“Smart Nanoparticles”
Stimuli Sensitive Hydrogel Particles

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Hydrogels

Crosslinked water soluble polymers – a physically restricted, dimensionally-stable, polymer solution
Responsive Hydrogels

Polymeric gels can be designed to undergo environmentally-initiated phase separation events (volume phase transition).

Change in local environment
- pH, Photons, Temperature, Ionic Strength, Electric Fields, Pressure, [Analyte]

Collapsed state
- Chain-chain interactions dominate

Swollen state
- Solvent-chain interactions dominate
Typical Responsive Gel

\textit{poly}(N\text{-isopropylacrylamide}) (pNIPAm) – Thermoresponsive Gel

Swollen/Hydrophilic \quad \rightarrow \quad \text{Collapsed/Hydrophobic}

31 \, ^\circ \text{C}
Phase separation of poly-$N$-isopropylacrylamide occurs via an entropically-driven coil to globule transition.

Xiaohui Wang; Xingping Qiu; Chi Wu
Responsive Hydrogels

Volume phase transitions in simple gels can be modeled as a crosslinked polymer in a vdw fluid.

A change in osmotic pressure on either side of the interface induces a solvation/desolvation response

\[
\frac{\pi}{k_B T} = \frac{\pi_{el} + \pi_M}{k_B T} = \frac{n_0}{N_x} \left[\frac{1}{2} \left(\frac{n}{n_0}\right) - \left(\frac{n}{n_0}\right)^{\frac{1}{3}}\right] - \frac{1}{v} \left[\ln(1 - nv) + nv + \chi n^2 v^2\right]
\]
“Smart” Polymers


pNIPAm Microgel/Nanogel Synthesis

Controllable Parameters:
- particle porosity/solvent content (crosslinker identity/conc.)
- size – 50 nm to 5 μm (initiator, surfactant conc.)
- phase transition magnitude
- volume phase transition shape

Precipitation Polymerization

Oligoradical → Precursor Particle → Growing Particle → Microgel

70 °C >4 hrs.

SDS

APS
Hydrogel Design

Particle design via copolymerization

- pH sensitive/polyelectrolytes
- Thermosensitive

Crosslinker length
Hydrogel Design: Responsivity/Sensitivity

Electric Field

Light

Metal Ions
Hydrogel Particle Characteristics

Infinite Spherical Network

High water content (90-99% v/v)
a microgel is effectively all surface area

Highly Monodisperse
Volume Phase Transitions

Dynamic Light Scattering (Photon Correlation Spectroscopy)

2 mol% crosslinked pNIPAm in water
Multiresponsive Hydrogels

pNIPAm-co-Acrylic Acid – pH and temperature dependent
Core/Shell Synthesis

Collapsed core particles act as preexisting hydrophobic nuclei onto which growing polymer (*the shell*) adds.

Must control hetero-nucleation vs. homonucleation to achieve monodisperse populations.
Core/Shell Particle Characterization

Light scattering data typically show an increase in particle size between core and core/shell with invariant polydispersity.
Multiresponsive Core-Shells

\begin{align*}
\text{p-NIPAm Core} \\
\text{p-NIPAm -co- AAC Shell} \\
\text{pH 6.5}
\end{align*}

Phase Transition Tuning

Phase transition temperature determined by hydrophilic/hydrophobic balance.

\[ \text{X} = \text{N-tert-butyl} \]

Ratio of \textit{N}-isopropyl to \textit{N}-tert-butyl determines transition point.
Phase Transition Tuning

○ 1 mol-%, (●) 5 mol-%, (□) 10 mol-%, (■) 20 mol-% and (△) 40 mol-% TBAm

Phase Transition Tuning – pH and Hydrophobicity

Poly($N$-isopropyl acrylamide-$co$-$N$-tert-butyl acrylamide-$co$-acrylic acid) microgels – electrostatic repulsion mediates hydrophobic collapse.
Multi-Functional Nanogels

PEG-grafted “core” and core/shell particles

How does PEG-grafting impact protein adsorption?
“Bare” pNIPAm microgels (no PEG) display strong T-dependent protein adsorption. Below phase transition = hydrophilic; above phase transition = hydrophobic.
Multi-Functional Nanogels

PEG-Modification renders collapsed particles hydrophilic.

Multi-Functional Nanogels

NMR Analysis indicates a relative change in polymer hydration – PEG “core” phase separates to shell surface.
Polyelectrolyte/Microgel Multilayers

=Anionic Microgel

=Polycation (PAH)

\[ \text{H}_2\text{N} \]
Microgel Film Formation

Passive Adsorption

Spin Coating

pNIPAm-AC = polyanion
poly(allylamine)•HCl (PAH) = polycation

Co-Deposition of Macromolecules

Insulin-impregnated films obtained via incubation of particle solution with peptide.
Labeled Insulin Incorporation

Linear increase in insulin content with particle layer number.

Pulsatile Insulin Release

Medium Replacement

9-layer film in 0.02M PBS pH=7.4

Heat to 40 C

Fast, pulsatile insulin release during film deswelling.
Bio-Functional Nanogels with Designed Topology

Cleavable diol crosslinks (DHEA)

Biotinylated core beneath a shell with tunable pore size.
Bio-Functional Nanogels with Designed Topology

HABA assay for biotin-avidin binding

Partially degraded shell $\rightarrow$ MW dependent binding.
Towards a Smarter Nanogel

Drug/Gene/RNA delivery

Goals:
1. Long Circulation Time
2. Cell-Specific Targeting
3. Receptor Mediated Endocytosis
4. Endosomal Escape
5. Cytosolic or Nucleus-Localized Release

These steps comprise a state-dependent “program”
Cancer Targeting with Nanogels

Folic acid - an effective ligand for targeting solid tumors.
Cancer Targeting with Nanogels

Dual staining (particle+lysotracker) illustrates endosomal escape.

Cancer Targeting with Nanogels

Thermal trigger induces cytotoxicity

![Graph showing viable cell percentage at different concentrations and temperatures](image)

![Diagram illustrating the targeting and uptake of nanogels by KB cells](image)
Other Stimuli: Photons

Photosensitive microgels via T-jump dyes

\[ \varepsilon = 150,000; \phi = 0 \]

\[ \lambda = 632.8 \text{ nm} \]
Increasing dye concentration = greater photoheating.
Hydrogel Micro-Optics

Substrate-supported microgels behave as microlenses.

Tunable Aqueous Microlenses

pNIPAm-co-AAc – temperature and pH tunable lensing.
Photoswitchable Microlenses

Laser heating of gold nanoparticles provides route to photoswitching
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