Hydrogels in drug delivery & biomedical engineering

WHITE PAPER

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Hydrogels consist of three-dimensional, hydrophilic, polymeric networks capable of holding large quantities of solvated hydrophilic drugs. Since the early 1960s they have been considered for controlled release of trapped drugs, both small molecule and macromolecular drugs, through slow diffusion. They possess tuneable properties and the capability to protect labile drugs from degradation controlling their release. Their resemblance to living tissue opens up many opportunities for biomedical applications. Currently, hydrogels are used for manufacturing contact lenses, hygiene products, wound dressings, tissue engineering scaffolds and drug delivery systems.

Hydrogels

Hydrogels have attracted significant interest for their use in drug delivery due to their unique physical properties. The high porosity that characterizes hydrogels can easily be adjusted by controlling the density of cross-links in their matrix and their affinity to water. Their porous structure also allows drugs to be loaded and then released. The advantages offered by hydrogels for drug delivery applications include the possibility for sustained release, which results in maintaining a high local concentration of an active pharmaceutical ingredient over a long period[1]. The drug, or a secondary delivery vehicle, can be loaded into a hydrogel and then its release may proceed through several mechanisms: diffusion controlled, swelling controlled, chemically controlled and environmentally responsive release[2].

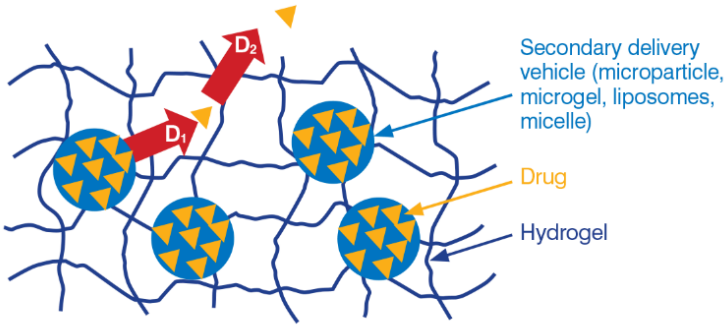


Fig 1: "Plum pudding" composite hydrogels containing drug encapsulated in a secondary controlled release vehicle (e.g. microparticles, nanoparticles, microgels, liposomes, micelles).

Hydrogels may be classified based on their sources (natural or synthetic hydrogel), their polymeric compositions (homo-polymer, co-polymer and multi-polymer hydrogels), physical structure (amorphous, semi-crystalline and crystalline hydrogels), cross-linkers (physical and chemical cross-linked hydrogels), electrical charge (nonionic, cationic, anionic, amphoteric and zwitterionic hydrogels) and release controllers (time controlled hydrogels and stimuli-induced or smart hydrogels)[3].

Hydrogels are generally used for their morphology, elasticity and swelling properties, modulation of each of which the drug release mechanism. Tailored release rates and dissolution profiles can be achieved with hydrogels with different hydrophobicity/hydrophilicity and structural characteristics. Further developments can be expected in the specific use of hydrogels for delivery of therapeutic proteins and peptides.

Diffusion controlled release systems are characterised by reservoir or matrix hydrogels[4].

- A reservoir delivery system includes a drug-containing core coated with a hydrogel membrane, commonly available as capsules, cylinders, spheres or slabs. The concentration of the drug is higher in the centre of the system to allow a constant release rate.
- In matrix systems the drug is dispersed or dissolved uniformly throughout the three-dimensional structure of the hydrogel. Drug release is achieved through the hydrogel's pores. The initial release rate in this instance is proportional to the square root of time.
- In swelling-controlled release, a variant on matrix systems, the process is also called Case II transport and shows constant, time-independent kinetics of release. It combines swelling-controlled release with diffusion, when the hydrogel allows drug diffusion concurrently with relaxation of the polymer chains

According to PubMed there are over 3500 published papers on hydrogel drug delivery systems. While there has also been a high intensity of patent filing relatively few hydrogel-based drug products have reached the market. Examples of the use of hydrogels in drug delivery are given in the table below;

[1] Caló et al 2015, "Biomedical applications of hydrogels: A review of patents and commercial products", *European Polymer Journal 65 252–267*
[2] Hoare et al 2008, "Hydrogels in drug delivery: Progress and challenges", *Polymer 49 1993-2007*
[3] Ghasemiyeh et al 2019, "Hydrogels as Drug Delivery Systems; Pros and Cons", *Trends in Pharmaceutical Sciences 2019: 5(1).*
[4] Zarzycki et al 2010, "Drug release from hydrogel matrices", *Ecological Chemistry And Engineering 17, 2 117-136*

Product	Type of Hydrogel	Therapeutic Application	Drug Delivered
Sericin	Dextran	Optically trackable drug delivery system for malignant melanoma	Doxorubicin
Hyalofemme	Carbomer propylene glycol. Hyaluronic acid derivative	Vaginal dryness, estrogen alternative	Hyaluronic acid derivative
Dextenza	Polyethylene glycol	Intra-canalicular delivery for postoperative ophthalmic care	Dexamethasone
Regranex	Carboxymethyl cellulose	Diabetic foot ulcer	Recombinant human platelet derived growth factor
muGard	2% Poloxamer	Cervical cancer recurrence	Carboplatin

Fig 2: Examples of hydrogels translated to clinical use[5]

In April 2019 the FDA approved a cellulose and citric acid hydrogel capsule, Plenity, for obesity[5].

Hydrogels are also of increasing interest in biomedical engineering applications, particularly for tissue engineering and regenerative medicine. The appropriate combination of materials and synthetic techniques of hydrogels has contributed to the development of scaffolds and generation of tissues with application-based mechanical and biochemical properties. In application of hydrogels to tissue engineering their mechanical properties play a pivotal role in regulating interactions between cells and their microenvironment, and thereby control the cell adhesion, proliferation, motility, differentiation, migration and growth. For applications like engineering of heart valves and vessels, hydrogels need to tolerate shear stresses. Also, complex mechanical gradients exist in many of relatively complex tissues of the body. Hydrogel scaffolds need to resemble the mechanical profile of natural tissues to be accurate biomimetics of cell function[6].

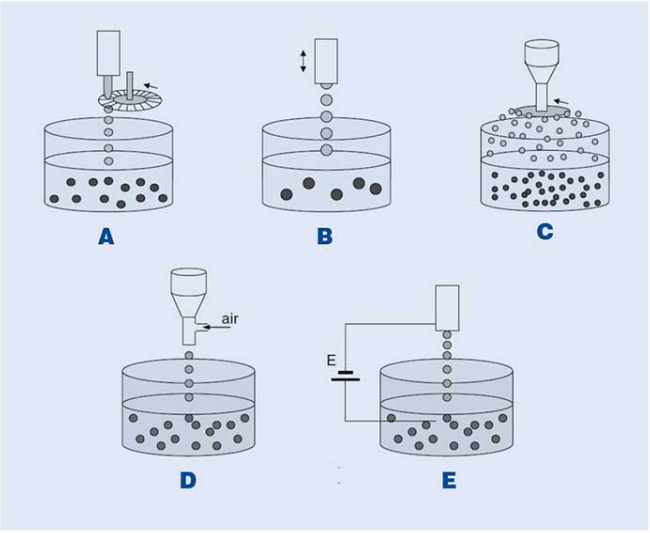
Hydrogels can be delivered in a variety of manners, such as surgical implantation, local needle injection or systemic delivery via intravenous infusion. The choice of delivery method for a given application is based on maximizing the overall efficacy and patient compliance[7].

Manufacture of hydrogels

Hydrogels are usually prepared from polar monomers. Depending on their starting materials, they can be divided into natural polymer hydrogels, synthetic polymer hydrogels, and combinations of these.

Any technique which can be used to create a cross-linked polymer can be used to produce a hydrogel. Copolymerisation/cross-linking free-radical polymerisations are commonly used to produce hydrogels by reacting hydrophilic monomers with multifunctional cross-linkers. Water-soluble linear polymers of both natural and synthetic origin are cross-linked to form hydrogels in a number of ways:

- 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.



While many different monomers can be used, the most common hydrogels are lightly cross-linked copolymers of an acrylate and acrylic acid, and grafted starch-acrylic acid polymers[8].

Cytotoxicity tests are used to evaluate the toxicity of hydrogels. Most of the problems with toxicity associated with hydrogels are unreacted monomers, oligomers and initiators that leach out during application. Understanding the toxicity of the various monomers used as the building blocks of the hydrogels is, therefore, very important[9].

[5] 2019, www.myplenity.com
[6] Vedadghavami et al 2017, "Manufacturing of hydrogel biomaterials with controlled mechanical properties for tissue engineering applications", *Acta Biomaterialia 62 42–63*
[7] Li et al 2016, "Designing hydrogels for controlled drug delivery", Nat Rev Mater 1(12)
[8] Ahmed 2015, "Hydrogel: Preparation, characterization, and applications: A review", *Journal of Advanced Research (2015) 6, 105–121*
[9] Vadithya et al 2012, "As A Review on Hydrogels as Drug Delivery in the Pharmaceutical Field", *International Journal Of Pharmaceutical And Chemical Sciences 1 (2) 642-661*

Aside from application specific morphologies (e.g. hydrogel sheets for wound care), for drug delivery, microspheres are the preferred option. Many dripping techniques are available, ranging from a) jetcutter b) oscillatory nozzle c) spinning disk d) pulsed airflow e) electrostatic. Although each of these approaches are more efficient than just using gravity alone, they are all limited in terms of the minimum droplet size possible (~200µm+) and control of the particle size distribution. In addition, deformation of the droplets on impact with the collection bath, can cause undesirable morphologies.

The Micropore difference

Membrane emulsification sidesteps these challenges by forming hydrogel droplets directly as a w/o emulsion, precise size control can be achieved, with perfectly spherical droplets in sizes less than 50µm.

Thermal gelation is the simplest curing mechanism, materials like agar-agar, carrageenan and gelatine can be processed at elevated temperature and cooled in a controlled manner. Ionic gelation or precipitation is relatively straightforward when using a dripping technique, however with membrane emulsification an alternate approach is required. The preparation of a fine emulsion or dispersion of the relevant curing solution (w/o) is prepared and added to the w/o hydrogel system. The relative proportions of curing agent and polymer concentration is an important consideration. As the hydrogel droplets encounter the fine dispersion of curing agent, surface curing takes place, without significant absorption of additional aqueous phase, therefore the droplet volume is not significantly increased, maintaining the initial favoured size distribution.

This allows for generation of sub-200µm hydrogel microspheres with a consistent particle size distribution. This, in turn, has an influence on consistent delivery of API volume, mechanical stability and biodegradation rate of the particle.

In addition to the hydrogels listed earlier, alginate, chitosan, carrageenan, agar-agar, systems are naturally derived hydrogels, used in an array of drug delivery systems. Knowledge of each polymers relative stability or weakness helps to design a system that will degrade and release API under the desired conditions.

We're ready to help you with your hydrogel challenges.