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Predictive modelling of the swelling behaviour of polyelectrolytic chitosan hydrogels

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ABSTRACT

This study concerns the development of a model to predict the pH dependent swelling behaviour of a polyelectrolyte gel. Flory and Tanaka swelling theory was used to calculate a value of r_{swell}, the swelling ratio at equilibrium. Swelling equilibrium is reached when the mixing, elastic and ionic forces in the gel are balanced. Each of these contributing factors were considered separately and the swelling ratio at which all three contributions balanced was calculated. The calculations were modelled on a chitosan–genipin/glutaraldehyde/polygenipin system, and the results were compared to experimental data. The dependence of swelling and pH and crosslinker was successfully modelled, but the absolute degree of swelling was higher than found experimentally. This is most likely because of underestimation of the elastic contribution of the non-Gaussian nature of the network chains. The information awarded by the model is valuable for the design of targeted swelling hydrogel drug delivery systems.

1. Introduction

Several attempts have been made to model the swelling behaviour of polyelectrolytic gels (Colombo, 1993), but studies are often limited. This is because, as a finite gel, the crosslinks and polymer segments are all influenced by and, in turn influence, the ionisation of the fixed charges on the network and the diffusing counter ions. In this study, an attempt has been made to calculate the effect of each of the influential ionic groups separately and thus gain an understanding of the dissimilar behaviour of the different systems. This was done using swelling theory developed by Flory and Tanaka et al. and builds on similar work in the literature (Butler & Pudney, 2003). In the previous study by Butler et al., the swelling behaviour of similar crosslinked chitosan systems was modelled and compared it with experimental data but correlation was limited because not all possible ionisable groups were considered. In this study the effect of each ionisable group is calculated as a function of the local pH. In this way, the pH dependent swelling behaviour is calculated for gels of chitosan crosslinked with genipin, glutaraldehyde and polygenipin and successfully compared with experimentally determined data.

Swelling equilibrium is attained when a free energy balance is achieved between the several contributing forces (Shroader & Opermann, 1996):

$$0 = \mu_{mix} + \mu_{elastic} + \mu_{ionic} \quad (1)$$

The strategy of this model is to evaluate μ_{mix}, $\mu_{elastic}$ and μ_{ionic} in terms of the swelling ratio, r_{swell}, and to find the value of r_{swell} for which, Eq. (1) is true for a chosen set of conditions.

1.1. The mixing potential, μ_{mix}

The mixing potential is created by the mixing of the polymeric segments with each other and with the solvent when placed in the swelling environment. This contribution can be derived from Flory–Huggins solution theory. It is stated that (Flory, 1953; Flory & John Rehner, 1943b) the free energy of mixing for a system, ΔG_m, at a constant temperature and external pressure is

$$\Delta G_m = \Delta H_m - T\ \Delta S_m \quad (2)$$

where ΔH_m is the change in enthalpy of the system, T, the temperature and ΔS_m, the change in entropy upon mixing (Flory, 1953; Flory & John Rehner, 1943b). From this, Flory derived an expression for the free energy for a mixing system in terms of the number of moles of solvent and the polymer volume fraction. This

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is most commonly a positive driving force for swelling and can be expressed as in Eq. (3),

$$\mu_{\text{mix}} = RT\left(\frac{\ln(1-\phi_2)+\phi_2+\chi(\phi_2)^2}{V_s}\right) \quad (3)$$

where R is the gas constant, the commonly used Boltzmann constant, χ is the Flory–Huggins interaction parameter, V_s is the molar volume of the solvent and ϕ_2 is the polymer volume fraction. The polymer volume fraction was derived from the product fraction of each polymer component and its partial specific volume.

1.2. The elastic potential, $\mu^{elastic}$

An opposing force to swelling is the elastic contribution. As swelling increases, so does the chain stiffness, with a corresponding reduction in entropy (Flory & John Rehner, 1943a). It is found that elastic contribution often determines the overall degree of swelling and so the maximum achievable swelling ratio. This is a negative contribution, which considers the modulus and nature of the chain as well as the swelling ratio. Eq. (4) was used to describe the elastic potential:

$$\mu_{\text{elastic}} = -G'\left(\frac{1}{2}r - \frac{(1-(1/N)+(0.4/N^2)+(0.32/N^3))}{r^{1/3}} + \left(-\frac{1}{N}+\frac{2.6}{N^2}-\frac{1.72}{N^3}\right)r^{1/3} + \left(-\frac{2.2}{N^2}+\frac{8.84}{N^3}\right)r + \left(\frac{6.84}{N^3}\right)r^{5/3}\right) \quad (4)$$

where G' is the shear elastic modulus and N the average number of segment lengths per elastically active network chain.

1.3. The ionic potential, μ_{ionic}

In polyelectrolyte systems there is an additional and often dominating contribution due to the presence of counter-ions. It is the ionic potential that generally determines the differential swelling over the pH range and hence the positions of the maxima and minima of the swelling curve. The chemical potential of the water inside the gel and outside must be equal i.e. they must obey Donnan's equilibrium. However, a difference in the concentration of ions inside and outside the matrix is caused by the charges on the polymer chain, which are fixed and immobile, but require an equivalent number of counter-ions to remain within the gel to achieve electroneutrality.

From this principle, Tanaka et al. (Ohmine & Tanaka, 1982; Tanaka & Fillmore, 1979) and Brannon-Peppas et al. (Peppas, 2000) described the ionic potential thus

$$\mu_{\text{ionic}} = RT\sum_i (c^i_{\text{out}} - c^i_{\text{in}}) \quad (5)$$

where c^i_{out} is the concentration of each ionic species out of the gel and c^i_{in}, the concentration of each ionic species in the gel.

The above theoretical relationships between the polymer physical characteristics and the contributing potentials towards swelling were used to predict the swelling behaviour of chitosan based networks in aqueous environments. This particular system is of interest as a pH specific drug delivery system and, as such, a strong understanding of the factors effecting swelling are desirable. The experimental conditions were modelled on experimental systems already reported (Jahren, Butler, Adams, & Cameron, 2010).

2. Experimental methods

The model is used to make predictions based on chitosan–genipin/glutaraldehyde/polymerised genipin (polygenipin) networks as described previously in literature (Jahren et al., 2010). The crosslinked chitosan systems form polyelectrolytic gel networks with cationic amine groups on chitosan polymer chains and anionic carboxyl groups on genipin or aldehyde groups on the glutaraldehyde. The ionic nature of the network results in pH responsive swelling, the degree of which is dependent on the nature and concentration of the crosslinker. From this point on, the theory will be discussed in the context of a chitosan–monomer genipin network (except where specified) but the same principles have used to model the chitosan–glutaraldehyde and chitosan–polygenipin systems and should be equally applicable to a whole range of other polyelectrolytic gels.

In this study we were looking at a 2 part system, chitosan and then a crosslinker, both of which contribute to the volume fraction as shown in Eq. (6):

$$\phi_2 = \frac{(\%c_c\upsilon_c + \%c_g\upsilon_g)/(\%c_c\upsilon_c + \%c_g\upsilon_g + (100-(\%c_c+\%c_g))\upsilon_w)}{r} \quad (6)$$

where $\%c_c$ and $\%c_g$, are the concentration of chitosan and genipin respectively expressed as a weight percentage, υ_c, υ_g, and υ_w are the partial specific volume of chitosan, genipin and water and r is the gel equilibrium swelling ratio = $(M_f - M_s)/M_s$ where M_f and M_s are the final and starting mass of the gel sample.

N can be quantitatively defined by the number of chitosan saccharide units between each crosslink, i.e. in a single elastically active chain. It is found as

$$N = \frac{c_c}{c_g} \quad (7)$$

where c_c and c_g are the molar concentrations of chitosan and genipin respectively. The value for the gels used in this study varied from 1.09 to 10.9 saccharide units per chain. This is also a useful indicator of the proportion of amino groups per crosslinker, as each saccharide has a single amino group.

The mobile ions outside the gel are dependent on the solute used. For example, in these experiments hydrochloric acid and sodium hydroxide were used respectively for acid and basic conditions with no additional salt in the solvent. The model assumes that the swelling environment is in such excess to remain unchanged during the swelling process, i.e. is an infinite bath. The concentration of each ionic species outside the gel was found as

$$c_{H^+_{out}} = 10^{-\text{pH}} \quad (8)$$

$$c_{Cl^-_{out}} = 10^{-\text{pH}} \quad (9)$$

$$c_{Na^+_{out}} = 10^{-(14-\text{pH})} \quad (10)$$

$$c_{OH^-_{out}} = 10^{-(14-\text{pH})} \quad (11)$$

where c_{H^+}, c_{Cl^-}, c_{Na^-} and c_{OH^-} are the concentrations of protons, chloride ions, sodium ions and hydroxyl ions respectively and pH is the pH of the solvent. As we are in this case considering the solvent conditions exterior to the gel only there is no contribution from the hydrogel ions. Hydrochloric acid and sodium hydroxide are strong acid and bases respectively and as such were considered to undergo complete dissociation.

The ionic species within the network space are dependent on the type of ionic species bound on the polymer chains and those of the freely diffusing solute. As mentioned above, the concentration of the counter ions is dependent on obeying Donnan's equilibrium (Butler and Pudney, 2003) which states that

$$[A^+]_{out}\cdot[B^-]_{out} = [A^+]_{in}\cdot[B^-]_{in} \quad (12)$$

Table 1
The gel constituents and concentrations and the linear relationship of G′ and r are determined experimentally (Jahren et al., 2010).

	Chitosan		Crosslinker		G′
	wt%	mol/dm^{-3}	wt%	mol/dm^{-3}	
a. 1 wt% chitosan–5 mM genipin	1	11.73×10^{-6}	0.1131	0.005	$354.5r + 507.3$
b. 1 wt% chitosan–7.5 mM genipin	1	11.73×10^{-6}	0.1691	0.0075	$900.5r + 1634.3$
c. 1 wt% chitosan–10 mM genipin	1	11.73×10^{-6}	0.2262	0.01	$1783.3r + 2457.6$
d. 1 wt% chitosan–25 mM genipin	1	11.73×10^{-6}	0.5655	0.025	$5158.2r + 5609.2$
e. 1 wt% chitosan–50 mM genipin	1	11.73×10^{-6}	1.131	0.05	$24617r + 70502$
f. 1 wt% chitosan–5 mM glutaraldehyde	1.5	17.59×10^{-6}	0.5006	0.005	$62449r + 22089$
g. 1 wt% chitosan–10 mM polygenipin	1	11.73×10^{-6}	0.2262	0.01	$2058r + 17795$

Taking this into account, the concentration of each ionic species within the gel was found thus

$$c_{c^+_{in}} = \left(\frac{c_{c^+} - c_{g^-}}{r}\right)\left(\frac{c_{H^+_{out}}}{c_{H^+_{out}} + 10^{-pK_{ac}}}\right) \quad (13)$$

$$c_{g^-_{in}} = \left(\frac{c_{g^-} - c_{c^+}}{r}\right)\left(\frac{c_{H^+_{out}}}{c_{H^+_{out}} + 10^{-pK_{ag}}}\right) \quad (14)$$

$$c_{H^+_{in}} = 10^{-pH} \quad (15)$$

$$c_{Cl^-_{in}} = \frac{c_{H^+_{out}} c_{Cl^-_{out}}}{(c_{H^+_{in}} + c_{c^+_{in}})} \quad (16)$$

$$c_{Na^+_{in}} = \frac{c_{OH^-_{out}} c_{Na^+_{out}}}{(c_{OH^-_{in}} + c_{g^-_{in}})} \quad (17)$$

$$c_{OH^-_{in}} = 10^{-(14-pH)} \quad (18)$$

where c_{c^+} is the concentration of available ionisable groups on the chitosan chains and c_{g^-} on the genipin chains (glutaraldehyde/polygenipin) and pK_{a_c} and pK_{a_g} are the dissociation constants of chitosan and genipin (glutaraldehyde/polygenipin) respectively.

During the gelation process, some of the ionisable groups that would contribute to swelling are bound up on the crosslink and thus unable to contribute to swelling. This is accounted for in Eqs. (13) and (14) by the subtraction of the number of available reaction groups. As is logically true, it is a condition of the model that

- should c_{g^-} exceed c_{c^+} then $c_{c^+_{in}}$ is equal to zero and
- should c_{c^+} exceed c_{g^-} then $c_{g^-_{in}}$ is equal to zero.

The swelling ratio appears in Eqs. (13) and (14) as an increase in swelling reduces the volume concentration of the ionic groups bound within the swelling gel and the pK_{a_c} and pK_{a_g} are required since both chitosan and genipin are only weak acid and bases respectively and so will only partially dissociate to a degree depending on the swelling environment pH.

G' was determined experimentally in (Jahren et al., 2010) where a linear approximation was applied relating the G' linearly to r, as described in Table 1.

The other parameters and scientific constants that were incorporated into the model calculations are listed in Table 2.

The pK_a value of chitosan is quoted in the literature as 6.3 (Park & Choi, 1983), and there are no quoted values for genipin and glutaraldehyde. As these values are singularly important in determining the swelling behaviour, values were determined using pK_a prediction software. It was found that the pK_a of each constituent of the network, varied depending on the type of crosslinking. The pK_a of each gel type was predicted using ACD/pK_a v8.0 for windows courtesy of the ACD/I-lab service. This software used the Hammett method for pK_a prediction (Perrin et al., 1981). The following pK_a values were assigned (Table 3).

Table 2
The parameters and scientific constants included in the calculations.

	Parameter	Value	Units
T	Temperature	298	K
pH		1–14	
R	Gas constant	8.3143	J K^{-1} mol^{-1}
χ	Interaction parameter	0.48[a]	
V_s	Molar volume of solvent	0.00612[b]	m^3 mol^{-1}
υ_c	Partial specific volume chitosan	0.702[c]	m^3 kg^{-1}
υ_g	Partial specific volume genipin	0.7433[c]	m^3 kg^{-1}
υ_{gt}	Partial specific volume glutaraldehyde	0.53[c]	m^3 kg^{-1}
υ_w	Partial specific volume water	1	m^3 kg^{-1}

[a] Obtained from literature [2].
[b] Approximated to that of water.
[c] Calculated by the method descried by Durchschlag and Zipper, based on the addition of volume increments of the constituent atoms (Durchschlag & Zipper, 1997).

Using Eqs. (1)–(18) and the values above we can calculate the individual values of μ_{mix}, $\mu_{elastic}$, and μ_{ionic}. The value of r for which these three terms balance and sum to zero (Eq. (1)) is the equilibrium swelling ration was determined by a basic iteration and optimisation calculation.

3. Results and discussion

Each of the contributing potentials, μ_{mix}, $\mu_{elastic}$ and μ_{ionic}, were calculated in terms in terms of r, which was increased or decreased incrementally until the condition (1) was met i.e. the sum of these terms was equal to zero. It was found, in all cases, that the mixing potential was constant and of negligible value, but the ionic and elastic potentials increased and decreased relative to each other and increased in magnitude with r_{swell}. Fig. 1a and b shows a typical graphical representation of how each of these factors varied with pH and r. The figure shown is data modelled on a 1 wt% chitosan and 5 mM genipin system; all of the other system followed similar behaviour.

Using all the terms listed above, the equilibrium swelling for 1% chitosan gels crosslinked with 5-50 mM genipin were calculated and compared with the experimental findings as shown in Fig. 2.

As shown, the calculated values show a reasonable correlation with the experimental values. The modelled r at low pH is

Table 3
The assigned pK_a values for each ionisable group in the gel networks, as determined using the Hammet method for pK_a prediction (Perrin et al., 1981).

Network type	Ionising group	Assigned pK_a value
Chitosan–genipin	Chitosan's amine	5.0
	Genipin's carboxyl	12.0
Chitosan–glutaraldehyde	Chitosan's amine	7.1
	Glutaraldehyde's aldehyde	15.1
Chitosan–polygenipin	Chitosan's amine	8.3
	Genipin's carboxyl	12.0

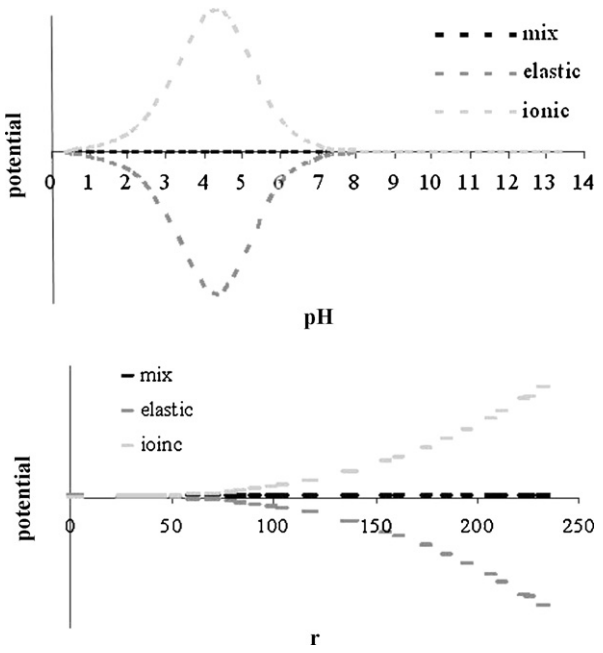

Fig. 1. The 3 contributing potentials as a function of (a) pH and (b) r_{swell} as modelled on a 1 wt% chitosan and 5 mM genipin gel.

higher than the experimental values, which are all close to zero or even negative. Between pH 3 and 6, where the maximum swelling occurs, the modelled data closely follows the experimental data. At around pH 7 there is again a slight deviation from the experimental data, but the model then falls to a minimum at the higher pH's recapturing the behaviour observed experimentally. Several limitations of this model can be observed. The model was designed on the assumption that $r = 0$ was the most relaxed, lowest energy state the network could assume. In reality the gel samples can shrink to reach the swelling equilibrium giving a negative r value which is not observable in the model. This limitation has a negligible effect on the gels of lower crosslink density, but is more noticeable with the higher crosslink density, more highly elastic networks. Despite this limitation the model adequately describes and compares the effects of different crosslinker concentrations at the maximum swelling.

When the two scales of Fig. 2 are compared, it is apparent that the prediction of the model was a consistent factor of 30 too large. As previously discussed, it is the elastic properties of the material which are dominant in determining the magnitude of the swelling, so it is probable that at this stage the elastic potential contribution has been underestimated. Chain entanglements can form a physical crosslink, which has an identical effect on elasticity as a chemical crosslink (Sperling, 2001) so increasing the number of effective crosslinks. Using the model to calculate the crosslinking density, n, that would be required to produce the experimentally determined r, suggests approximately 80 times the original genipin crosslinking density in each system. However, such a large contribution due to physically entanglements is unlikely, as chain entanglements have limited lifetime and could be expected to reorganise over time and under action of stress. A more likely explanation is that the gels do not exhibit rubber like behaviour as presumed. Previous studies have demonstrated that polysaccharide systems do not obey the rubber elasticity theory because the polysaccharide chains are too stiff for short chain lengths to show Guassian behaviour which is essential if rubber elasticity theory is to be obeyed (Bailey, Mitchell, & Blanshard, 1977). It has been proposed that instead of network of flexible chains, a highly crosslinked polysaccharide gel resembles a network of stiff rods (Davidovich-Pinhas & Bianco-Peled, 2010; Mitchell, 1980).

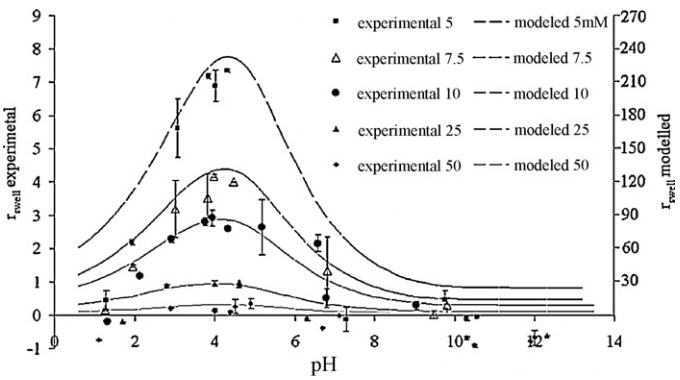

Fig. 2. The experimental and calculated r_{swell} as a function of pH for a 1 wt% chitosan and 5–50 mM genipin gel.

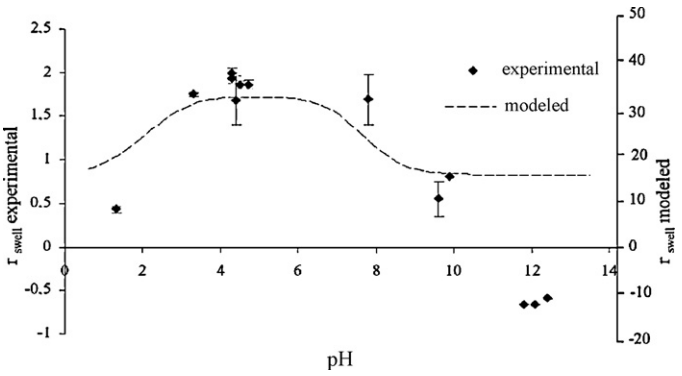

Fig. 3. The experimental and calculated r_{swell} as a function of pH for a 1.5 wt% chitosan and 5 mM glutaraldehyde gel.

Fig. 3 shows the calculated predictions of r for 1.5 wt% chitosan and 5 mM glutaraldehyde gels compared to the experimentally obtained data (Jahren et al., 2010).

For the chitosan–genipin gels, the best fit is achieved at the maximum swelling range, which in this case is extended over a large pH range, 3–7. As in the case before, at the extreme low pH the modelled data is higher than the experimental and at pH 12 the modelled data reaches a plateau to a minimum much higher than the negative swelling observed experimentally.

Fig. 4 shows the calculated prediction of r for the 1% chitosan, 10 mM polygenipin gels compared with the values determined experimentally.

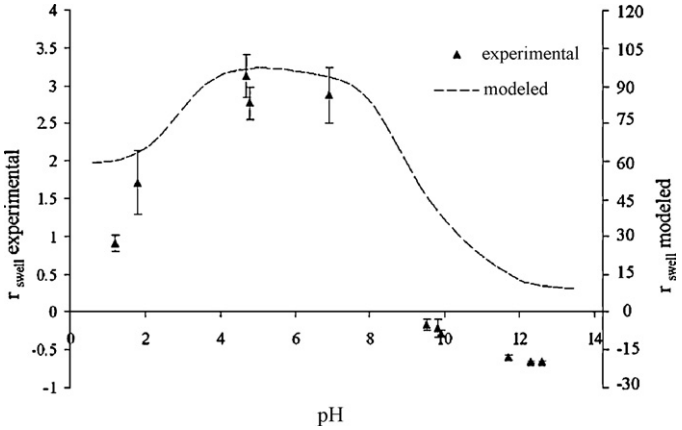

Fig. 4. The experimental and calculated r_{swell} as a function of pH for a 1 wt% chitosan and 10 mM polygenipin gel.

The modelled data is again slightly higher than the experimental data at the extreme low pH, but a better fit is achieved at the maximum swelling range between pH 4 and 8, the modelled data then mimics the experimental data with a steeper fall to a minimum value at the extreme high pH. However, as before, the modelled data does not show a negative swelling value as is observed in the experiment.

Although in each case there are some deviations, the general shape of the swelling curves is well described by the calculated r values. The relative difference in maximum swelling ratio between gels within a systematic series (Fig. 2) is also well captured by the model which would allow the model to be used in a semi predictive fashion to predict the behaviour of new, compositions within the series.

A significant increase in the confidence of the model could be gained by a more rigorous determination of some of the experimental parameters such as material pK_a, degree of crosslinking in the networks and molecular weight in the case of polymerised genipin. This could not be carried out within the scope of this work, but would certainly improve the reliability of the calculations.

4. Conclusions

Using swelling theory, a model was developed to calculate the equilibrium swelling ratio, r, of polyelectrolyte gels. A relatively successful prediction was made of the pH dependent swelling behaviour of chitosan crosslinked with genipin, glutaraldehyde and polygenipin gels. The calculated results were compared to data obtained experimentally and a reasonable fit was made, particularly in the regions of maximum swelling. There are several limiting factors of the model, such as unknown definitive values of pK_a, r_0 and elastic contribution by physical entanglements and the non rubber like behaviour of polysaccharides. Overall, the swelling model gives a good qualitative description of the data and quantitative prediction of the relative maximum swelling ratio of a systematic series of gels as well as some quantitative analysis of each swelling contribution and each of the factors affecting it.

The model provides an insight into the relative importance of each of the parameters. It has been shown that the mixing potential, μ_{mix} has a negligible effect compared with the elastic and ionic potentials, $\mu_{elastic}$ and μ_{ionic}. The major features of the graph can be attributed to certain material condition. It was revealed that the ionic potential, particularly the pK_a, has been shown regulate the pH dependent response whereas it is the elastic potential and specifically the number of chemical and physical crosslinks combined, which governs the overall magnitude of the swelling. The overall magnitude of swelling was lower than the model predicted. This is most likely because of underestimation of the elastic contribution of the non-Gaussian nature of the network chains. This knowledge can be used during material selection when designing specialised pH responsive delivery devices.

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