HYDROGELS

KMU 407

Polymer Science and Technology II

2016-2017 Fall Semester

What is a Hydrogel?

Hydrophilic polymer material that can absorb large amounts ***without dissolving***.

A **network** composed of physical or chemical crosslinkers that are prepared from monomers, pre-polymers, or already hydrophilic polymers.

Cross-links produced through:

- Chemical reaction to form covalent bonds
- Entanglement of polymers
- Ionic interactions, hydrogen bonds, or hydrophobic interactions or van der Walls forces

- Developed from the early 1960. Poly(2-hydroxiethyl methacrylate).
- Principal applications in the biomedical and pharmaceutical fields
- Initially developed as a substitute of natural living tissue due to their rubber nature and high water content
- Properties 👍: swelling behaviour and network permeability
- Principal applications:
  - contact lenses, biosensoris, sutures and dental materials
  - controlled drug delivery

Hydrogels Classification

Classification according to polymeric composition

- Homopolymer hydrogel (derived from a single species of monomer)

- Multipolymer interpenetrating polymeric hydrogel (made of two independent cross-linked synthetic and/or natural polymer component, contained in a network form)

- Copolymer hydrogel (comprised of two or more different monomer species with at least one hydrophilic component, arranged in a random, block or alternating configuration)

Classification based on type of cross-linking

Hydrogels can be divided into two categories based on the chemical or physical nature of the cross-link junctions,

- Linking polymer chains via chemical reaction.
- Using ionizing radiation to generate main-chain free radicals which can recombine as cross-link junctions.
- Physical interactions such as entanglements, electrostatics and crystallite formation.
- Photo-polymerization

Physically crosslinked hydrogels
• Ionic interactions (alginate etc.)
• Hydrophobic interactions (PEO–PPO–PEO etc.)
• Hydrogen bonding interactions (PAAc etc.)
• Stereocomplexation (enantiomeric lactic acid etc.)
• Supramolecular chemistry (inclusion complex etc.)

Chemically crosslinked hydrogels
• Polymerization (acryloyl group etc.)
• Radiation (γ-ray etc.)
• Small-molecule crosslinking (glutaraldehyde etc.)
• Polymer–polymer crosslinking (condensation reaction etc.)

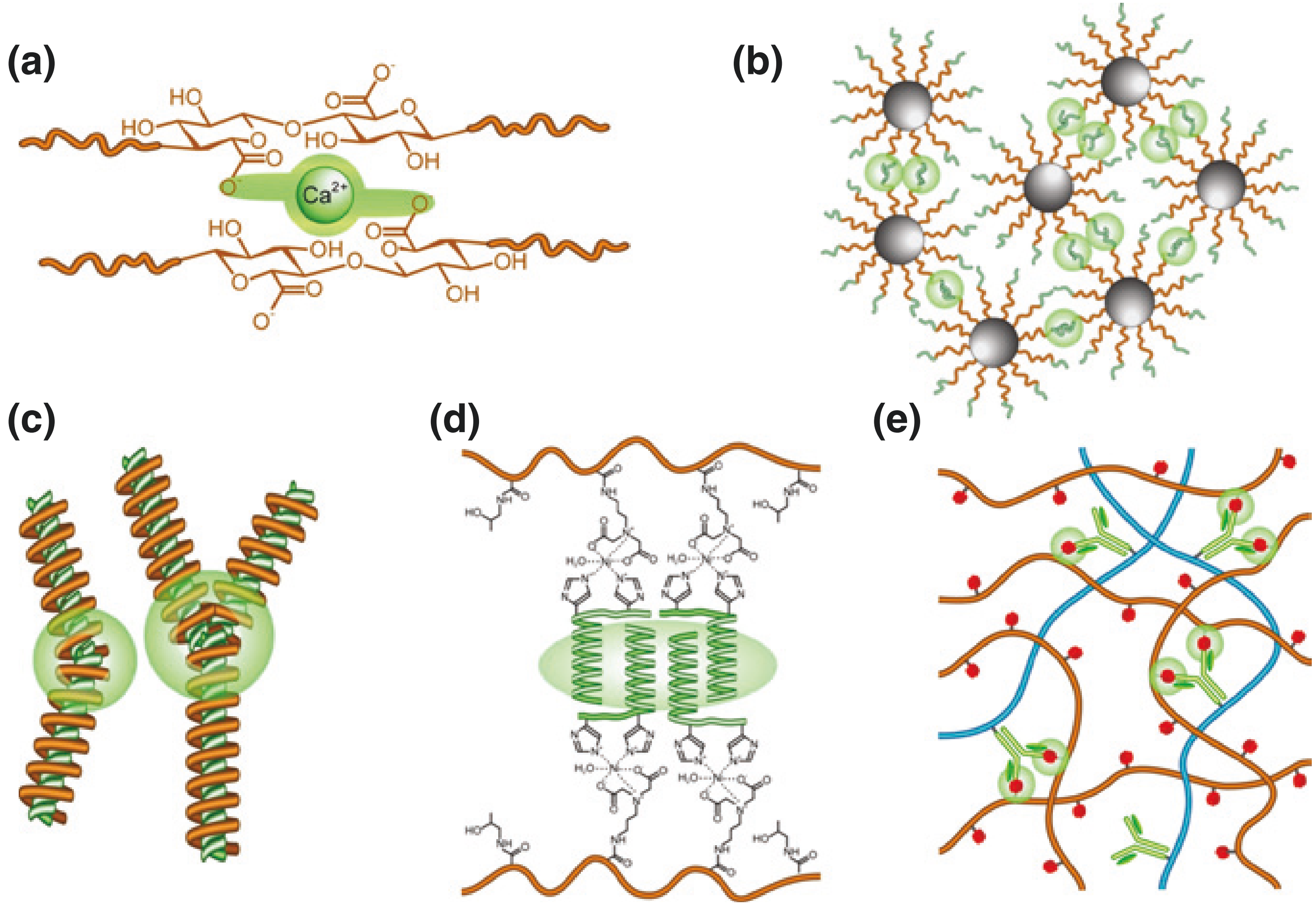


Fig. 2.2 Schematic of methods for formation of physically crosslinked hydrogels via. **a** Ionic interactions, **b** hydrophobic interactions, **c** self-assembling of stereocomplex formation, **d** coiled-coil interactions, **e** specific molecular recognition

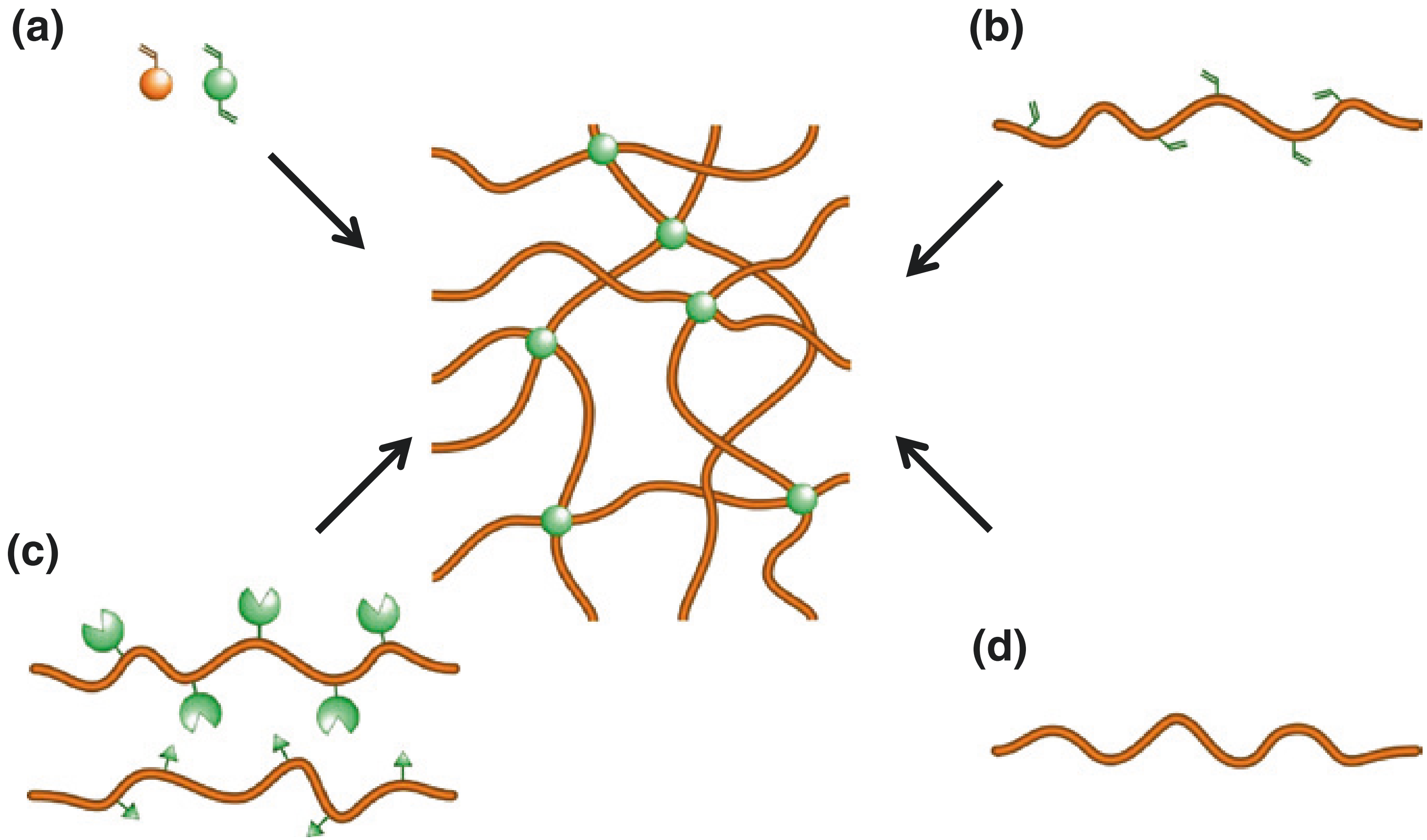


Fig. 2.3 Schematic of methods for formation of chemically crosslinked hydrogels by radical polymerization of **a** vinyl monomers and **b** macromonomers **c** reaction of pendant functional groups, and **d** high-energy radiation

Classification according to network electrical charge

Hydrogels may be categorized into three groups on the basis of presence or absence of electrical charge located on the cross- linked chains:

- Nonionic (neutral).
- Ionic (including anionic or cationic).
- Amphoteric electrolyte (ampholytic) containing both acidic and basic groups.

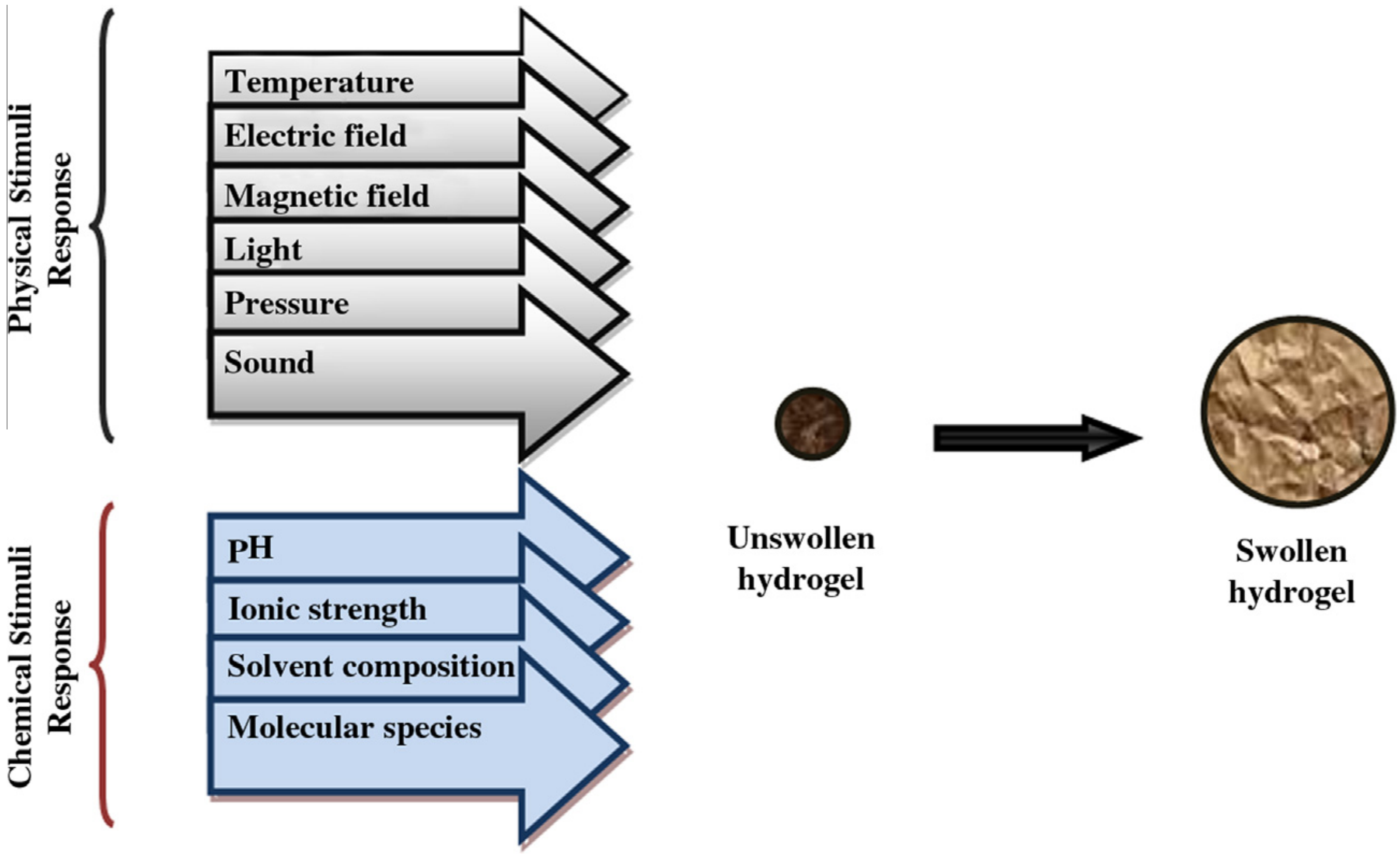
Classification based on configuration

The classification of hydrogels depends on their physical structure and chemical composition can be classified as follows:

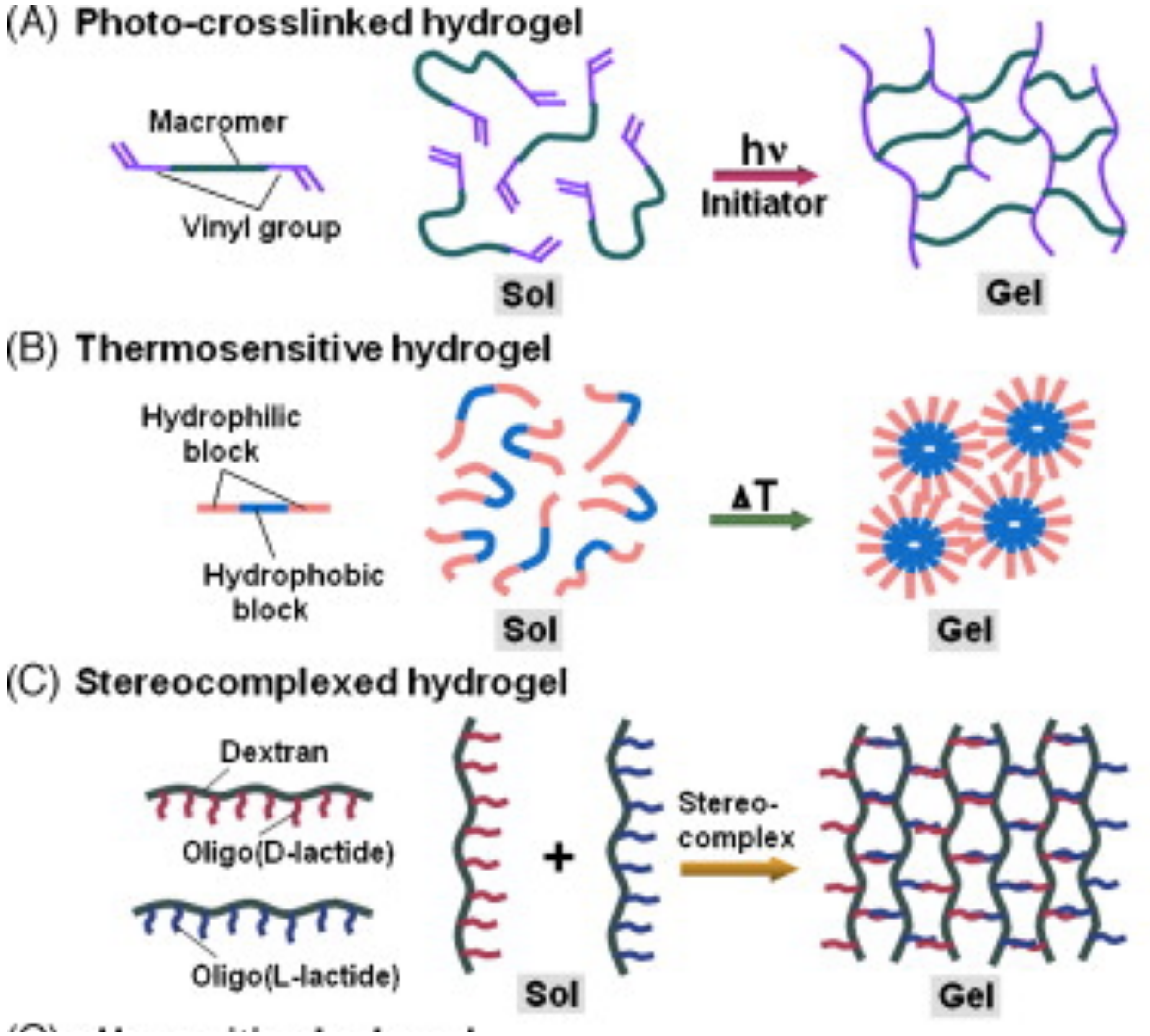
- Amorphous (non-crystalline)
- Semi-crystalline: A complex mixture of amorphous and crystalline phases
- Crystalline.

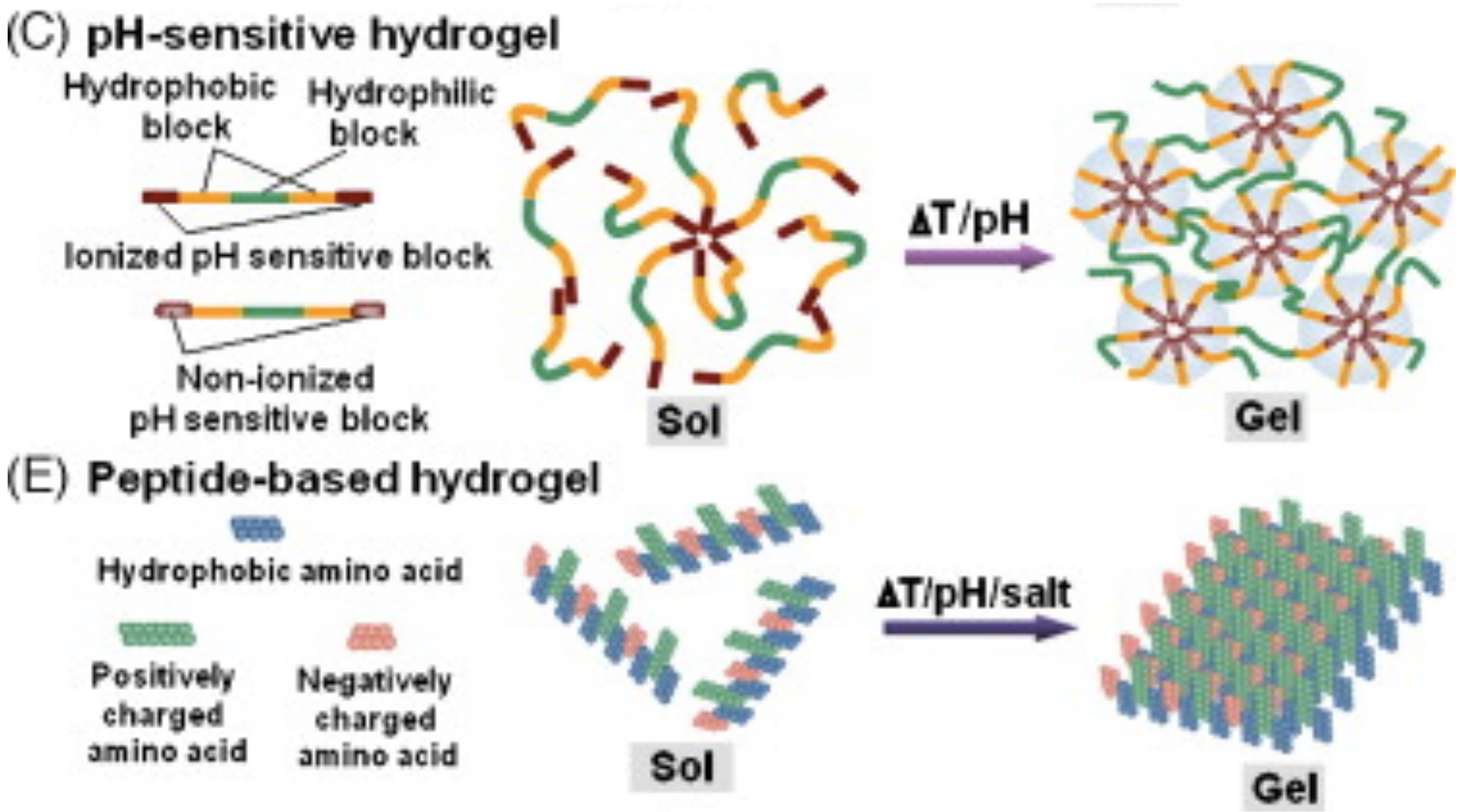
Hydrogels sensitive to environmental conditions

- Hydrogels are capable of swelling or de-swelling reversibly in water and retaining large volume of liquid in swollen state.
- They may perform dramatic volume transition in response to a variety of physical and chemical stimuli:
  - temperature, electric or magnetic field, light, pressure, and sound
  - pH, solvent composition, ionic strength, and molecular species
- Hydrogels can be designed with controllable responses as to shrink or expand with changes in external environmental conditions.


Physical Stimuli Response
Temperature
Electric field
Magnetic field
Light
Pressure
Sound
Chemical Stimuli Response
PH
Ionic strength
Solvent composition
Molecular species
Unswollen hydrogel
Swollen hydrogel

- pH-sensitive hydrogels
- Temperature-sensitive hydrogels
- Complexing hydrogels
- Materials sensitive to chemical or enzymatic reaction
- Magnetically responsive systems


(A) Photo-crosslinked hydrogel
Macromer
Vinyl group
hν
Initiator
Sol
Gel
(B) Thermosensitive hydrogel
Hydrophilic block
Hydrophobic block
ΔT
Sol
Gel
(C) Stereocomplexed hydrogel
Dextran
Oligo(D-lactide)
Oligo(L-lactide)
+
Stereo-complex
Sol
Gel


(C) pH-sensitive hydrogel
Hydrophobic block
Hydrophilic block
Ionized pH sensitive block
Non-ionized pH sensitive block
Sol
ΔT/pH
Gel
(E) Peptide-based hydrogel
Hydrophobic amino acid
Positively charged amino acid
Negatively charged amino acid
Sol
ΔT/pH/salt
Gel

Temperature-responsive hydrogels

- Physically crosslinked thermosensitive hydrogels may undergo sol–gel phase transitions instead of volume change at a critical solution temperature.

- Positive temperature-responsive hydrogels show phase transition at a critical temperature called the upper critical solution temperature (UCST). Hydrogels made from polymers with UCST shrink when cooled below their UCST.

- Negative temperature- responsive hydrogels have a lower critical solution temperature (LCST). These hydrogels shrink upon heating at above their LCST .

pH-responsive hydrogels

- pH-responsive hydrogels are made of polymeric backbones with ionic pen- dant groups that can accept or donate protons in response to an environmental pH change.

- As the environmental pH changes, the degree of ionization in a pH-responsive hydrogel is dramatically changed.

- There are two types of pH- responsive hydrogels: anionic and cationic hydrogels:
  - PAAc becomes ionized at high pH
  - Poly(*N, N'*-diethylaminoethyl methacrylate) (PDEAEM) becomes ionized at low pH.

Technologies adopted in hydrogel preparation

Any of the various polymerization techniques can be used to form gels, including bulk, solution, and suspension polymerization.

In general, the three integral parts of the hydrogels preparation are

- monomer
- initiator
- cross-linker

Technologies adopted in hydrogel preparation

Bulk polymerization

- Bulk polymerization is the simplest technique which involves only monomer and monomer-soluble initiators.
- The polymerization reaction is normally initiated with radiation, ultraviolet, or chemical catalysts.
- High rate of polymerization and degree of polymerization occur because of the high concentration of monomer.
- The bulk polymerization of monomers to make a homogeneous hydrogel produces a glassy, transparent polymer matrix which is very hard.
- When immersed in water, the glassy matrix swells to become soft and flexible.

Technologies adopted in hydrogel preparation

Solution polymerization/cross-linking

- In solution copolymerization/cross-linking reactions, the ionic or neutral monomers are mixed with the multifunctional cross- linking agent.
- The polymerization is initiated thermally by UV-irradiation or by a redox initiator system.
- The presence of solvent serving as a heat sink is the major advantage of the solution polymerization over the bulk polymerization.
- Typical solvents used for solution polymerization of hydrogels include water, ethanol, water–ethanol mixtures, and benzyl alcohol.

Technologies adopted in hydrogel preparation

Suspension polymerization

- In this technique, the monomers and initiator are dispersed in the hydrocarbon phase as a homogenous mixture.
- The viscosity of the monomer solution, agitation speed, rotor design, and dispersant type mainly governs the resin particle size and shape.
- Dispersion polymerization is an advantageous method since the products are obtained as powder or microspheres (beads), and thus, grinding is not required.

Technologies adopted in hydrogel preparation

Grafting to a support

- Generally, hydrogels prepared by bulk polymerization have inherent weak structure.
- To improve the mechanical properties of a hydrogel, it can be grafted on surface coated onto a stronger support.
- This technique that involves the generation of free radicals onto a stronger support surface and then polymerizing monomers directly onto it as a result a chain of monomers are covalently bonded to the support.

Natural Hydrogel Polymers

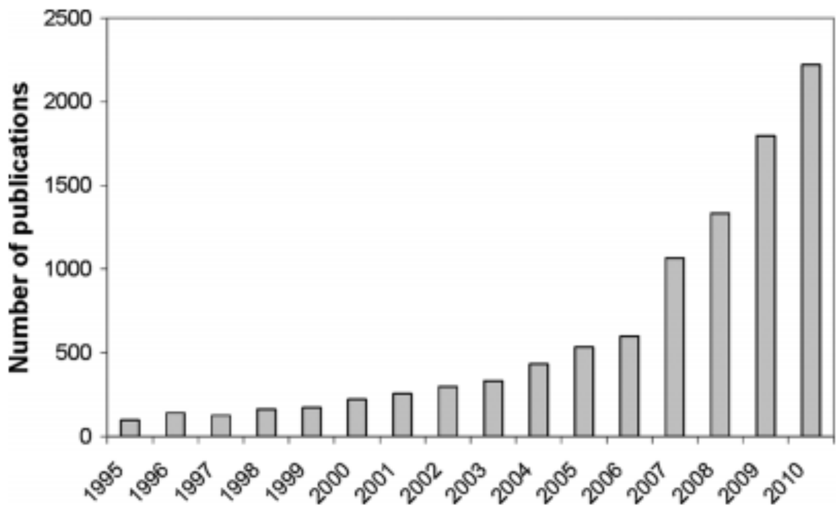
- **Formed from proteins and ECM components**
  - Collagen, Hyaluronic acid, Matrigel
- **Biological sources**
  - Chitosan, Alginate, Fibroin
- **Pros**
  - Inherently biocompatible and bioactive
  - Promote many cellular functions
  - Embedded proteins, growth factors, and enzymes
- **Cons**
  - Vary by batch
  - High affinity to proteins present in serum
  - Lacks tunability

Synthetic Hydrogel Polymers

- **Non-natural materials**
  - Examples: poly(ethylene glycol), poly(vinyl alcohol), and poly(2-hydroxy ethyl methacrylate)
- **Pros**
  - Minimal tendency to adsorb proteins
  - Highly reproducible
  - Readily available
  - Opportunity to control presentation of mechanical properties and biochemical cues
- **Cons**
  - Lacks cell adhesion sites
  - Tight crosslinks render cells immobile
  - Protein diffusion is limited preventing cells from secrete ECM

Motivation for Hydrogels

- Drug delivery, scaffolds, food preservation, biosensors
- Biomaterial, coatings for medical devices, contact lenses
  - Biologically compatible
- Study cell and tissue physiology
  - Large water content and rubbery consistency makes hydrogels great mimics for living tissue



Drug delivery systems

- Permeability and swelling depend strongly on:
  - chemical nature of the polymer
  - structure
  - morphology
- Drug delivery systems classification:
  - swelling controlled
  - chemically controlled
  - environmentally responsive
- Smart and responsive hydrogels are ideally suited as intelligent drug delivery systems

Contact lenses

- New high permeability lenses made of silicone based hydrogels
- Wear resistance has been improved thanks to specific surface treatments
- The hydrophobic surface of the silicone is converted into hydrophilic to avoid eye adesion and protein accumulation
- These systems have a higher permeability to oxygen
- Can be used up to 30 days without removing them
- They are covering now more than 2/3 of the market

Important Properties

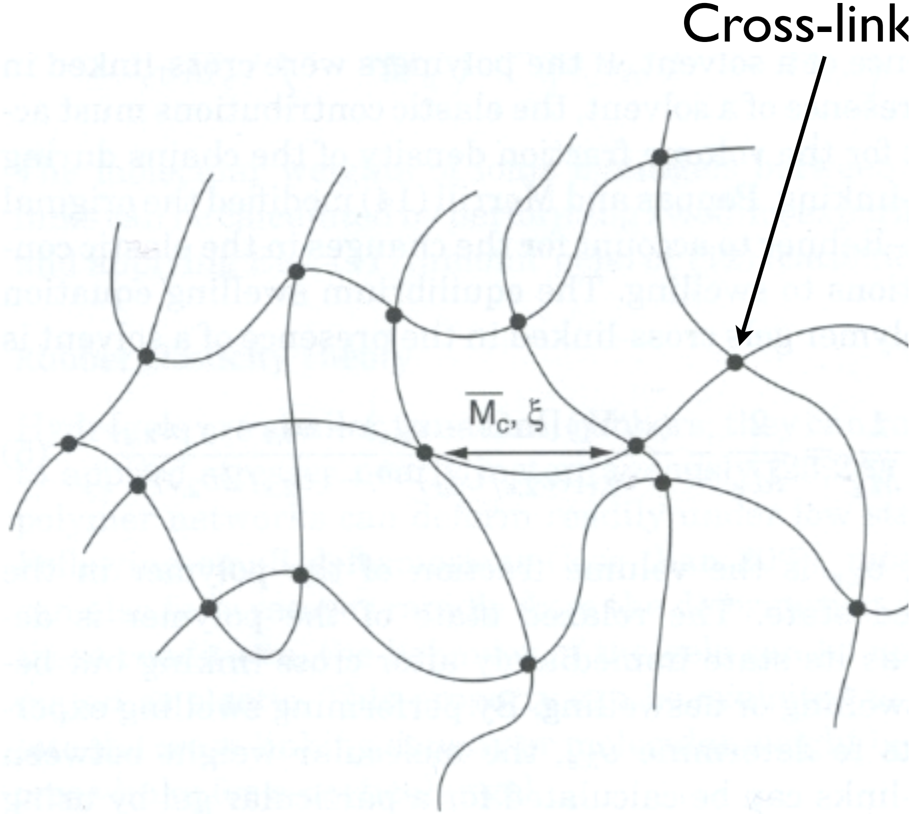
- Swelling
  - Solute diffusion
  - Surface properties and mobility
  - Optical properties
  - Mechanical properties

Most important parameters that define structure and properties of swollen hydrogels are

- **polymer volume fraction in swollen state, $v_{2,s}$**,
- effective molecular weight of polymer chain between cross-linking points, M_c, and
- correlation distance between two adjacent cross-links, ξ.

Rubber-elasticity theory and equilibrium-swelling theory are extensively applied to describe these three dependent parameters.

- From morphology the structure is defined by:
    - Pores size: ξ
    - Molecular weight between cross-links: $\overline{M}_c$
    - Volume fraction of the polymer in the swollen gel:



$$\upsilon_{2,s} = \frac{\text{Volume of polymer}}{\text{Volume of swollen gel}} = \frac{V_p}{V_{gel}} = \frac{1}{Q}$$

Degree of cross-linking:

$$X = \frac{M_0}{2\overline{M}_c}$$

$$\frac{1}{\overline{M}_c} = \frac{2}{\overline{M}_n} - \frac{\left(\frac{\upsilon}{V_1}\right)\left[\ln\left(1-\upsilon_{2,s}\right)+\upsilon_{2,s}+\chi_1\upsilon_{2,s}\right]}{\upsilon_{2,r}\left[\sqrt[3]{\frac{\upsilon_{2,s}}{\upsilon_{2,r}}}-\frac{\upsilon_{2,s}}{\upsilon_{2,r}}\right]}$$

$\overline{M}_n$: molecular weight of linear chains without cross-linking

$\upsilon_{2,r}$: volumetric fraction of polymer in the relaxed state

υ : specific volume of the polymer

χ_1 : polymer-solvent interaction parameter

V_1 : molar weight of the solvent

The equilibrium swelling ratio or water content is generally used to describe the swelling behavior of hydrogels:

$$Equilibrium\ swelling\ ratio = W_{swollen}/W_{dry}$$

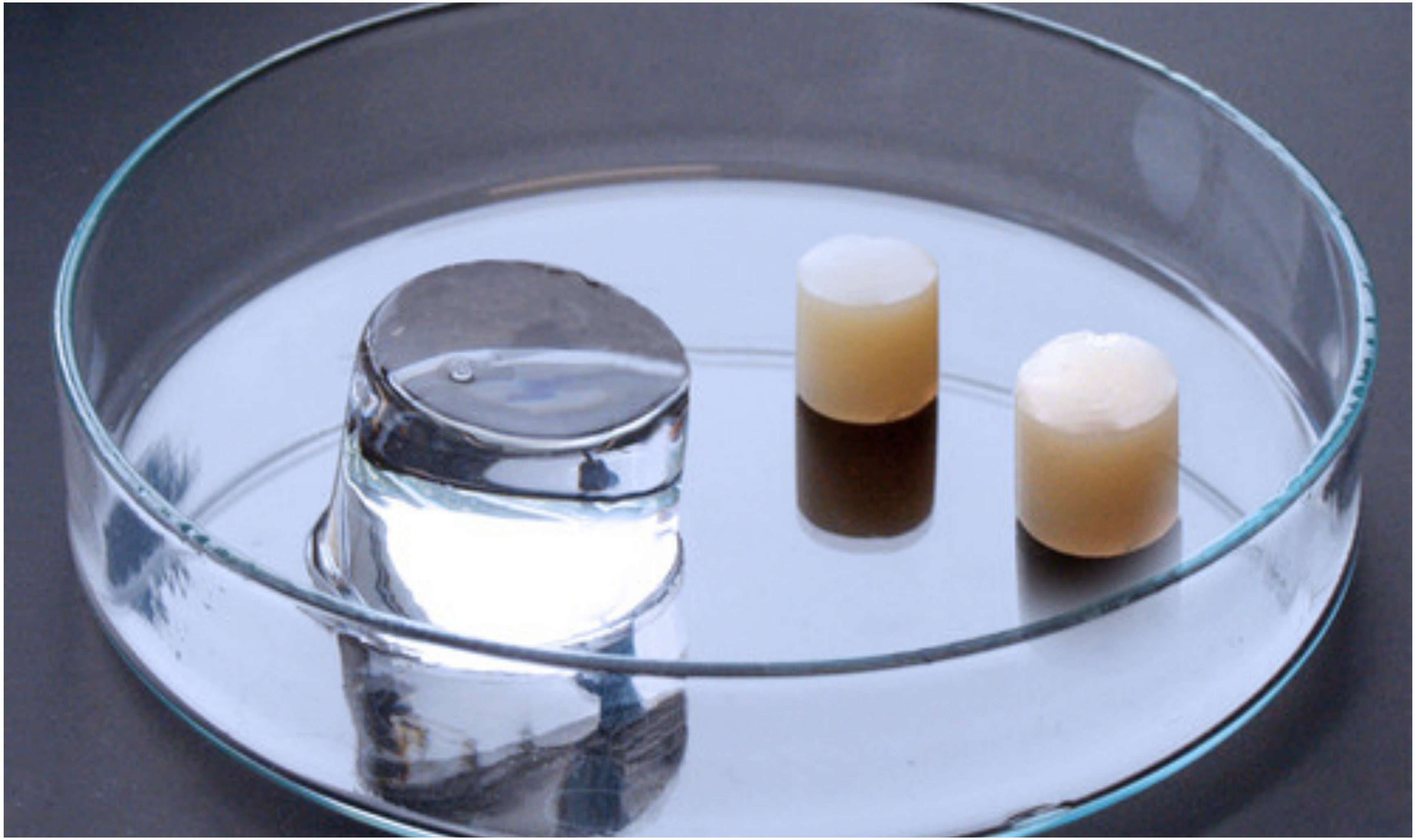
The swelling kinetics of hydrogels can also be determined from the swelling kinetic curves.

$$Swelling\ ratio = \left(W_t - W_0\right)/W_0$$

The swelling characteristics are crucial to the use of hydrogels in biomedical and pharmaceutical applications since the equilibrium swelling ratio affects:

- the solute diffusion coefficient
- surface wettability
- mobility
- optical and mechanical properties of the hydrogel.

Swelling Properties



Type	Morphology	Type of absorbed water	Major swelling mechanism	Swelling rate	Application
Non-porous	Without network porosity	Mostly bound	Diffusion through free volumes	Very slow, sample size-dependent	Various uses from contact lenses to artificial muscles, etc.
Micro-porous	Various porosity with closed-cell structure (100-1000 Å)	Mostly bound	Combination of molecular diffusion and convection in the water filled pores	Slow, sample size-dependent	Mainly in biomedical applications and controlled release technology
Macro-porous	Various porosity with closed-cell structure (0.1 -1 μm)	Mostly bound	Diffusion in the water filled pores	Fast, sample size-dependent	Mainly in form of superabsorbents in baby diapers, etc.
Super-porous	High porosity with interconnected open-cell structure	Mostly free	Capillary forces	Very fast, sample size-independent	DDS (particularly in the gastrointestinal tract), tissue engineering, etc.

Slow swelling is due to slow diffusion of water into glassy matrix of dried hydrogels. Sometime fast swelling polymer is more desirable; therefore, Chen et al., 1999 and Park developed a new kind of superabsorbent polymers so called superporous hydrogels.

Superporous hydrogels (SPHs) are porous hydrophilic crosslinked structures with the ability of absorbing aqueous fluids up to a few hundred times their own weight.

Superporous hydrogels (SPHs) were originally developed as a novel drug delivery system to retain drugs in the gastric medium. These systems should instantly swell in the stomach and maintain their integrity in the harsh stomach environment, while releasing the pharmaceutical active ingredient.

Table 3 General features of superabsorbent (SAPs) and superporous (SPHs) hydrogels.

Point of comparison	SAPs	SPHs
Commonly used monomer	Acrylamide, acrylic acid, salts of acrylic acid including sodium and potassium acrylates	Acrylamide, acrylic acid, salts of acrylic acid including sodium and sulfopropyl acrylates, 2-hydroxyethyl methacrylate
Method of synthesis	Bulk, solution, inverse-suspension	Mostly aqueous solution
Initiating system	Thermal, redox	Mostly redox
Porous structure	Random closed to semi open cells	Interconnected open cells
Final product	Particles	Any shape including particles, sheet, film, rod.
Applications	Where high swelling, fast-medium rate of swelling is required	Where size-independent high and very fast swelling is required

Table 4 Typical formulations of aqueous solution polymerization for SAPs and SPHs preparation.

Starting material	Role	Nonporous SAP	Porous SAP	Superporous SPH
Acrylamide, acrylic acid	Monomer	✓	✓	✓
Bisacrylamide	Cross-linker	✓	✓	✓
Deionized water	Solvent	✓	✓	✓
Ammonium persulphate	Oxidant	✓	✓	✓
Tetramethyl ethylenediamine	Reductant	✓	✓	✓
Glacial acetic acid	Foaming aid		✓	✓
Sodium bicarbonate	Foaming agent		✓	✓
PEO-PPO-PEO block copolymer	Foam stabilizer			✓
Starting reaction temperature (°C)		25	25	25
Reaction temperature		Within 30 s (after 15 s of inhibition period) the reaction temperature rises from 25 to about 75 °C with the rate of about 2 °C/s	Within 66 s (after 80 s of inhibition period) the reaction temperature rises from 25 to about 65 °C with the rate of about 1 °C/s	Within 78 s (after 80 s of inhibition period) the reaction temperature rises from 25 to about 55 °C with the rate of about 0.7 °C/s
Reaction product after synthesis		Solid rigid hydrogel	Solid flexible unstable foam	Solid flexible Stable foam

The functional features of an ideal hydrogel material

- The highest absorption capacity (maximum equilibrium swelling) in saline.
- Desired rate of absorption (preferred particle size and porosity) depending on the application requirement.
- The highest absorbency under load (AUL).
- The lowest soluble content and residual monomer.
- The lowest price.
- The highest durability and stability in the swelling environment and during the storage.

The functional features of an ideal hydrogel material

- The highest biodegradability without formation of toxic species following the degradation.
- pH-neutrality after swelling in water.
- Colorlessness, odorlessness, and absolute non-toxic.
- Photo stability.
- Re-wetting capability (if required) the hydrogel has to be able to give back the imbibed solution or to maintain it; depending on the application requirement (e.g., in agricultural or hygienic applications).