Lecture 8: Physical Hydrogels

Last Day:	Overview of biomedical applications of hydrogels Structure of covalent hydrogels Thermodynamics of hydrogel swelling
Today:	Bonding in physical hydrogels Structure and thermodynamics of block copolymer hydrogels
Reading:	L.E. Bromberg and E.S. Ron, 'Temperature-responsive gels and thermogelling polymer matrices for protein and peptide delivery,' *Adv. Drug Deliv. Rev*., **31**, 197 (1998)

Associative forces in physical hydrogels

Cross-link structure in physical hydrogels

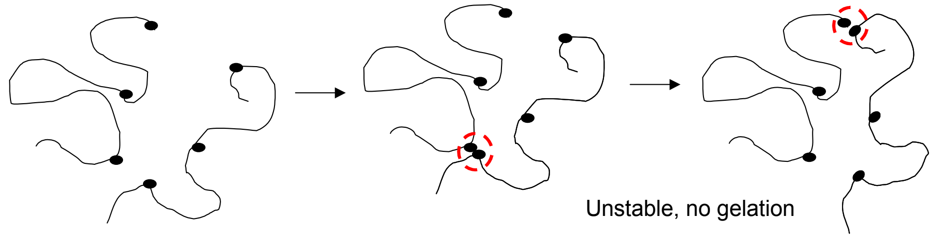
- Driving associative forces:
  1. Hydrophobic associations/ Van der Waals forces
     i. LCST polymers, hydrophobic-hydrophilic block copolymers
  2. Micellar packing
  3. Hydrogen bonding (Rubner)
  4. Ionic bonding (later lecture)
  5. crystallizing segments
  6. Combinations of the above interactions
     - Peptide interactions (e.g. coiled coils)(1)

- Stability requires cooperative bonding interactions(2) (Guenet, Thermoreversible gelation of polymers and biopolymers)

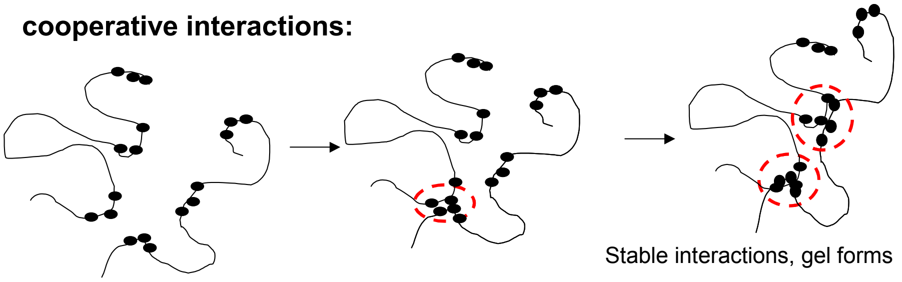
  - Individual non-covalent bonds are relatively weak:
    - Strength of covalent bond:
    - Hydrophobic association:
    - Ionic bond:
    - Hydrogen bond in water:
    -
  - Cooperativity: lowered energy barrier for second and subsequent bonds after first has formed
    - Used in biological associations

- Alpha helix, beta sheet

non-cooperative interactions:

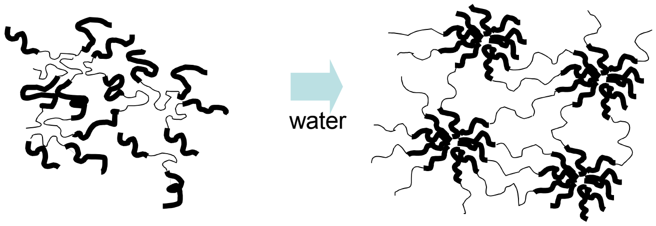


cooperative interactions:

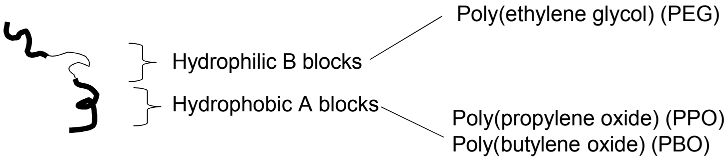


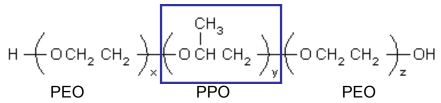
General characteristics of physical gel biomaterials

- ○ **Dehydration of hydrophobes/hydrophobic association**
  - ○ Examples:
    - PEO-b-PPO-b-PEO, PPO-b-PEO-b-PPO (commercially known as Pluronics (BASF))[2]
      - ○ Similar associative properties from PLGA-PEG-PLGA copolymers and PEG-PLGA-PEG copolymers

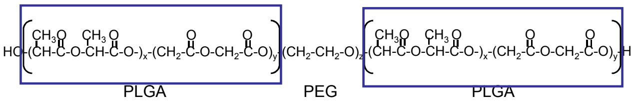


Example blocks:



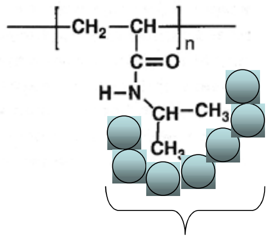


$H\!-\!(OCH_2CH_2)_x\!-\!(OCH(CH_3)CH_2)_y\!-\!(OCH_2CH_2)_z\!-\!OH$



$HO\!-\!\left[(\overset{CH_3}{CH}\!-\!\overset{O}{\overset{\|}{C}}\!-\!O\!-\!\overset{CH_3}{CH}\!-\!\overset{O}{\overset{\|}{C}}\!-\!O\!-)_x\!-\!(CH_2\!-\!\overset{O}{\overset{\|}{C}}\!-\!O\!-\!CH_2\!-\!\overset{O}{\overset{\|}{C}}\!-\!O)_y\right]\!-\!(CH_2\!-\!CH_2\!-\!O)_z\!-\!\left[(\overset{CH_3}{CH}\!-\!\overset{O}{\overset{\|}{C}}\!-\!O\!-\!\overset{CH_3}{CH}\!-\!\overset{O}{\overset{\|}{C}}\!-\!O\!-)_x\!-\!(CH_2\!-\!\overset{O}{\overset{\|}{C}}\!-\!O\!-\!CH_2\!-\!\overset{O}{\overset{\|}{C}}\!-\!O)_y\right]\!-\!H$

- Poly(N-isopropylacrylamide)

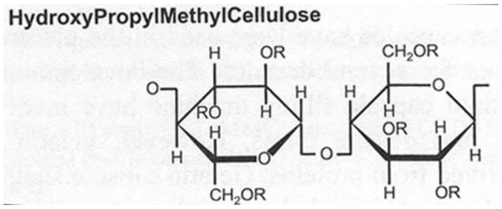


ordered water molecules
(minimize water-hydrophobe contacts)

Dehydration allows water to disorder (*entropically-driven*)

$$\Delta S = S_{dehydrated} - S_{hydrated} > 0$$

- Hydroxypropylmethyl cellulose (natural biopolymer)
    - Hydroxypropyl groups dehydrate to associate and form a gel



- **Micellar packing**
    - Examples:
        - Pluronics PEO-PPO-PEO block copolymers
        - Cubic lipid gel phases(3)

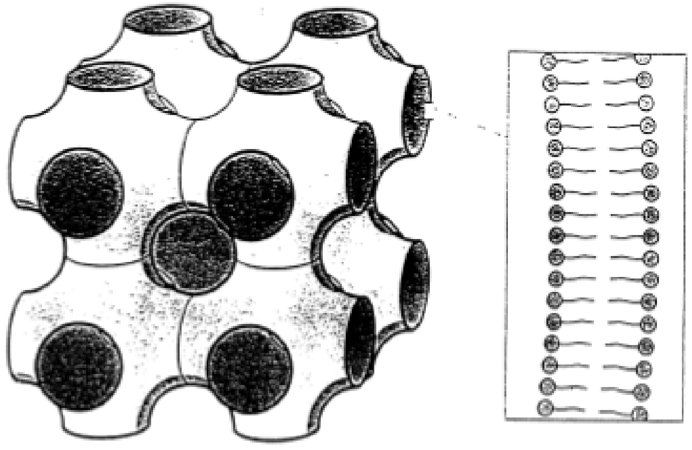


Fig. 2. Structure of glycerylmonoleate–water cubic phase in three dimensions with inset showing the lipid bilayer. (Adapted with modifications from Refs. [4,39].)

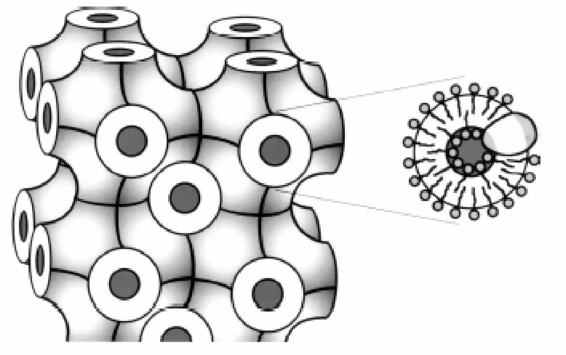
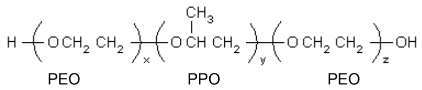
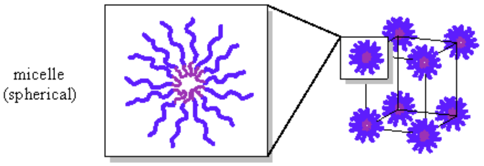


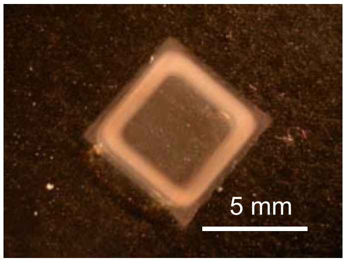
FIG. 1. Schematic model of a bicontinuous cubic phase composed of monoolein, water, and a membrane protein. The matrix consists of two compartments, a membrane system with an infinite three-dimensional periodic minimal surface (*Left*), interpenetrated by a system of continuous aqueous channels (shown in black). The enlarged section (*Right*) shows the curved lipid bilayer (with an inserted membrane protein molecule) enveloping a water conduit. In a cubic phase consisting of 60–70% (wt/wt) monoolein or monopalmitolein and water, hydrophobic proteins diffuse laterally in the bilayer, while water-soluble components diffuse freely through the intercommunicating aqueous channel system (see text). Adapted from plate 9, ref. 27, with kind permission of Elsevier Science–NL, Sara Burgerhartstraat 25, 1055 KV Amsterdam, The Netherlands.

(Landau and Rosenbusch 1996(4))



$H\left(OCH_2CH_2\right)_x\left(O\overset{CH_3}{CH}CH_2\right)_y\left(OCH_2CH_2\right)_zOH$

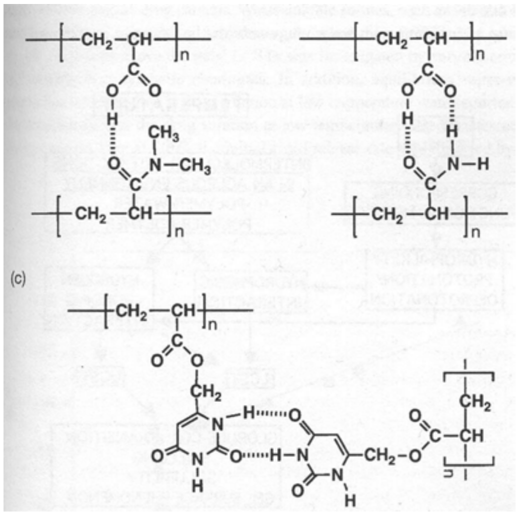




(micellar crystal figure from website, Matthew, Bhatia, and Roberts; http://www.ecs.umass.edu/hamilton/matthew_julie.htm)

- 5mm hydrogel shown above is a composite box formed by Sciperio printer from Pluronic F-127 and PPF-co-PEG

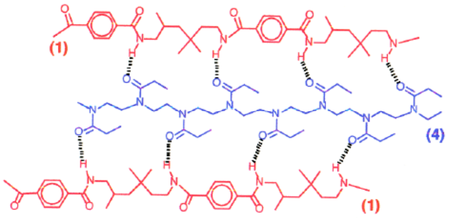
- **Hydrogen bonding**
  - Hydrogen bonds can form between H and C, N, O, and F
  - Examples:
    - Poly(vinyl alcohol)
    - Poly(vinyl alcohol)/PEO blends

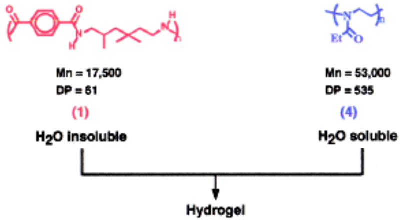


- Polymers that can form hydrogen bonded gels(5):
  - Poly(vinyl alcohol)
  - Gelatin (natural biopolymer)
    - From Sigma product sheet:
      - Gelatin is a heterogeneous mixture of water-soluble proteins of high average molecular weights, present in collagen. The proteins are extracted by boiling skin, tendons, ligaments, bones, etc. in water. Type A used as a stabilizer, thickener and texturizer in foods; in the manufacture of rubber substitutes, adhesives, cements, lithographic and printing inks, plastic compounds, artificial silk, photographic plates and films, matches, and light filters for

mercury lamps; in textiles; to inhibit crystallization in bacteriology and prepare cultures; in PCR hybridization in molecular biology; in the pharmaceutical industry as a suspending agent, encapsulating agent and tablet binder; and in veterinary applications as a plasma expander and hemostatic sponge.

- **Percec:** form hydrogels by H-bonding between water-insoluble short chains and long water-soluble chains





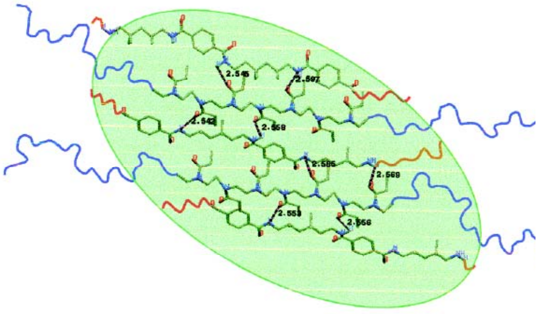


Figure 4. Schematic representation of H-bonding interaction between 1 and 4 obtained from molecular modeling experiments.

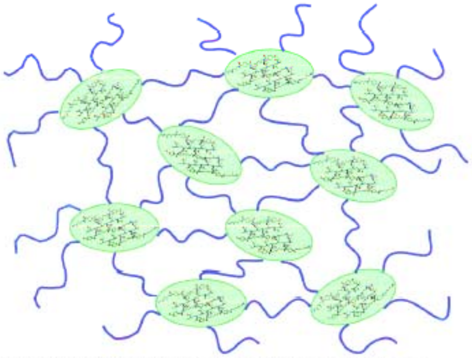
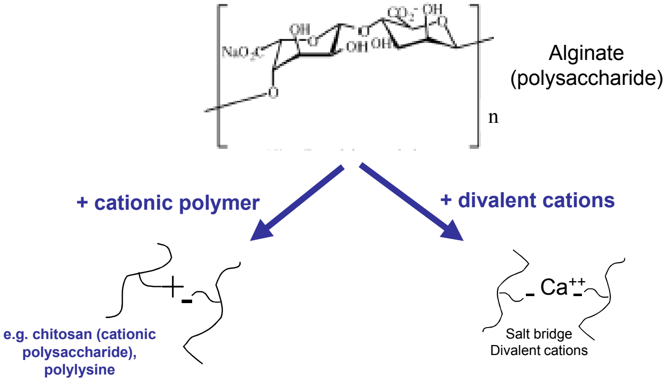


Figure 5. Schematic representation of supramolecular networks generated by the blend of 1 with 4 solely via H-bonding.

(Percec and Bera(6))

- **Ionic bonding**
  - Examples:
    - Sodium alginate(7) (Grant, Morris, FEBS Lett. 32, 195 (1973))
      - Crosslinked by divalent cations, forming salt bridges
        - Sensitive to salt concentration in physiological locations
      - Crosslinked by blending with cationic polymer
        - E.g. chitosan, polylysine
      - Used extensively for gentle cell encapsulation



- **Crystallizing segments**
  - Examples:
    - Isotactic Polyvinyl alcohol (Merrill/Bray(8))
    - Isotactic Poly(methacrylic acid)

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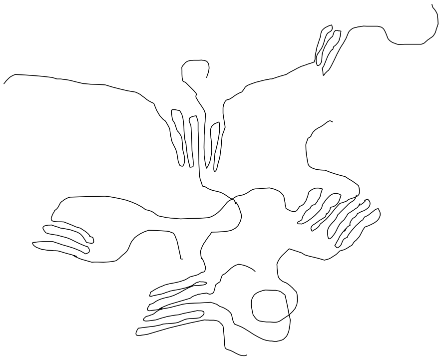


- **Protein interactions**
  - Examples:
    - Avidin cross-linked particle networks(9)
    - Associating alpha helices (Wang et al.): coiled-coil peptide cross-links

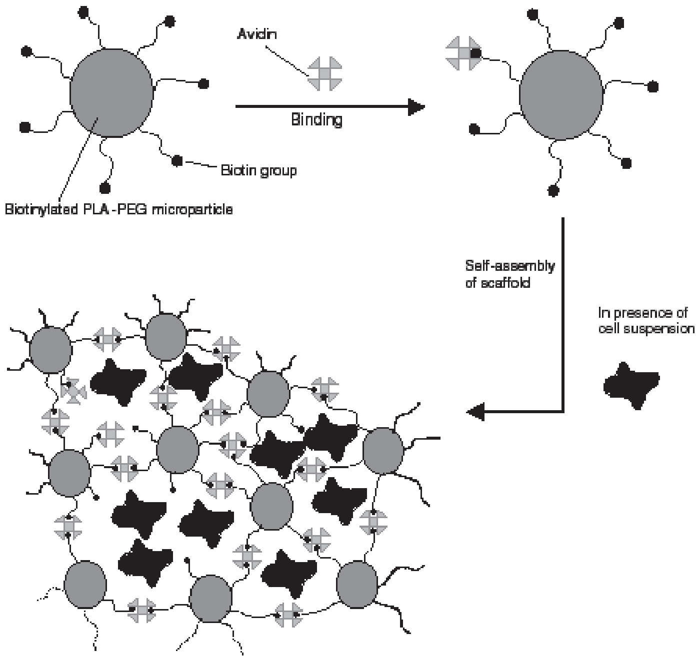


Fig. 1. A schematic representation of scaffold self-assembly.

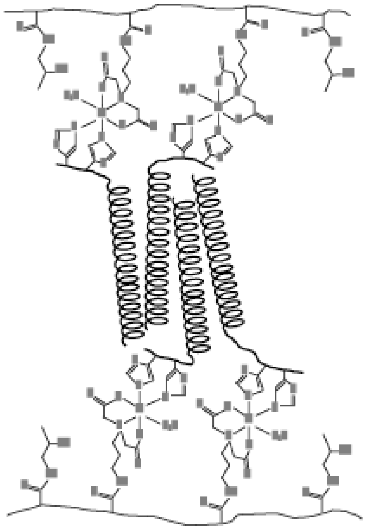
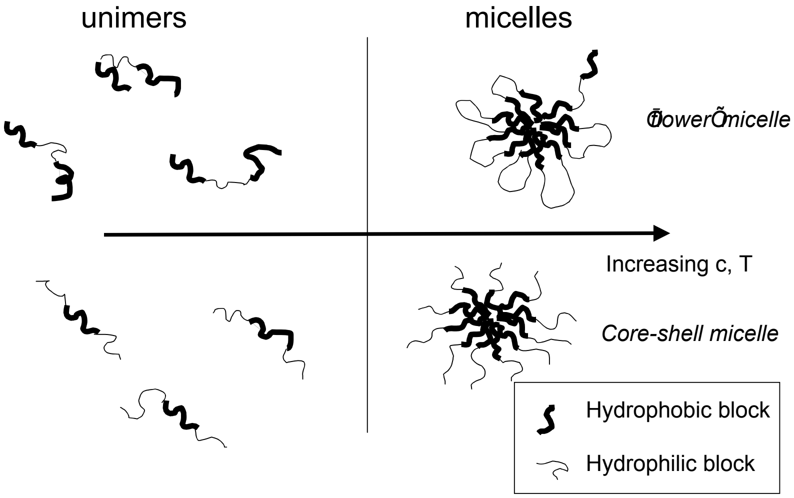


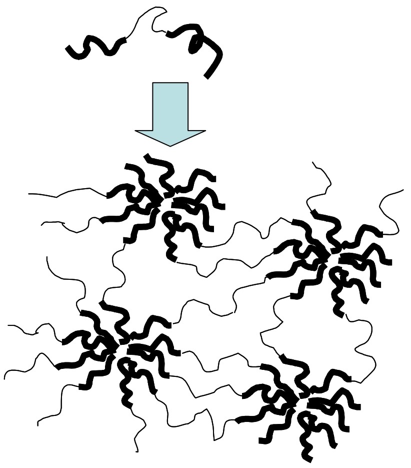
Figure 1 Structural representation of the hybrid hydrogel primary chains and the attachment of His-tagged coiled-coil proteins. Poly(HPMA-co-DAMA) is shown here as the primary chains. The pendant iminodiacetate groups form complexes with transition-metal ions, such as Ni■, to which the terminal histidine residues of the coiled coils are attached. A tetrameric coiled coil (not drawn to scale), consisting of two parallel dimers associating in an antiparallel fashion, is shown here as an example of many of the possible conformations.

Structure of Associating Block Copolymer Hydrogels[4]

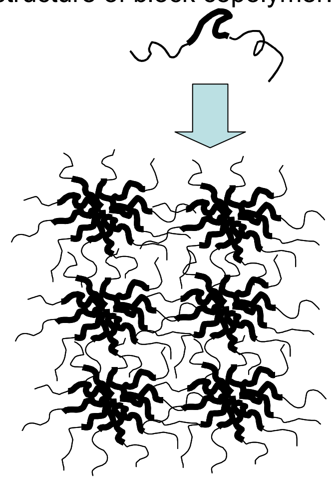
- Pluronics (trade name, BASF) are an important class of hydrophobically-associating block copolymers: FDA approved for use *in vivo*
- Starting at relatively low concentrations, Hydrophilic-hydrophobic block copolymers form micelles upon passing a critical concentration (cmc) or temperature (cmt)[2]
    - ***ON BOARD:***



- At higher concentrations, micelles overlap and gelation can occur:
    - Micelles pack together
        - Interactions between micelles depend on structure of block copolymer:



Intermicelle physical cross-links



Entanglement of packed micelle coronas

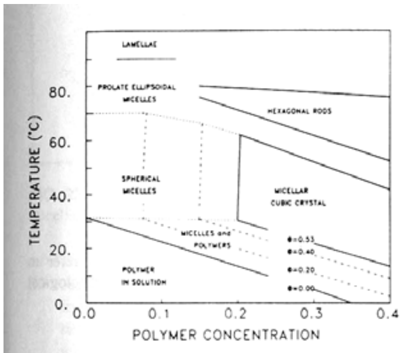


FIG. 20 Temperature-concentration phase diagram showing the characteristics of $E_{25}P_{40}E_{25}$ fully dissolved in D_2O. In the low-concentration, low-temperature range, the polymers are dissolved Gaussian chains. Above the $\Phi = 0$ line of critical micellation concentration/temperature, a liquid of micelles is formed with micellar volume fraction (Φ) as shown by contour lines in the figure. When the $\Phi = 0.53$ line is crossed, the micellar liquid "freezes" into a hard-sphere cubic crystal. (*Source*: from [36], with permission.)

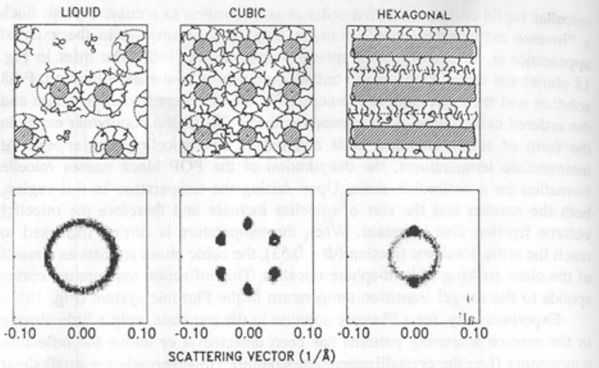


FIG. 19 Top row: Schematic illustration of interacting micelles, spherical at low temperature, characterized by the core-radius R_c and hard-sphere interacting radius R_{hs}, and rod-like at high temperature. Bottom row: Two-dimensional scattering functions as obtained perpendicular to the shear plane of 25% solution $E_{25}P_{40}E_{25}$. The three columns represent P-85 at $T = 25$ °C, $T = 27$ °C, and $T = 68$ °C. (*Source*: from [39], with permission.)

Experiments by Hatton group at MIT:

PEO-PPO-PEO micellization at different temperatures measured by adding a hydrophobic dye that absorbs UV light when bound in a hydrphobic environment (e.g. micelle core) but not free in solution

Transition range: micelles in equilibrium with unimers

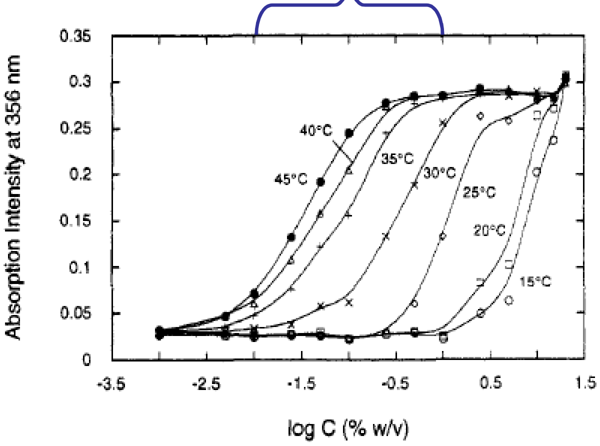
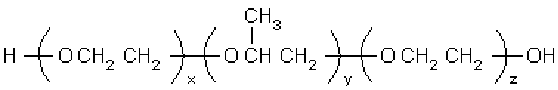


Figure 3. Effect of concentration, with temperature as parameter, on the absorption intensity of DPH at 356 nm in aqueous solutions of Pluronic P104. The critical micellization concentrations can be estimated from the first break in the curves.

- Block length determines gel structure



$$H\left(OCH_2CH_2\right)_x\left(O\overset{CH_3}{\overset{|}{C}H}CH_2\right)_y\left(OCH_2CH_2\right)_zOH$$

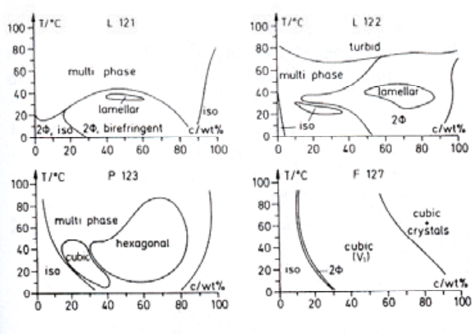


FIG. 14 Phase diagrams of the systems of $(EO)_x(PO)_y(EO)_x$ block copolymers with $y = 69$ and x increasing from 5 to 106. (*Source*: from [13], with permission.)

(Chu 1996)

- Relation between structure and applications in bioengineering
  - Cubic phase gels studied most often (pluronic F-127 at concentrations circa 20% w/vol)
  - Applied to:
    - Hydrogel scaffolds for tissue engineering of cartilage(10)
    - Drug delivery
      - Cubic phase gels erode by surface dissolution
        - Provides zero-order drug release(11)

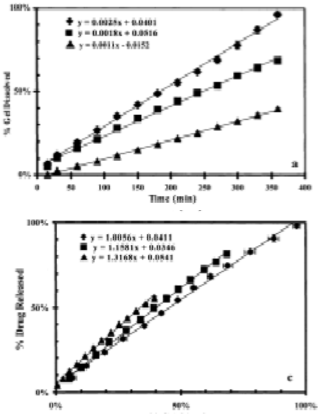
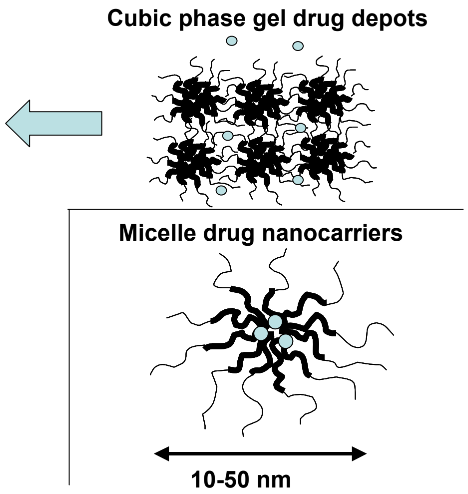


Fig. 1. Influence of P407 concentration (♦ 25% (w/v), ■ 30% (w/v), and ▲ 35% (w/v)) on gel dissolution and ceftiofur release at 37 °C. (a) Cumulative percent of P407 dissolved versus time, (b) cumulative percent ceftiofur released versus time, and (c) correlation of cumulative percent gel dissolved and cumulative percent ceftiofur released. Data are expressed as means ± S.D. for $n = 3$.



- Drugs can be incorporated into micelles as nano-carriers
  - E.g. Kim et al. PEO-PLGA-PEO block copolymers for drug delivery (Nature paper)(12)

Thermodynamics of Hydrophobic Association vs. H-Bonding Gels[2,5]

LCST polymers(5)

- Amphiphilic copolymers like PEO/PPO block copolymers associate on increasing temperature
  - They belong to a class of materials exhibitin **LCST** (lower critical solution temperature) behavior
  - LCST materials phase separate from their solvent with increasing temperature, in contrast to the more common UCST materials, that phase separate at low temperatures:

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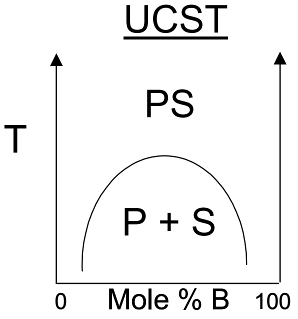

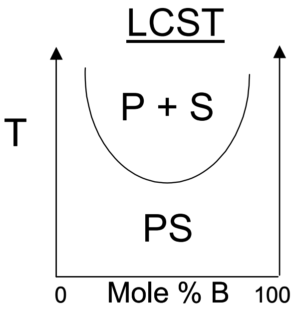

PS = polymer solution
P + S = two-phase region: polymer-rich, polymer-poor

- Homopolymers can also exhibit LCST behavior
  - E.g. poly(N-isopropylacrylamide)
    - Soluble in water at low temperatures, but collapses at 32 deg. C
- Thermodynamically, any polymer that phase separates from water on increasing temperature *must* be driven by entropy
  - Go into theory?

Associating block copolymers(13, 14)

- The association of hydrophobic blocks in aqueous solution is described by the *closed association* model
  - Micelles form in a transition from unimers directly to multimolecular structures, with no intermediate bi-mer/tri-mer/etc.
- Examining the driving force for copolymer self-assembly
  - What is the free energy change for formation of micelle structures?

Eqn 1 $\Delta G^0 = G_{micelle} - G_{unimer}\Big|_{cmc/cmt} = \Delta H^0 - T\Delta S^0 = RT\ln c_{cmc}$ **Foundations of colloid Science R.J. Hunter**

Eqn 2 $\Delta H^0 = R\left[\frac{\partial \ln c_{cmc}}{\partial(1/T)}\right]_{T,P}$

- Association of hydrophobic blocks driven by increasing concentration is exactly equivalent to association driven by increasing temperature, thus:

$$\frac{\partial \ln(c_{cmc})}{\partial(1/T)} = \frac{\partial \ln(c\ )}{\partial(1/T_{cmt})}$$

(determined experimentally)

- From X, a plot of ln c vs $1/T_{cmt}$ allows ΔH^0 to be determined:(15)

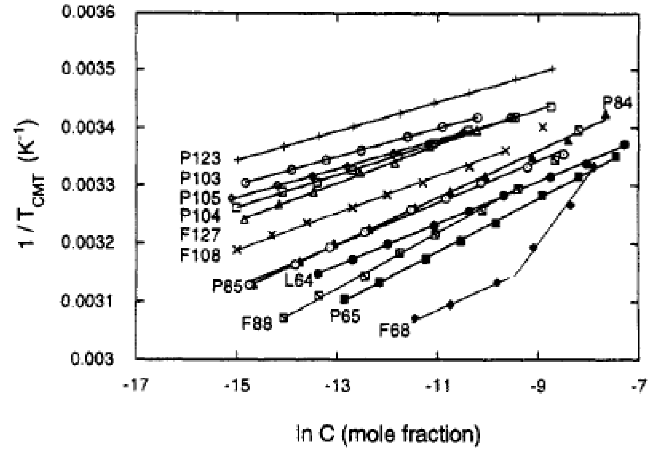

Figure 6. Reciprocal T_{cmt} vs copolymer concentration plots for various Pluronics, used for the determination of the micellization enthalpy in terms of the closed association model.

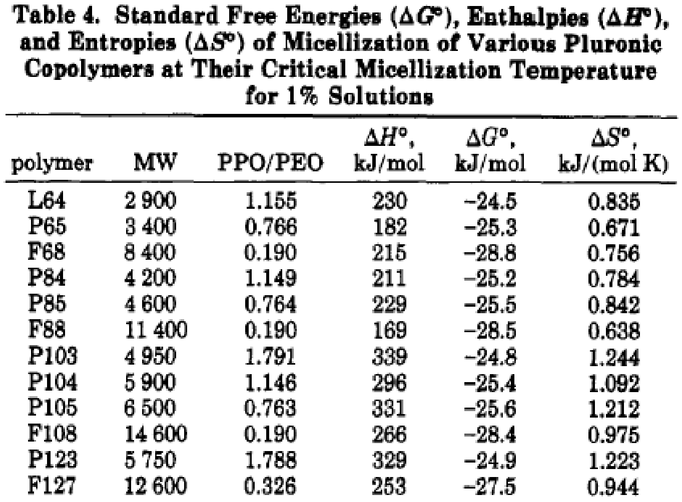

Table 4. Standard Free Energies ($\Delta G°$), Enthalpies ($\Delta H°$), and Entropies ($\Delta S°$) of Micellization of Various Pluronic Copolymers at Their Critical Micellization Temperature for 1% Solutions

polymer	MW	PPO/PEO	$\Delta H°$, kJ/mol	$\Delta G°$, kJ/mol	$\Delta S°$, kJ/(mol K)
L64	2 900	1.155	230	−24.5	0.835
P65	3 400	0.766	182	−25.3	0.671
F68	8 400	0.190	215	−28.8	0.756
P84	4 200	1.149	211	−25.2	0.784
P85	4 600	0.764	229	−25.5	0.842
F88	11 400	0.190	169	−28.5	0.638
P103	4 950	1.791	339	−24.8	1.244
P104	5 900	1.146	296	−25.4	1.092
P105	6 500	0.763	331	−25.6	1.212
F108	14 600	0.190	266	−28.4	0.975
P123	5 750	1.788	329	−24.9	1.223
F127	12 600	0.326	253	−27.5	0.944

- Positive slope of $1/T_{cmt}$ plot indicates ΔH^0 is positive: but ΔG^0 is negative (micellization is a spontaneous process at the cmc/cmt)
  - Thus, association is *enthalpically unfavorable*
    - *?*

        - Driven by favorable *entropy change*
            - Ordered water around hydrophobic groups is released to disorder if hydrophobic blocks associate, and this entropy gain outweighs the entropy penalty for confining the blocks to the micelle core
    - Consistent with *direction* of transition temperature change:
        - Any entropically-driven process will occur with *increasing* temperature, since G = H - TS
    - Entropy/hydrophobic effect-driven gelation contrasts with hydrogen-bonding association of gels
        - Hydrogen bonded gels break cross-links with increasing temperature (gel formed driven by enthalpy gain on H-bonds)
            - H-bonds weak; thermal energy can become greater than bonding energy
            - H-bonding transition gels (gels dissociate with increasing temperature): Nature 349, 400 (1991)
        - Opposite temperature behavior- gel is dissociated/swells with increasing temperature
        - E.g. gelatin/PVA are fluid at elevated temperatures and gelled at lower temperatures, while pluronics are fluid at low temperature and gel at elevated temperatures

References

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