Phase Behavior, Rheology, Erosion Kinetics and Biomedical Applications of Fluoroalkyl-Ended PEGs

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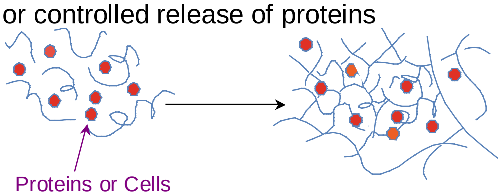
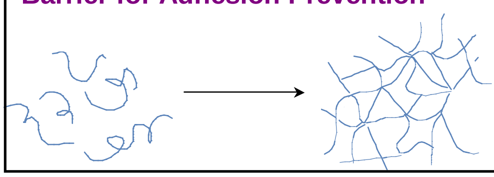
Motivation: In-Situ Transforming Hydrogels

Applications

1) Delivery Carrier: Immobilization of cells or controlled release of proteins

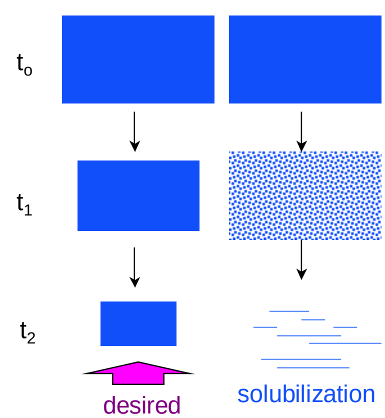


2) Soft Structural Support or Barrier for Adhesion Prevention



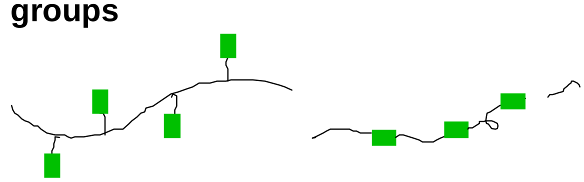
Erosion type

Surface vs. Bulk

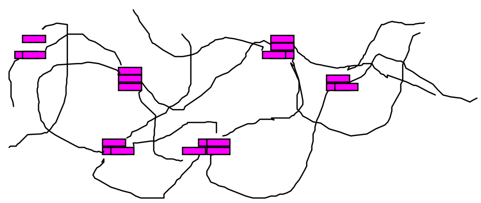


Associative polymers

- **With attracting groups**

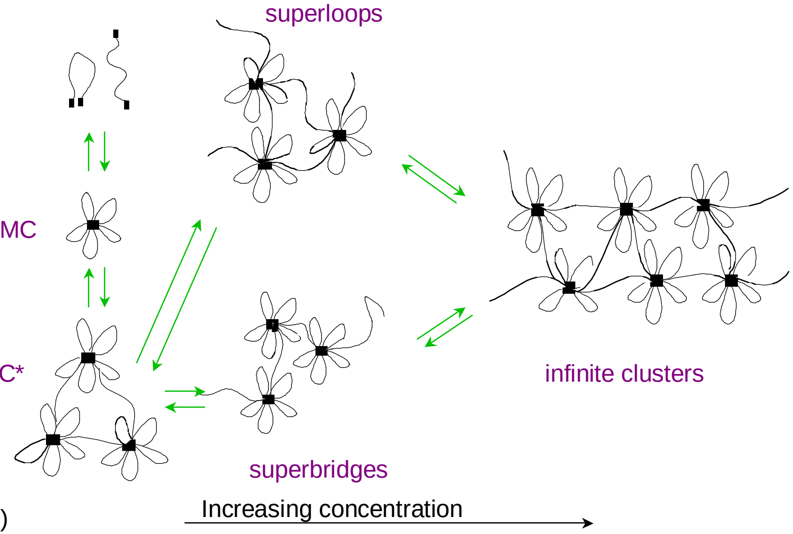


- Physical junctions :
  electrostatic
  hydrogen bonding
  hydrophobic



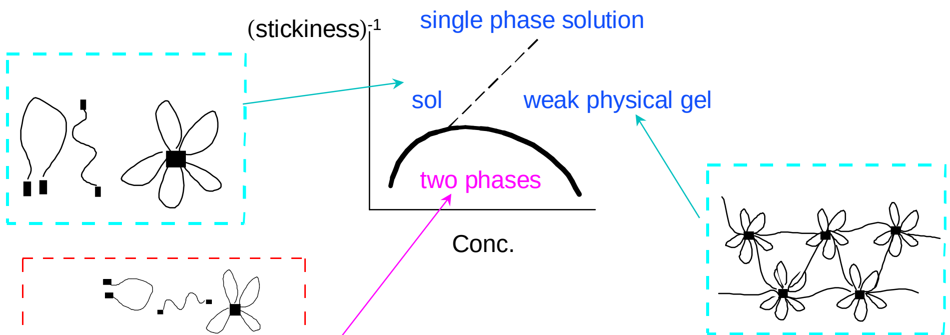
- Model system :
  End-group modified polymer in good solvent

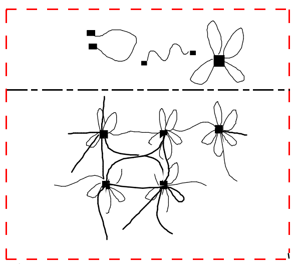
Topology of Associative Network for “Single Phase” Systems



(Annable, ‘93)

Phase Behavior of End-Associating Polymers





Phase behavior governed by
- **attraction** due to exchange entropy: increases with aggregation number of core N_{agg}
- **repulsion** due to excluded volume interaction: independent of chain length *N*

(Semenov, '95; Russel and coworkers, '98-'99)

Structure-Property Relations & Materials Design

- **Midblock type & length**
- **Hydrophobe type & length**

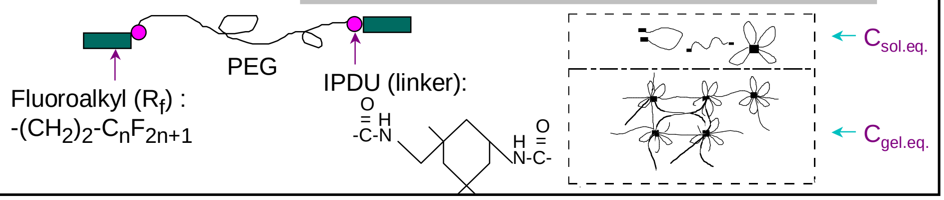
→

- **Phase behavior**
- **Rheology**
- **Erosion behavior**
- **Triggered solidification**

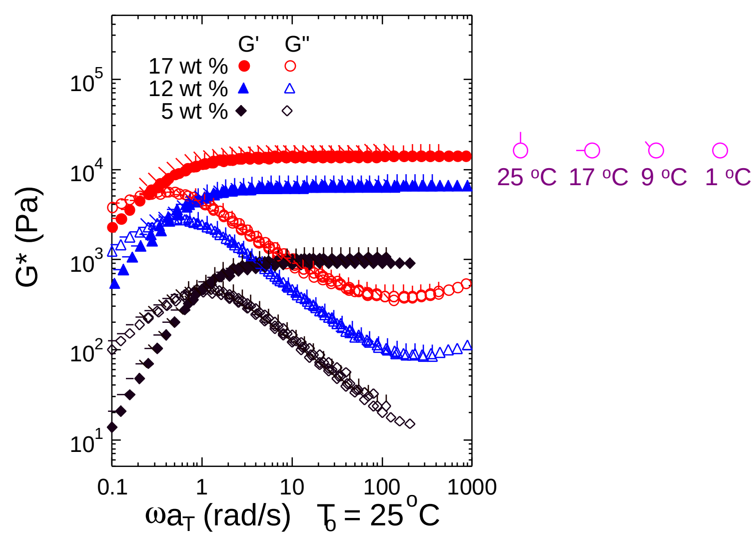
- **Midblock: PEG**
  - why? biocompatible
  - length ∅ mesh size of gel
- **Hydrophobe: fluoroalkyl, R_f**
  - why? hydrophobic and biocompatible
  - length ∅ strength of aggregation

Materials and Phase Behavior

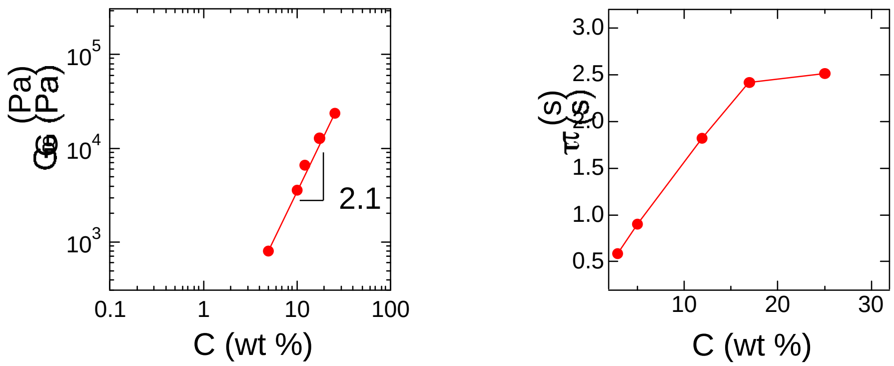
Sample	type of behavior	equilibrium composition in water (wt %) $C_{gel.eq.}$	equilibrium composition in water (wt %) $C_{sol.eq.}$	equilibrium composition in PBS (wt %) $C_{gel.eq.}$	equilibrium composition in PBS (wt %) $C_{sol.eq.}$ at 25 ºC
20KC8	1 phase				
20KC10	1 phase				
10KC8	2 phase	**6.5**±0.2	**0.075**±0.005	**7.8**±0.2	**0.055**±0.002
10KC10	2 phase	**6.8**±0.7	**0.019**±0.008	**8.1**±0.7	**0.011**±0.003
6KC6	2 phase	**9.5**±0.5	**0.066**±0.006	**10.5**±0.6	**0.038**±0.002
6KC8	2 phase	**11.0**±0.3	**0.042**±0.007	**12.5**±0.3	**0.017**±0.001
6KC10	insoluble				



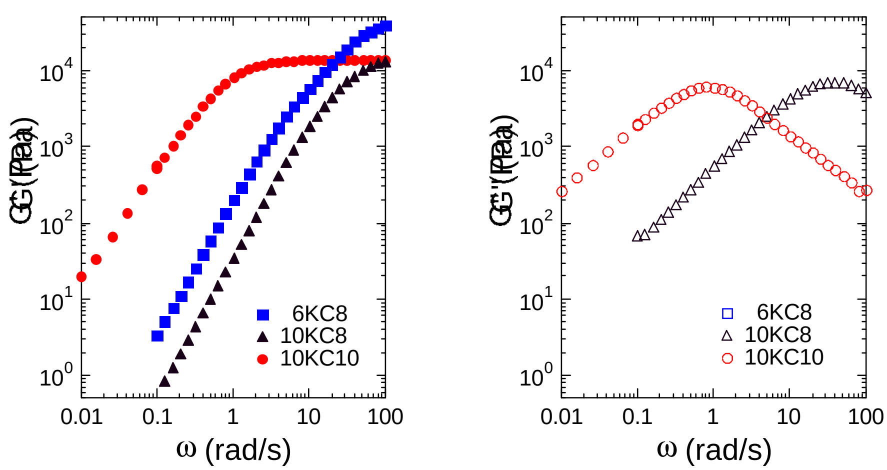
Dynamic moduli of "single phase" species (20KC10)



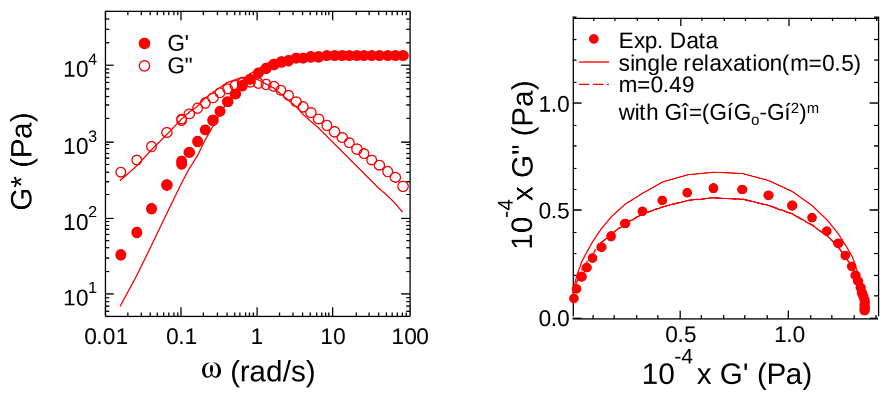
Concentration dependence of G_o and τ for "single phase" species (20KC10)



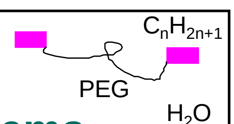
Dynamic moduli of the equilibrium gels of species that show sol-gel coexistence

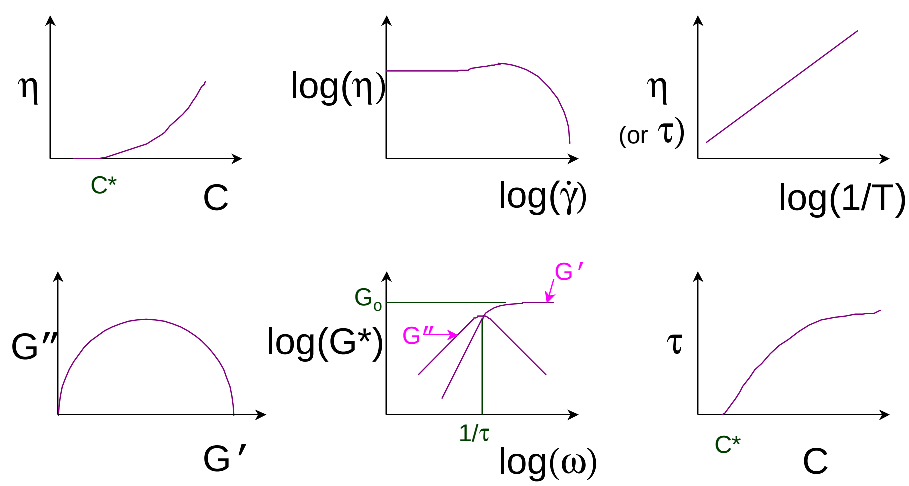


Nearly single relaxation behavior at $C_{gel,eq.}$ (10KC10)

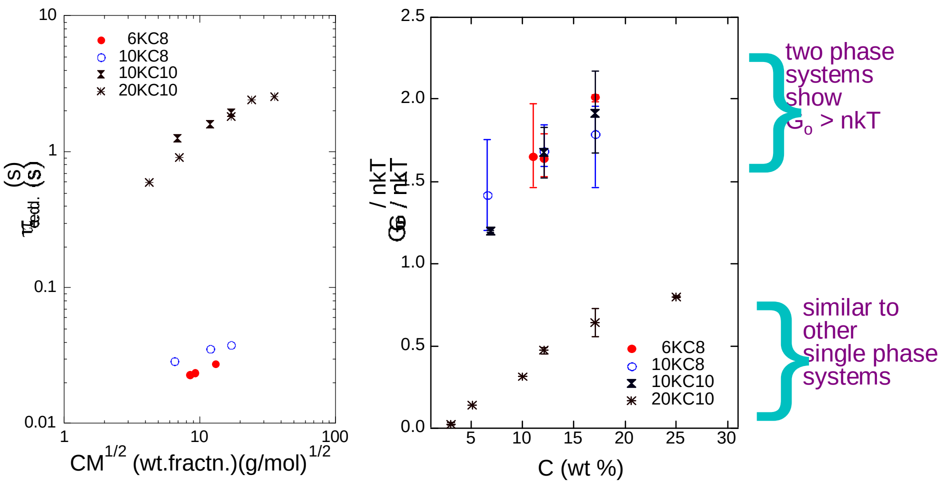


Literature on Rheology of Alkyl-ended "Single Phase" Systems

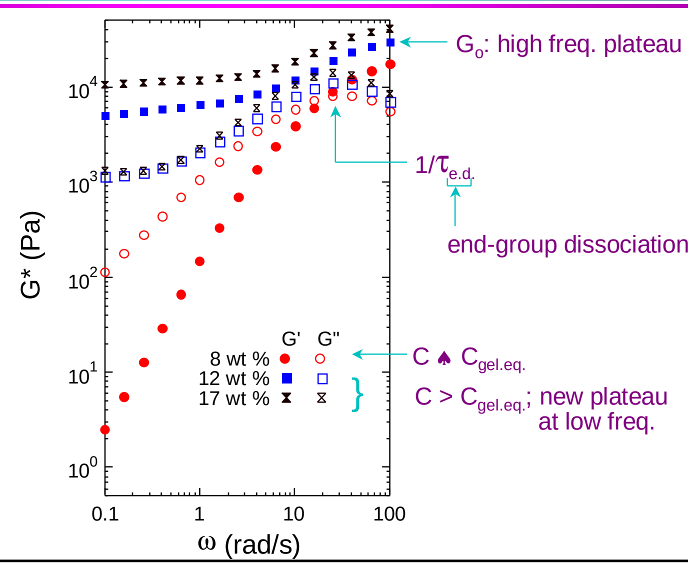




End-Dissociation Time and Apparent "Effective Fraction" of Chains in the Gel

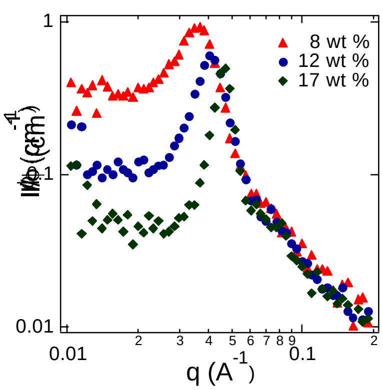


Formation of a new plateau at C > $C_{gel,eq.}$ (10KC8)



Ordering Transition in the Gel Phase

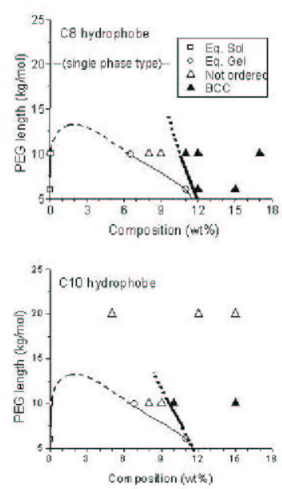
SANS (10KC8 at 25 ºC)



	Aggregation number	
Species	(wt %)	N_{agg}
6KC8	(15)	32±4
10KC8	(8)	32±4
10KC8	(12)	32±4
10KC8	(17)	34±4
10KC10	(12)	50±6
20KC10	(12)	51±9
5KmC8	(0.5)	28 ±4
5KmC10	(0.5)	48 ±5

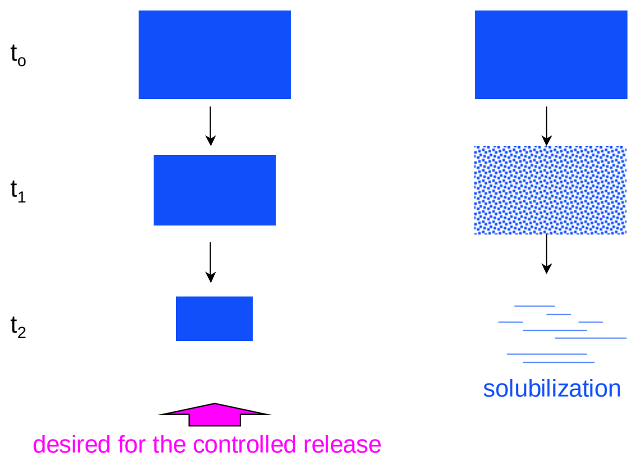
Implications for Theory

- **Rheology of single-phase systems:**
  - » Annable's could be improved by better description of bridge:loop and inclusion of micelle-micelle repulsion
- **Phase behavior:**
  - » Aggregation number is not the primary determinant of the phase behavior as Semenov and Russel assume; deeper understanding of the effect of chain length on micelle-micelle repulsion is needed.

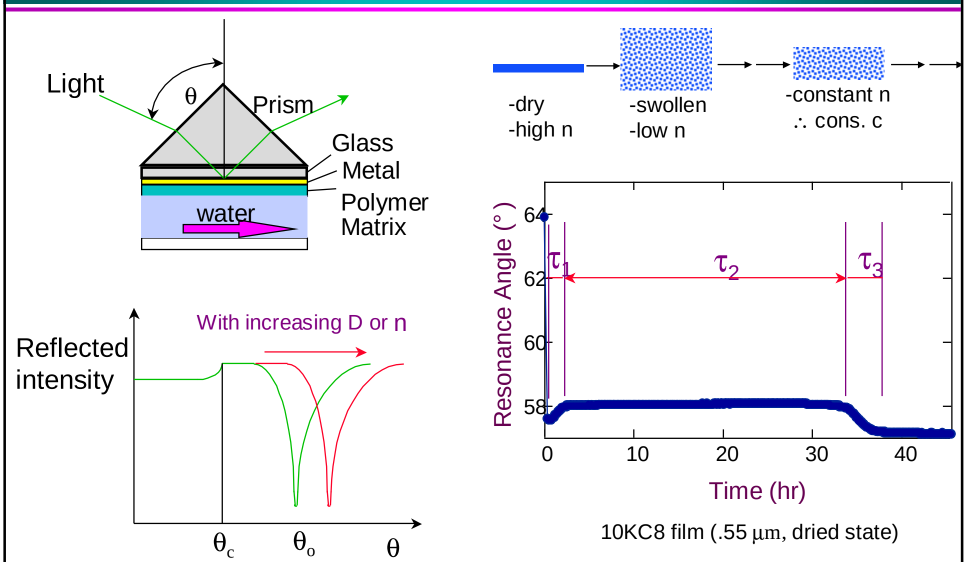


Polymer matrix erosion

Surface(heterogenous) vs. Bulk(homogeneous) erosion



Dissolution characteristics of polymer matrix by SPR in a flow system



Erosion Rates Correlate with Phase Behavior

Sample	phase behavior	composition (wt %)	dissolution rate ($mg/cm^2/hr$)
5K-M-C10	lyotropic gel	12.8	0.201
20KC10	single phase	10.0	0.168
6KC8	sol-gel coex.	11.0	3.33×10^{-4}
10KC8	sol-gel coex.	6.5	1.67×10^{-3}
10KC10	sol-gel coex.	6.8	too slow to measure by SPR

Summary of Gel Properties in the Sol-Gel Coexistence Regime

- Mechanical properties (modulus, viscosity) can be controlled by the manipulation of hydrophilic and hydrophobic parts.
- Erosion of the matrix is achieved from the surface (heterogeneous type).
- Dissolution rates are much slower ($\sim 10^{-3}$ times) than systems with no phase separation.
- Dissolution is an activated process governed by end group length (10KC10 vs. 10KC8).

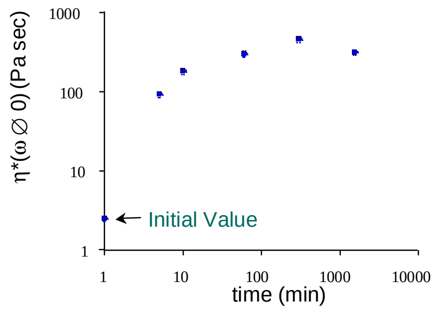
Sol-Gel Transition with Water-Miscible, Bio-Tolerable Organic Solvent
(N-methyl pyrrolidone (NMP))

Conc. solution in NMP (Injectible)

Gel

Viscosity change at 37 °C after exposing 50 % 10KC8 in NMP to water reservoir.

For initial thickness d ~ 1.5 mm transition occurs within 10 min.

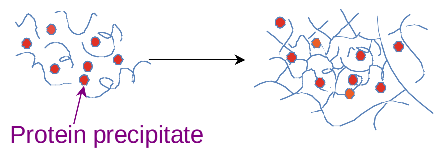


Human growth hormone (hGH)

- A single-chain polypeptide of 191 AAs with 2 disulfide bonds. M.W. ~ 22 KD
- Synthesized and secreted into storage granules as dimer with 2 Zn^{2+} ions and then released from the anterior pituitary.
- Deficiency prevents normal growth, so the recombinant form (rhGH) is used to treat hGH deficient children.
- Current clinical administration : daily injections for several years => need for sustained release systems.

Release of hGH from In-Situ Forming Hydrogels of PEG with Fluorocarbon Ends

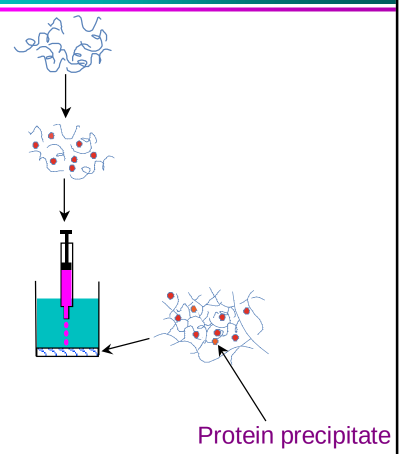
- The equilibrium gel phase of PEG modified with fluorocarbon ends shows slow, surface erosion.
- Injectible state by dissolving in NMP.
- Gelation after injection by diffusion of NMP out and water in.



- Sustained release of protein through the hydrogel.

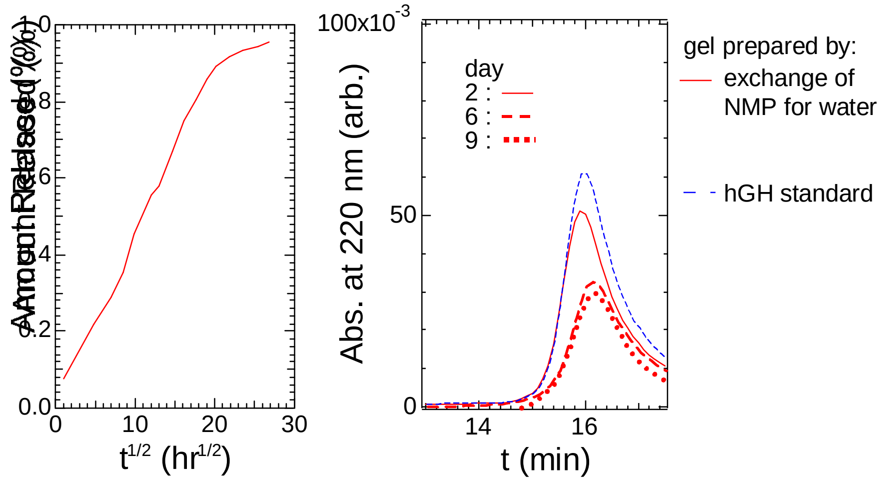
Release experiment protocol for NMP formulation

- Dissolve PEG-R_f in NMP.
- Add protein powder (protein:PEG-R_f :NMP = 1:10:10).
- Inject the suspension into PBS
- Collect the supernatant at intervals and refill.
- Measure total protein concentration.



hGH-Zn release from injectible NMP formulation

6KC8 at 37 °C to PBS buffer, thickness of gel at eq. ~ 0.25 cm
initial gel state of 1 :10:10 (weight) of hGH:Polymer:NMP



Blood response to foreign materials

FOREIGN SURFACE

Flowing blood

PROTEIN ADSORPTION

Higher flow rate
; arterial

Lower flow rate
; venous

PLATELET AGGREGATION
(WHITE THROMBOSIS)

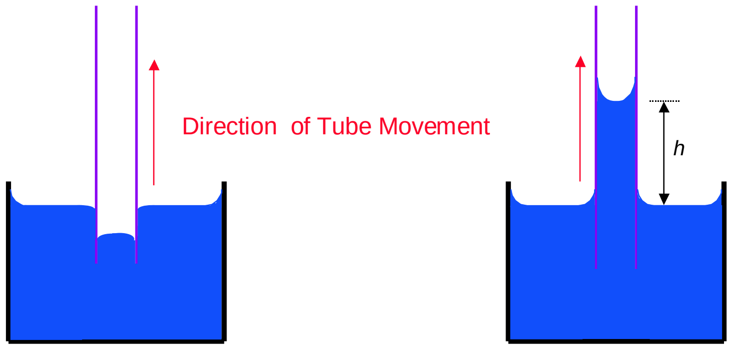
FIBRIN FORMATION
+
PLATELET AGGREGATION
+
TRAPPED RED CELLS
(RED THROMBOSIS)

Ref.; Hoffman, A.S., Polymeric Materials and Artificial Organs, 1984, p.27

R_f-PEGs as surface-modifying materials for PTFE

- R_f-PEGs with long enough R_f showed slow (6KC8, 10KC8, 10KC10) or no (6KC10) erosion. → Adsorbed R_f-PEGs on PTFE can give a long-lasting surface-modifying coating.
- Suggests easy route to PEG surface layer on teflon:
  - 1.Immerse PTFE part in a solution of R_f-PEG in ethanol (1 wt %).
  - 2. Remove to leave a viscous liquid film on the surface, and
  - 3. immerse in water to induce association of the R_f groups with each other and the PTFE surface.
- Observe that PTFE surface is hydrophilic after adsorption.

Capillarity of small PTFE tube



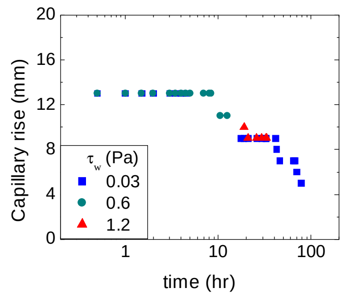
**(a) Before Coating (Bare PTFE)
; Capillary Depression (Non-Wetting)**

**(b) After Coating
; Capillary Rise (Wetting)**

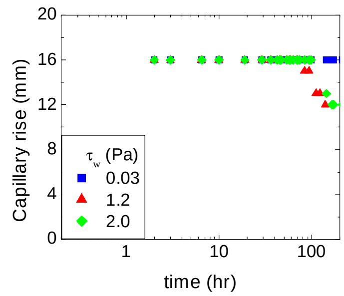
Change of capillary rise of modified PTFE tube with time under flow

(I.D =1.35 mm,varying shear rate (sec^{-1}))

10KC10



6KC10



Results for PTFE modification

- Surface adsorption of R_f-PEGs onto PTFE effectively modifies the surface from being hydrophobic to hydrophilic.
- Capillary rise method is a sensitive tool to monitor the change in the surface properties of a narrow tube.
- Stability of this physisorption under flow correlates with the phase behavior and erosion rate of the bulk state of R_f-PEGs. In particular, an R_f-PEG that is insoluble in water provides the most stable modification.

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