Dual Control Fluorophore release from viscoelastic enhanced Ionogels

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Temperature and pH triggered release characteristics of water/fluorescein from 1-ethyl-3-methylimidazolium ethylsulfate based ionogels†

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A crosslinked poly(*N*-isopropylacrylamide) ionogel encapsulating an ionic liquid exhibits improved transmittance properties, enhanced water uptake/release, greater thermal actuation behaviour and distinct solvatomorphology over its hydrogel equivalent. It was also found that the rate of release of fluorescein pre-loaded into membranes was considerably enhanced for ionogels compared to equivalent hydrogels, and could be triggered through changes in pH and temperature.

the polymer component combining the favourable characteristics of both independent phases in one material.

As pNIPAAM is well known as a platform for drug delivery, dyes have been used such as Methylene blue[10] and Orange II[11] to monitor the uptake and release properties of these hydrogels. The study of release of pre-loaded organic molecules is of great interest for example as a model platform for precise delivery (space, time, amount) of active drugs (*in vitro*). In order to study the effect of

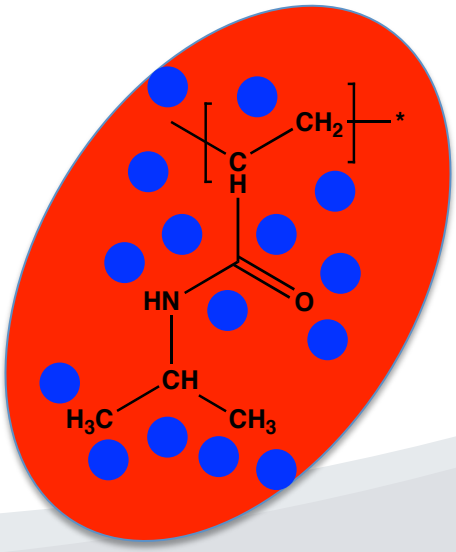
Contents

- Thermo-responsive gels
- Ionic Liquid-based Poly(*N*-Isopropylacrylamide) gels
- Comparison of $[C_2mIm][EtSO_4]$-Ionogel and Hydrogel
  - Actuation
  - Dye Release
- Conclusion

Thermo-responsive Gels

- Poly(N-Isopropylacrylamide) or **"PNIPAAM"**, display inverse solubility upon heating.
- Hydrophilic to Hydrophobic transition occurs at lower critical solution temperature (LCST), 30-35°C.
- Below LCST, gel swells by intake of water molecules through hydration of aliphatic groups and hydrogen bonding with amide group.
- Above LCST, gel collapses along backbone before water molecules are expelled, process is driven by the conversion from polymer-solvent bonds to polymer-polymer and solvent-solvent bonding.

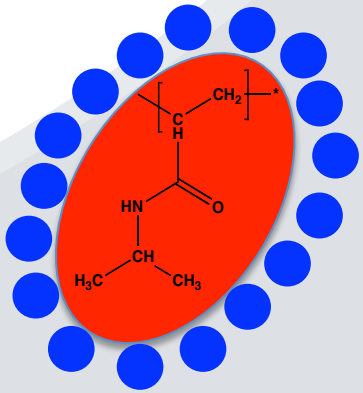
Hydrophilic (below LCST)



ΔT

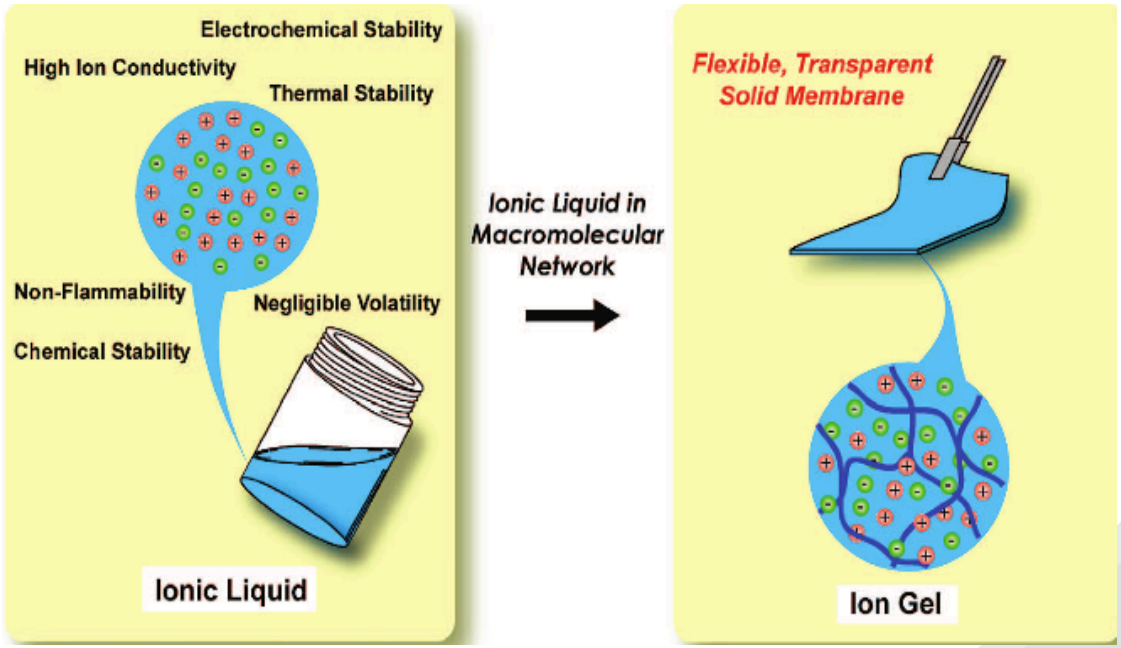
Time

Hydrophobic (above LCST)



H.G Shild, Prog. Polym. Sci., Vol. 17, 163-249, 1992

Ionogels



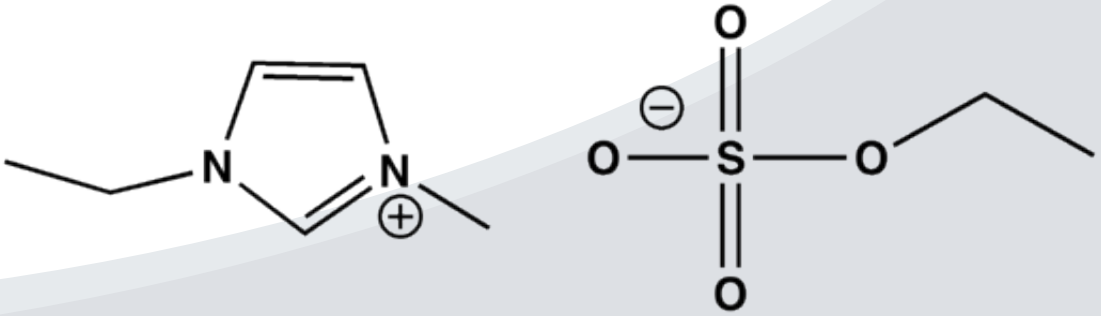
- Solid state devices that retain unique IL properties
- Polymer is formed in IL, which acts as the liquid phase of the gel
- Applications include solid-state electrolytes and optical displays

T. Ueki and M. Watanabe, *Macromolecules*, 2008, **41**, 11.
A. Kavanagh, R. Byrne, D. Diamond and K. J. Fraser, *Membranes*, 2012, **2**, 16-55.
J. Le Bideau, L. Viau and A. Vioux, *Chemical Society reviews*, 2011, **40**, 907-932.

Why study these Gels?

- Smart hydrogel materials have not been successful in open atmosphere for wide range of temperatures.
- Due to solvent contained in the network (volatility and phase change e.g freezing).
- Introduction of IL provides first step to a environmentally stable polymer gel, where swelling/shrinking can be observed in open atmosphere.[5]

$[C_2mIm][EtSO_4]$



T. Ueki and M. Watanabe, *Macromolecules*, 2008, **41**, 11.

Why study these Gels?

- pNIPAAM is used as platform for drug delivery
- Dyes used to monitor uptake and release properties
- Model platform for precise delivery of active drugs

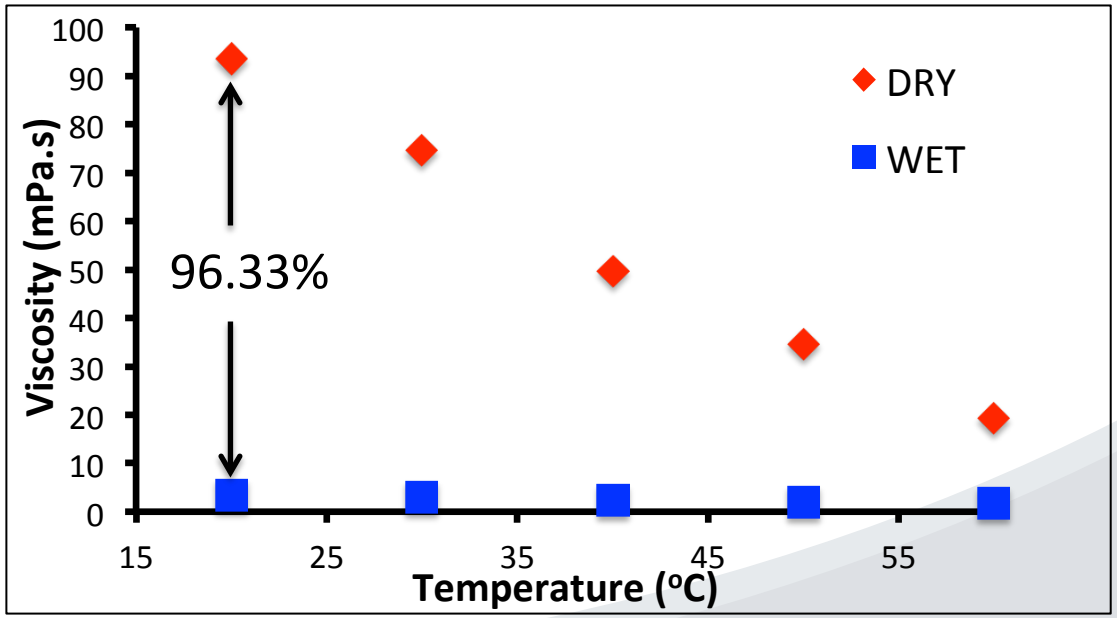
M. R. Guilherme, R. Silva, E. M. Girotto, A. F. Rubira and E. C. Muniz, *Polymer*, 2003, **44**.

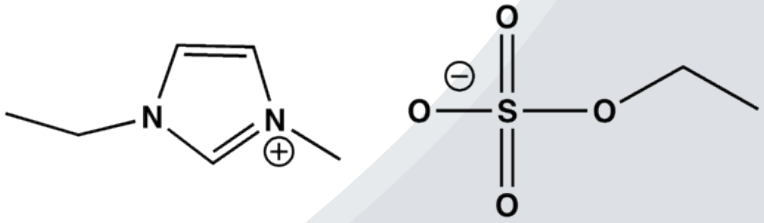
Actuation Experimental

- Gels were photo-polymerised in 12mm teflon moulds
- Placed in water at room temperature overnight
- Swollen gels then placed in water above LCST for 1 min

Actuation Properties

IL	LCST (°C)	After Hydration/ mm @20 °C (n=3)	***Swelling Increase (%)***	Above LCST/mm @45 °C (n=3)	***Contraction Decrease (%)***
Ionogel	26	4.57 (0.09)	**28.7**	2.97 (0.03)	**31.4**
Hydrogel	31	3.87 (0.05)	**18.6**	3.36 (0.09)	**21.5**





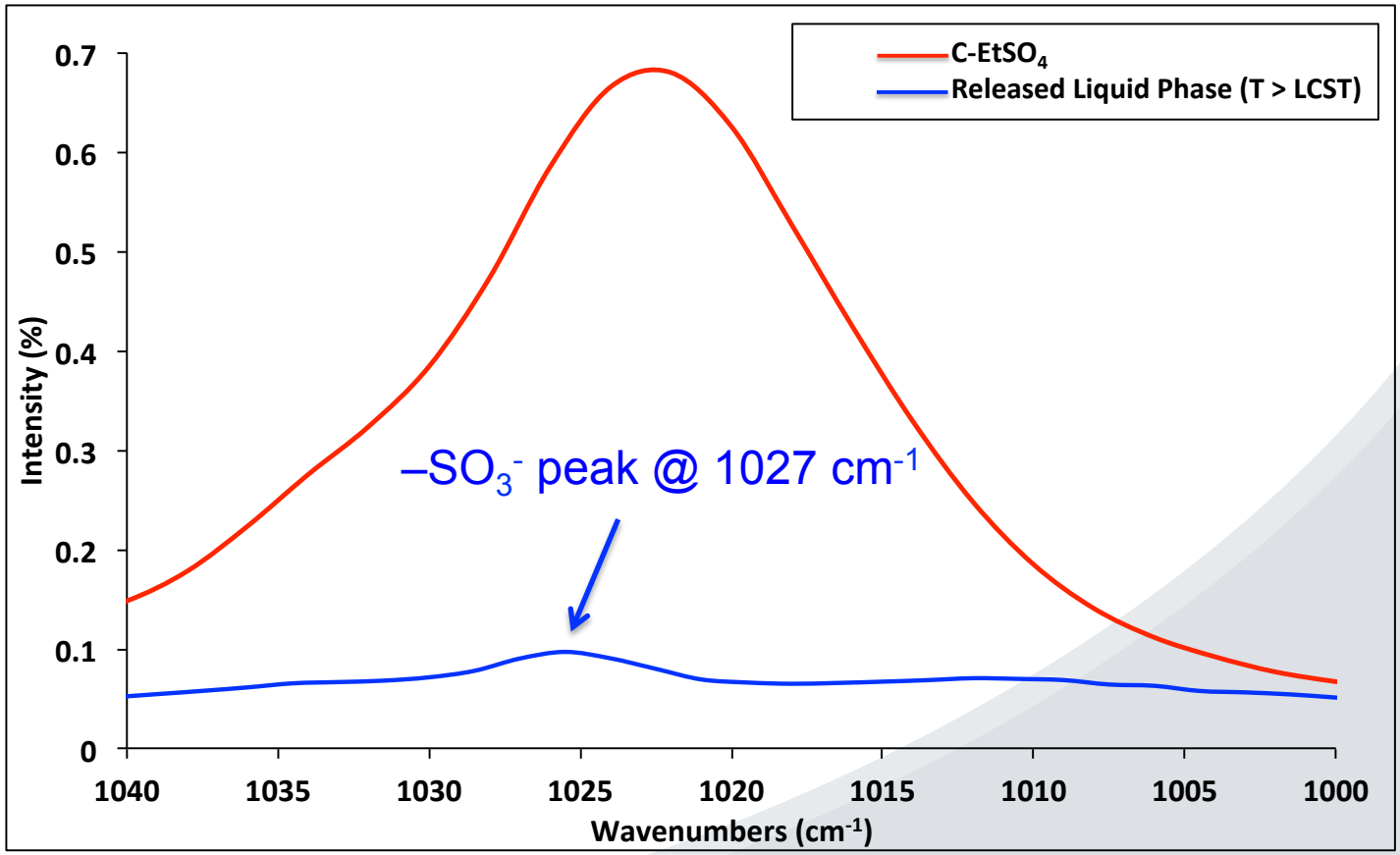
1:1 (v/v) water/IL measured as function of temperature

~ 96 % change in viscosity in the liquid phase, drive for water absorption into hydrophillic IL is large

H. G. Schild, *Progressive Polymer Science*, 1992, **17**, 163-249.

Actuation Properties

- Raman spectra of $-SO_3^-$ peak of $[C_2mIm][EtSO_4]$ appearing at 1022 cm^{-1}



- Released liquid above the LCST contains trace amounts of IL
- Increases polymer-polymer interactions, resulting in more compact format

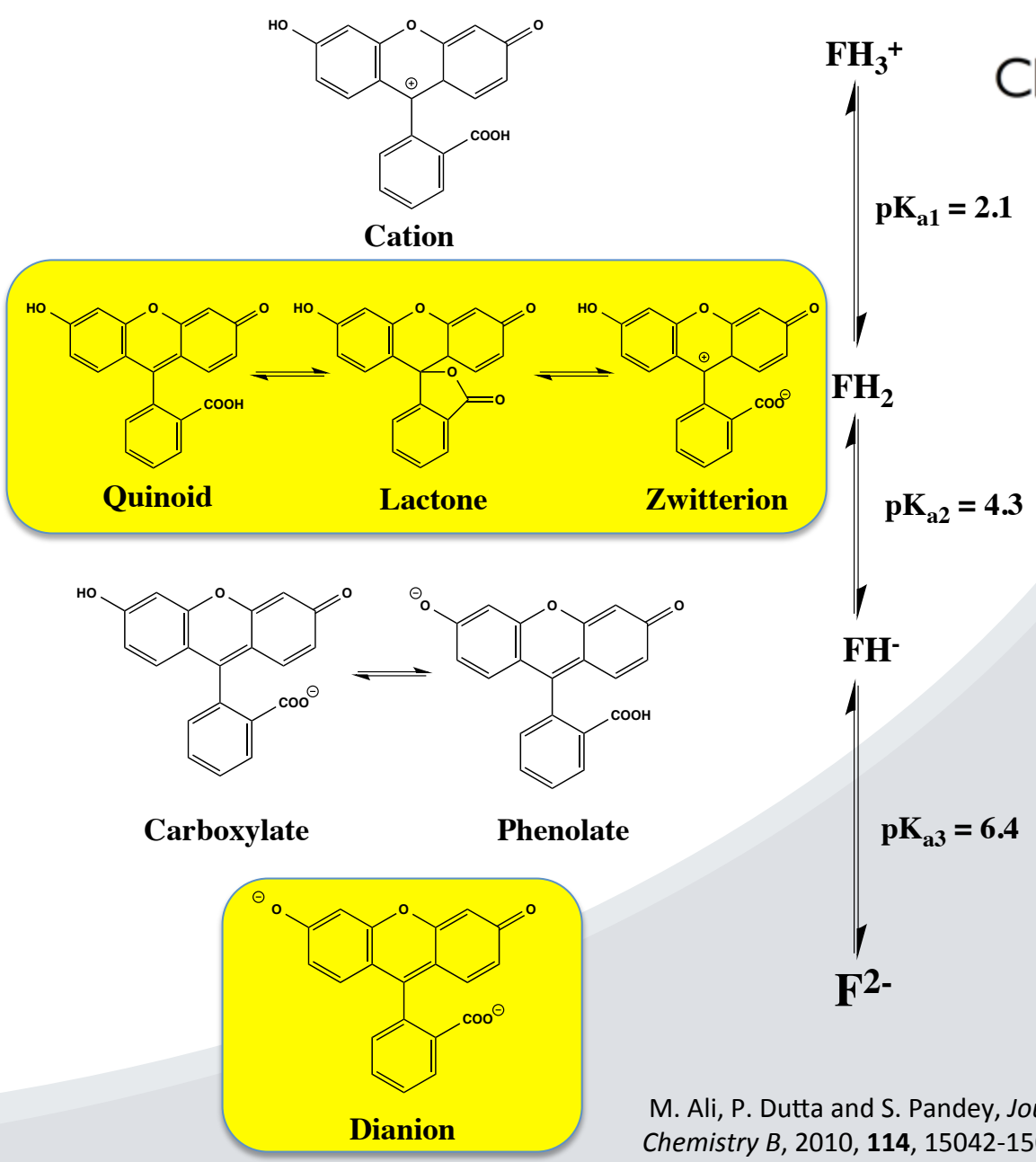
Dye release experimental

- Both gels **preloaded** with 3 mM of Fluorescein
- Swelled overnight in selected pH
- Swollen gels were placed in same solution at 40 ^{o}C (> LCST) and 20 ^{o}C (< LCST) for 1 min
- Bathing solution stirred for homogeneity and then cooled to room temperature

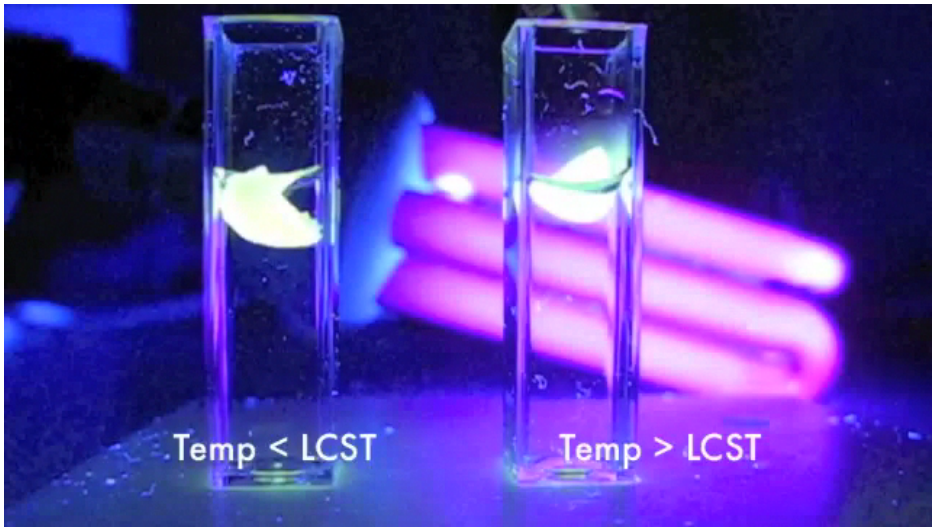
Fluorescein

- Fluorescein exists in solution as 7 distinct isomers, collective pKa of 6.4
- Each prototropic form shows characteristic absorbance peaks
- Fluorescein is used as a mock drug for in-vivo and in-vitro research due to its optical visualization

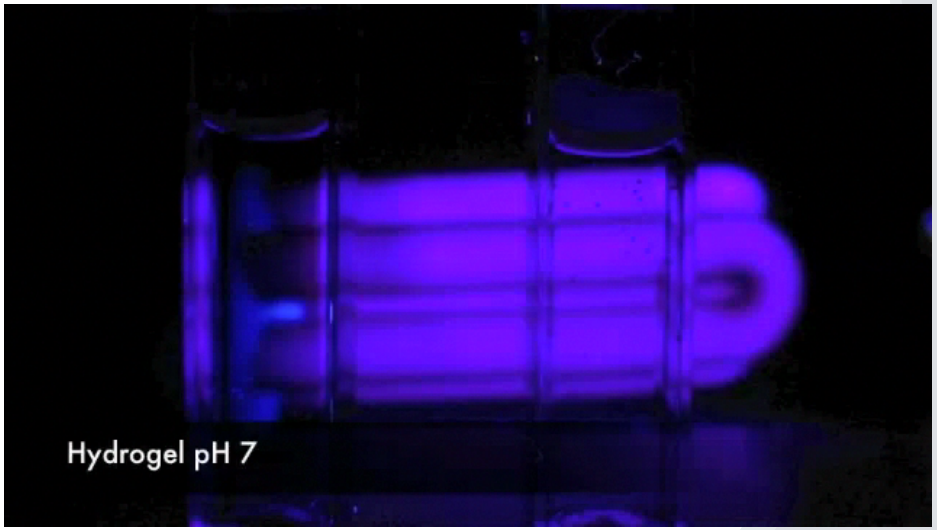
M. Ali, P. Dutta and S. Pandey, *Journal of Physical Chemistry B*, 2010, **114**, 15042-15051.
H.-R. Lin, W.-J. Chen and M.-H. Ling, *Journal of nanoscience and nanotechnology*, 2011, **11**, 1823-1833.



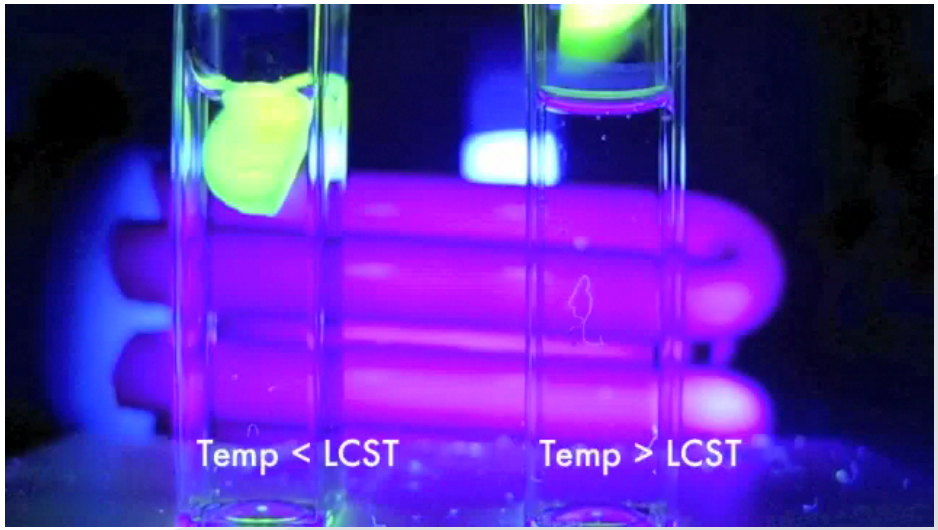
M. Ali, P. Dutta and S. Pandey, *Journal of Physical Chemistry B*, 2010, **114**, 15042-15051.



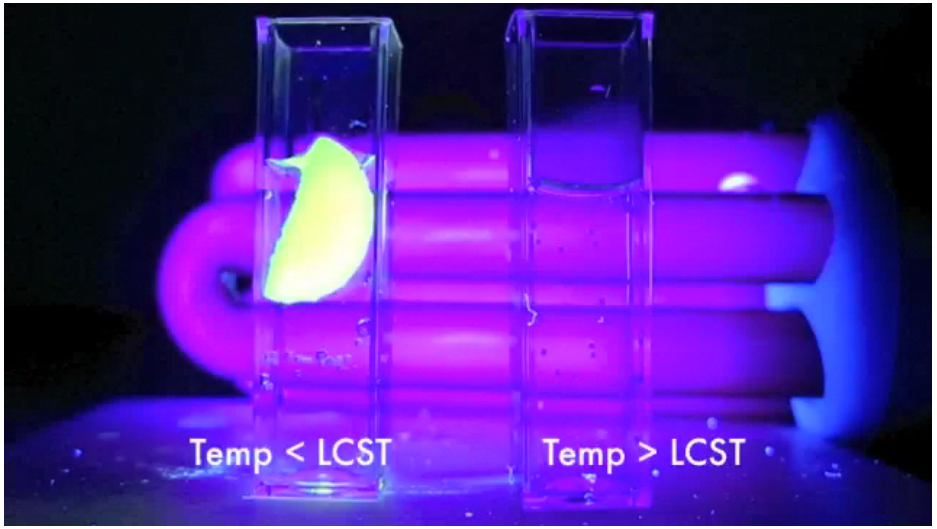
Hydrogel pH 4



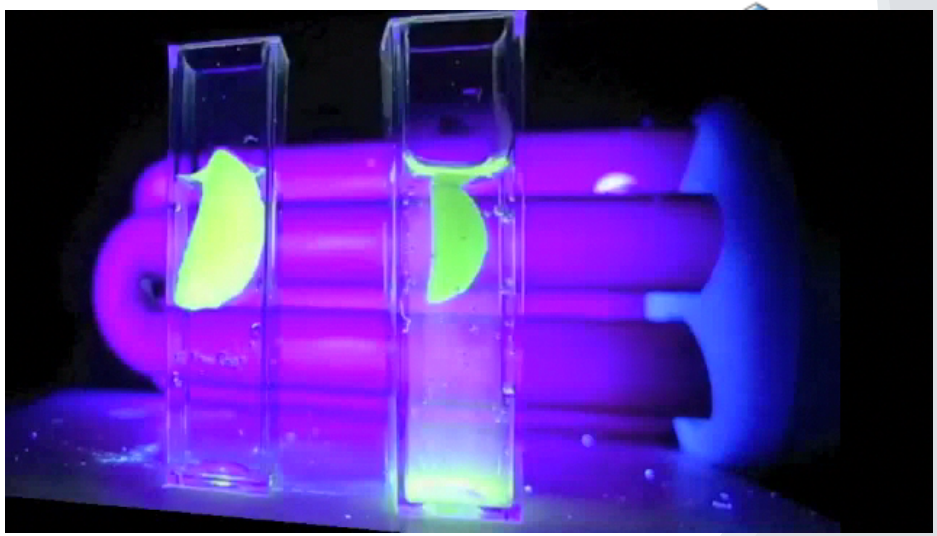
Hydrogel pH 7



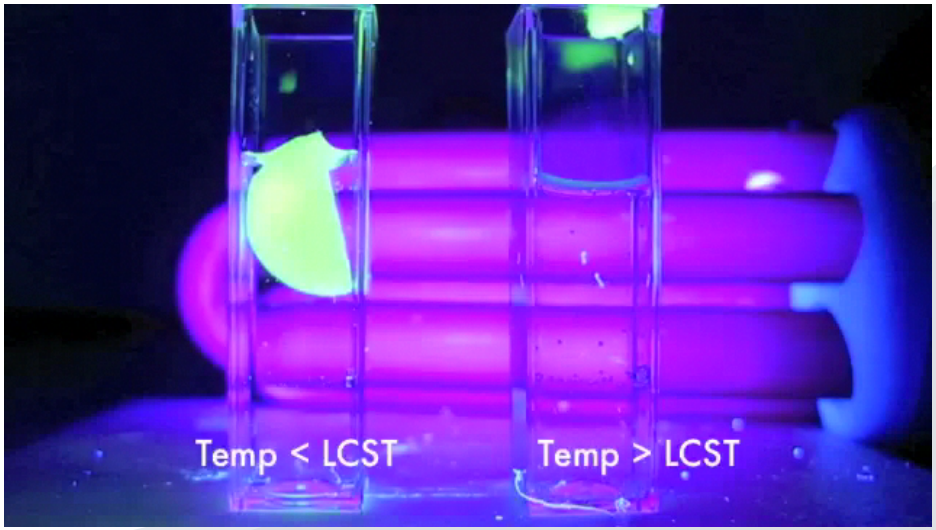
Hydrogel pH 9.2



Ionogel pH 4



Ionogel pH 7



Ionogel pH 9.2

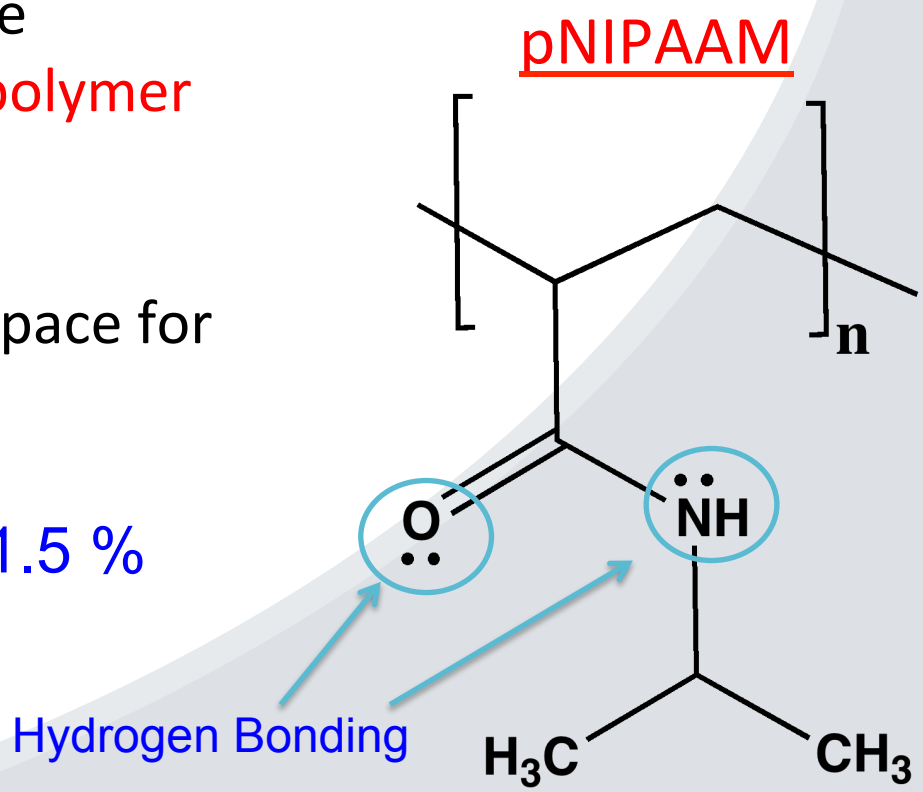
Dye release after 1 min

Solution	Hydrogel (mM) / (n = 3)		Ionogel (mM) / (n = 3)	
	< LCST	> LCST	< LCST	> LCST
pH 4	-	-	-	0.30 (2.96×10^{-4})
pH 7	-	0.01 (4.97×10^{-5})	-	0.35 (1.57×10^{-2})
pH 9.2	-	0.20 (1.20×10^{-3})	-	0.54 (4.49×10^{-2})

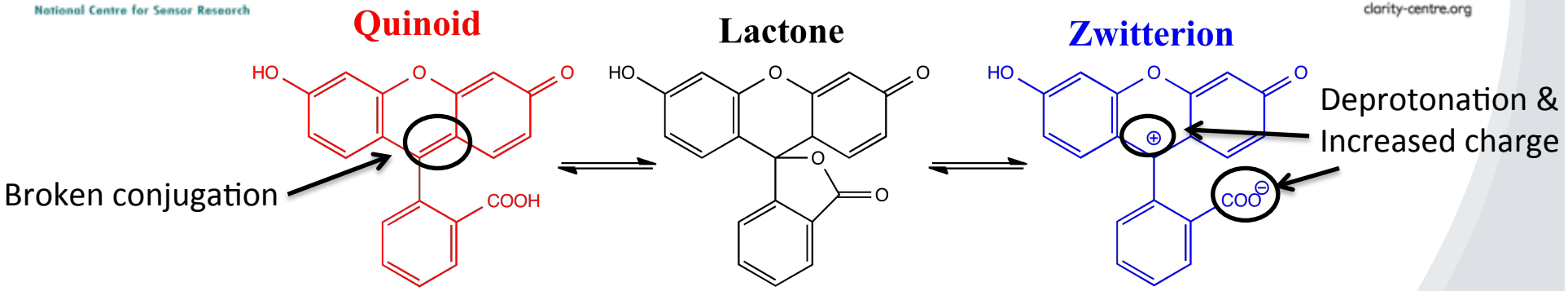
- Fluorescein that is released is strongly favoured above the LCST
- Dye release is enhanced as the pH is increased
- Also enhanced by the presence of $[C_2mIm][EtSO_4]$ in the gel

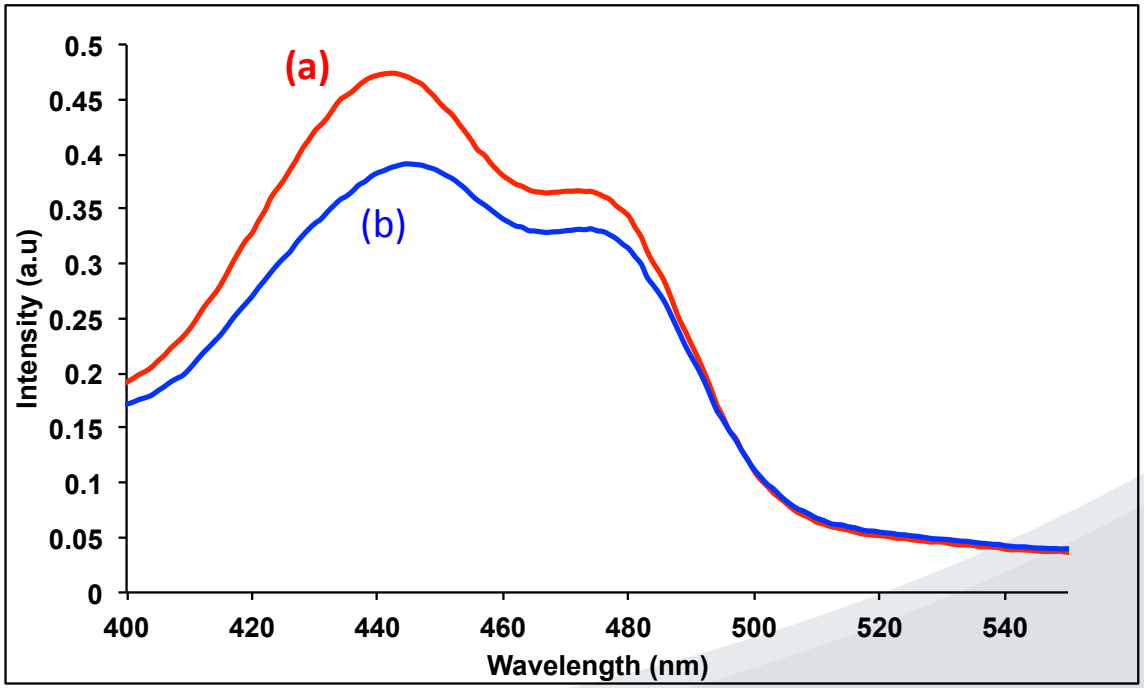
Increase due to Contraction

- Above the LCST, solvent (IL, water) and solute (fluorescein) interactions are diminished in favour for polymer-polymer interactions
- Decrease of free volume reduces space for solvent/solute
- Ionogel 31.4 % and Hydrogel 21.5 %



Increase at pH 4 (Neutral)





(a) Fluorescein in pH 4 buffer shows neutral form in hydrogel at 444 nm and 475 nm

(b) Fluorescein in pH 4/IL mixture shows decrease in absorption

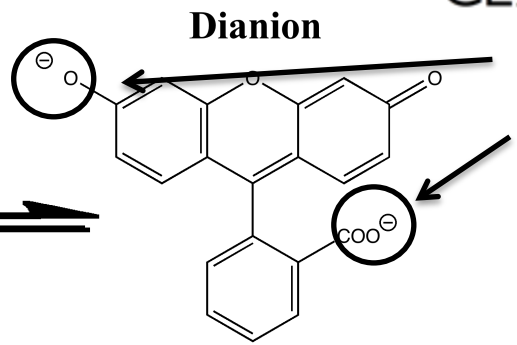
IL effect breaks conjugation of Quinoid, increasing concentration of non-absorbing, **more soluble** Zwitterion.[7]

Deprotonation reduces hydrogen interaction with polymer backbone

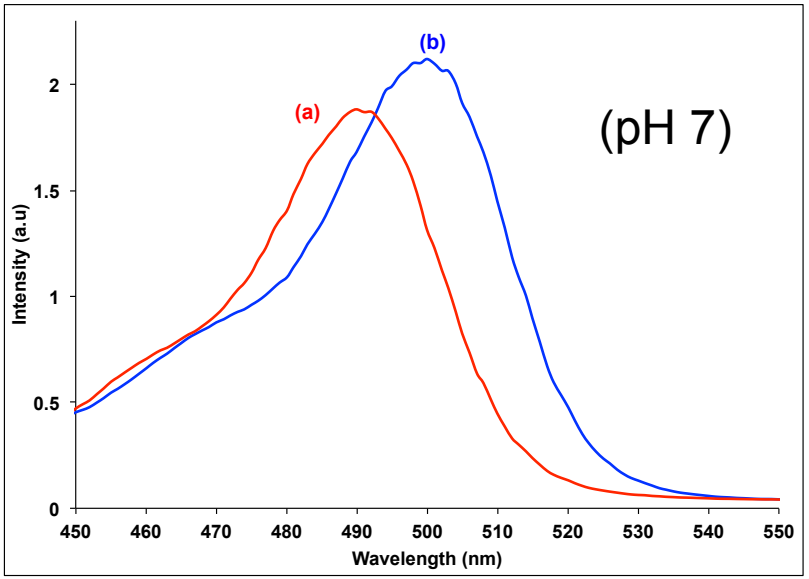
M. Ali, P. Dutta and S. Pandey, *Journal of Physical Chemistry B*, 2010, **114**, 15042-15051.

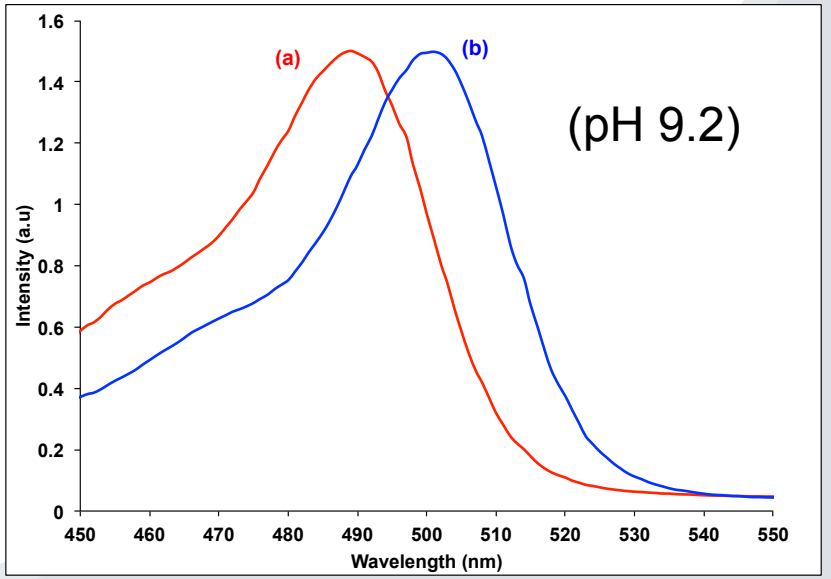
Increase at pH 7 & 9.2 (Dianion)

$FH^2 \xrightleftharpoons{pK_{a2} = 4.3} FH^- \xrightleftharpoons{pK_{a3} = 6.4}$



(a) pH buffer and (b) pH buffer / IL mixture





- Both pH 7 and 9.2 are found to contain the more charged dianion isomer at 490 nm
- Addition of IL leads to stabilization by IL of isomer
- Release is enhanced compared to hydrogel

Conclusions

- $[C_2mIm][EtSO_4]$ ionogel was found to display increased thermal actuation, compared to its hydrogel equivalent
- These enhancements found to contribute to increased delivery of dye used for biomedical applications, Fluorescein.
- Addition of electrostatic interactions between dye and IL increase delivery amount of dye.
- Release shown to be controlled by **pH/IL environment** and **thermal activity**

Acknowledgements

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- Prof. Doug MacFarlane

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Thank you for your attention!