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Soft nanocomposites: nanoparticles to tune gel properties

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Soft nanocomposites: nanoparticles to tune gel properties

Marcelo A. da Silva,[b] Cécile A. Dreiss[a]*

[a] King's College London, Institute of Pharmaceutical Sciences, 150 Stamford Street, SE1 9NH, UK

[b] MNP, School of Physics & Astronomy, University of Leeds, 8.61 E.C. Stoner Building, Leeds, LS2 9JT, UK

*Corresponding author: cecile.dreiss@kcl.ac.uk

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Abstract

The demand for new, soft materials with bespoke physical and biological characteristics and functionality has fuelled the research into nanocomposite hydrogels. 'Soft' nanocomposites – nanoparticles within a hydrated, polymeric gel matrix – offer a simple, yet versatile, platform for the design of materials with specific – and tunable – properties. Indeed, the 'soft' properties of the matrix can be combined with the inherent functionality of the nanoparticles (drug loading, antimicrobial, light refraction…) or give rise to altogether new characteristics (toughness, optical properties, self-healing…), evolved from the synergistic interaction of the polymer chains with the particles. In this review, we report the evolution and achievements of nanocomposite gels, with a focus on mechanisms and structure. The review therefore is structured around the *properties* resulting from the gel/nanoparticles association – rather than a classification based on applications or specific types of polymer or nanoparticles. *How* can nanoparticles tune mechanical, optical, biological properties or impart stimuli-responsiveness to a polymer gel matrix - and how is this behaviour linked to the underlying structure?

Abbreviations: NC (nanocomposite); NP (nanoparticle); poly(ethylene oxide) (PEO); poly(propylene oxide) (PPO); N-isopropyl acrylamide (NIPAAm); poly(*N*-isopropyl acrylamide) (PNIPAAm); polyacrylamide (PAAm); poly(*N*,*N*-dimethylacrylamide) (PDMA); crystalline colloidal arrays (CCA); near-infra red (nIR); Small-angle neutron scattering (SANS)

1. Introduction

This review is about the marriage between two areas of soft matter that both separately have experienced a tremendous growth over the past couple of decades: hydrogels and nanotechnology. Both have been stimulated by the demand for new materials with very specific characteristics for a plethora of applications – as sensors, actuators, for drug delivery, tissue repair etc – as well as the simple fascination for building new structures, functions and properties. While hydrogels have been known and made for a very long time, the more recent surge in hydrogel research has been largely driven by their similarity with bodily tissues (thus offering a favourable environment to grow cells and deliver active compounds) as well as their versatile nature, making them unique candidates to impart responsiveness to specific triggers in so-called 'smart' materials,[1-3] while nanotechnology also encompasses a vast range of rapidly expanding sectors, from microelectronics, catalysis to diagnostic and drug delivery.[4-10] The combination of hydrogels with nanoparticles therefore opens up enormous opportunities for creating new materials and properties, which may simply arise from the added properties of the bulk and the dispersed phase, but also from a synergistic interaction between the two components, leading to totally new characteristics (**Table 1**).

Table 1. Examples of gel matrix-nanoparticles used to obtain gel nanocomposites and their outcomes

Gel nanocomposites				
Aspect	matrix	NP	effect	Ref
Mechanical	PNIPAAm	inorganic Clays	enhanced resilience and extensiveness	23-25, 27, 28
	PAAm	graphene oxide	enhanced resilience and extensiveness	30, 31
	PAAm	Silica	enhanced tensile modulus	32, 33
	PAc-DMAA	Titania	enhanced resilience and extensiveness	34

	PAAm	layered double hydroxide platelets	enhanced tensile modulus	35
	PDMA	cellulose nanocrystals	enhanced tensile modulus	55
Optical	Gelatin	Silver	colour change	11
	Gelatin	Copper	colour change	60
	Inorganic polymers	Sulfides	refractive index manipulation	66-68
	Inorganic polymers	Titanium oxide	refractive index manipulation	58
	Inorganic polymers	laponite	domains formation	78
	Inorganic polymers	crystalline colloidal arrays	colour changes	71, 72, 82, 83
	Inorganic polymers	inverse opal structures	colour changes	74, 85, 86
Biological	Inorganic polymers	Silver-graphene oxide	Antimicrobial, accelerates healing	16
	collagen and gelatin	Silver	antimicrobial	90, 91
	modified hyaluronic acid	calcium phosphate	bone regeneration	92
	hyaluronan	poly(lactide-co-glycolide)	sustained drug delivery	93
	PNIPAAm-AAm-PEGDA	graphene oxide and iron oxide	controlled drug delivery	94
	Inorganic polymers	few-walled carbon nanotubes	localized mechanical actuation	95
Stimuli-responsiveness	PNIPAAm	clay	temperature	24, 26, 103
	double-network PNIPAAm	silica	improved temperature response	97
	PNIPAAm	PNIPAAm	improved temperature response	98
	PNIPAAm	Iron oxide	magnetic response	6, 104
	P(NIPAAm-co-AAm)	gold nanoshells	optical response	105
	PNIPAAm	gold	optical response	107
	PNIPAAm	SW carbon nanotubes	optical response	108
	PNIPAAm	Graphene oxide	optical response	109
	polypeptide PC10P	gold nanorods	optical response	110
	F127	super paramagnetic iron oxide	improved temperature response	113

Apart from a few historic examples,[11] gel nanocomposites are a much younger topic than their elder sibling – and not to be confused with - ‘nanocomposites’, where the matrix is pure polymer. A search on Web of Science database shows that ‘nanocomposite gels’ only attracted a handful of hits pre-2000s, but publications have risen steeply in the last 10 years, reaching ca. 1500 papers and > 30,000 citations p.a. (**Figure 1**). As with nanocomposites (NC), the most traditional purpose of adding nanoparticles (NPs) into a gel matrix (and still a highly productive area of research) has been to improve mechanical properties. Indeed, it has now been successfully demonstrated that the introduction of NPs can open new avenues towards material design, leading to gels which, while containing at least 90% water, can display extraordinary toughness.[5, 12] An area where both hydrogels and nanoparticles, independently, have generated intense research is in biomedicine. As a result, a plethora of NC gels have been proposed to address challenges in tissue engineering and drug delivery,[8, 13-15] for instance for antimicrobial applications (with metal NPs),[16] controlled drug release,[17] regenerative medicine[9] (in particular with ceramic fillers, such as calcium phosphate), carbon-based nanomaterials,[18] and biopolymers as the gel matrix.[8, 19] Increasing activity has also been focused on ‘smart’ materials, and we show in this review that NC gels provide an ideal platform to impart responsiveness to soft materials.

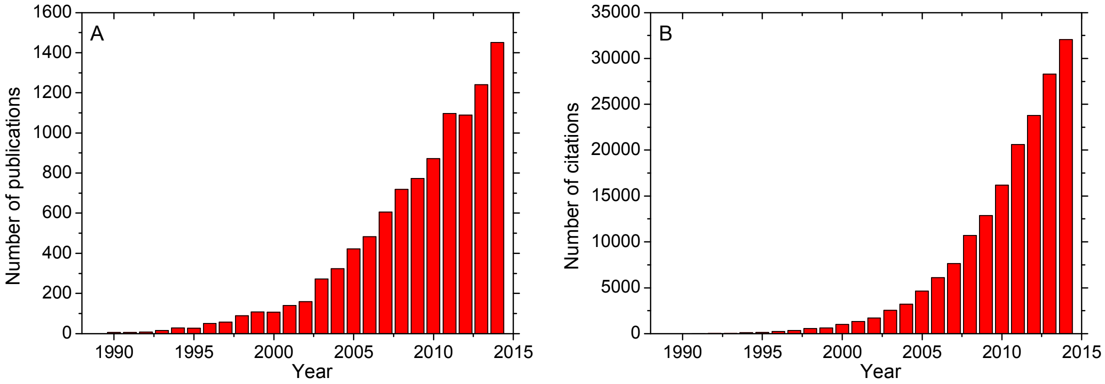

Figure 1. Number of publications (A) and citations (B) containing the search keywords 'nanocomposite' and 'gel' in the last 15 years according to ISI web of science (Sept/2015). It reveals an exponential growth in both number of papers and citations.

This review is structured around *properties* (**Table 1**): how can nanoparticles be used to modulate the characteristics of a gel matrix? Hence our aim is not to give recipes for sophisticated preparation and synthesis protocols, or indeed report on the use of gels as templates for in situ fabrication of NPs, but rather to show how a range of new interesting properties can be built by associating nanoparticles and gels, specifically: mechanical, optical, biological and responsiveness to stimuli. We conclude with a section which summarises some of the – still very few - insights into the structure of NC gels underlying these unique properties.

2. Mechanical properties

The first and still most widespread intention when introducing nanoparticles in a gel matrix is the improvement of mechanical properties. Traditional chemically crosslinked gels have a number of limitations, due to the intrinsically random crosslinking process, resulting in morphological inhomogeneity (opacity) and poor mechanical performance (brittleness, limited elongation, lack of toughness etc). Compared to other types of strategies towards the design of strong hydrogels (such as interpenetrated networks,[20] sliding gels,[21] tetraPEG[22]), hydrogels made by combining polymer chains with inorganic fillers offer a relatively simple answer, added to the possibility of easily tuning properties by varying composition. The discovery of gels with high toughness and extensibility has revived interest in these materials, and led to applying to the field of hydrogels techniques and theories previously developed for rubbers.

Haraguchi[23-26] was the first to propose solving the conundrum of controlling both the density of crosslinks (ν) and inter-crosslinks molecular weight. This was achieved by designing a nanocomposite hydrogel where the polymerisation of *N*-alkylacrylamide derivatives (such as *N*-isopropyl acrylamide, NIPAAm) was initiated from water-swellable inorganic clay platelets (**Figure 2 A**).[23] This novel class of NC hydrogels, with high transparency, results in remarkable properties, in particular toughness, capacity to withstand high levels of deformation, high elongation[23, 27] (ca. 1500%) with near-complete recovery and self-healing (**Figure 2 B,C**).[28] In these materials, neighbouring clay platelets are connected by polymer chains so that they act as high-functionality crosslink points; therefore, clay-clay interparticle distance is equivalent to inter-crosslink distance and thus controlled (**Figure 2 A**).The nature of the grafting points on the clay surface is attributed to a combination of ionic interactions between an anionic end of the polymer chain bonded to SO_3^- and K^+ (from the potassium peroxodisulfate initiator) on the platelets, and coordination interaction between nucleophilic N(H)CO from PNIPAAm and Si from the clay surface. Since the polymer chains are not restricted by the presence of chemical crosslinks, they behave like free, linear polymers, resulting in very high swelling ratios (W_w/W_{dry} = 110)[23] and rapid deswelling with temperature changes. The structure of these gels, at rest and under elongation, obtained from small-angle neutron and X-ray scattering, is discussed further in section 6 (and **Figure 7**), which is dedicated to NC gels architecture.

Following the work of Haraguchi, many other nanocomposite gels have been developed (**Figure 2**), using the same strategy of in-situ polymerisation from layered inorganic nanoparticles, either with clay,[29] graphene oxide,[30, 31] silica,[32, 33] titania[34] or layered double hydroxide platelets (LDH) (**Figure 2 E**),[35] all showing remarkable mechanical toughness, elongation and self-healing properties. The LDH/polyacrylamide (PAAm) hydrogels developed by Hu et al[35] show elongations at break > 4000% at low LDH content (2.3%) with an unexpected yielding phenomenon upon stretching, attributed to an unusual hierarchical porous morphology with interconnected pores; the swelled hydrogels display increased tensibility (> 6236%, beyond measuring range), while yielding disappeared. The enhanced mechanical properties are again attributed to a highly dense network of chains crosslinked by NPs, where the polymer retains a high flexibility and mobility between multi-functional crosslink points (**Figure 2**).

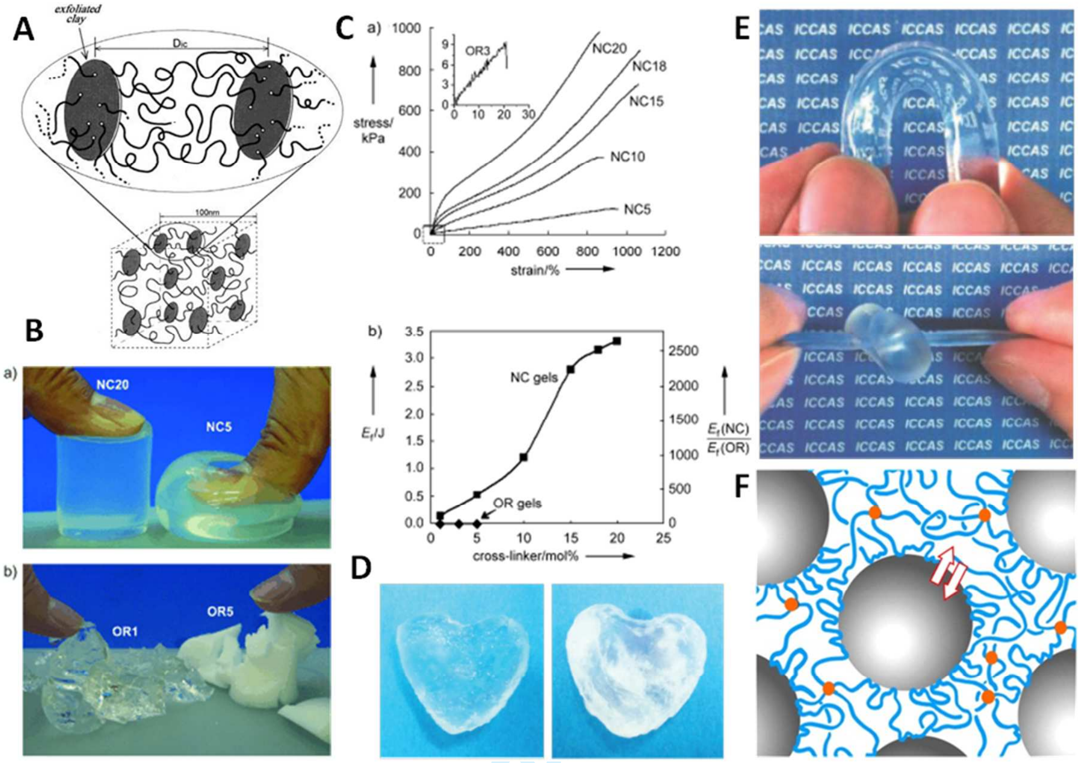

Figure 2. Examples of nanocomposite (NC) gels presenting remarkable mechanical properties. **A.** Organic/inorganic networks developed by Haraguchi, consisting of uniformly dispersed (exfoliated) inorganic clay sheets with PNIPAAm (reprinted with permission from reference 26. Copyright 2002 American Chemical Society). **B.** The resulting NC gels do not rupture under repeated compression by hand, compared to conventional chemically crosslinked gels of PNIPAAm (OR, bottom picture) (reprinted from reference 24 with permission from John Wiley & Sons, Inc.). **C.** a) Tensile stress versus strain curves with increasing amounts of clay (NC5-NC20) show that initial modulus of elasticity (*Ei*) and tensile strength (σ) increase monotonically with increasing clay content. NC20 displays a $\sigma \sim$ 1000 kPa, *Ei* ~ 400 kPa and ca. 1000% elongation at break (inset: magnified view of equivalent OR gel, which is very brittle). b) The fracture energy *Ef* of NC20 is 2650-times higher than OR gels (reprinted from reference 24 with permission from John Wiley & Sons, Inc.). **D.** NC gels based on clay and dendritic binders retain their shape after being moulded into a heart shape, even after full exchange of water with THF (reprinted by permission from Macmillan Publishers Ltd from reference 36, copyright 2010) **E.** NC gels based on layered double hydroxide platelets (LDH)/PAAm also exhibit remarkable mechanical toughness – here shown under torsion or knotting (reprinted from reference 35 with permission from John Wiley & Sons, Inc.). **F.** Physical adsorption can also be used to create strong NC gels, here with covalently crosslinked (orange) PDMA on silica NPs. The chemical network controls

strain recovery through the entropic restoring forces and silica NPs promote transient and recoverable connectivity (reprinted with permission from reference 37. Copyright 2013 American Chemical Society).

Xie et al developed poly(acrylic acid) hydrogels from silica NPs, where the elasticity arises from the entanglements of the polymeric chains and the silica NPs play the role of 'analogous crosslinking points'.[38] The tensile strength and elongation at break of the NC gels could be modulated (up to 313 kPa and 3420%) by varying the mass fraction and/or diameters of the vinyl hybrid silica NPs (VSNP), which transfer stress to the polymeric chains.[39] When a NC gel is subjected to stress, the intermolecular hydrogen bonds dynamically break and recombine to dissipate energy, resulting in a reorganisation of the polymer chains, while the VSNP maintain the gel network and tolerate stress, even when part of the intermolecular hydrogen bonds start to break. After gel network homogenization, the applied stress can be rapidly and uniformly distributed over the entire network with the multifunctional VSNP acting as transfer centres, thus explaining the remarkable mechanical performance.

Recently, the group of Aida[36, 40] has developed NC gels that can be moulded into shape-persistent, free-standing objects, with high mechanical strength and rapidly self-heal (**Figure 2 D**). These gels are either based on mixtures of clay nanosheets, a dendritic molecule based on PEO, and sodium polyacrylate[36] or photocatalytic titania nanosheets with NIPAAm (**Figure 5 A**), which becomes polymerised *in situ* upon exposure to light,[40] leading to modulable hydrogels with photolatently reactive crosslinking points.

The NC gels described above all show superior mechanical properties, however they do require a non-trivial level of preparation, and in particular in-situ polymerisation in the presence of a suspension of inorganic particles. Some effort therefore has also been concentrated in developing NC gels from 'off-the-shelf' materials or simpler materials, in particular through mixing of polymer and particles, where the reinforcement originates from *physical* interactions between the polymer and particles (often clay or silica), where the polymer chains are either non or lightly crosslinked, or possibly exist as a pre-existing physical gel; this approach has been particularly explored by Hourdet, Creton and Marcellan (**Figure 2 F**).[33, 37, 41-45] A striking demonstration of the strength of particle-polymer interactions are 'shake-gels' - solutions of PEO and silica nanoparticles that instantly turn to gels after being shaken or sheared[46] – or the recent demonstration that silica colloid solutions alone can 'glue' gels or even tissues, due to the adsorption of polymer chains on their surfaces, their reorganisation and capacity to dissipate energy under stress.[44] The challenge with NC gels based on the adsorption of polymer chains on NPs lies in the adequate dispersion of the particles to avoid flocculation, in the presence of physical forces which can be very high. Indeed, the mixing protocol is critical and different preparation pathways can lead to different outcomes,[47] while the strength of the interactions can also be used as a parameter to control final structures. NC gels based on physical interactions have been obtained with a wide variety of polymer architectures: block-copolymers,[48-51] polymers grafted with sticky groups,[41] star polymers[52] or single-stranded DNA,[53] and a range of NPs: laponite,[49, 54] silica,[41, 42, 45] cellulose nanocrystals,[55] graphene oxide sheets,[53] metal oxide NPs.[51] In some cases, the interactions, despite being non-covalent, are so strong that the gelation process is virtually irreversible.[41, 53]

Based on the results that the adsorption of polymer on NPs alone can lead to a physical network,[41] Creton et al[45] have developed networks where the polymer chains (poly(*N*,*N*-dimethylacrylamide), PDMA) are slightly crosslinked, thus combining covalent links (polymer-polymer) to physical links (polymer-NP), an adaptation of a strategy already used for rubbers.[56] These hybrid gels show an increase in compression strength and fracture toughness of notched samples by one order of magnitude when compared to unmodified PDMA gels,[45] while the modulus increases by a factor of 6 with 7% particles. They also exhibit no permanent damage after several load–unload compression cycles - a very unique property for such tough hydrogels. The exceptional increase in toughness in the chemically crosslinked gels is attributed mainly to the combined effect of breakable silica–polymer bonds and a wide distribution of elastic chain lengths.[45] The toughening mechanisms, similarly to the double-networks developed by Gong,[20] are attributed to a combination of stress redistribution (due to the high functionality of the NP-crosslinks) and the existence of dissipative mechanisms slowing down crack tip propagation (in this case, the break-up/readsorption of PDMA chains to the silica, which are weaker links than the polymer-polymer bonds). In systems where the polymer chains do not interact with the silica particles, such as PAAm/silica hydrogel hybrids, no large increase in strength or modulus is observed, the particles acting as inert fillers.[57]

3. Optical properties

The possibility of exploiting hydrogel/nanoparticle interactions to modulate gels optical properties was reported by Kirchner and Zsigmondy over a hundred years ago.[11] They discovered that the colour of gelatin hydrogels with embedded gold nanoparticles would depend on the gel hydration level; the colour change was ascribed to changes in interparticle distance as the hydrogel network expanded and contracted due the incorporation or loss of water, showing a very early example of stimuli-induced optical change in a nanocomposite gel.

A first approach to modify the optical properties of a gel consists in randomly dispersing isotropic NPs within the matrix. One of the most intuitive changes resulting from changes in interparticle spacing is colour - or the absorption of visible light. Several examples can be found in the literature of the modulation of UV-visible absorption[58-62] or photoluminescence[63-65] of bulk gel optical properties induced by the incorporation of nanoparticles. For instance, Jeevika and Shankaran developed a colorimetric Cu^{2+}-sensor using silver NPs-loaded gelatin hydrogels.[60] The gelatin matrix offers a stable scaffold to prevent the aggregation of Ag NPs. The sensing mechanism is based on the complexation of Cu^{2+} and the Ag NPs, leading to the agglomeration of the NPs and hence a colour change. A different approach was developed by Qing and co-workers:[61] in this case, functionalized agarose gels were used as templates for the in situ formation of Cu NPs from external Cu^{2+} diffusing into the gel matrix, which, in turn, changed the optical properties of the gel, in this case imparting fluorescence. The group of Caseri reported several studies where they combined polymeric matrices and inorganic nanoparticles (PbS,[66, 67], FeS [68] and TiO_2 [58]) in order to increase the range of refractive indices that could normally be obtained using the polymer gel alone. For a more in-depth discussion of these systems, the reviews of Caseri[4, 69, 70] are a good starting point.

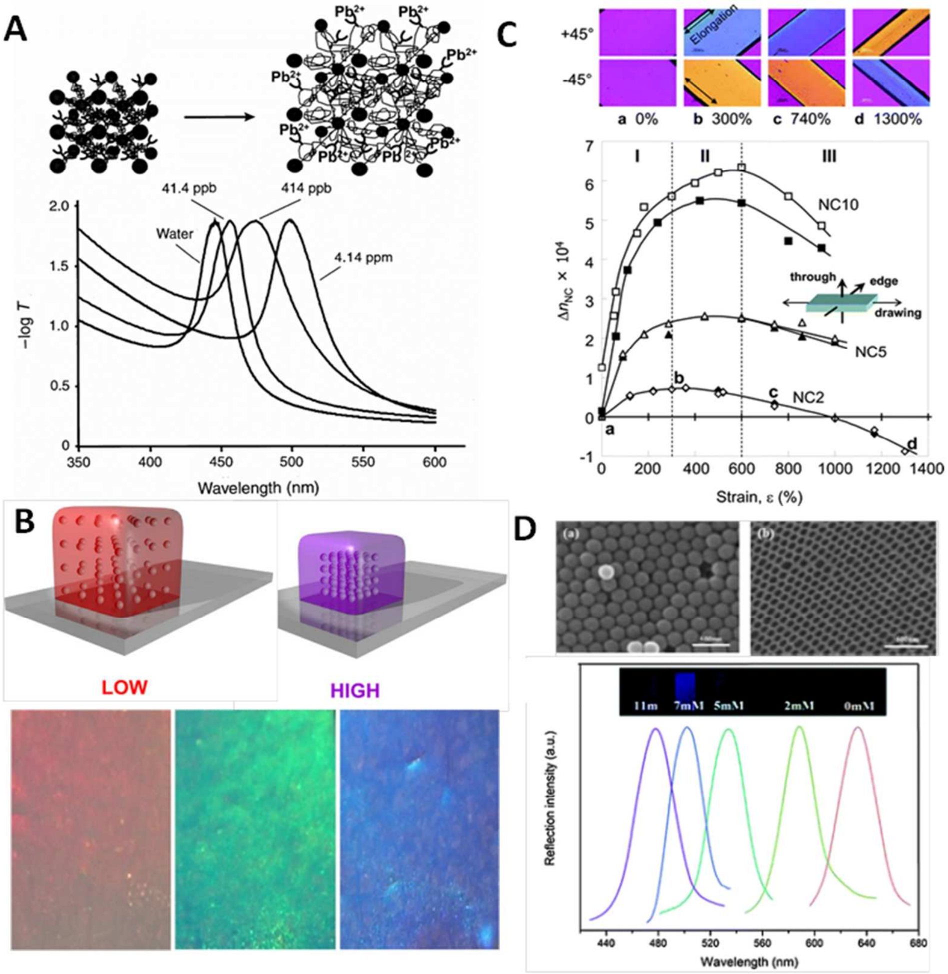

Figure 3. Examples of approaches to impart optical properties to NC gels. **A.** A chemical sensor, capable of detecting different analytes through colour change, was developed based on a crystalline colloidal array of polystyrene (PS) NPs that diffracts light at a wavelength that is determined by lattice spacing. In this example, the visible extinction spectra are shown at various concentrations of Pb(CH_3COO) (reprinted by permission from Macmillan Publishers Ltd from reference 71, copyright 1997). **B.** Based on the same principle, photonic crystals made of PS NPs embedded in a PAAm gel were used as sensors of the ionic strength. The periodical arrangement of NPs reflects light, and ions permeating through the gel matrix modify the lattice structure, affecting the wavelength of reflected light. As a result, films of the gel are red when placed in pure water, turn green or purple in the presence of 1 mM or 100 mM electrolyte, respectively, and these can be recorded with a digital camera (reprinted with permission from reference 72. Copyright 2013 American Chemical Society). **C.** The anisotropy of clay NP can be used to impart birefringence - dependent on the amount of clay (NC2-NC10) - when the gel matrix is deformed uniaxially. Photo images show polarized-light micrographs of stretched gels under crossed polarizers (reprinted from

reference 73 with permission from the Royal Society of Chemistry). **D.** Hydrogel films with an inverse opal structure were prepared from SiO_2 colloidal arrays (a) used as a sacrificed template (b) within a gel based on PAAm. The gel responds to varying concentrations of glucose by an increasing blue-shift of the reflection peak (reprinted from reference 74 with permission from the Royal Society of Chemistry).

Changes in optical properties arise from the ability of the gel matrix to support and spatially stabilize NPs, locking the particles in place, in distributions which depart from an isotropic arrangement, thus imparting new properties to the nanocomposites, such as birefringence[75] or Bragg diffraction (**Figure 3 A**).[71] For instance, starting from an isotropic distribution of the nanoparticles, mechanical deformation of the gel can induce properties not present in the quiescent state, e.g., strain-induced fluorescence,[76] or lead to anisotropic properties due to strain-induced organization, for instance, infra-red (IR) dichroism[77] or optical anisotropy (**Figure 3 C**).[73]

A clever example of using a gel matrix to create domain segregation with distinctive optical properties was shown by Raghavan and co-workers,[78] who developed a hybrid gel made of two components, containing the same monomer but different crosslinkers. Gel 1 contained a chemical crosslinker while gel 2 contained the same monomer, but was physically crosslinked by laponite NPs, inspired from the gels discovered by Haraguchi[5, 23] described in section 1. The presence of the NPs imparts different properties to the second gel component, such as selectively adsorbing a cationic dye, or birefringence with respect to gel 1, which allowed the researchers to embed a hidden pattern (or 'message') of gel 2 into gel 1, which only becomes visible under cross-polarisers.

Microfluidics have also been used as a tool to generate non-isotropic distributions of NPs in gel matrices. Floyd-Smith and co-workers demonstrated how microfluidic devices could be used to create non-uniform nanoparticle dispersions in pre-polymer solutions that are preserved upon gelation,[79] and how this could then be exploited to modulate optical properties, for instance, to create an optical index gradient in polymeric gels loaded with Ti nanoparticles.[80]

Another example of patterned nanoparticles distribution used to impart optical properties of gel nanocomposites arises from the combination of crystalline colloidal arrays (CCA) and polymeric matrices. CCA are self-assembling colloidal particles that form spatially ordered lattices, which show intense Bragg diffraction based on the lattice spacing.[81] It is possible, by embedding the CCA within a gel matrix, to create a nanocomposite with CCA optical properties but also sensitive to changes in the polymeric matrix (**Figure 3 A**).[71] Differently from embedded gold or silver nanoparticles - where the colour changes arise from changes in Plasmon resonance - the optical properties of CCA depend on the lattice spacing, yet, in both cases, it is a change of volume in the polymeric matrix that triggers the optical response. Those systems are particularly useful for diagnostic application, to sense specific analytes, ionic strength, pH, among other properties (**Figure 3 B**).[71, 72, 82, 83] Another approach is to build so-called ‘inverse opal structures’, by preparing hydrogels with embedded CCA and then removing the nanoparticles, thus, creating an array of mesopores in the polymeric matrix.[84] Inverse opal hydrogels offer the advantage of improving the transparency of the hydrogels, at the expense of the cost of removing the nanoparticles. Several examples of tunable inverse opal hydrogels have been described in the literature (**Figure 3 D**).[74, 85, 86]

4. Biological response

The previous two sections were focused predominantly on the modulation of *physical* properties that can be induced by nanoparticles. However, this is not the only possible outcome of combining NPs and gels: indeed, the biological behaviour of nanocomposites can also be selectively tuned by combining bulk hydrogels and NPs (**Figure 4**).[2, 8, 13-15, 18] The simplest way to achieve this is by combining materials that already have inherent biological properties into a nanocomposite with desirable physical properties. For instance, the antimicrobial properties of metal NPs is well established.[87] Therefore, incorporating metal NPs into bulk hydrogels is an easy route towards gels with antimicrobial properties.[88] For example, Yang and co-workers[16] produced Ag–graphene hydrogels from Ag NPs, graphene oxide and acrylic acid crosslinked by N,N′-methylene bisacrylamide. They demonstrated *in vivo* the hydrogel nanocomposite suitability as skin graft replacement in mice, as well as its antibacterial properties. By combining both polymers of biological origin ('biopolymers') and bio-active NPs, it is possible to obtain so called 'bionanocomposites', which have been reviewed in detail elsewhere.[6, 8, 10, 18, 89] For example, both collagen[90] and gelatin (denatured collagen)[91] have been combined to Ag NP, with the objective of exploiting gelatin intrinsic biological properties while also imparting antimicrobial activity (**Figure 4 A**). Another layer of complexity can be added to obtain 'smart' bionanocomposites (see also section 5). Leeuwenburgh and co-workers have produced self-healing hydrogels by combining modified hyaluronic acid and calcium phosphate NPs (**Figure 4 B**).[92] The resultant nanocomposite is particularly suited to bone regeneration as the hyaluronan derivative provides a suitable scaffold for cell growth, the calcium phosphate NPs induce mineralization, while the combination of both in a nanocomposite shows improved mechanical behaviour compared to the blank hyaluronic acid gel, and the self-healing ability helps preserve the nanocomposite under stressful conditions.[92] A large range of design options for bionanocomposites is available, and examples can be found elsewhere.[1, 2, 6, 9, 13, 15, 18]

Nanocomposite hydrogels are particularly well-suited for drug delivery, as drugs can be solubilised into polymeric nanoparticles, which are themselves embedded into the gel matrix, resulting in sustained release.[2, 6, 13] Shoichet and co-workers have demonstrated the *in vivo* applicability of hyaluronan-based nanocomposites loaded with poly(lactide-co-glycolide) NPs for intrathecal delivery after spinal cord injury in mice.[93] However, passive release is not the only biological response that can be obtained. Stimuli responsive nanocomposites are particularly useful for targeted drug delivery;[17] these are covered in the next section. A recent example of how stimuli responsive NC gels can provide unique solutions for engineered drug delivery is given by the 'self-folding nanorobots' developed by Sakar and co-workers, designed for navigation through body orifices and able to release drug on demand (**Figure 4 C**).[94] The team of researchers produced a shape-responsive NC gel based on bilayers of poly(ethylene glycol) diacrylate (PEGDA) and PNIPAAm-AAm-PEGDA loaded with either graphene oxide (responsive to near-IR light) or iron oxide NPs (magnetically activated). The shape of the resulting NC gels can be changed on demand and the efficiency of the release of the loaded drugs can, therefore, be modulated.[94]

The object of stimuli-responsive NCs in the biomedical field is not limited to drug delivery. Lu and Zeng produced a nIR stimuli-responsive NC gel based on PNIPAAm loaded with few-walled carbon nanotubes, further coated with a top layer of collagen-functionalized poly(acrylic acid)-co-PNIPAAm in order to improve cell adhesion. This

NC allowed very precise local mechanical stimuli induced by nIR exposure. The mechanical forces produced can be used to actuate cells (**Figure 4 D**).[95]

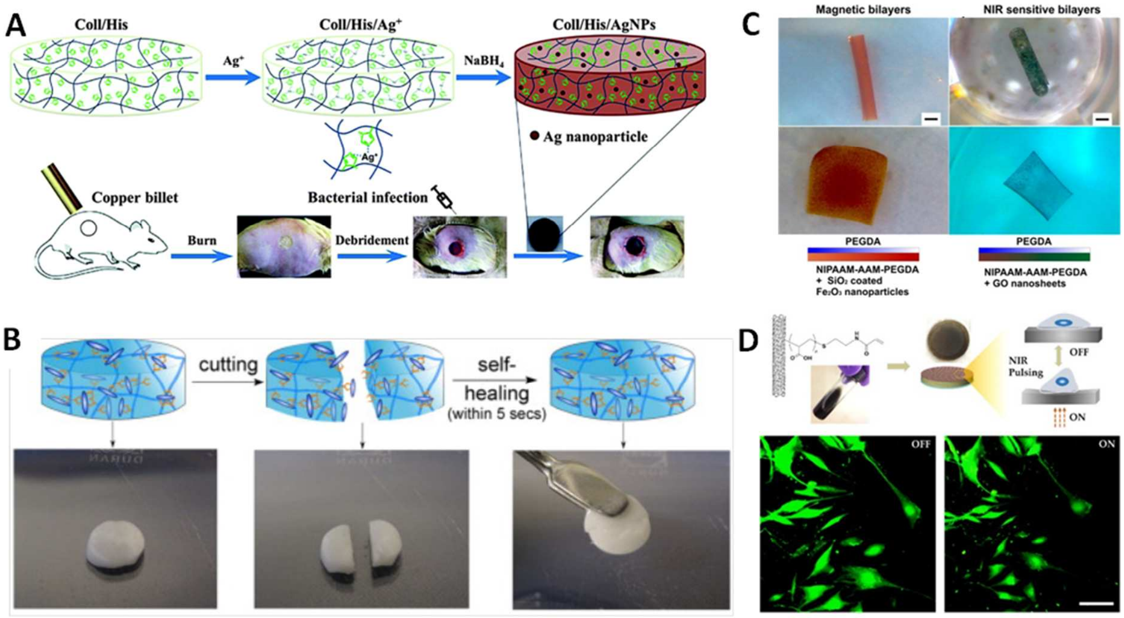

Figure 4. Applications of NC hydrogels to induce a biological response. **A.** Histidine (His) covalently crosslinked to collagen (Coll) scaffolds were employed as a template to chelate silver ions which were reduced in situ to form Ag NPs-hybridized Coll scaffolds. These hybrid materials exhibited enhanced mechanical properties, biocompatibility and antibacterial properties compared to the naked Coll substrate, when used in the regeneration of infected full-thickness burn skin rats (reprinted from reference 90 with permission from the Royal Society of Chemistry) **B.** The synergistic combination of calcium phosphate NPs with a biocompatible matrix of bisphonate-functionalised hyaluronic acid provides an injectable, yet robust, biodegradable material, displaying self-healing as well as adhesiveness to mineral surfaces. (reprinted from reference 92 ,copyright 2014, with permission from Elsevier) **C.** Self-folding hydrogel bilayers (or 'microrobots') that can switch shape - here shown in tubular and rectangular configurations - contain either GO or silica-coated superparamagnetic iron oxide NPs, which provide either nIR responsiveness or magnetic actuation for triggered and targeted drug release, respectively. Scale bar is 500 μm (reprinted with permission from reference 94. Copyright 2015 American Chemical Society). **D.** A NC gel that can deliver spatially and temporally defined mechanical forces to cells was designed by combining uniformly distributed carbon nanotubes to thermally responsive PNIPAAm. nIR stimulation induces changes in strain that can be transmitted remotely to cells and thus offer the

potential to accurately design force sequences for tissue engineering applications (reprinted with permission from reference 95. Copyright 2014 American Chemical Society).

5. Responsiveness to stimuli

In the field of soft matter, so-called ‘smart’ materials have become - over the last decade or so - the object of increasingly intense research. ‘Smart’ materials are materials that alter their function, properties, shape, etc by responding to specific stimuli.[1, 96-99] Polymer gels are natural candidates to act as stimuli-responsive materials, since polymer chains can be designed to react to environmental changes, thus altering their solubility, conformation, degree of crosslinking etc, and consequently altering the properties of the gel matrix.[1, 2, 18, 40, 100, 101] The addition of nanoparticles provides a handle to either impart responsiveness to a ‘blank’ substrate or alter functionality when embedded in an already ‘responsive’ gel.[1, 5] This switchability of stimuli-responsive NC makes them a particular focus of research for controlled drug delivery applications.[2, 17]

Several strategies have been proposed to impart responsiveness to gel nanocomposites (**Figure 5**). The most obvious approach is to incorporate nanoparticles to improve the applicability of an inherently responsive hydrogel. For this purpose, PNIPAAm and other alkyl-substituted acrylamides have been widely studied, as they undergo a natural thermally-reversible volume transition.[1, 102] However, on their own, the mechanical properties of chemically crosslinked PNIPAAm hydrogels are poor, displaying brittleness and low elasticity.[98] In order to improve their properties, several groups have investigated PNIPAAm gels with embedded NPs (**Figure 5 A**).[24, 26, 33, 40, 45] Haraguchi[7, 24, 26, 103] and co-workers have produced super-tough alkyl-substituted acrylamide hydrogels embedded with clay

NPs (section 2, **Figure 2 A,B,C**). As already discussed in section 2, the PNIPAAm/clay nanocomposites showed good transparency, higher malleability and ductility than the blank hydrogel, whilst preserving the thermal-responsiveness of the polymer. In a similar vein, Chu and co-workers managed to improve mechanical performance by crosslinking PNIPAAm in the presence of PNIPAAm-based nanogels, thus combining thermo-responsive bulk gel and nanogels in a single system, which resulted in an improvement in response time.[98] One of the most interesting aspects of gel nanocomposites is the potential to combine different elements in order to obtain synergistic improvements. The work of Grunlan and co-workers[97] provides a good example; they obtained a double-network (DN) PNIPAAm hydrogel, where both interpenetrating networks were composed of PNIPAAm with different crosslink densities, with embedded silica NPs. The manipulation of both crosslink densities and NP concentration opened access to a large range of physical properties, as well as improving the swelling/deswelling kinetics, while preserving the phase volume transition of PNIPAAm.

Another approach to stimuli responsive gel NCs consists in using nanoparticles to improve the response, either by increasing its magnitude or coupling it with a response that is easier to detect. For instance, volume changes are more difficult to measure than colorimetric changes; therefore, by coupling a visual change to a volumetric one, the whole process is more readily detected or quantified. In the optical section, a typical example was presented that involved polymers embedded with Au or Ag NPs, which colour depends on the interparticle distance: as a result, gel swelling and deswelling provides an easy handle towards colour changes.[11, 60]

A more sophisticated strategy is where the NPs themselves are the source of the stimuli; this is generally obtained by converting an external stimulus to which the polymer bulk is insensitive (e.g. light) into a stimulus to which the matrix will respond (e.g. heat). Hilt and co-workers have developed PNIPAAm gels embedded with coated Fe_2O_3 nanoparticles (**Figure 5 B**).[6, 104] The iron oxide NPs could be stimulated by an alternating magnetic field (AMF), which caused them to vibrate in place and locally generate heat, which, in turn, was able to trigger the expected phase volume transition of the PNIPAAm bulk matrix; this could be used to induce the controlled unloading of hydrophobic drugs encapsulated in the gel matrix.[104] West and co-workers have developed a P(NIPAAm-co-AAm) hydrogel with gold nanoshell NPs for specific drug delivery applications. The gold nanoshells are nIR absorbers, therefore impacting the polymer phase transition, and enabling optically triggered drug release.[105] Similarly, Okano and co-workers[106] have used copolymerization with hydrophobic alkyl methacrylate or hydrophilic acrylamides to either lower or increase the LCST of the final copolymer. Au NPs efficiently convert absorbed light to heat, thus generating local hot spots which in turn triggered P(NIPAAm-co-AAm) transition. A curious example of a response triggered by NPs is provided by the work of Hayward and his group:[107] by using pattern distribution of light-absorbing gold NPs in PNIPAAm hydrogel sheets, they were able to induce local buckling of the sheets and reversibly change the 3D shape of the sheets (**Figure 5 C**). With a similar approach, Javey and co-workers[108] produced light-activated actuators of PNIPAAm hydrogels loaded with single-walled carbon nanotubes (SWNT) combined with low density polyethylene (LDPE). The SWNT can absorb nIR radiation and dissipate heat, which, in turn, can be used to trigger the PNIPAAm volume change by nIR exposure. By copolymerizing strips of PNIPAAm/SWNT on sheets of LDPE, they were able to build large foldable structures. Graphene oxide (GO) has also been shown to be a good light-sensitive trigger for PNIPAAm volume transition. Jiang and co-workers[109] produced light-responsive PNIPAAm hydrogels loaded with functionalized GO NPs. The NC showed a good light-triggered volume response, as well as a larger swelling degree than blank PNIPAAm gels; they also demonstrated that the NCs were suitable as microvalves for microfluidic devices.

While PNIPAAm and other alkyl-substituted acrylamide hydrogels are clearly dominating the field of stimuli-responsive NC gels, other responsive polymers have been investigated as gel matrices. Burdick and co-workers[110] produced light-sensitive NCs of polypeptides with embedded gold nanorods (**Figure 5 D**). The polypeptide used, PC10P, forms a physical gel at room temperature and melts at ca. 60°C. Under nIR exposure, PC10P physical gels loaded with Au nanorods melt at room temperature, due to heat dissipation from the nanorods. Another classic example of thermally responsive polymer is the family of Pluronics, triblock copolymers of PEO-PPO-PEO, which undergo a sol-gel transition in aqueous solution and form micelles into which drugs can be solubilised.[111, 112] Muhammed and co-workers[113] prepared injectable F127 Pluronic hydrogels loaded with super paramagnetic iron oxide NPs. When submitted to a magnetic field, the NPs re-orientate themselves and cluster together, causing a shrinkage of the bulk gel. This volume contraction accelerated the release of drugs solubilised in the polymer micellar core.

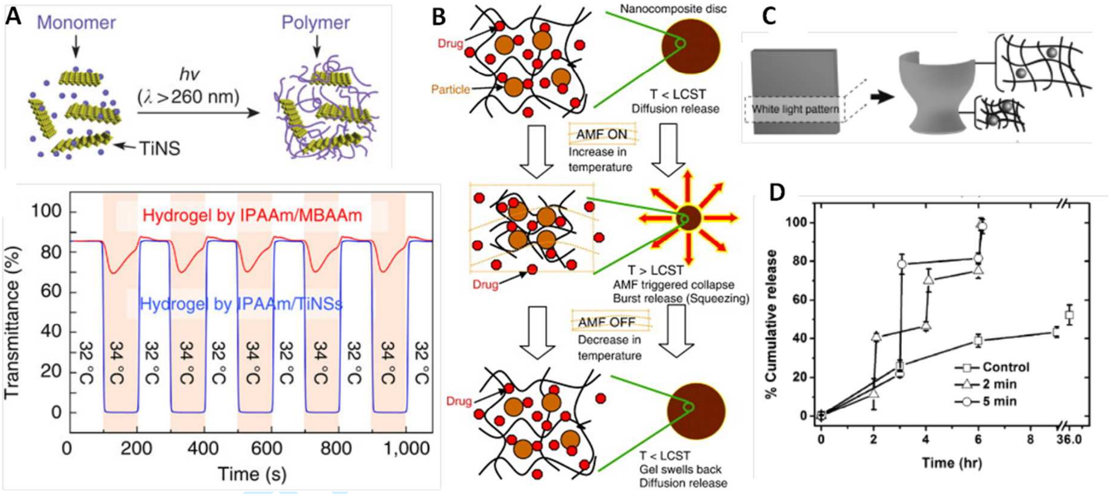

Figure 5. Responsive NC gels. **A.** Schematic structure of titania nanosheet (TiNS)-mediated photoinduced hydrogelation of PNIPAAm (λ>260 nm at 25°C for 20 min) and resulting improved temperature-modulated optical transmittance (300 nm) of a 50 μm hydrogel film (blue) compared to a reference hydrogel with no TiNS (red) (reprinted by permission from Macmillan Publishers Ltd from reference 40, copyright 2013). **B.** Effect of ON-OFF cycles of alternating magnetic field (AMF) on NC gels of PNIPAAm comprising superparamagnetic Fe_3O_4 NPs. AMF triggers uniform heating leading to collapse and resultant burst release of the drug (reprinted from reference 104, copyright 2008, with permission from Elsevier). **C.** Photothermally reprogrammable gels that exploit the thermal deswelling of PNIPAAm networks containing Au NPs, which generate heat when irradiated by light through the SPR effect (reprinted from reference 107 with permission from John Wiley & Sons, Inc.). **D.** Based also on the local heating generated by gold nanorods, a polypeptide gel NC enables step-wise release of FITC-dextran triggered by nIR exposure, compared to a typical diffusion-mediated release when trigger is OFF (reprinted from reference 110 with permission from John Wiley & Sons, Inc.).

6. Structure

While there has clearly been an explosion of new designs for NC gels, either for the creation of transparent, ultra-tough, super extensible gels, or to impart responsiveness, mainly with biomedical applications in mind, the understanding of the intricate structural arrangements that lead to these superior properties is still lagging behind. Small-angle X-ray and neutron scattering (SAS) are unique techniques that can probe gel morphology[114, 115] and nanoparticle arrangement, and probably the only tools to achieve nanoscale level information on nanocomposite structure.[116-119] This final section summarises information obtained on selected NC gels, some which have been described above. There are clear difficulties with obtaining structural information, the most obvious one being to deconvolute contributions arising from the particles and the gel matrix.

Most of the structural work on NC gels has been published on thermally-responsive block-copolymers,[48, 49, 51, 117, 118] such as Pluronics, whose gelation occurs through the arrangement of micelles into a macro-lattice.[120] SANS can therefore be used to assess whether the presence of NPs disrupts this arrangement (even if only qualitatively), and - if sufficient contrast is available between the polymer and the NPs - provide some insight into the localisation of the NPs within this highly ordered structure.

Ogata and co-workers[118] have developed organic–inorganic nanocomposite gels as an in situ gelling biomaterial for injectable accommodative intraocular lens, based on a hydrophobically modified PEG containing hydrophilized silica. SANS was used to ascertain that the incorporation of the NPs (2-5 nm) did not disrupt the micellar ordered structure at the origin of the gel phase.[118] Instead, when Fe_3O_4 particles were introduced into a closed-packed network of F108 Pluronic micelles (25%),[51] it was found that the NPs (of size comparable to the micelles) disrupted the macrocrystalline order, resulting in the clustering of the nanoparticles.[48, 51]

Raghavan and co-workers have used SANS to help elucidate the mechanism of gelation in mixtures of Pluronic and laponite, either thermally induced[49] or by lowering the pH, through the UV-triggered activation of a photoacid generator,[117] at polymer concentrations well below the close-packing of micelles (**Figure 6**). SANS data show that at either low temperature or high pH the laponite particles are dispersed in solution, stabilised by Pluronic chains adsorbed through its hydrophobic segments. Upon increasing the temperature or reducing the pH, the polymer desorbs and form micelles in solution, which drive the clustering of laponite into a volume-filling network[49] or house-of-card structure (**Figure 6**).[117]

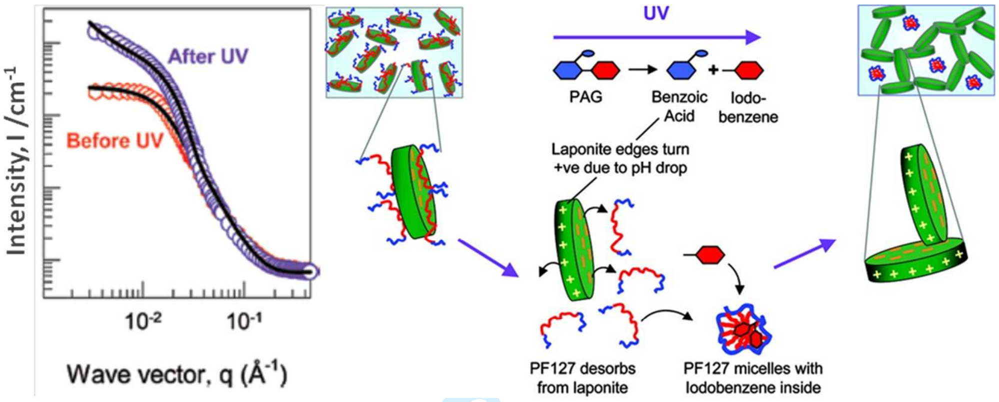

Figure 6. Scheme representing the photogelling mechanism in mixtures of F127 Pluronic, laponite and a photoacid generator (PAG). Initially, laponite NPs are stabilised by the polymer, with the hydrophobic PPO (red) segments adsorbed on their surface and the SANS data (left) can be fitted by a disk-shape with an adsorbed polymer shell. Upon UV irradiation of the PAG, the pH drops, laponite edges become positively charged, F127 desorbs and forms micelles in solution while interactions between laponite NPs result in a house-of-cards structure, which appears as an increase in the scattered intensity at low-q, corresponding to a fractal dimension of 2 (reprinted with permission from reference 117. Copyright 2009 American Chemical Society).

Still in mixtures of laponite with another Pluronic (P123), but over a much higher concentration regime (50%), SAXS data have been used to show that the addition of laponite drives a transition from a hexagonal phase of rodlike micelles at low temperature to a lamellar phase at high temperature.[54]

SANS offer the advantage over X-rays (SAXS) to contrast-match specific parts of the system by selective deuteration, or by simple tuning of solvent composition (H_2O/D_2O mixture). This is particularly applicable where the NPs are inorganic and thus have a neutron scattering length density quite different from the polymer, thus their organisation within the gel matrix can be visualised with the polymer made ‘invisible’. Marcellan and co-workers[37] thus were able to ascertain that silica NPs – acting as multifunctional crosslinks - were well dispersed in a PDMA matrix - even after cyclic mechanical loading. Another benefit of SAS techniques is the possibility to visualise structural changes while stretching a material. With the system just mentioned,[37] it was possible to show that under an applied strain the silica particles arranged themselves perpendicular to the stretching direction, but the isotropic pattern was recovered when at rest.

A large amount of structural work was performed by the group of Shibayama[22, 119, 121-125] to elucidate the origin of the exceptional mechanical properties of the clay/polymer nanocomposite gels developed by Haraguchi and described in section 2[5, 23, 28, 121] (**Figure 7 A,B**), using a combination of SANS, SAXS and light scattering. With SANS and contrast variation on stretched NC gels (**Figure 7**), an abnormal-butterfly pattern was observed, which is commonly seen in chemical gels under strain and assigned to inhomogeneities, but was here assigned to the orientation of the clay platelets with their surface parallel to the stretching direction (**Figure 7 C,D**).[122] These structural studies thus made it possible to attribute the remarkable extensibility and strength at break of these pioneering NC gels to the following factors: a very large inter-crosslink distance (which is set by the inter-platelet distance); the length of the topological chains $<R^2>^{1/2}$, where R is the end-to-end distance in PNIPAAm chains between crosslinks; and, finally, the number of ‘effective’ crosslinks’ - much larger than in conventional gels -, because most polymer chains are anchored to clay platelets and therefore elastically active (**Figure 7**).

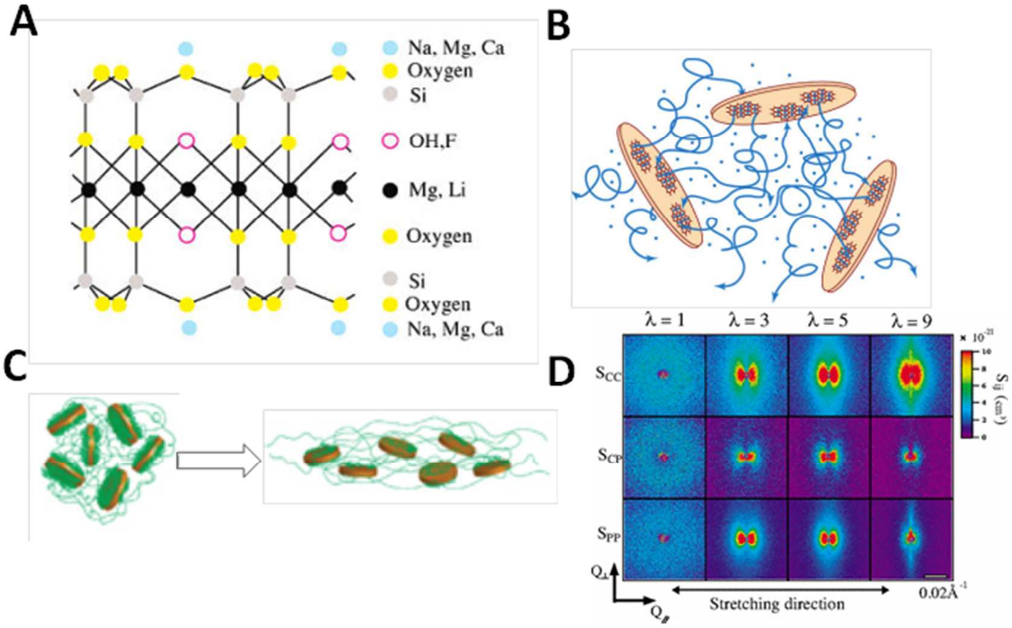

Figure 7. Schematic representing the structure of the clay/PNIPAAm gels. **A.** Chemical structure of the clay platelets showing the various types of atoms. The oxygen atoms may form hydrogen bonds with the carbonyl oxygen of NIPAAm monomer, binding them to the surface, (reprinted with permission from reference 122. Copyright 2005 American Chemical Society) **B.** hence PNIPAAm is polymerised from the surface thus creating bridging chains between the platelets. (reprinted with permission from reference 122. Copyright 2005 American Chemical Society) **C.** Upon stretching, the platelets orient with their surface parallel to the strain direction – as established by (reprinted by permission from Macmillan Publishers Ltd from reference 126. Copyright 2011) **D.** the two-dimensional SANS partial structure factors of the NC gels obtained by systematic contrast variation (S_{CC}: clay scattering; S_{CP}: clay polymer cross term; S_{PP}: polymer scattering) at varying stretching ratios λ. The remarkable mechanical properties of these NC gels are thus assigned to the length of the chains between the platelets, which act as multifunctional crosslinks, and the high density of elastically active polymer chains (reprinted with permission from reference 125. Copyright 2009 American Chemical Society).

7. Conclusions

This review has demonstrated the huge variety of structures, designs, properties that can arise from the combination of nanoparticles with hydrogels. Nanocomposite gels provide a relatively simple and flexible concept to generate specific properties and modulate them by varying composition, often circumventing the need of complex chemistry. It is noticeable that considerable effort has been targeted towards biomedical materials, where the 'softness' and hydrated environment offered by hydrogels provide a mimic of natural tissues, which, in turn, can be modulated by nanoparticles for improved robustness, elasticity, biocompatibility, or to add features such as antimicrobial, self-healing, controlled release, etc. A very strong focus of soft matter research has been in the design of 'smart' materials: materials which alter their behaviour in response to a trigger. Evidently, nanocomposite gels offer an ideal platform to do just this: synergistic interactions between the gel matrix and the nanoparticle dispersion offer a formidable handle to impart responsiveness to environmental factors such as temperature, pH, light, strain – as demonstrated in this review. As a result, a whole new generation of soft nanocomposites promises to find useful applications as tools for diagnostic and as scaffold biomaterials for 3D cell culture, which can guide cell behaviour through a variety of physical cues. Overall, the trend is towards increasingly multi-functional, complex materials which can modulate their behaviour as a response to several, rather than one, stimuli. It is however important to emphasize that the combination of simple materials alone can lead to very interesting outcomes, as demonstrated recently with silica sols acting as strong adhesives for gels and biological tissues,[44] which is simply due to the dynamic adsorption of multiple polymer chains on the nanoparticles surface. In addition, in this race towards ever-more sophisticated, cutting-edge materials, one should not forget the necessity of fundamental mechanistic and structural understanding.

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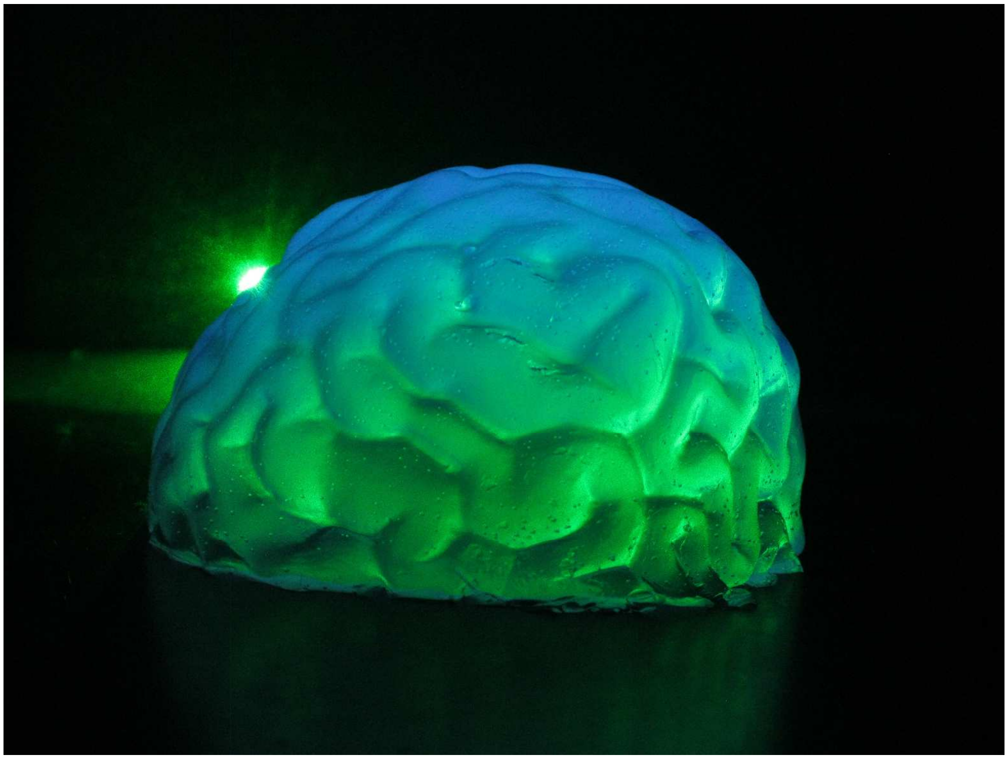
‘Soft’ nanocomposites: nanoparticles to tune gel properties

Marcelo A. da Silva, Cécile A. Dreiss*

Gel nanocomposites offer a simple yet powerful concept towards material design, with the combination of nanoparticles functionality (here: luminescence) with the ‘soft’ properties of a gel matrix (here: shape retention and mechanical support).



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Soft nanocomposites: nanoparticles to tune gel properties

Authors' biographies

Cécile A. Dreiss obtained her PhD in Chemical Engineering from Imperial College London, followed by a postdoc in colloid science at the University of Bristol. Now based at King's College London, her research focuses on understanding and exploiting self-assembly in soft matter, spanning colloidal, polymeric and biological systems, by establishing relationships between properties on the macro-scale (such as rheology) and the organization on the nanoscale, using mainly techniques such as small-angle neutron scattering.

Marcelo A. da Silva obtained his PhD in physical-chemistry from the State University of São Paulo, Brazil, with a project on solvent-induced protein gelation. After his PhD, he worked as a postdoctoral researcher on surfactants as drag-reduction additives at the State University of Campinas. He then took up a postdoctoral position at King's College London working on biopolymer gels for tissue engineering applications, and is currently a research associate at the University of Leeds studying hydrogels of polyproteins.