Hydrogels in Drug Delivery

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Hydrogels

Hydrogels are hydrophilic polymer networks which may absorb from 10–20% (an limit) up to thousands of times their dry weight in water.
Hydrophilic polymers used to synthesize hydrogel matrices

Natural polymers and their derivatives (±crosslinkers)
Anionic polymers: HA, alginic acid, pectin, carrageenan, chondroitin sulfate, dextran sulfate
Cationic polymers: chitosan, polylysine
Amphipathic polymers: collagen (and gelatin), carboxymethyl chitin, fibrin
Neutral polymers: dextran, agarose, pullulan

Synthetic polymers (±crosslinkers)
Polyesters: PEG-PLA-PEG, PEG-PLGA-PEG, PEG-PCL-PEG, PLA-PEG-PLA, PHB, P(PF-co-EG)±acrylate end groups, P(PEG/PBO terephthalate)
Other polymers: PEG-bis-(PLA-acrylate), PEG±CDs, PEG-g-P(AAm-co-Vamine), PAAm, P(NIPAAm-co-AAc), P(NIPAAm-co-EMA), PVAc/PVA, PNVP, P(MMA-co-HEMA), P(AN-co-allyl sulfonate), P(biscarboxy-phenoxy-phosphazene), P(GEMA-sulfate)

Combinations of natural and synthetic polymers
P(PEG-co-peptides), alginate-g-(PEO-PPO-PEO), P(PLGA-co-serine), collagen-acrylate, alginate-acrylate, P(HPMA-g-peptide), P(HEMA/Matrigel®), HA-g-NIPAAm
Applications of Hydrogels in Drug Delivery

- Benefits of controlled drug delivery
  - more effective therapies with reduced side effects
  - maintenance of effective drug concentration levels in the blood
  - patient’s convenience as medicines as taken less frequently
  - increased patient compliance
Release mechanisms of drug molecules:

diffusion, dissolution, osmosis, ion exchange
(1) Polymer matrix, drugs are loaded in the water-insoluble Polymer matrices

(2) Reservoir system, Drugs are loaded in reservoirs that are subsequently covered by water-insoluble polymer membrane
The same monolithic and reservoir devices can be prepared by using water-soluble or biodegradable polymers and hydrogels, in which the drug release is controlled by dissolution of the polymers and hydrogels. As in Figure 5.2a, highly cross-linked hydrogels can be used as monolithic devices, or the hydrogel core can be covered with a water-insoluble polymer membrane to form reservoir devices (Figure 5.2b).
In osmosis-controlled drug delivery systems, the core of the devices is often made of hydrogels as a source of osmotic pressure.

In ion-exchange-based drug delivery systems, water-soluble polyelectrolytes are highly cross-linked, and these are basically hydrogels with very high cross-linking densities, which prevents the system from swelling.
Controlled drug delivery by diffusion, dissolution, osmosis, and ion exchange allows continuous delivery of drugs at predetermined rates. In many instances, however, drug delivery has to be noncontinuous, or pulsatile. For example, delivery of insulin should not be continuous; rather, a bolus of insulin has to be delivered only when the blood glucose level is increased. Such delivery, known as modulated or self-regulated delivery, requires hydrogels with properties recognizing the changes in environmental conditions, i.e., “environment-sensitive hydrogels.”
Applications of Hydrogels in Drug Delivery

- Environment-Sensitive Hydrogels
  - respond to environmental change: temperature, pH, specific molecule
  - reversible volume phase transition or sol–gel phase transition
  - “intelligent” or “smart” hydrogel

Diagram:
- Change in pH for gel swelling
- Drug-loaded gel
- Change in temperature for gel collapse
- Drug release through the swollen network
- Drug release by the squeezing action
As shown in Figure 5.3, a smart hydrogel can undergo swelling due to a change in the pH of the environment, resulting in easier diffusion of drug molecules through the expanded polymer network. Alternatively, the temperature of the environment can be increased to shrink the temperature-sensitive hydrogels for faster release of the drugs through a squeezing action. Typical examples of the environment-sensitive hydrogels are listed in Table 5.2, and the structures of selected polymers are shown Figure 5.4.
### Environmental-Sensitive Hydrogels used for Drug Delivery

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Applications of Hydrogels in Drug Delivery

• Molecular structures of environmental-sensitive hydrogels

(1) Temperature sensitive hydrogel

Poly(N-isopropylacrylamide) (PNIPAAm)

Poly(NIPAAm-co-butyl methacrylate) (P(NIPAAm-co-BMA))

Poly(ethylene oxide-co-propylene oxide-co-ethylene oxide) (PEO-PPO-PEO)

(2) pH sensitive hydrogel

Poly(acrylic acid) (PAA)

Poly(N,N'-diethylaminoethyl methacrylate) (PDEAEM)

(3) Biodegradable hydrogel

Poly(ethylene glycol-b-L-lactide-co-glycolide-b-ethylene glycol) (PEG-PLGA-PEG)

(4) Glucose sensitive hydrogel

Poly(N-vinylpyrrolidone-co-phenyl boronic acid) (Poly(NVP-co-PBA))

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Hydrogel

- polymer N-isopropylacrylamide (NIPAAm) is thermal responsive in water
- below the Low Critical Solution temperature 32°C (LCST), NIPAAm is swollen – hydrophilic
- above the LCST, it is shrunk - hydrophobic
Applications of Hydrogels in Drug Delivery

(1) Temperature-Sensitive Hydrogel: volume phase transition

ex) PNIPAAm → changed around LCST:
• negative thermosensitivity (competition between hydrogen bonding and hydrophobic interaction)

\[
\begin{array}{c|c|c|c}
\text{Conc.} & \text{Temp.} & \text{Hydrogen bonding} & \text{swelling or solubility}\uparrow \\
\hline
\text{Hydrophobic interaction} & \text{shrinking} & \Rightarrow \text{'on/off' drug delivery system}
\end{array}
\]

ex) IPNs of poly(acrylic acid)
• positive thermosensitivity

\[
\begin{array}{c|c|c|c}
\text{Conc.} & \text{Temp.} & \text{Swelling or solubility} & \text{shrinking} \\
\hline
\text{UCST} & \Rightarrow
\end{array}
\]
Applications of Hydrogels in Drug Delivery

(2) pH-sensitive hydrogels-polyelectrolyte

ex) poly(N,N-diethylaminoethyl methacrylate)

\[
\begin{align*}
\text{CH}_2 & \quad \text{H} \\
\text{C} & \quad \text{C} \\
\text{C} & \quad \text{O} \\
\text{O} & \\
\text{CH}_2\text{CH}_2\text{N(CH}_2\text{CH}_3)_2 & \\
\end{align*}
\]

a. acidic or basic pendant group  
b. dissolve or swell at low pH  
c. relatively-high-swelling behavior  
→ electrostatic repulsive interaction

cf) pH difference between the stomach and the intestine

high pH → swell → intestine : neutral ⇒ drug release !

low pH → shrink → stomach : acidic

To protect acid-labile drugs in the stomach
Applications of Hydrogels in Drug Delivery

(3) pH & temperature-sensitive hydrogel:
- incorporating ionizable and hydrophobic functional groups
- dependent on both the temperature and the pH

\[
\text{pH of the medium} > pK_a \text{ of the carboxyl groups of polyanions}
\]

\[
\text{ionization} \quad \rightarrow \quad \text{increased LCST} \Rightarrow \text{increased hydrophilicity, charge repulsion}
\]
Applications of Hydrogels in Drug Delivery

(4) Specific molecule-sensitive hydrogel: glucose-sensitive hydrogel

- Glucose oxidase
- Glucose
- Insulin

![Diagram showing the components and interactions of the glucose-sensitive hydrogel system.](image)

- Neutral polymer: \( \text{N(CH}_3\text{)}_2 \)
- Charged polymer: \( + \text{N(CH}_3\text{)}_2 \text{H} \)

Glucose oxidase catalyzes the reaction between glucose and gluconic acid, leading to the release of insulin from the reservoir when pH decreases.
■ Biodegradable Hydrogels
  - Degradation mechanism: control the kinetics of drug release
  - Hydrolysis or enzyme-catalyzed hydrolysis
  - Hydrophobic and water insoluble
  - Eliminate the need of removing a drug delivery device
  - Biocompatibility and flexibility

Poly(lactic acid)

Poly(glycolic acid)

Poly(lactic-co-glycolic acid)

Poly(ε-caprolactone)

poly(ortho esters), polyanhydrides, polyphosphoesters
Specific applications of Hydrogels in Oral Drug Delivery

- Oral cavity
  - Tablet superdisintegrants
  - Mucoadhesive hydrogels

- Small intestine
  - Hydrotropic hydrogels
  - pH-sensitive hydrogels

- Large intestine
  - Enzyme-degradable hydrogels
  - pH-sensitive hydrogels

- Stomach
  - pH-sensitive hydrogels
  - Gastric retention devices
  - Gastric floating systems
  - Mucoadhesive systems
  - Superporous hydrogels
Hydrotropic Hydrogels for delivery of poorly soluble drug

- Hydrotropic agent: Diverse class of water soluble compounds at high concentration, enhance water solubilities of poorly soluble solutes ex) N,N-dimethylnicotinamide (3.5M), N,N-diethylnicotinamide

- Many drugs: poorly soluble in water
  low absorption and low bioavailability

- Low–molecular–weight hydrotropes: high concentration

- Polymeric forms of hydrotropes (e.g., hydrotropic hydrogels)
• Hydrogels have played role in the development of various controlled-release formulation
  → biocompatible and increasing the solubility of poorly soluble drug
• Hydrogels with novel properties will continue to play important role in drug delivery
  → smart hydrogels and new controlled-release formulation
Reference

• A. S. Hoffman, Hydrogels for biomedical application, Adv. Drug Delivery Rev. 54 (2002), 3-12
Improving the delivery of hydrogels
Improving the delivery of hydrogels

- Hydrogels used in drug delivery are usually formed outside of the body and impregnated with drugs before placement of the hydrogel drug complex in the body.

- A wide range of cross-linking strategies can be used, including UV photopolymerization and various chemical cross-linking techniques.
Improving the delivery of hydrogels

- Such cross-linking methods are useful only if toxic reagents can be completely removed prior to hydrogel implantation, which may be difficult to achieve without leaching loaded drug.

- In addition, bulk hydrogels have a defined dimensionality and often high elasticity which generally excludes extrusion through a needle.

- Because of these considerations, there has been considerable interest in *in situ* gelation.
In Situ gelation

1. Physically cross-linked hydrogels
2. Covalently cross-linked hydrogels
Physically cross-linked hydrogels

- Physical cross-linking can be achieved using a variety of environmental triggers (pH, temperature, ionic strength) and a variety of physicochemical interactions such as:
  1. Hydrophobic interactions
  2. Charge interactions
  3. Hydrogen bonding interactions
  4. Stereocomplexation
  5. Supramolecular chemistry
Hydrophobic interactions

✓ A gelator (the hydrophobic segment) is coupled to a hydrophilic polymer segment by post-polymerization grafting or by directly synthesizing a block copolymer to create a polymer amphiphile
Fig. 1. Mechanism of in situ physical gelation driven by hydrophobic interactions
Fig. 2. Chemical structures and abbreviations of common thermogelling hydrophobic blocks
Charge interactions

✓ Have been widely investigated for cross-linking in situ gelling polymers

✓ May occur between a polymer and a small molecule or between two polymers of opposite charge to form a hydrogel
Fig. 3. Mechanisms of in situ physical gelation based on charge interactions with an oppositely-charged polymer or an oppositely-charged small molecule cross-linker.
Charge interactions

Advantages:

1. Biodegradation can occur as ionic species in extracellular fluid bind competitively with the gel components
2. Cross-linking (or decross-linking) can also be triggered by pH changes
3. Can also be used to cross-link microparticle or nanoparticle gels to create three-dimensional particle assemblies with favorable drug delivery properties

✓ For example, dextran microspheres coated with anionic and cationic polymers exhibit spontaneous gelation upon mixing
Hydrogen bonding interactions

✓ Can be used to produce hydrogels in vitro by freeze-thawing, e.g. in the formulation of poly(vinyl alcohol)-based hydrogels

✓ Can also be used to formulate injectable hydrogels

✓ This synergism is typically a result of hydrogen bonding interactions between the polymer chains facilitated by the compatible geometries
Fig. 4. In situ physical gelation via hydrogen bonding interactions between geometrically-compatible biopolymers (methylcellulose and hyaluronic acid); the hydrogen bonds break under shear.
Hydrogen bonding interactions

Advantage:

✓ Generally exhibit excellent biocompatibility due to the absence of chemical cross-linkers and because the formulations are typically based on or resemble extracellular matrix polymers

However:

✓ Hydrogen-bonded networks can dilute and disperse over a few hours in vivo due to influx of water, restricting their use to relatively short-acting drug release systems
Stereocomplexation

✓ Refers to synergistic interactions which can occur between polymer chains or small molecules of the same chemical composition but different stereochemistry
Fig. 5. Mechanism of in situ physical gelation via stereocomplexation between L- and D- lactide polymer chains.
Stereocomplexation

- Resulting in excellent biocompatibility and biodegradability

- Without requiring the use of harsh/denaturing conditions such as organic solvents, chemical crosslinkers, or the formation of hydrophobic domains which may denature embedded proteins
Stereocomplexation

Significant limitation:

✔ Relatively restricted range of polymer compositions which can be used
Supramolecular chemistry

✓ The ordered arrangement of molecules into defined structures

Most common type:
✓ Formation of inclusion complexes between poly(alkylene oxide) polymers and cyclodextrins

✓ Cyclodextrins are molecules which have hydrophilic surfaces but hydrophobic pockets which are geometrically compatible with poly-(alkylene oxide)-based polymers such as PEO or PPO.
Fig. 6. Mechanism of in situ physical gelation via the formation of a supramolecular complex between poly(ethylene oxide) (PEO) and cyclodextrin.
Covalently cross-linked hydrogels

While physically cross-linked hydrogels have the general advantage of forming gels without the need for chemical modification or the addition of cross-linking entities in vivo,

They have some limitations:
Because the strength of a physically crosslinked hydrogel is related to the constituent gelators, it is difficult to decouple variables such as gelation time, network pore size, chemical functionalization, and degradation time.

The tissue dwell time is often poor due to dilution followed by dissipation.
Covalently cross-linked hydrogels

In contrast:

✓ Covalent cross-linking prevents both dilution of the hydrogel matrix and diffusion of the polymer away from the site of injection

✓ The cross-linking groups can be added to reactive pre-polymers as small molecules or conjugated directly to them.
Fig. 7. Typical in situ-cross-linking chemistries: (a) reaction of an aldehyde and an amine to form an imine group (or a Schiff base); (b) reaction of an aldehyde and hydrazide to form a hydrazone; (c) Michael reaction of an acrylate and either a primary amine or a thiol to form a secondary amine or a sulfide.
Small-molecule cross-linking

 ✓ Human serum albumin was cross-linked with the active ester form of tartaric acid to create a highly tissue adhesive hydrogel capable of controlling doxorubicin release
 ✓ The drug itself may also in some cases be used as the cross-linker
 ✓ This approach is restricted to cases in which the drug has two reactive functional groups available for functional group chemistry
Small-molecule cross-linking

General disadvantages:

✓ The potential toxicity of residual unreacted small-molecule cross-linkers
✓ For example, glutaraldehyde is often used to form carbohydrate-based hydrogels but is also a tissue fixative
Polymer-polymer cross-linking

- Avoid the use of potentially toxic small-molecule cross-linking agents
- The main limitation of this approach is that significant polymer modification chemistry may be required to prepare the functionalized pre-polymers
- In addition, the pre-gel polymers are often themselves somewhat cytotoxic, even when prepared from highly biocompatible polymer precursors
Michael addition

✓ Between a nucleophile (i.e. an amine or a thiol) and a vinyl group
✓ Is particularly useful for in situ cross-linking hydrogels due to its rapid reaction time, its flexibility in forming multiple types of bonds, and the relative biological inertness of the polymeric precursors
✓ Has been used to cross-link vinyl sulfone- functionalized dextrans with thiolated poly(ethylene glycol)
Extending the effectiveness of hydrogels for drug delivery
Extending the effectiveness of hydrogels

✓ The high water content of most hydrogels typically results in relatively rapid release of drugs particularly in the case of hydrophilic drugs for which hydrogel delivery is typically applied

✓ This release profile is much shorter than those which can be achieved using microspheres or macroscopic devices

✓ Strategies have been explored to reduce the release rate
Extending the effectiveness of hydrogels

1. Drug-hydrogel interactions
2. Gel network engineering
Drug-hydrogel interactions

A. Physical interactions
B. Covalent bonding
Physical interactions

✓ Charge interactions have frequently been employed to increase the strength of the interactions between the gel and a target drug to delay drug release

✓ Phosphate-functionalized polymers are effective because of their multivalent anionic charge
Fig. 8. Physical strategies for enhancing the interaction between a loaded drug and a polymeric gel to slow drug release.

Example: Phosphate-containing soft contact lenses can bind the cationic drug naphazoline in quantities directly proportional to the phosphate content.
Covalent bonding

✓ Drugs can also be covalently conjugated to the hydrogel matrix

✓ For example, dexamethasone (anti-inflammatory and anti-allergenic) has been conjugated to a photoreactive mono-acrylated PEG through a degradable lactide bond
Fig. 9. Chemical strategies for enhancing the interaction between a loaded drug and a polymeric gel to slow drug release.
Covalent bonding

✓ Drug release may be regulated via the hydrolysis of the polymer backbone

✓ The cross-linker can be engineered to give specific durations of release

✓ For example, by changing the length of a sulfide-based cross-linker from three to four carbons, the time required to release from a hydrogel was increased from approximately 4 days to 2 weeks
Gel network engineering

1. Interpenetrating polymer networks (IPNs)
2. Surface diffusion control
3. Composite hydrogels
Interpenetrating polymer networks (IPNs)

- Second hydrogel network is polymerized within a pre-polymerized hydrogel

- Typically done by immersing a pre-polymerized hydrogel into a solution of monomers and a polymerization initiator

- IPNs can be formed either in the presence of a cross-linker to produce a fully interpenetrating polymer network (full IPN)
  - OR

- In the absence of a cross-linking mechanism to generate a network of embedded linear polymers entrapped within the original hydrogel (semi-IPN)
Fig. 10. Formation and structure of semi- and full interpenetrating polymer networks (IPN).
Interpenetrating polymer networks (IPNs)

Advantages:

1. Relatively dense hydrogel matrices can be produced which feature stiffer and tougher mechanical properties, more widely controllable physical properties, and more efficient drug loading compared to conventional hydrogels.

2. IPN pore sizes and surface chemistries can also be controlled.

3. Interpenetrating phases with different degradation profiles and/or different swelling responses to physiological conditions can be used.
Interpenetrating polymer networks (IPNs)

- Semi-IPNs can more effectively preserve rapid kinetic response rates to pH or temperature (due to the absence of a restricting interpenetrating elastic network)

While

- Still providing most of the benefits of IPNs in drug delivery (e.g. modifying pore size, slowing drug release, etc.)
Surface diffusion control

- Can be performed to generate a reduced-permeability “film” layer at the hydrogel surface, often in conjunction with a thermosensitive switch for on-off drug release
Fig. 11. Drug diffusion control by surface-modifying a hydrogel with an environmentally-responsive polymer graft.
Particle-based drug delivery vehicles have proven capacity for long-term release.

As a result, growing interest has focused on overcoming the inherent pharmacological limitations of hydrogels by coformulating particulate systems into the hydrogel matrix to form composite or “plum pudding” hydrogel networks.
Fig. 13. “Plum pudding”, composite hydrogels containing drug encapsulated in a secondary controlled release vehicle (e.g. microparticles, nanoparticles, microgels, liposomes, micelles). D1 and D2 represent the diffusion coefficients of drug out of the hydrogel
Composite hydrogels

Advantages:

1. May increase the biocompatibility of the particulate vehicle by “hiding” the microparticles

2. The hydrogel phase may also improve the kinetic release profile of microspheres by providing an additional diffusion barrier to drug release
References:


