

Review Article

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Usage of Hydrogels for Brain Imaging and Diagnostics

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Received Date: January 12, 2020

Published Date: January 16, 2020

Abstract

In the last decades, an exponential and rapid evolution has been seen in hydrogel studies. This all started when for the very first-time hydrogels were used in eye surgery. Hydrogels made their way in the medical application because of its biodegradable nature. Now a day's hydrogels applications can be found in many fields including contact lenses, wearable sensors for muscular activities, biodegradable hydrogels for reconstructive surgery and many more. All of these classes have been continuous studies with time to improve the efficiency and filed of applications. Beside all these applications, recently hydrogels were used for tissue engineering especially as a scaffold for stem cells. It was found that hydrogels play an important role in brain application including the treatment of brain tumors. This review covers the use of hydrogels in brain applications.

Introduction

A hydrogel is a three-dimensional network composed of polymers that are hydrophilic in nature. As a result, hydrogel structures can retain a substantial quantity of water. Functional groups like $-NH_2$, $-SO_3H$, $-OH$, $-CONH_2$, $-COOH$ provide hydrophilicity to hydrogels. Wichterle & Lím [1] reported hydrogels for the very first time in 1960. These structures are flexible and contain at least 10% of water (by volume or weight). Sometimes they are also named hungry networks. Hydrogels respond to external stimuli (physical or chemical) and undergo a phase transition. The external stimuli consist of pressure, magnetic field, light intensity, temperature,

chemical composition, and pH and more. But the transition is usually reversible which means hydrogels return to their initial state after the stimuli are removed. It should be noted that not all the monomers or hydrogels react similarly to different stimuli. The functional groups present in the hydrogels make them responsive to various stimuli [2-4]. Hydrogels have the potential to find their uses in many fields; oil recovery, agriculture, biosensors, biotechnology, pharmaceutical, to name a few. Other applications involve their use as superabsorbent diapers [5], drug delivery [6], tissue regeneration [7], cell cultures [8] and contact lenses [9].

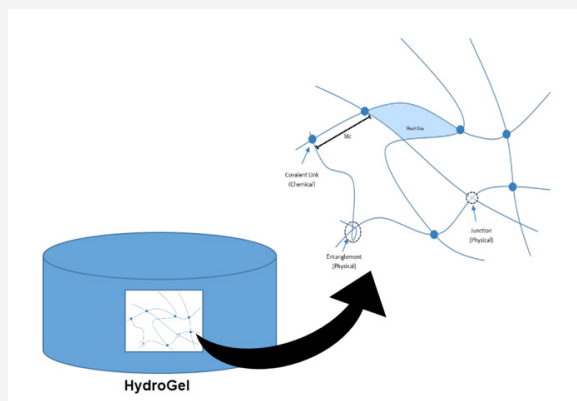


Figure 1: Schematic of a hydrogel network having mesh size ξ and polymeric chain molecular mass M_c [13].

Hydrogels can be classified into two categories; i) physically cross-linked, ii) chemically cross-linked. Chemically cross-linked hydrogels are insoluble in water unless the covalent bond in the network is broken first [10]. The network of physical hydrogels is formed by the non-covalent cross-linking of monomers, e.g., electrostatic interaction [11]. Usually, hydrogels are inert in nature which makes hydrogels one of the best candidates to be used as biomaterials [12]. The response of hydrogels depends on their composition, degree of cross-linking and type of cross-linking. Tailoring these properties may allow us to synthesize application-based hydrogels. Mesh size is an important factor that determines the space available for external particles to enter or leave the hydrogel network and is controlled by the degree of cross-linking (see Figure 1) [13].

There are certain properties of hydrogel structures that are hunted when being used for sensing applications; i) the degree of wetness and inertness of the structure that makes it qualified to be a hydrogel, ii) the degree of sensitivity or response to the external stimuli like change in swelling, and iii) the diffusion control of particles through their polymeric structures [14-16]. The theory of swelling needs to be understood which is essential for sensing applications of hydrogels. The following section will describe the swelling theory of hydrogels.

In hydrogel network, osmotic pressure is created by the hydrophilicity of monomers which results in the swelling of structure upon contact with water [17]. The swelling occurs in three stages; i) first the water diffuses into the structure, ii) after hydration, the polymer chains relax, and iii) lastly, they expand upon relation [17,18]. There is a limit to which hydrogels can absorb water. This limit or so-called equilibrium is attained when the osmotic pressure becomes equal to the elastic counteractive forces of polymeric chains in hydrogel structure. The expansion stops at this equilibrium state. When osmotic pressure changes due to any kind of activity, for example by breakage of bond or change in pH value, the equilibrium is disturbed which results in the swelling or shrinking of hydrogel structure to stabilize. Flory & Rehner [19,20] have described the theory of swelling in detail using the free energy and chemical potential of hydrogels.

The response of hydrogels, when they encounter external stimuli, is in the form of volume-phase transitions (VPT) which occurs due to sudden changes in the hydrogel network. These sudden changes are the product of molecular interactions with the external particles or stimuli. Therefore, it can be stated that the stimulus determines the response mechanism of hydrogels. There are several types of hydrogels that respond differently to different stimuli. Most researched hydrogels are those that respond to pH changes leading to volume-phase transitions. Consider having a system where we have a hydrogel that has a pH value equal to pK_a (acidic nature) and an environment having a pH value greater than pK_a . This difference results in the deprotonation of the hydrogel, causing a negative charge to appear on polymeric chains or functional groups attached to the monomers to be more

accurate which leads to the repulsion of polymeric chains and hence the swelling of the network. An example of this mechanism can be found with poly (methacrylic acid) (PMAA) structure [21]. However, if this ionized acidic network is protonated or the pH of the environment is lowered than the pH of the network, the structure returns from the swollen state to its initial state because of the reduction of electrostatic repulsive forces between the ions on the polymeric chains. Similar behavior exists in the hydrogel structures with cationic functional groups (basic nature), but in an opposite fashion [22].

Status of Development

Hydrogel sensors were reported for the detection of Glutamate in vivo [23]. Glutamate is one of the most important excitatory neurotransmitters in the brain. Osmium is recycled through a chemical reaction and acts as an electron transfer mediator. These sensors were hydrogel-based second generation sensors. They were obtained using carbon fiber which used redox mediator wired coating. They were reported previously reported by Kulagina et al. [24]. Anesthetized rats were used for this experiment. It was found that a very less amount of glutamate oxides was used in these sensors when compared to the first-generation sensors.

In 2009, a wearable brain cap was reported in the 4th International IEEE EMBS Conference on Neural Engineering [25]. This cap showed the ability to measure electroencephalogram (EEG) signals. Unlike other caps that use electric contact, this cap doesn't require any electric contact with the head. Hydrogel materials were used for cap manufacturing. These contacts do not need any electric contact between its surface and scalp. On the other hand, these contacts are flexible, and their integration is easy in the wearable cap. This cap plays a vital role in the basic brain-computer interfaces (BCI) system (See Figure 2a). On the other hand, (See Figure 2b). highlighted one reference approach using contactless electrodes. The electrode used an electro-active hydrogel, polyacrylamide hydrogel (PAAM), for sensing and modulation of the sensor. This work provided a solution to the uncomfortable attachment of caps for the BCI system to monitor the EEG signal by reducing the attachment procedure and time consumption. Right after this, another detailed report was published by the same authors with the same results in 2010 [26]. In addition to it, the conductive hydrogel has also been utilized as an electrode material for the peripheral neural interfaces. For example, PEDOT:PSS was mixed with ionic liquid, 4-(3-butyl-1-imidazolium)-1-butanedisulfonic acid triflate are used for micropatterned hydrogel arrays which showed the low-voltage modulation capabilities for mouse nerve [27].

One of the milestones for the usage of hydrogel for brain applications was reported by K. Chung in 2013 [28]. A new technique for the imaging of a brain, called Clear Lipid-exchanged, Anatomically Rigid, Imaging/immunostaining compatible, Tissue hydrogel (CLARITY), was developed in Stanford University. This technique made it possible to get the whole image of a mouse brain and make it possible to label a lot of molecules.

This technique involved the use of hydrogel to remove fat lipid layer without disrupting the cell structure and hold the rest of the components in place. This process is called hydrogel-hybrid tissue formation. This is done by the formation of formaldehyde-

acrylamide fixative-generated hydrogel mesh. By using this cellular lipid is removed using sodium dodecyl sulfate [29]. This makes the whole brain transparent to light but also permeable to molecules (Figure 2).

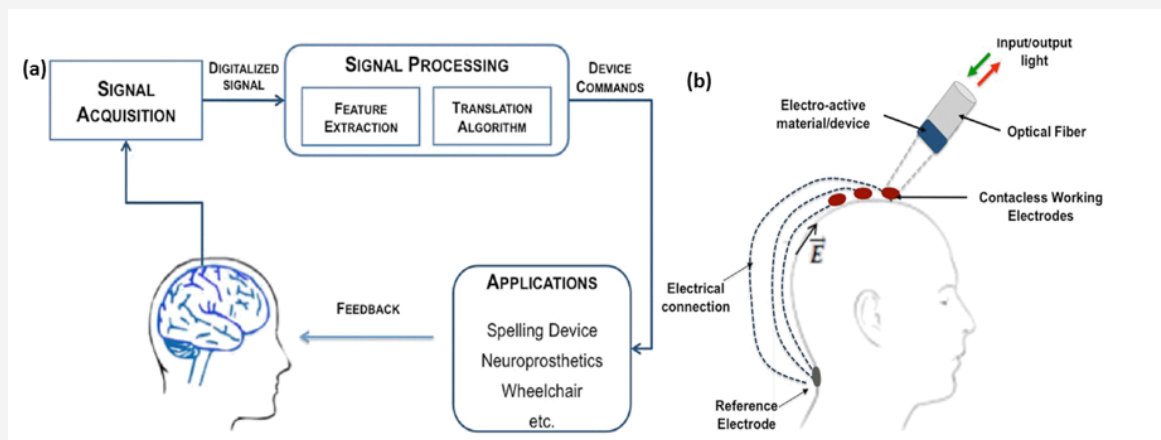


Figure 2: (a) Basic design and operation of a BCI system. (b) One-reference approach. The contactless electrode is highlighted. Reprinted with Permission from reference [24], Copyright © 1999 American Chemical Society.

This leads scientists to highlight specific features by adding molecular markers. By doing this one can create a brain library that can be studied by others. Figure 3 shows the 1mm block of the hippocampus where green, red and blue represent excitatory neuron, inhibitory neuron, and astrocytes, respectively. This was said that this technique works in the human brain too. By looking at someone's brain and match those with molecular information make it possible for scientists to know how a disease can make changes to the brain. Many other groups have presented different reports talking about how to find an ideal solution for the detection of fluorescent-labeled signal and tissue clearing [29,30].

Later, CLARITY was used together with magnetic resonance

imaging (MRI) [31] to investigate myelination contribution to measurable from diffusion tensor imaging. In neuroscience, diffusion tensor imaging (DTI) is widely used to estimate the white matter microarchitecture (WM). It was found that, in WM regions, fractional anisotropy is sensitive to myelination. The relationship between the diffusion signal and its biological underpinnings revealed for the very first time in the framework of brain-wide immunolabeling of WM targets using combined DTI-CLARITY.

Different case studies using CLARITY has been done on Parkinson's mouse model [32], Alzheimer's disease patients (post-mortem brain tissue) [33], post-mortem human brain tissue (died 6 years ago) [34].

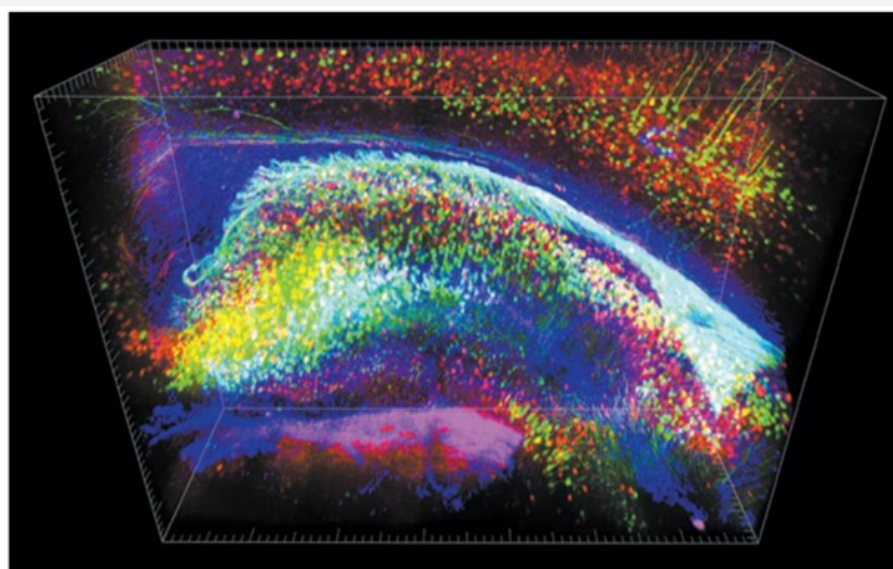


Figure 3: Neurons in an intact mouse hippocampus visualized using CLARITY and fluorescent labeling. Reprinted with the permission of Author [35], Copyright © 2013, The Author.

A report published in 2015 presented the hydrogel for the 3D printing applications [36]. This work reported the printing of complex external structures of the human brain using alginate. A high-quality 3D brain model was obtained using an MRI image of the brain. This model defined the different parts of the brain including temporal and frontal lobes of the cortex and the cerebellum. This printing technique using hydrogel has presented the unique ability to print complex structures.

In 2018, an injectable hydrogel was reported for the human umbilical cord mesenchymal stem cells (hUC-MSCs) implantation [37]. This hydrogel contained hyaluronic acid and sodium alginate. This provided a microenvironment for the implant by acting as a scaffold. This research was carried out using SD rats. The injecting performance was satisfied by the gelation time of more than 6 min. This hydrogel scaffold presented suitable rheological behavior for matching of brain tissue and decent compatibility for stem cells.

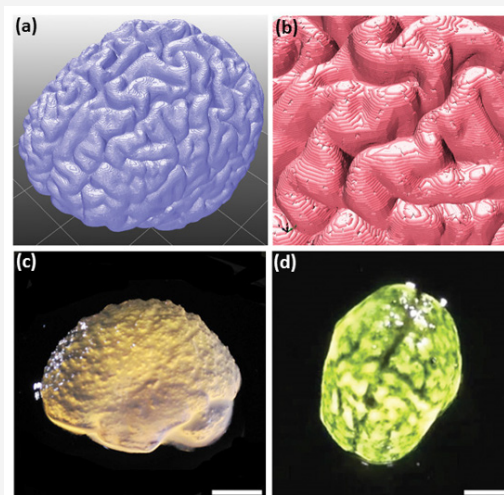


Figure 4: (a) A 3D rendering of a human brain from MRI data processed for FRESH printing. (b) A zoomed-in view of the 3D brain model showing the complex, external architecture of the white matter folds. (c) A lateral view of the brain 3D printed in alginate showing major anatomical features including the cortex and cerebellum. The brain has been scaled down to ~3 mm in length to reduce printing time and test the resolution limits of the printer. (d) A top-down view of the 3D printed brain with black dye dripped on top to help visualize the white matter folds printed in high fidelity. Figure and caption, Reprinted from reference [36], Copyrights © 2015, The Authors.

In the advancement of hydrogel application for brain application, a published report demonstrated the use of hydrogel for the treatment of brain tumors (glioblastoma) [38]. Local drug delivery Temozolomide (TMZ) into the brain was done using photopolymerizable PEG-DMA-based hydrogel. The systematic of injectable hydrogel drug delivery can be seen in Figure 5. The figure is self-explanatory where glioblastoma was treated with injectable polymerizable hydrogel loaded with TMZ- loaded

micelles. Photopolymerization was done using UV light which ends up killing cancer cells. In another study, the hydrogel was combined with paclitaxel (PTX) nanoparticles for the treatment of brain tumors (glioma) [38]. An MRI image was used to prepare the 3D structure of the tumor for the local delivery of paclitaxel. In the end, it was found that nanocomposite hydrogel can be used as a potential system in the improvement of the therapeutic efficacy of PTX (Figure 5).

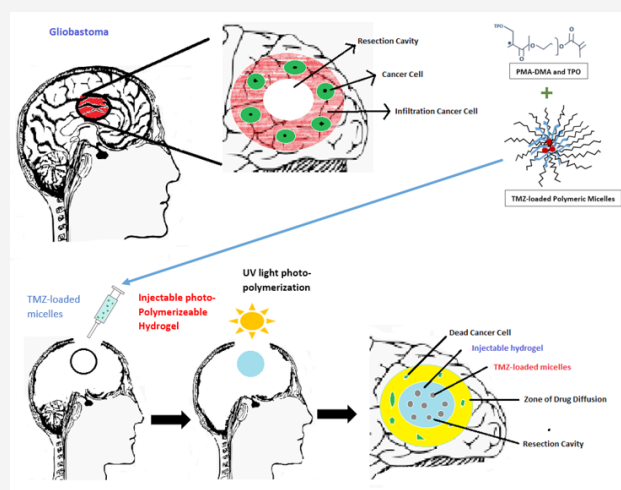


Figure 5: Schematic representing an injectable hydrogel with TMZ-loaded polymeric micelles that would be photopolymerized in situ and thus closely fitting the borders of the resected zone and would provide a sustained and local delivery [38].

The ultra-thermosensitive hydrogel was reported in 2017 which helps in brain tumor recurrence by developing a local drug delivery system [40]. Because of the ultra thermosensitivity (operational temperature $\leq 28^{\circ}\text{C}$) of these hydrogels make their use possible after surgical resection (temperature of operation theater is always $\leq 30^{\circ}\text{C}$). This solved the problem of conventional thermosensitive hydrogel which operates on temperature $\geq 32^{\circ}\text{C}$ that can cause the gel formation failure in tissue.

Besides the local drug delivery system, a remote drug delivery

system is also important for clinical needs and the patient's physiological response. A new nanoparticle hydrogel system was reported that can control the on-demand drug delivery of chemically defined small drug molecules [41]. The use of photo-triggerable chemical compounds makes it a remotely-triggerable system. Induced light triggers the photo-triggerable material to start intermolecular rearrangements. This leads to the separation and release of the drug from the hydrogel. The systematic of this process can be seen in Figure 6.

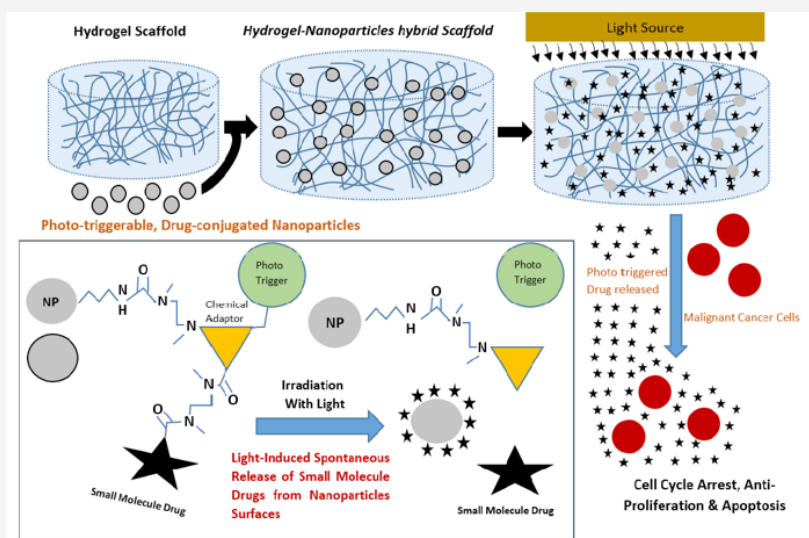


Figure 6: Schematic illustration depicting the fabrication and application of hydrogel-nanoparticle hybrid scaffolds. Photo-triggerable, drug conjugated silica nanoparticles were encapsulated within a PEG-based hydrogel. The subsequent photo-irradiation of the hybrid scaffold initiates a series of chemical rearrangements which ultimately releases the covalently bound drug to induce cancer cell death [41].

For the temperature/pH sensitivity brain tumors can be monitored by magnetic nanogels [42]. Magnetic nanogel was combined with Cy5.5-labeled lactoferrin (Cy5.5-Lf- MPNA nanogels). This nanogel presented the ability to change its size and hydrophilic/hydrophobic properties depending upon the surrounding temperature and pH. This property makes it possible to understand the surrounding environment of nanogel, whether it's physiological (normal) or acidic (tumor). This enhances the targeting ability for drug delivery.

Many other studies have also presented the use of hydrogels in for brain applications in different forms: magnetic nanoparticles [43-46], polymeric nanoparticle [47] and lipid-based DDS [48-50]. All of them are not possible to cover in this short review.

Conclusion

Hydrogels have attracted a lot of attraction in the medical field because of their easy processing, nano size, viscoelasticity, swelling capability, high drug encapsulation efficiency, and minimal toxicity [51,52]. In this review, we have tried to cover the max of hydrogel brain application including 3D printing, local and remote drug delivery, treatment methods for brain tumors and brain mapping. It was found that hydrogel is a promising material for brain applications. The research in this filed is still going on at full speed

to explore future opportunities in the field of medicine.

Acknowledgement

This work was supported by Smart Project Program through KAIST-Khalifa Joint Research Center (KK-JRC) (N11190250).

Conflict of Interest

No conflict of interest.

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