*Nirma Univ J Pharm Sci; 2018, 5(1) 73-84*

ISSN 2348 –4012

**REVIEW** ARTICLE

# HYDROGELS AS NOVEL ALTERNATIVE FOR THE MANAGEMENT OF VARIOUS DISEASES OF CENTRAL NERVOUS SYSTEM

***Kajol Sevak, Renuka Mishra*, Jigna Shah, Tejal Mehta***
*Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat*

**Abstract**

The word 'Hydrogel' includes 'Hydro' and 'Gel' indicating gel like property and water solubility. Hydrogel formation includes combining together of monomer units to form cross-linked structure which provides water insolubility. Hydrogel as a delivery system has gained wide acceptability due to its various applications. Based on the monomer used, hydrogel possess different properties and can be used for various diseases and disorders. Materials used for hydrogel formulation include Polyvinyl alcohol (PVA), Polyethylene oxide (PEO) and polysaccharides such as Chitosan, Cellulose, Agarose, Carragenan. Depending on the swelling behaviour, hydrogel can be used for different applications including controlled relase formulations The classification of hydrogel is based on the its physical, chemical, swelling, and source. Hydrogel based delivery system has application in effective management of various diseases of central nervous system like Alhzeimer; Parkinson's; Tumor of spinal cord; Down's syndrome and brain stroke. Different materials used in the formulation of the hydrogel provide different property thus making it suitable for management of different diseases and disorders besides central nervous system..

**Keywords:** Hydrogel, Cross linked polymers, Central nervous system, Controlled release.

***Corresponding Author:** Email: renukasharma81@rediffmail.com*

## INTRODUCTION

A Hydrogel can be described as amalgamation monomer units linked to form a water soluble polymer which is further cross-linked to form an insoluble network. It is a water swollen network polymer. Hydrogels are already used in manufacturing of soft contact lenses and gelatin desserts. These cross-linked bonds may be covalent, ionic, hydrogen or simply physical entanglements having important role in determining physical characteristics of it. Amount of water present in the swollen state of hydrogel determines its properties and characteristics. Usually, higher the water content, the material has higher application potential. It can be utilised in various forms such as absorbent material, soft tissue renewal material, membrane for separation and moisture retention in soil. In addition to that, there has been substantial interest in altering the unique characteristics of hydrogel in controlled release technological area.

## STRUCTURE AND PHYSICAL PROPERTIES OF HYDROGEL

Different water soluble monomers like hydrophilic vinyl-type monomers, sugars and amino acids which are obtained from natural resources are the fundamental building blocks of hydrogel. This monomer is then synthesised by a synthetic process. The crosslinking of the polymer generates hydrogel network might be carried out during polymerization or after the production of polymer. This final resulted monomer is characterised by the average distance between cross-links, which predominantly affects the properties of polymer.

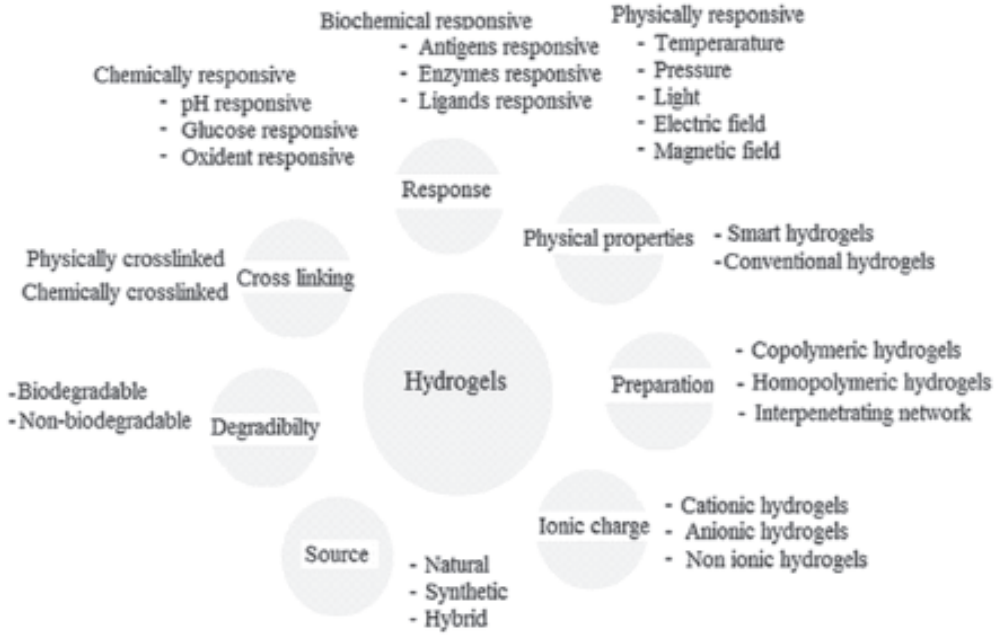


**Figure 1: Classification of hydrogels**

## MATERIALS USED IN HYDROGEL

Different materials can be used in hydrogel manufacturing. This includes polyvinyl acetate (PVA), Polyethylene oxide (PEO), Poly N-vinyl pyyrolidone (PNVP), polysaccharides and polyphosphazenes [1]. Brief information about the materials is provided as below-

### 1) PVA (Polyvinyl alcohol)

Hydrolysis of polyvinyl acetate generates polyvinyl alcohol (PVA) which is characterised based on the basis of molecular weight and degree of hydrolysis. It is proved that if the PVA is fully hydrolysed then it possesses the best crystallizing properties like water solubility and then only can be dissolved in hot water. If it is 85-90% hydrolysed, then maximum cold water solubility can be achieved. The hydroxyl group is another better candidate which can give marvellous sites for cross-linking with such difunctional reagents. It possesses some extraordinary properties like crystalizing at low temperatures in solution which does not happen in normal crystallisation procedures of polymers. Based on research on mechanical properties of PVA gels, it has been found out by researchers that both stress at break and modulus had higher characteristics with the increasing number of freeze thaw cycles. Elongation at break was having opposite characteristics. Along with that, mechanical strength was increased with increment in degree of hydrolysis and molecular weight.

### 2) PEO (Poly Ethylene Oxide) based materials

Polyethylene glycol (PEG) and Polyethylene oxide (PEO) have almost same structure but difference in molecular weights. The former has low weight and the latter has high molecular weight. Similar to the PVA, PEO can also crystalize with keeping in its rather low temperature. Along with that, to have good hydrogel composition, chemical cross-linking is necessary which can be attained by di isocyanate compound. The aftermath product can be called a polyurethane with huge number of hydrophilic soft bank. A normal diffusion kinematics were observed from the release of caffeine and prostaglandin from diisocyanate cross-linked PEO by Graham but on the other hand a more complex release was found if the same was released from thee dry gels which ultimately showed a constant release rate. The equilibrium of the materials used to manufacture those ranges from 0.2 to 19 with respect to dry polymer. A very amusing material was prescribed by Stadler and Weber which helped linking PBD chains to PEO cross-links with the percentage varying from 3.2 to 16.2% wt and a large number of these products showed volume swelling more than 1.25 and some of the samples even reached the 1.5 scale. The results of transmission electron microscopy elaborated that materials had 2 continuous phases, the property by means of which they are capable enough of loading hydrophobic drugs into a water solvable system.

**3) Poly N-Vinyl Pyrrolidone (PNVP) / PVP**

Poly N-Vinyl Pyrrolidone (PNVP) / PVP which was initially used as a blood plasma extender has more hydrophilic gels polyhydroxy ethyl methacrylate (PHEMA) and swell to particular limit. The presence of water in the equilibrium position can be as high as 95% and the interaction parameter varies from 0.49 to 56 under the certain conditions. PNVP is often found to be copolymerized with less hydrophilic monomers because of its high hydrophobicity.

**4) Polysaccharides**

It includes the natural materials, which includes the bacterial fermentations and also taken from the plants. Generally the polysaccharides in the natural materials are used more than the other synthetic polysachharide materials. It also includes the functional groups like the acidic groups like the COOH in the gum arabic, Sulfate group in the caragenanas. The basic group contains the polymer like the chitosan, which is also frequently used.

1) Cellulose

It is one of the most frequently used polymer and forms the highly swellable gels. It is highly soluble in water and also compatible with it.

2) Agarose and Carrageenan

They are sulfated galactans. Both the polymers adopt linear and the helical structure. Thermally reversible gels are formed with the Aragose and the Carrageenan.

**5) Polyphosphazene**

It has very less application in the hydrogel applications. It forms rubbery type of the material and also cross-linked with the di and trivalent cations. It absorbs the high amount of water and generate the highly swollen gels.

## HYDROGELS USED IN VAROIUS CNS DISEASE

INTRODUCTION

- Hydrogel in Down's Syndrome
- Hydrogel in Spinal Cord Disease
- Hydrogel in Alzheimer's Disease
- Hydrogel in Stroke
- Hydrogel in Tumour
- Hydrogel in Parkinson's Disease

Due to presence of blood brain barrier (BBB) and blood spinal cord barrier (BSCB), the transfer of molecules to the Central Nervous System is a confronting issue. There are some instances where direct cerebral spinal fluid injections into the extracellular fluid is also proposed and used in clinical and pre-clinical or experiments. The present research in the same field encompasses examining bio-inert as well as biocompatible polymers as base for controlled release of biologically active molecules inside the central nervous system for controlled drug delivery. It is

necessary to mention that there is an interim leak in the BBB and BSCB after injury or stroke to the spinal cord and brain, which permit molecules and cells to get into the Central Nervous System from the circulating blood than normal physiological conditions. It is still unforeseeable that up to which extent, this "leakiness" can be useful for cell and drug delivery. Polymeric hydrogels which have some automated characteristics with nervous tissue, can be placed in the intra spinal space so that it can balance homogeneous mechanical landscape with all adjacent soft central nervous system tissue. Hydrogels which are prepared from different synthetic and natural polymers are explored for its capability to deliver therapeutic activity directly into the spinal cord and brain.[2]

Fibrin-based hydrogels have been more used and progenitor/stem cells in combining with growth factors in rodent models of spinal cord injury and scar inhibiting enzyme chondroitinase ABC Injecting in- situ gelling form of agarose in combination with lipid microtubules filled with bioactive molecules after spinal cord injury have been used. Chitosan-based hydrogels incorporating micro particles or nanoparticles have been reported Refer Figure 2, Hydrogels in CNS. Molecules having bioactivity are delivered to the CNS using micro or nanoparticles of chitosan based hydrogels but chitosan-based biomaterials have widely been used for delivery through the nasal route.

This example of delivery is lucrative since the nasal passage has porous endothelial membrane.

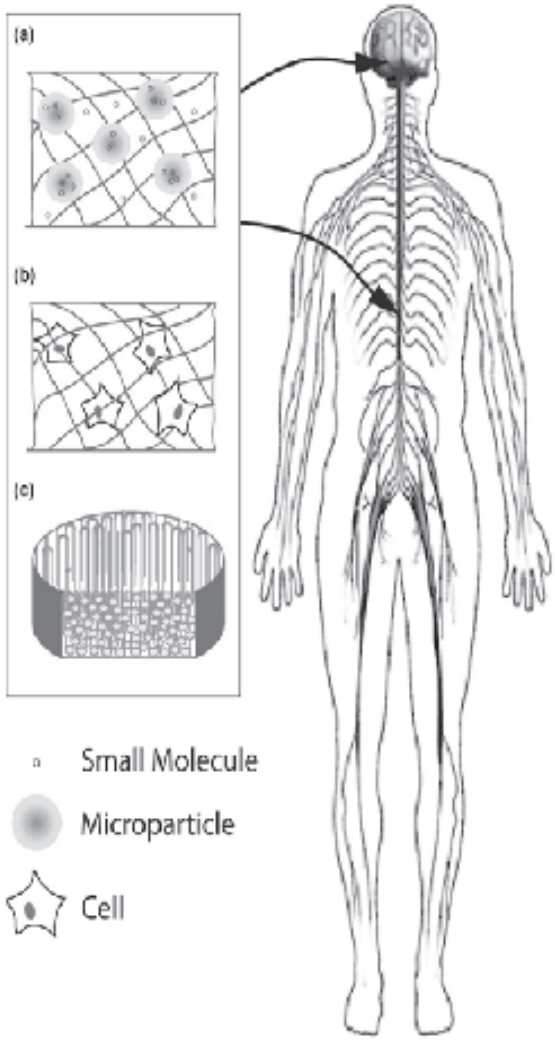


**Figure 2: Hydrogel in CNS1**

The figure represents the ways in which the hydrogels are developed for the therapies to repair the nervous system, here the microparticles used to create the highly tunable delivery platform for the small molecules in CNS, also hydrogels can also be used to deliver the cells in the CNS.

## 1) HYDROGEL IN SPINAL CORD

Spinal Cord Injury (SCI) is a condition for which still we got no cure. Individuals experiencing SCI have long lasting glitch of body parts and lessened personal satisfaction. Consistently as low as 2.3 to as high as 83 for each million occupants experience the ill effects of this. The auxiliary occasions after the essential damage comes about into increase in the multifaceted nature of the malady and because of that SCI treatment ends up harder. The present drug a spinal string injury is constrained. A few medications named the decompression of the rope and in the end the organization of calming medications and adjustment of the spine are accessible. Along these lines, the improvement of novel restorative systems focusing on this condition is urgent and exceptionally essential. Cell based treatments are a standout amongst the most as often as possible actualized and investigated among the diverse methodologies depicted previously. Fat tissue-inferred Stromal/Stem Cells (ASCs) and Olfactory Ensheathing Cells (OECs) have indicated better and confident outcomes. For instance, intra spinal transplantation of murine ASCs, which additionally actuated apparent picks up in engine execution, in a SCI creature show, one week after damage, advanced the assurance of stripped axons presumably by keeping oligodendrocytes' degeneration and by taking an interest in the recovery of the myelin sheath.[3]

The idea of the ASC's secretome chooses the useful results. ASC's secretome is the board of atoms discharged by these cells to the extracellular milieu. Truth be told, multitudinous confirmations demonstrated that ASC's secretome contains critical neuro administrative atoms, for example, Nerve Growth Factor (NGF), Glial cell line-inferred Neurotrophic Factor (GDNF), Brain-determined Neurotrophic Factor (BDNF), Insulin-like Growth Factor 1 (IGF1), Vascular Endothelial Growth Factor (VEGF), Hepatocyte Growth Factor (HGF), essential Fibroblast Growth Factor (bFGF), Transforming Growth Factor Beta 1 (TGF-b1). Notwithstanding that, it is discovered that the particles emitted by ASCs have the ability to tweak and influence the reaction of the safe framework. Then again, OECs are primarily separated by partaking in the development and direction of essential olfactory neurons. Their aggregate root with Schwann cells may expand some coordinating qualities appeared between these two cell composes, specifically the limit of OECs to encompass olfactory axons, shape fascicular forms and orchestrate fringe like myelin. The potential OEC transplantation as a treatment for CNS harm has just been investigated in vivo. Most examinations utilizing these cells demonstrated the upgrades in conduct comes about. For instance, murine OECs could remyelinate axons in spinal string harmed rats which extreme prompt practical improvement of electric conduction in already demyelinated axons.

In this manner, it is considered that OECs can make a tolerant feel with the goal that axonal can be recovered, in the typically unfriendly milieu of the harmed CNS. For every one of these grounds, autologous transplantation of OECs in SCI patients has just been completed. There was a one clinical trialing which it was seen that autologous OECs are sheltered following three years post-transplantation. For the most part since they are effectively available, ASCs (which can be gotten in extensive amounts from lipoaspirates) and OECs (which can be securely disconnected from nasal biopsies) introduce themselves as promising contender for SCI cell treatment and can be connected in an autologous way with evading moral concerns and the requirement for immunosuppression. We picture exploiting the useful qualities of every cell compose at the same time by consolidating both.

## 2) HYDROGEL IN ALZHEIMER

There are various serious causes generated with the Alzheimer disease, which includes the various symptom like memory problem, thinking problem, behavioral problem, so it's brain disorder. In the United States the Alzheimer's disease is ranked at the 6th position. It's important to in the Alzheimer disease to relieve the neurodegenerative progression. Early diagnosis of the Alzheimer clinical analysis done of the cerebrospinal fluid and protein such as the beta amyloid peptide. Positron emission tomography is done for the AD. In the clinical examination there is the high cost for the PET and also the cerebrospinal fluid. MicroRNA is important so the attention is paid to it in AD, because of it modulate translation of messenger RNAs to protein by cleaving or destabilizing the mRNAs. Extracellular vesicles are enriched with the

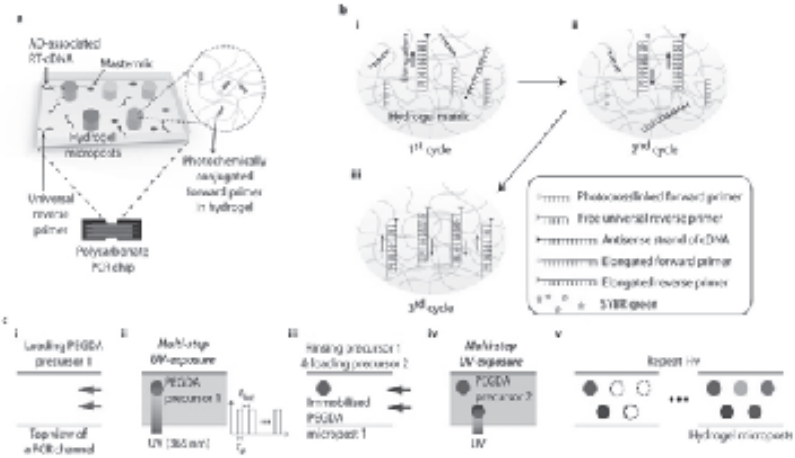


**Figure 3: Hydrogel in Alzheimer's disease**

Here, the diagram represents the (a) Schematic illustration of hydrogel microposts immobilized in a polycarbonate (PC) PCR chip in the presence of universal reverse primers and reverse transcribed (RT)-cDNAs associated with Alzheimer's disease (b) Schematic illustration depicting the principle of PCR confined within a hydrogel matrix. (c) Fabrication process to immobilize polyethylene glycol (PEGDA) microposts in the PCR chip.

micro RNAS by recent research which are the biomarker for the AD. Range within 10-fold seen between AD patients and healthy controls.[4]

## 3) HYDROGEL IN 3D TUMOR ENGINEERING

Now a days Hydrogels are used more also for the tissue engineering and also for the 3D culture cells because they possess very high biocompatibility and they have distinct characteristics which matches with that of living tissue which gives a compatible ambience for cells and make their response matching with that observed into the living organism. Changes in the hydrogel can be done with the help of the chemical modification to do the same thing as done by living tissues so resulting into more biocompatibility and enhance their in vivo working. Various kinds of polymers have been used to form the different hydrogel. Poly lactic acid (PLA) like synthetic materials, polyethylene oxide(PEO) , polyethylene glycol (PEG), polyvinyl alcohol (PVA), agarose and alginate, organosilicon-based nanocomposites and chitosan have been investigated so that they can be used with various kind of tissues. [4]

Likewise pores of these hydrogels and nano-sized strands emulate the structure of living tissues in-vivo which at last gives a domain that can procedure in-vivo cell–cell and cell-platform connections. Alongside that, fibre crosslinking by which hydrogels frame from these peptides don't require any synthetic added substances and UV light or warmth treatment which may prompt lower cell biocompatibility, not at all like the circumstance with other biopolymer-based hydrogels. Toward the end, infusion can create these peptide hydrogels which make them empower them to embody cells for 3D societies. Till now, different sorts of self-amassing peptide hydrogels have been used for biomedical applications going from hydrogels for tissue designing to nano-vehicles for hostile to malignancy medication and si-RNA conveyance.

## 4) HYDROGEL IN BRAIN AFTER STROKE

To substitute the lost tissue, ex vivo generation of engineered organs by means of classical tissue engineering technique can be implanted. As it requires the invasive implantation of the tissue construct, this approach is not well organized and proper for brain repair. [5] Another technique is In situ tissue regeneration which aims to completely bypass the ex vivo generation of the engineered organ. It does so by implanting a scaffold directly at the site of injury just to stimulate endogenous tissue repair by mean of local or transplanted progenitors. Although earlier the materials for brain repair used implantable materials, contemporary tries have been focused on engineered injectable hydrogels. [5]

The hydrogels can be designed to match the mechanical properties of the normal

brain by modulating the crosslinking density and to serve as local drug delivery depots. The crosslinking point and network mesh size depends upon the polymer chain length and its tendency to percolate and these are factors by which the characteristics if it can be modulated, which at the end and ultimately modulates nutrient diffusion and cell motility. [6]

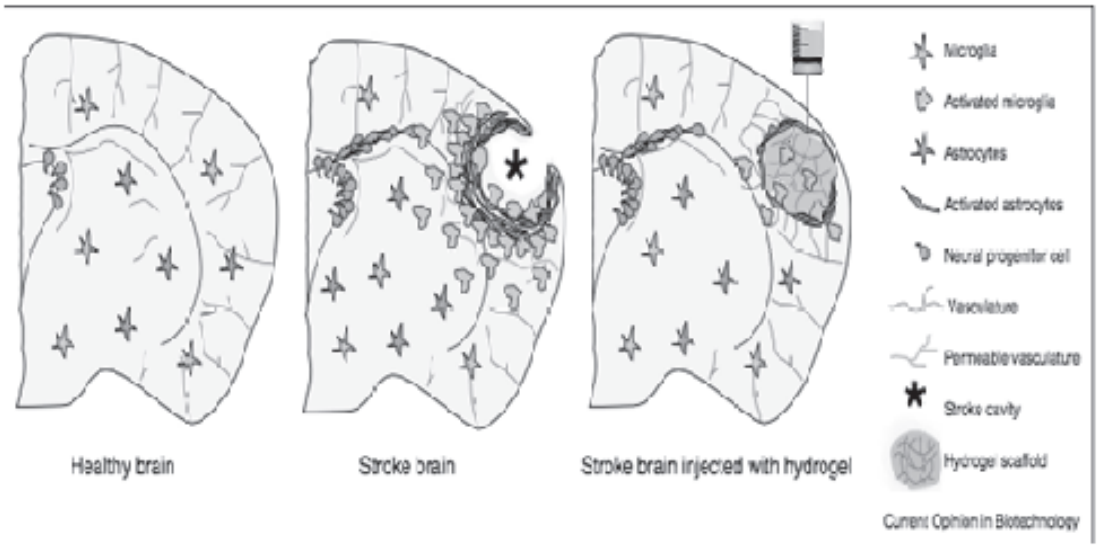


**Figure No. 4: Hydrogel in Brain Stroke**

Diagram represents the coronal brain section and the major physio-pathological events occurring after an ischemic stroke.

## 5) THE HYDROGEL IN STEM CELLS

To treat different diseases, adult stem cells, which are capable enough of being self-renewable, are good option to go with as they provide therapeutic applications in a nice way. To treat the neurodegenerative diseases (Parkinson's disease, stroke, Alzheimer's disease, and spinal cord injury) recently, neural stem cell, which are technically difficult when the matter comes to isolation and characterization thus leading them to be less used, therapy has been taken into consideration as a whole new approach. Adult stem cells, in addition to that, possess an inherent capacity to differentiate into many cell types such as fibroblasts, osteoblasts, adipocytes, yocytes, and neurons, and due to this property, these adult stem cells could act as an unlimited source of stem cells which is highly useful in treating neurodegenerative diseases.[7]

Among the all viable sources of adult stem cells like bone marrow, adipose tissue, muscle and human umbilical cord, considerable attention has been centered on skeletal muscle because it is a convenient and abundant source of adult stem cells due to its considerable mass in

the body. If the strategies to isolate and characterise skeletal muscle from muscle-derived stem cell is developed then it will pave the way towards generation of unlimited stem cells. This could be achieved by MDSC because it can differentiate into neurons and glial cells, e.g. oligodendrocytes and astrocytes. To treat epilepsy and bipolar disorder, Valproic acid (VA), which can even act as a pleiotropic histone deacetylase (HDAC) inhibitor which helps contributing into differentiation in process, is a proliferatively used because it is an anticonvulsant and mood stabilizing drug but the previous results are not that much convincing as they showed low cell survival. However, the survival issue of adult stem cells can be eliminated if a number of 3 dimensional scaffolds with geometric or topographical features are provided. The hydrogel could be a 3-dimensional scaffold as it can be fabricated even with scaffold geometry's complexity's existence. Chitosan, which is abundant and natural, is another attractive candidate for the same purpose. Hydrogels which are based on chitosan are kown to have some better features like biodegradability, biocompatibility and non-immunogenic which lead it to the best candidate for scaffold tissue engineering processes such as cell encapsulation and cell culture. Recent studies have shown that a mixture of chitosan and glycerol phosphate disodium salt (GP) can form a hydrogel in situ at body temperature. However still, no scientific studies have tested the differentiation of MDSCs in the presence of VA on chitosan-based hydrogels, yet to be completed. The ultimate and final aim of this work was to treat the neurodegenerative diseases through tissue engineering in rat MDSCs in the presence of VA on chitosan-based hydrogels.

**6) LYMPHOMA:**

Methotrexate (MTX) is crucial therapeutic to treat number of malfunctionalities of central nervous system, but has a slight fall that it passes poorly through blood-brain barrier. Fortunately, muco-adhesive chitosan based nano-formulation if accompanied by intranasal Administration could be a key to this hurdle. **Methods:** Nanogel having MTX was differentiated on the basis of morphology, drug loading, particle size, drug release behaviour and zeta potential after it was prepared by ionic gelation method. The resulted were compared with the eight maths models such that a particular phenomenon could be understood. The the solution with deionized water was administered into the nasal cavity of rats and after 15, 30, 60, 240 minutes, the plasma and brains were analysed for MTX quantity. **Results:** Particle size = 100 nm, zeta potential = 18.65 ± 1.77 mV, loading efficiency = 65.46 ± 7.66, loading capacity = 3.02 ± 0.34. The release phenomenon was found to be complying Swelling and Fickian diffusion. Results of *in vivo* studies : Drug Targeting Efficiency = 424.88%, Direct Transport Percentage for Nanogel (test)

and Drug free solution (Control) are 76.46% and 34842.15% and 99.71% respectively. **Conclusion:** More amount of MTX was generated by Nanogel in brain but not in plasma if compared with free drug solution. Further, it was found that Intranasal Administration increases the brain concentration of MTX.[8]

## CONCLUSION AND FUTURE PERSPECTIVE

The research on hydrogels have witnessed a tremendous enhancement for therapeutic delivery, producing new hydrogels which are application oriented like multi responsive hydrogels and tandem gelling hydrogels, along with simultaneously achieving unprecedented things by means of exceptional qualities like facile administration in the same field. The advancement move towards Top notch technological development in which the world is being engulfed is now leading to the 3D printed hydrogels. If combined with biologically active agents, then lucid sway over cellular behaviour could be obtained in the field of tissue engineering. The nano-cells having rapid response and high adaptability to ambience is another lucrative candidate for the same field responded with intracellular clues, making bio-orthogonal crosslinking superior to classical linking because of its fast reaction kinetics. Hydrogel systems has some basic requirements like formation of in situ is a basic requirement, use of bio-orthogonal reactions to fasten the environmental response and drug delivery in specified quantity, all which could be easily obtained by modulation of release of hydrogels administration leading to greater control in drug concentration.

There are some critical issues related to manufacturing and stability which need to be resolved. However, these new advancements in therapeutic hydrogels have potential to develop safe, efficient and scalable drug delivery which could to be commercialized.

## REFERENCES


[1] Tarcha, Peter J. Polymers for controlled drug delivery. CRC press, 1990.

[2] Z. Z. Khaing, R. C. Thomas, S. A. Geissler, and C. E. Schmidt, “Advanced biomaterials for repairing the nervous system : what can hydrogels do for the brain?,” *Biochem. Pharmacol.*, vol. 17, no. 7, pp. 332–340, 2014.

[3] E. D. Gomes *et al.*, “Biomaterials Combination of a peptide-modi fi ed gellan gum hydrogel with cell therapy in a lumbar spinal cord injury animal model,” vol. 105, pp. 38–51, 2016.

[4] W. Choi *et al.*, “Biosensors and Bioelectronics Hydrogel micropost-based qPCR for multiplex detection of miRNAs associated with Alzheimer’s disease,” *Biosens. Bioelectron.*, vol. 101, no. March, pp. 235–244, 2017.

[5] L. R. Nih, S. T. Carmichael, and T. Segura, “ScienceDirect Hydrogels for brain repair after stroke/ : an emerging treatment option,” *Curr. Opin. Biotechnol.*, vol. 40, pp. 155–163, 2016.

[6] T. Jin, F. J. Nicholls, W. R. Crum, H. Ghuman, S. F. Badylak, and M. Modo, “Biomaterials Diamagnetic chemical exchange saturation transfer (diaCEST) affords magnetic resonance imaging of extracellular matrix hydrogel implantation in a rat model of stroke,” *Biomaterials*, vol. 113, pp. 176–190, 2017.

[7] J. S. Kwon *et al.*, “International Journal of Biological Macromolecules Chitosan-based hydrogels to induce neuronal differentiation of rat muscle-derived stem cells,” *Int. J. Biol. Macromol.*, vol. 51, no. 5, pp. 974–979, 2012.

[8] L. P. Jahromi, S. Mohammadi-samani, R. Heidari, A. Azadi, and P. Sciences, “in vitro - and in vivo Evaluation of Methotrexate-Loaded Hydrogel Nanoparticles Intended to Treat Primary CNS Lymphoma via Intranasal Administration,” no. 9, pp. 305–317, 2018.