, with the swelling values found experimentally ($S_{i,e}$ and $S_{f,e}$) and calculated from Eq. (2) ($S_{i,c}$ and $S_{f,c}$) are given.

The values in Table 3a show no difference in pH-responsive swelling of SRH-O without ionizable pendant group(s) at temperatures above (37 °C) or below LCST (25 °C). Therefore, it can be safely said that SRH-O is not responsive to pH. Also, the swelling of SRHs with ionizable pendant carboxyl groups appears to depend on the pH of the surrounding solution. At small pHs, since the pendant carboxyl groups in the hydrogel are not yet anionized, the swelling value is small and intra- and intermolecular complexation can be seen through H-bonds (physical cross-linking).

All response values of hydrogels containing pendant carboxyl groups in Table 3a, 3b, 3c show differences regardless of temperature and the difference of side groups such as -COOH, -CH_3, -CH_2COOH added to acrylic acid. Many parameters such as the chemical structures of the co-monomers, pK_a values, ease of dissociation, degree of ionization, ability to make hydrogen bonds, hydrophobicity-hydrophilicity properties, intra-chain and inter-chain molecular interactions, polymer architect, may be the reasons for these differences [3,23]. Considering the use of SRHs as a possible biomaterial, differences in these parameters will present a wide array of possibilities to the end-user.

The swelling values of these SRHs, which are considered and recommended to be used as biomaterials, were calculated at body temperature (37 °C) for the parameters found from Eq. (2) in the pH values of various body fluids and systems [33,35] and are presented in Table 4a, and 4b.

The calculated swelling values of SRH-O are not affected in all systems. Except for the skin and vagina, there is not much change in the calculated swelling values of SRHs at the lower and upper limit pHs of body fluids. Therefore, SRHs that can be used as biomaterials in these body fluids can be used easily if a certain swelling is desired. When SRHs are used as a biomaterial such as a wound dressing, artificial skin additive, and controlled release material on the skin, the swelling value will change in the pH range of the skin and will provide convenience in the desired process. Similarly, for intrauterine devices that can be produced from SRHs, it may also be beneficial to change the swelling with the effect of pH. In addition, while SRHs calculated less swelling in the pH range of the stomach, more swelling was calculated in the small intestine. Thus, SRHs can be considered as suitable materials for drug release systems that are undesirable in the stomach but desired in the small intestine.

3.2.2. *Determination of LCST and magnitude of responsivity by swelling*

To calculate the temperature responsivity parameters of SRHs, using the swelling values found in the temperature range 10–60 °C, at pH 3 (below the inflection points) or pH 8 (above the inflection points), and I = 0.05 M, swelling-temperature graphs were plotted and some sample plots are presented in Fig. 7 and Fig. 8.

In the plots for SRHs, the relationships between temperature and swelling [36] are in the form of a sigmoidal curve. The sigmoidal 4-parameter relationship [23], adapted by Saraydın's approach, was arranged as follows to calculate the parameters of the transition zone in temperature-sensitive swelling of SRHs;

$$S = S_o + \frac{\phi}{1 + e^{-\left(\frac{T - LCST}{\Psi}\right)}} \tag{3}$$

where S_o (g g_{SRH}^{-1}) is the minimum swelling value and S_{max} (g g_{SRH}^{-1}) is the maximum swelling value (asymptotic values of the function). ϕ (g g_{SRH}^{-1}) is the magnitude of the responsivity of the hydrogel, that is, the change in the swelling value of the stimulus. It is equal to the difference $S_o - S_{max}$. LCST (°C) is the lower critical solution temperature. Ψ is the slope factor that defines the steepness of the curve, and a small Ψ indicates a narrow transition zone, while a large one indicates a wide transition zone. The sign of Ψ (- or +) determines the direction (negative

Table 3a
The parameters of pH-responsive swelling of only –COOH containing SRHs.

T	25 °C			37 °C		
Parameter	SRH-O	SRH-P	SRH-B	SRH-O	SRH-P	SRH-B
α ± SE	–	0.757 ± 0.016	1.195 ± 0.092	–	1.316 ± 0.024	1.040 ± 0.020
β ± SE	–	0.484 ± 0.034	0.974 ± 0.171	–	0.347 ± 0.284	0.673 ± 0.039
IP ± SE	–	3.964 ± 0.036	5.423 ± 0.162	–	5.426 ± 0.038	5.587 ± 0.042
S_o ± SE	–	2.920 ± 0.013	2.877 ± 0.056	–	2.125 ± 0.017	2.189 ± 0.012
r^2	–	0.999	0.995	–	0.999	0.999
S_{max}	–	3.677	4.072	–	3.441	3.133
S_{IP}	–	3.295	3.476	–	2.783	2.933
$S_{i,e\ (at\ pH\ =\ 2)}$	2.810	2.940	2.190	2.020	2.090	2.190
$S_{i,c\ (at\ pH\ =\ 2)}$	–	2.933	2.912		2.215	2.194
$S_{f,e\ (at\ pH\ =\ 9)}$	2.790	3.690	4.040	2.010	3.440	3.230
$S_{f,c\ (at\ pH\ =\ 9)}$	–	3.677	4.042	–	3.441	3.223
pH_i	–	2.980	3.573	–	4.656	4.165
pH_f	–	5.042	7.103	–	6.190	6.883
pH_a	–	2.062	3.529	–	1.534	2.718

Table 3b
The parameters of pH-responsive swelling of –COOH and –CH_3 containing SRHs.

T	25 °C			37 °C		
Parameter	SRH-C	SRH-M	SH-F	SRH-C	SRH-M	SH-F
α ± SE	0.313 ± 0.011	0.401 ± 0.012	0.385 ± 0.005	0.551 ± 0.027	0.793 ± 0.034	0.229 ± 0.008
β ± SE	0.480 ± 0.060	0.507 ± 0.053	0.619 ± 0028	0.921 ± 0.109	0.537 ± 0.081	0.695 ± 0.062
IP ± SE	5.593 ± 0.074	5.397 ± 0.063	5.438 ± 0.031	5.334 ± 0.106	5.244 ± 0.090	4.124 ± 0.071
S_o ± SE	3.755 ± 0.007	3.387 ± 0.008	3.160 ± 0.004	2.582 ± 0.017	2.097 ± 0.023	2.468 ± 0.007
r^2	0.997	0.998	0.995	0.997	0.996	0.999
S_{max}	4.068	3.788	3.862	3.133	2.890	2.688
S_{IP}	3.904	3.586	3.297	2.860	2.490	2.578
$S_{i,e\ (at\ pH\ =\ 2)}$	3.750	3.380	3.160	2.600	2.080	2.480
$S_{i,c\ (at\ pH\ =\ 2)}$	3.755	3.388	2.993	2.599	2.099	2.478
$S_{f,e\ (at\ pH\ =\ 9)}$	4.080	3.800	3.540	3.130	2.910	2.690
$S_{f,c\ (at\ pH\ =\ 9)}$	4.068	3.788	3.861	3.121	2.889	2.688
pH_i	4.590	4.334	4.191	3.531	4.107	2.847
pH_f	6.570	6.443	6.672	6.926	6.350	5.511
pH_a	1.980	2.109	2.481	3.394	2.243	2.684

Table 3c
The parameters of pH-responsive swelling of –COOH and –CH_2COOH containing SRHs.

T	25 °C		37 °C	
Parameter	SRH-I	SRH-A	SRH-I	SRH-A
α ± SE	0.877 ± 0.022	0.259 ± 0.021	1.437 ± 0.052	0.621 ± 0.007
β ± SE	0.617 ± 0.049	1.017 ± 0.174	0.621 ± 0.056	0.481 ± 0.020
IP ± SE	4.866 ± 0.053	5.046 ± 0.167	3.817 ± 0.067	4.503 ± 0.025
S_o ± SE	2.985 ± 0.016	2.933 ± 0.014	1.803 ± 0.046	1.786 ± 0.049
r^2	0.999	0.995	0.999	1.000
S_{max}	3.862	3.192	3.240	2.407
S_{IP}	3.270	3.062	2.522	2.095
$S_{i,e\ (at\ pH\ =\ 2)}$	2.980	2.940	1.880	1.790
$S_{i,c\ (at\ pH\ =\ 2)}$	2.993	2.945	1.876	1.789
$S_{f,e\ (at\ pH\ =\ 9)}$	3.870	3.180	3.280	2.410
$S_{f,c\ (at\ pH\ =\ 9)}$	3.861	3.187	3.240	2.407
pH_i	3.598	3.157	2.827	3.531
pH_f	6.071	6.884	5.113	5.495
pH_a	2.481	3.726	2.489	1.964

or positive) of the responsivities.

By using the temperature-responsive swelling values of SRHs at pH 3 and 8, the transition zone parameters were calculated from Eq. (3). The r^2 values were determined to be 1 or very close to one. This shows that the adapted sigmoidal 4-parameter equation can be used to calculate the transition zone parameters of SRHs.

Tables 5a, 5b, and 5c give the ϕ, Ψ, LCST, and S_o with SE and r^2 calculated by using Eq. (3). Maximum swelling (S_{max}), swelling at LCST (S_{LCST}), the transition zone interval (T_a), the initial (T_i) and the finish (T_f) temperature values of the transition zone, with the swelling values found experimentally ($S_{i,e}$ and $S_{f,e}$) and calculated from Eq. (3) ($S_{i,c}$ and $S_{f,c}$) are given.

The LCST value of SRH-O was calculated around 27.7 °C at both pH 3 and pH 8 (Tables 5a, 5b, 5c). The reason for the difference between the LCST calculated from the swelling method of SRH-O and the LCST determined from DSC (31.2 °C) may be environmental effects such as pH and ion on the swelling of the gel. In addition, the LCST values of all SRHs containing carboxyl groups were generally calculated as greater than this value of SRH-O. As a result of incorporation of acidic co-monomers into NIPAAm/acrylamide network, LCST values shifted towards higher temperatures. In addition, the LCST values of all SRHs containing carboxyl groups were generally calculated as greater than this value of SRH-O. As a result of the incorporation of acidic co-monomers into the NIPAAm/acrylamide network, LCST values shifted towards higher temperatures. On the other hand, LCST values of SRHs, as well as IP values, differ from each other regardless of pH and pendant groups in co-monomers. The reasons for these differences may be the same as those described in pH-responsive swelling. The LCST values of SRH-I, SRH-A, SRH-P, and SRH-F at pH= 8 are between 32 and 35 °C, indicating that the transition points of these hydrogels are close to human body temperature.

The negative sign of Ψ values indicates that SRHs give a negative response in temperature-sensitive swelling.

When SRHs should be used as a possible biomaterial in the field of biomedicine, the LCST values of some SRHs being close to body

Table 4a
Swelling values calculated for pH ranges of human body fluids at 37 °C.

Body fluid	Blood	Saliva	Skin	Tears	Vaginal Fluid
SRH↓ pH→	7.35–7.45	6.40–7.00	4.10–5.80	7.25–7.45	3.80–4.40
SRH-O	2.042–2.043	2.039–2.041	2.032–2.037	2.042–2.043	2.031–2.033
SRH-P	3.437–3.438	3.373–3.429	2.150–3.117	3.435 – 3.438	2.125–2.135
SRH-B	3.158–3.168	2.990–3.115	2.292–2.791	3.148–3.168	2.257–2.341
SRH-C	3.072–3.077	2.995–3.049	2.703–2.922	3.066–3.077	2.676–2.734
SRH-M	2.875–2.877	2.807–2.861	2.181–2.682	2.872–2.877	2.147–2.223
SRH-F	2.686–2.686	2.680–2.685	2.576–2.670	2.686–2.686	2.553 – 2.600
SRH-I	3.235–3.236	3.218–3.232	2.682–3.138	3.234–3.236	2.512–2.836
SRH-A	2.405–2.406	2.395–2.404	1.974–2.368	2.405–2.406	1.903–2.063

Table 4b
Swelling values calculated for pH ranges of gastrointestinal and urinary fluids at 37 °C.

Body fluid	Stomach $_{(empty)}$	Small intestine	Colon	Urine $_{(acidic)}$	Urine $_{(basic)}$
SRH	1.00–1.50	7.20–7.50	7.90–8.50	6.50–7.00	7.50–8.00
SRH-O	2.022–2.024	2.024–2.043	2.044–2.046	2.040–2.041	2.043–2.046
SRH-P	2.125–2.125	3.434–3.438	3.440–3.441	3.390–3.429	3.438–3.440
SRH-B	2.190–2.191	3.142–3.172	3.197–3.215	3.016–3.115	3.172–3.201
SRH-C	2.588–2.592	3.063–3.080	3.096–3.113	3.006–3.049	3.080–3.100
SRH-M	2.097–2.098	2.870–2.878	2.884–2.888	2.820–2.861	2.878 – 2.885
SRH-F	2.470–2.473	2.685–2.686	2.687–2.688	2.681–2.685	2.686–2.688
SRH-I	1.818–1.837	3.234–3.236	3.238–3.239	3.211–3.221	3.236–3.238
SRH-A	1.786–1.787	2.405–2.406	2.406–2.407	2.397–2.404	2.406–2.407

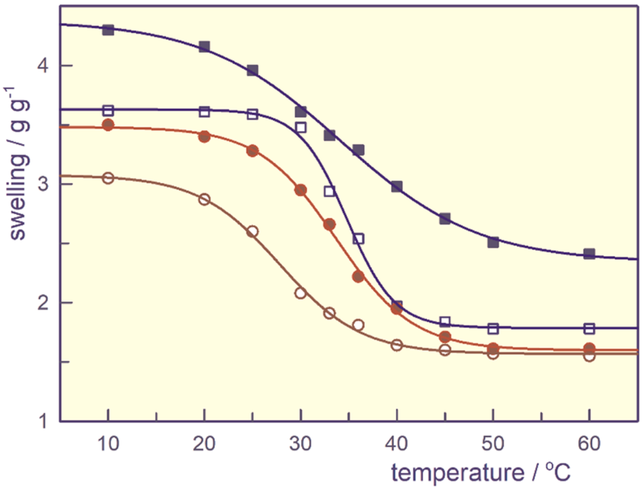


Fig. 7. Temperature-responsive swelling of some SRHs at pH= 8, ○; SRH-O, ■; SRH-P, ●; SRH-A, □; SRH-F, and – ; model fit.

temperature and the differences in these parameters will provide users with a wide variety of options.

3.3. Determination of magnitude of ion-responsivity by swelling

Ionic strength strongly influences the swelling of SRHs [36–38]. Ion-sensitive swelling of SRHs was made at 25 °C at increasing concentrations (M) of salts that can give the same or different anions and cations such as $NaNO_3$, NaCl and $CaCl_2$, and ionic strength-swelling graphs were created, and some of these plots are given as sample graphics in Fig. 9 and Fig. 10.

The swelling of SRH-O remained approximately constant with increasing ionic strength of the medium, while the swelling of other SRHs decreased. This behavior may be due to the electrostatic repulsion of the ionizable pendant groups in the hydrogel chains and the concentration difference between the SRH and the mobile ions in the surrounding solution [29,39]. On the other hand, swelling degrees of SRH-F and SRH-A in $NaNO_3$ solution, and swelling values of all carboxylic acid-containing hydrogels in NaCl and $CaCl_2$ solutions fall below the swelling value of SRH-O when above a certain ionic strength. When this limit value is exceeded, the interactions between the cations in the outer solution and the anionizable pendant carboxyl groups of SRHs prevent the formation of hydrogen bonds, and swelling decreases.

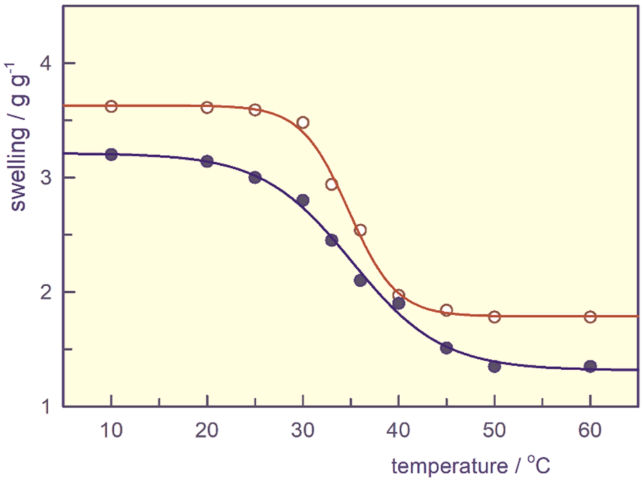


Fig. 8. Temperature-responsive swelling of SRH-F, ●; pH= 3, ○; pH= 8, and – ; model fit.

The ion-sensitive swellings of SRHs, examples of which are presented in Fig. 9 and Fig. 10, are similar to the exponential decay curves. The exponential decay (single, 3-parameter) equation was adapted with Saraydın's approach to calculating the parameters of the ion-sensitive swelling of SRHs as follows;

$$S = S_o + \xi e^{-\lambda I} \tag{4}$$

where S_o is the swelling (g g_{SRH}^{-1}), i.e. the offset or minimum swelling. ξ is the swelling amplitude (g g_{SRH}^{-1}), i.e. the magnitude of the hydrogels' response to the ionic strength. λ is the exponential slope coefficient (M^{-1}) and is a measure of how swelling decreases with increasing ionic strength. I is the ionic strength (M).

Using Eq. (4), the parameters of the ion-sensitive swelling of SRHs

Table 5a
The parameters of temperature-responsive swelling of only –COOH containing SRHs.

pH	3			8		
Parameter	SRH-O	SRH-P	SRH-B	SRH-O	SRH-P	SRH-B
$\phi \pm$ SE	1.999 ± 0.031	2.342 ± 0.122	2.362 ± 0.118	1.510 ± 0.047	2.042 ± 0.083	2.226 ± 0.031
$\Psi \pm$ SE	-3.929 ± 0.152	-4.077 ± 0.535	-5.954 ± 0.592	-4.219 ± 0.318	-7.152 ± 0.284	-3.321 ± 0.133
LCST ± SE	27.601 ± 0.191	28.303 ± 0.653	27.026 ± 0.691	27.835 ± 0.392	34.215 ± 0.535	28.798 ± 0.164
$S_o \pm$ SE	1.588 ± 0.014	1.247 ± 0.056	1.558 ± 0.045	1.567 ± 0.021	2.340 ± 0.047	1.904 ± 0.015
r^2	0.999	0.993	0.996	0.998	0.998	0.999
S_{max}	3.507	3.589	3.920	3.077	4.382	4.130
S_{LCST}	2.507	2.418	2.739	2.322	3.361	3.017
$S_{i,e}$ (at T = 10 °C)	3.480	3.620	3.760	3.050	4.300	4.140
$S_{i,c}$ (at T = 10 °C)	3.484	3.563	3.792	3.055	4.315	4.122
$S_{f,e}$ (at T = 60 °C)	1.510	1.260	1.500	1.550	2.410	1.920
$S_{f,c}$ (at T = 60 °C)	1.508	1.248	1.567	1.568	2.394	1.904
T_i	20.364	20.476	18.515	19.947	22.376	22.061
T_f	35.442	36.610	38.246	36.661	45.816	35.767
T_a	25.078	16.135	19.732	16.714	23.440	13.707

Table 5b
The parameters of temperature-responsive swelling of –COOH and –CH_3 containing SRHs.

pH	3			8		
Parameter	SRH-C	SRH-M	SH-F	SRH-C	SRH-M	SH-F
$\phi \pm$ SE	2.589 ± 0.132	2.304 ± 0.037	1.896 ± 0.080	2.587 ± 0.035	1.886 ± 0.075	1.843 ± 0.051
$\Psi \pm$ SE	-5.200 ± 0.610	-3.789 ± 0.177	-4.690 ± 0.504	-3.270 ± 0.126	-3.480 ± 0.389	-2.485 ± 0.250
LCST ± SE	30.233 ± 0.659	31.930 ± 0.186	35.120 ± 0.516	28.546 ± 0.158	29.032 ± 0.472	34.797 ± 0.272
$S_o \pm$ SE	1.561 ± 0.064	1.440 ± 0.021	1.317 ± 0.050	1.991 ± 0.017	2.204 ± 0.036	1.787 ± 0.034
r^2	0.995	0.999	0.996	0.999	0.995	0.997
S_{max}	4.150	3.744	3.213	4.578	4.090	3.630
S_{LCST}	2.856	2.592	2.265	3.285	3.147	2.709
$S_{i,e}$ (at T = 10 °C)	4.030	3.730	3.200	4.560	4.070	3.620
$S_{i,c}$ (at T = 10 °C)	4.098	3.737	3.204	4.569	4.082	3.630
$S_{f,e}$ (at T = 60 °C)	1.560	1.450	1.350	1.980	2.150	1.780
$S_{f,c}$ (at T = 60 °C)	1.569	1.440	1.326	1.991	2.204	1.787
T_i	21.364	24.337	25.657	21.634	21.898	29.518
T_f	39.994	39.628	44.393	35.503	36.509	39.994
T_a	18.630	15.292	18.736	13.869	14.611	10.476

Table 5c
The parameters of temperature-responsive swelling of –COOH and –CH_2COOH containing SRHs.

pH	3		8	
Parameter	SRH-I	SRH-A	SRH-I	SRH-A
$\phi \pm$ SE	2.196 ± 0.089	3.051 ± 0.149	1.655 ± 0.051	1.885 ± 0.041
$\Psi \pm$ SE	-3.761 ± 0.450	-6.859 ± 0.646	-2.722 ± 0.293	-4.010 ± 0.247
LCST ± SE	33.106 ± 0.461	29.502 ± 0.668	32.233 ± 0.306	33.608 ± 0.252
$S_o \pm$ SE	1.195 ± 0.053	0.961 ± 0.064	2.356 ± 0.030	1.598 ± 0.025
r^2	0.995	0.997	0.996	0.999
S_{max}	3.391	4.012	4.021	3.483
S_{LCST}	2.293	2.487	3.189	2.541
$S_{i,e}$ (at T = 10 °C)	3.450	3.870	4.020	3.500
$S_{i,c}$ (at T = 10 °C)	3.386	3.844	4.021	3.478
$S_{f,e}$ (at T = 60 °C)	1.350	1.000	2.330	1.610
$S_{f,c}$ (at T = 60 °C)	1.197	0.966	2.356	1.601
T_i	25.342	19.043	26.501	25.495
T_f	40.634	42.696	37.931	41.955
T_a	15.292	23.653	11.431	16.460

were calculated. r^2 values were found above 0.99. These r^2 values close to unity are an indication of the usability of the exponential decay single, 3-parameter equation in determining the ion-responsive swelling parameters of the prepared hydrogels.

S_o, ξ, and λ values obtained from Eq. (4) are presented in Tables 6a, 6b, and 6c together with their standard error (SE) values. In addition to the calculated S_{max}, the experimentally determined $S_{i,e}$ and $S_{f,e}$ (initial and final equilibrium swelling) are also added to Tables 6a, 6b, and 6c.

The responsibility value (ξ) of SRH-O is 3.3–6.7 times smaller than that of hydrogels containing acidic co-monomer (Tables 6a, 6b, 6c). Thus, hydrogels containing acidic co-monomers exhibit ion-responsivity, while SRH-O is not ion-responsive.

The swellings of SRHs in water and ion solutions were decreased in the order water > $NaNO_3$ > NaCl > $CaCl_2$. When SRHs are swollen in salt solutions, the pendant –COOH groups in the SRH are neutralized by the cations (Na^+ or Ca^{2+}) in the external solution, and therefore the swelling values are reduced. When the fixed charges in the hydrogels are completely neutralized, SRHs containing pendant –COOH group show non-ionic behavior like SRH-O. In various salt solutions, the hydrogels exhibited the Donnan effect when the charges on the pendant groups in

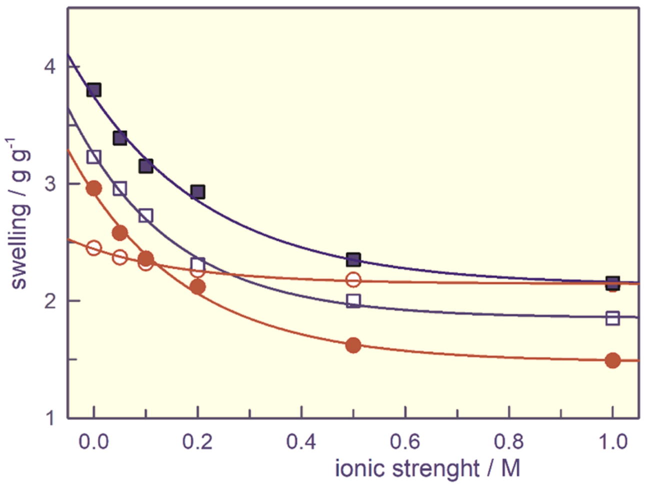


Fig. 9. Ionic strength-responsive swelling of some SRHs at 25 °C, ○; SRH-O, ■; SRH-C, □; SRH-F, ●; SRH-A, and – ; model fit.

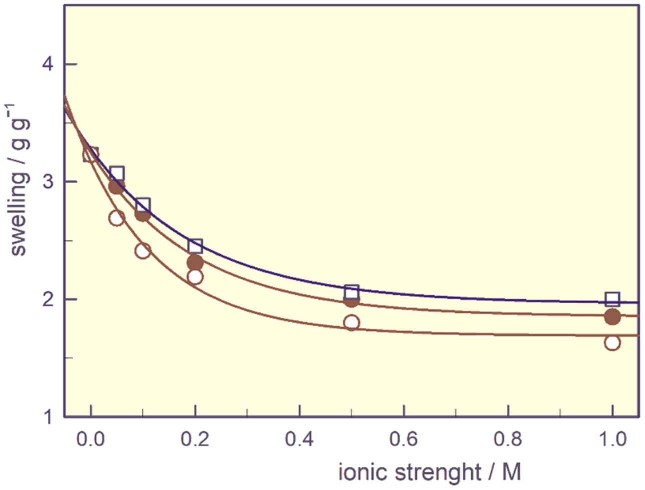


Fig. 10. Ion and counter ion-responsive swelling of SRH-F, □; NaNO$_3$, ●; NaCl, ○; CaCl$_2$, and – ; model fit.

the polymer chain are neutralized, followed by a salting effect as the gels transition to a non-ionic state [37–40].

The monovalent Na$^+$ ion interacts with only one of the pendant –COO$^-$ groups in the polymer chain, while the divalent Ca^{2+} ion interacts with two of them. As a result of neutralization, the charges on the polymeric chain in CaCl$_2$ solutions will decrease even more than in NaNO$_3$ or NaCl solutions. Thus, the polymer chains will behave like uncharged chains and swelling will decrease. At the same time, Cl$^-$ ions in salt solutions show stronger precipitant (salting out) than NO$_3$$^-$ ions. Therefore, due to the inducing effect of the water molecules surrounding the polymer, swelling of the hydrogel is more in NaNO$_3$ solution than in NaCl solution.

The ion-response values of the hydrogels containing the carboxyl group(s) presented in Tables 6a, 6b, 6c also differ regardless of the difference in pendant groups such as –COOH, –CH$_3$, –CH$_2$COOH added to the acrylic acid. The reasons for these differences were stated in pH and temperature-responsive swellings.

The swelling values of these SRHs, which are considered and recommended to be used as biomaterials, were calculated from Eq. (4) for saline (NaCl) solutions of various tonicity [41] (hypertonic, isotonic, hypotonic) and presented in Table 7.

Using the swelling values presented in Table 7, the hydrogel suitable for the tonicity of the physiological fluids or organs in the body can be easily selected.

3.4. Comparison of responsivities of SRHs

The comparison of temperature, pH, and ion responsivities of SRHs is shown in a bar graph given in Fig. 11.

All SRHs are responsible for temperature, while pH and ion- are responsible for SRHs except SRH-O. SRH-O, on the other hand, is not responsible for pH, but for a little bit of ionic strength. The mean value of temperature responsivity of hydrogels containing acidic co-monomer is 1.2 times higher at pH 3 and 1.3 times higher at pH 8 than SRH-O. The reason for this difference is that SRHs are also pH- and ion-responsive. The mean value of ion responsivity of hydrogels containing pendant carboxyl groups is 4.2 times higher in NaNO$_3$ solution, 5.0 times higher in NaCl solution and 6.0 times higher in CaCl$_2$ solution compared to SRH-O. The reasons for these differences are due to the interaction of different anions and cations in the solution with the suspended carboxyl groups in the hydrogel.

Prepared SRHs responded as temperature > ionic strength > pH stimulus, respectively. The high NIPAAm and low acidic comonomer content in the SRHs, and the interaction of the pendant carboxyl group (s) in the hydrogels with the ions that generate the ionic strength, may have resulted in such a sequence of T, I, and pH stimuli [42].

These copolymeric hydrogels, prepared by using the temperature sensitivity of N-isopropyl acrylamide monomer, the pH- and ion-sensitivity of carboxylic acid-containing monomers, and the resistance of acrylamide monomer to disintegration during swelling, have a very sensitive, durable, and homogeneous appearance to stimuli. Because of these properties, the prepared gels can be called environmentally sensitive, stimuli-responsive, smart, or intelligent hydrogels.

4. Conclusions

The parameters of the coil-globule or globule-coil transition zones, which are known to be very important in the use of temperature, pH, ion-responsive hydrogels as biomaterials in the biomedical field, are used by using the Sigmoidal (for temperature- or pH-responsive) or exponential decay (for ion-responsive) equations. found to be easy to

Table 6a
The parameters of ion-responsive swelling of only –COOH containing SRHs.

	NaNO$_3$			NaCl			CaCl$_2$		
Parameters	SRH-O	SRH-P	SRH-B	SRH-O	SRH-P	SRH-B	SRH-O	SRH-P	SRH-B
$S_o \pm SE$	2.146 ± 0.010	2.240 ± 0.044	2.236 ± 0.035	2.146 ± 0.010	1.763 ± 0.041	2.051 ± 0.036	2.123 ± 0.013	1.455 ± 0.092	1.816 ± 0.033
$\xi \pm SE$	0.297 ± 0.012	1.497 ± 0.064	0.970 ± 0.054	0.297 ± 0.012	1.970 ± 0.063	1.155 ± 0.058	0.279 ± 0.013	2.235 ± 0.139	1.404 ± 0.054
$\lambda \pm SE$	4.966 ± 0.537	7.427 ± 0.775	8.299 ± 1.096	4.966 ± 0.537	8.737 ± 0.664	10.206 ± 1.186	2.680 ± 0.340	8.199 ± 1.186	11.148 ± 0.054
r^2	0.995	0.995	0.991	0.995	0.9969	0.9926	0.996	0.990	0.996
S_{max} (S_o+ξ)	2.443	3.744	3.206	2.443	3.733	3.206	2.402	3.689	3.220
$S_{i,e}$ (at I = 0 M)	2.450	2.450	3.230	2.450	3.760	3.230	2.410	3.760	3.230
$S_{f,e}$ (at I = 1 M)	2.140	2.190	2.200	2.140	1.740	2.020	2.140	1.380	1.780

Table 6b
The parameters of ion-responsive swelling of –COOH and –CH_3 containing SRHs.

		NaNO$_3$			NaCl			CaCl$_2$	
Parameters	SRH-C	SRH-M	SH-F	SRH-C	SRH-M	SH-F	SRH-C	SRH-M	SRH-F
S_o ± SE	2.462 ± 0.028	2.150 ± 0.151	1.962 ± 0.054	2.132 ± 0.081	2.033 ± 0.070	1.854 ± 0.042	1.833 ± 0.110	1.723 ± 0.058	1.691 ± 0.078
ξ ± SE	1.437 ± 0.041	1.327 ± 0.139	1.315 ± 0.064	1.611 ± 0.018	1.397 ± 0.075	1.395 ± 0.052	1.987 ± 0.117	1.716 ± 0.057	1.480 ± 0.108
λ ± SE	8.033 ± 0.555	1.634 ± 0.372	4.667 ± 0.629	4.004 ± 0.631	3.828 ± 0.592	5.020 ± 0.502	3.746 ± 0.117	3.139 ± 0.304	6.424 ± 1.179
r^2	0.998	0.994	0.993	0.992	0.992	0.9960	0.991	0.997	0.990
S_{max} (S_o ξ)	3.899	3.477	3.277	3.743	3.431	3.248	3.820	3.439	3.171
$S_{i,e\ (at\ I\ =\ 0)}$	3.900	3.480	3.230	3.800	3.480	3.230	3.900	3.480	3.230
$S_{f,e\ (at\ I\ =\ 1)}$	2.430	2.400	2.000	2.150	2.050	1.850	1.870	1.78	1.630

Table 6c
The parameters of ion-responsive swelling –COOH and –CH_2COOH containing SRHs.

		NaNO$_3$		NaCl		CaCl$_2$
Parameters	SRH-I	SRH-A	SRH-I	SRH-A	SRH-I	SRH-A
S_o ± SE	1.962 ± 0.054	1.962 ± 0.059	1.947 ± 0.047	1.479 ± 0.053	1.852 ± 0.026	1.566 ± 0.032
ξ ± SE	1.315 ± 0.064	0.959 ± 0.058	1.337 ± 0.057	1.442 ± 0.063	1.459 ± 0.043	1.379 ± 0.050
λ ± SE	4.667 ± 0.629	7.427 ± 0.775	4.546 ± 0.569	4.806 ± 1.186	11.039 ± 0.749	9.171 ± 0.775
r^2	0.993	0.995	0.995	0.995	0.997	0.996
S_{max} (S_o + ξ)	3.277	2.921	3.284	2.921	3.311	2.945
$S_{i,e\ (at\ I\ =\ 0)}$	3.300	2.960	3.300	2.960	3.300	2.960
$S_{f,e\ (at\ I\ =\ 1)}$	2.520	1.980	1.950	1.490	1.830	1.520

Table 7
Variation of ion-stimulated swellings of SRHs with tonicity.

	hypertonic saline		isotonic saline	hypotonic saline	
SRH	3%	2%	0.9%	0.045%	0.0225%
SRH-O	2.169	2.200	2.284	2.348	2.391
SRH-P	1.785	1.862	2.276	2.769	3.170
SRH-B	2.057	2.087	2.292	2.578	2.831
SRH-C	2.338	2.541	3.002	3.316	3.513
SRH-M	2.230	2.411	2.809	3.074	3.239
SRH-F	1.960	2.104	2.498	2.802	3.003
SRH-I	2.055	2.197	2.576	2.864	3.054
SRH-A	1.620	1.785	2.197	2.497	2.690

calculate. At pH= 8, the LCST values of SRH-P, SRH-F, SRH-I, and SRH-A were calculated over 32 °C, while the LCST values of SRH-P and SRH-F were found to be close to the physiological temperature.

To determine in which physiological fluids or body organs/tissues the biomaterials intended to be used in the body can be used, parameters such as transition point, responsiveness, transition zone width calculated from these equations can be predicted before the procedure.

In conclusion, calculating the parameters of the transition zones with the proposed sigmoidal and exponential decay equation approach can be a useful tool for chemists, chemical engineers, bioengineers, biomedicine, biomaterials, polymer, and plastics scientists to find the transition zone parameters of stimuli-responsive hydrogels.

We can also predict that smart hydrogels hold great promise in the biological evaluation of temperature-, pH-, and ionic strength-sensitive

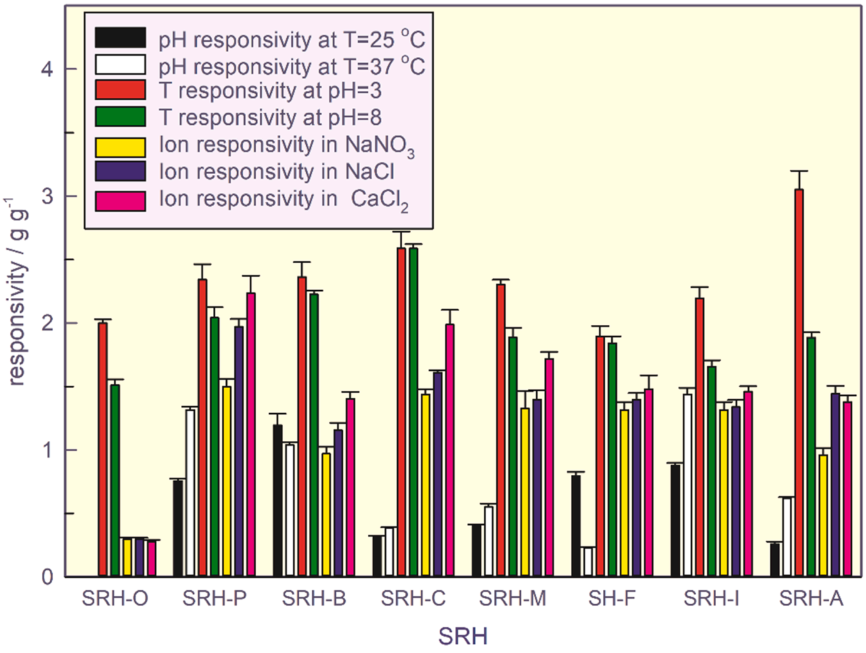


Fig. 11. Comparison of stimuli responsivities.

swelling behaviors, as a tool to fit experimental results with mathematical model correlations.

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Author contributions

The authors declare no conflict of interest.

CRediT authorship contribution statement

Dursun Saraydın: Conceptualization, methodology, software, formal analysis, investigation, resources, data curation, writing—original draft preparation, writing—review and editing, visualization, supervision, project administration, funding acquisition. **Yasemin Işıkver:** Conceptualization, methodology, software, formal analysis, investigation, resources, data curation, writing—original draft preparation, writing—review and editing, visualization. All authors have read and agreed to the published version of the manuscript.

Author statement

We are submitting an original unpublished article, "Calculations of the magnitude of responsiveness in pH-, temperature- and ion- responsive hydrogels," to your journal Materials Today Communications for review and, when appropriate, publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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