EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 10
116-120
Year: 2018

OVERVIEW ON NANOGEL DRUG DELIVERY SYSTEM

Mayuri D. Deshmukh* and Dr. S. S. Saboo

Pharmaceutics Department[1], Pharmacognosy Department[2]
Government College of Pharmacy, Aurangabad.

***Corresponding Author: Mayuri D. Deshmukh**
Pharmaceutics Department, Government College of Pharmacy, Aurangabad.

Article Received on 28/07/2018 **Article Revised on 18/08/2018** **Article Accepted on 07/09/2018**

ABSTRACT
Nanogel drug delivery system containing materials which having high drug loading capacity,biocompatibility and biodegradability these properties help to design a drug delivery system effectively. The aim of this review article is to study the polymers used in the preparation of nanogel along with their classification. Various evaluation parameters of the prepared nanogel are also studied here. Nanogels have also attracted a big interest due to their size and surface properties. Nanogels are promising and innovative drug delivery system that can play a vital role by addressing the problems associated with old and modern therapeutics such as nonspecific effects and poor stability. This review highlights the use of self-assembled nanogel for hydrogel nanoparticles for drug delivery applications. Nanogels,or hydrogel nanoparticles have gained considerable attention as one of the most promising nanoparticulate drug delivery systems owing to their unique properties that combine the characteristics of hydrogel systems.

KEYWORDS: Nanogel, Polymer, Drug delivery, Synthetic Procedure, Evaluation.

INTRODUCTION

'Nanogels' are the nanosized particles formed by physically or chemically crosslinked polymer networks that is swell in a good solvent. This involves polymer systems which are either copolymerised or monomers. Nanogel system is used to deliver drug in controlled, sustained and targetable manner. Nanogels are the semisolid formulations with three dimensional network of organic system containing fluids and drugs. These systems have been the part of traditional systems of topical drug delivery for local effects.

Nanogels are superior drug delivery systems than others because

- Ability to reach the smallest capillary vessels, due to their tiny volume and to penetrate the tissues either through the paracellular or the transcellular pathways.
- Highly biocompatible and biodegradable.
- Due to high drug loading capacity.

Routes of administration

- Topical
- Oral
- Pulmonary
- Nasal
- Parenteral
- Intra-ocular

Properties of Nanogel

- **Biocompatibility and biodegradability**

Nanogel based drug delivery system is highly biocompatible and biodegradable.

- **Higher drug loading capacity**

Higher drug loading capacity of nanogel depend on the functional group present in the polymeric unit. These functional group affect the drug carrying and drug releasing properties. Also the presence of functional group at interface with drug/ protein molecules is also responsible for higher loading.

- **Swelling property in aqueous media**

The most important property of nanogel is their rapid swelling/deswelling in aqueous media.

- **Particle size**

The size of nanogel ranges from 20 – 200 nm in diameter. And due to the small size they have good permeation capabilities.

- **Solubility**

Nanogels have ability to solubilize hydrophobic drugs and diagnostic agents in their core or networks of gel.

- **Electromobility**

Sonication or homogenization which are the harsh conditions and critical for encapsulating biomacromolecules are not needed for the preparation of nanogel.

- **Colloidal stability**

Nanogels having the better stability over the surfactant micelles and also they exhibit lower critical micelle concentration, slower rates of dissociation and longer retention of loaded drugs.

- **Non-immunologic response**

Nanogel drug delivery system does not produce any immunological response.

- **Others**

Both types of drugs that is hydrophilic and hydrophobic drugs and charged solutes can be given through nanogel. These properties of nanogel are influenced by temperature ,presence of hydrophilic/hydrophobic groups in the polymeric networks, cross linking density of gel, surfactant concentration and type of cross links present in the polymer network.

Polymers used in the preparation of nanogel

Polymers are large molecules in which repeating structural units or monomers which are connected by covalent chemical bonds are present. These compounds acts like the building blocks of natural (e.g. paper and amber), biological (e.g. proteins and nucleic acid), or synthetic (e.g. plastics and polyethylene) materials. In dermatology, there are new acrylic acid polymers they turn into gel in the presence of water, by trapping water into microcells. In these aqueous microcells, hydrophilic compounds can remain in a solution, whereas non-hydrophilic compounds may be dispersed in suspension. Stable gel like formulation is formed by this process that is easy to use and when this formulation applied on skin it releases the active compounds. Also these polymer based gel used to provide additional clinical benefits by mixing with other excipients such as moisturizers and emollients. By using this novel polymer- based technology, recently an anti acne formulation is introduced which is a combination of clindamycin 1% and benzoyl peroxide 5% that exhibit efficacy and excellent tolerability.

Gel forming polymers are classified as below:

A] Natural polymers:

I. **Proteins:-** e.g.- Collagen, Gelatin, Xanthin, Gellum gum
II. **Polysaccharides:-** e.g. - Agar, Alginic acid, Sodium or potassium, Corrageenas, Tragacanth, Pectin, Guar gum, Cassia tora.

B] Semisynthetic polymers

I. **Cellulose Derivatives:-** e.g. - Carboxymethyl cellulose, Methyl cellulose, HPC, HPMC, HEC.

C] Synthetic polymers

I. Carbomer:- e.g. - Carbopol-940, Carbopol-934, Carbopol-941
II. Poloxamer
III. Polyacrylamide
IV. Polyvinyl Alcohol
V. Polyethylene and its copolymers

D] Inorganic substances:- e.g. - Aluminium Hydroxide, Bentonite.

E] Surfactants:- e.g. – Cetosteryl alcohol, Brij -96

Techniques for the synthesis of Nanogel

- **Photolithographic Technique**

Photolithographic technique has been explored to fabricate 3D hydrogel particles and microgel or nanogel rings for drug delivery. Photolithography consist of five steps.

In the first step, the UV cross linkable polymer, which possesses low surface energy, as a substrate is released on the pre-baked photo resist-coated water. Next step involves molding the polymer into patterns on the silicon wafer by pressing the quartz template onto the polymer and exposed it to the intense UV light. In the third step , the particles with a thin residual interconnecting film layer are uncovered by removing the quartz template. In fourth step, residual thin layer is removed by a plasma containing oxygen that oxidizes it. In last step the fabricated particles are directly collected by dissolution of the substrate water of buffer.

- **Fabrication of biopolymers**

Chitosan (CS), hyaluronan (HA), and Dex are naturally occurring carbohydrate-based biopolymers. Microgels of these biopolymers are prepared by using various methods.

They can be classified into four different categories: Water- in- oil (W/O) heterogeneous emulsion, aqueous homogenous gelation, Spray drying method,and chemical cross linking of Dex.

- **Water-in –oil (w/o) heterogenous emulsion method**

This method of preparation of nanogel completed in two steps: One is the emulsification of aqueous droplets of water soluble biopolymers in continuous oil phase with an aid of oil-soluble surfactants and other is cross linking of biopolymers with water soluble cross linkers.

- **Inverse (mini) emulsion method**
- A W/O emulsion is formed from a mixture of aqueous biopolymer droplets and a continuous oil phase using either a homogenizer or a high speed mechanical stirrer.
- Resulting aqueous droplets of biopolymers are then crosslinked with appropriate crosslinking agents.

- Then crosslinked microgel particles are prepared as dispersion in organic solvents.
- Purified by different processes like precipitation, centrifugation, washing with organic solvents such as isopropanol and lyophilization.
- The size of the prepared microgel particles can be controlled by amount of surfactants and crosslinking agents as well as stirring speed during the formation of inverse emulsion.

- **Micromolding method**

Micromolding method is an as similar to photolithographic technique. However, they can minimize the need to use costly lithographic equipment and clean room fascilities. In this process, cells were suspended in a hydrogel precursor solution consisting of either methacrylated hyaluronic acid (MeHA) or PEGDA or a photoinitiator in water. The resulting mixture was deposited onto plasma cleaned hydrophilic PDMS patterns and then photocrosslinked via exposure to UV light. The resulting cell-laden microgels were removed, hydrated and then harvested. They were also molded into various shapes including square prisms, disks and strings.

- **Reverse micellar method**

Reverse micellar method also involves a W/O dispersion as similar to the inverse (mini) emulsion method; however, to form a thermodynamically stable micellar solution in which aqueous droplets dispersed in the continuous oil phase, large amount of oil soluble surfactants is used. The resulting micellar droplets having submicron size ranged from 10-100 nm in diameter.

- **Membrane emulsification**

In this technique of membrane emulsification, the to-be-dispersed phase is passed through the membrane (glass or ceramic), which possesses uniform pore size. Under certain conditions the emulsion droplets or microgels with specific morphology are formed on the surface of the membrane and afterwards, with a continuous phase that is flowing across the membrane, these fabricated emulsion droplets or microgels are recovered. These fabricated emulsion droplets can be in different emulsion formation such as water-in-oil (W/O), oil-in-water (O/W), oil-in-water-in-oil (O/W/O), and water-in-oil-in-water W/O/W). The size of the formed droplet is controlled by the membrane pore size, velocity of the continuous phase, and pressure of the trans-membrane.

- **Chemical cross linking**

Biodegradable Dex- based microgels and hydrogels were prepared by various methods based on chemical cross linking including Carbodiimide coupling, Michael addition reaction, Free radical polymerization.

- **Heterogenous free radical polymerization**

Various heterogenous polymerization reactions of hydrophilic or water-soluble monomers in the presence of either difunctional or multifunctional crosslinkers have been mostly utilized to prepare well-defined synthetic microgels. They include precipitation, inverse (mini) emulsion, inverse micro emulsion, and dispersion polymerization utilizing an uncontrolled free radical polymerization process.

- **Precipitation polymerization**

Precipitation polymerization involves the formation of homogenous mixture at its initial stage and the occurrence of initiation and polymerization in the homogenous solution. As the formed polymers are not swellable but soluble in the medium, the use of crosslinker is necessary to crosslink polymer chains for the isolation of particles. As a consequence, the resulting crosslinked particles often have an irregular shape with high polydispersity. Peppas et al., synthesized narrow size distribution poly (methacrylic acid-g-ethylene glycol) (P (MAA-g-EG)) nanospheres through precipitation polymerization for the oral delivery of proteins. They obtained better control over particle size and particle size distribution by controlling monomer concentration in water. They also revealed that increasing the cross-linker concentration during polymerization decreased the equilibrium swelling of the nanospheres.

Evaluation of nanogel

1. Drug content

In a 50 ml of volumetric flask 1gm of nanogel was taken to which 20ml purified water was added with continuous shaking. Mixture of 10% methanol in water used to adjust the volume. Similarlly, for blank determination plain bases were also treated. By using UV spectrophotomer absorbance of the solution with the blank was measured at 360nm.

Homogeneity of drug content

For homogeneity of drug contents, six tubes were taken randomly and assayed for the drug content as stated above. Studies were performed in triplicate and mean values were used for the analysis of data.

2. Measurement of p^H

The p^H of nanogel were determined by digital p^H meter. One gram of nanogel was dissolved in 100 ml of distilled water and stored at 4^0C for two hours. The measurement of p^H of each formulation was in triplicate and the average values are presented.

3. Viscosity

Viscosity of nanogel was determined by using Brookfield viscometer. Nanogels were filled in jar and spindle was lowered perpendicularly, care should be taken that the spindle do not touch to the bottom of the jar. The spindle was rotated in gel at increasing shear rates 0.5,1,2.5 and 5 rpm. At each speed, note down the corresponding dial reading. The reverse reading also noted and average was taken for these two readings. The viscosity of the gel was obtained by the multiplication of

the dial reading with the factors given in the Brookfield viscometer catalogues.

4. Spreadability

A modified apparatus consisting of two glass slides containing gel in between with the lower slide fixed to a wooden plate and the upper slide attached to a balance by a hook was used to determine spreadability.

5. Extrudability

A simple method was adopted for determination of extrudability in terms of weight in grams required to extrude a 0.5 cm ribbon of gel in 10 seconds from the collapsible tube.

Marketed formulation of nanogel

- Zyclin Nanogel
- Adalene Nanogel
- Oxalgin Nanogel
- Zyflex Nanogel

Application of Nanogel

Nanogel-based drug delivery formulations improve the effectiveness and safety of certain anti –cancer drugs, due to their chemical composition, which have been confirmed from in vivo study in animal models.

Now-a-days nanogel drug delivery system is used in various disorders like cancer, Autoimmune disease, Opthalmic, Diabetes, Neurodegenerative. In stopping bleeding. It gives an anti-inflammatory action.

CONCLUSION

Nanogels are promising and innovative drug delivery system that can play a vital role by addressing the problems associated with old and modern therapeutics such as nonspecific effects and poor stability. Future design and development of effective nanogel based drug delivery system for in vivo application requires a high degree of control over properties. Nanogels appear to be excellent candidates for brain delivery. One future goal of research in this area should be the improved design of microgels/nanogels with specific targeting residues to enable highly selective uptake into particular cells. This will be especially important for the targeting of cancer cells, thereby reducing nonspecific uptake into healthy cells. More and more in vivo and in vitro study should be needed to confirm the use of this delivery system on human being.

REFERENCES

1. Sultana, F., Manirujjaman, M., Imran-Ul-Haque, M.A. and Sharmin, S., 2013. An overview of nanogel drug delivery system. *J Appl Pharm Sci*, *3*(8): 95-105.
2. Dandagi, P., Kerur, S., Mastiholimath, V., Gadad, A. and Kulkarni, A., 2010. Polymeric ocular nanosuspension for controlled release of acyclovir: in vitro release and ocular distribution. *Iranian Journal of pharmaceutical research*, 79-86.
3. Kabanov, A.V. and Vinogradov, S.V., 2008. Nanogels as pharmaceutical carriers. In *Multifunctional pharmaceutical nanocarriers* (pp. 67-80). Springer, New York, NY.
4. Gonçalves, C., Pereira, P. and Gama, M., 2010. Self-assembled hydrogel nanoparticles for drug delivery applications. *Materials*, *3*(2): 1420-1460.
5. Dorwal, D., 2012. Nanogels as novel and versatile pharmaceuticals. *Int J Pharm Pharm Sci*, *4*(3): 67-74.
6. Oh, J.K., Drumright, R., Siegwart, D.J. and Matyjaszewski, K., 2008. The development of microgels/nanogels for drug delivery applications. *Progress in Polymer Science*, *33*(4): 448-477.
7. Shimizu, T., Kishida, T., Hasegawa, U., Ueda, Y., Imanishi, J., Yamagishi, H., Akiyoshi, K., Otsuji, E. and Mazda, O., 2008. Nanogel DDS enables sustained release of IL-12 for tumor immunotherapy. *Biochemical and biophysical research communications*, *367*(2): 330-335.
8. Xiangli, Q., Zhenjia, Z. and Side, Y., 2006. Preparation of initiator and cross-linker-free poly (N-isopropylacrylamide) nanogels by photopolymerization. *Journal of Photochemistry and Photobiology A: Chemistry*, *177*(2-3): 191-196.
9. Xu, D., Hong, J., Sheng, K., Dong, L. and Yao, S., 2007. Preparation of polyethyleneimine nanogels via photo-Fenton reaction. *Radiation Physics and Chemistry*, *76*(10): 1606-1611.
10. Yan, L. and Tao, W., 2010. One-step synthesis of pegylated cationic nanogels of poly (N, N′-dimethylaminoethyl methacrylate) in aqueous solution via self-stabilizing micelles using an amphiphilic macroRAFT agent. *Polymer*, *51*(10): 2161-2167.
11. Oishi, M., Sumitani, S. and Nagasaki, Y., 2007. On−Off Regulation of 19F Magnetic Resonance Signals Based on pH-Sensitive PEGylated Nanogels for Potential Tumor-Specific Smart 19F MRI Probes. *Bioconjugate chemistry*, *18*(5): 1379-1382.
12. Hasegawa, U., Shin-ichiro, M.N., Kaul, S.C., Hirano, T. and Akiyoshi, K., 2005. Nanogel-quantum dot hybrid nanoparticles for live cell imaging. *Biochemical and biophysical research communications*, *331*(4): 917-921.
13. Hayashi, C., Hasegawa, U., Saita, Y., Hemmi, H., Hayata, T., Nakashima, K., Ezura, Y., Amagasa, T., Akiyoshi, K. and Noda, M., 2009. Osteoblastic bone formation is induced by using nanogel-crosslinking hydrogel as novel scaffold for bone growth factor. *Journal of cellular physiology*, *220*(1): 1-7.
14. Semenzato, A., Casellato, M., Amabile, G., Faga, A. and Fratter, A., Formulation and Evaluation of a Nanogel System for the Skin Delivery of Hyaluronidase.
15. Nukolova, N.V., Oberoi, H.S., Cohen, S.M., Kabanov, A.V. and Bronich, T.K., 2011. Folate-decorated nanogels for targeted therapy of ovarian cancer. *Biomaterials*, *32*(23): 5417-5426.

16. Shah, P.P., Desai, P.R., Patel, A.R. and Singh, M.S., 2012. Skin permeating nanogel for the cutaneous co-delivery of two anti-inflammatory drugs. *Biomaterials*, *33*(5): 1607-1617.
17. Wu, W., Mitra, N., Yan, E.C. and Zhou, S., 2010. Multifunctional hybrid nanogel for integration of optical glucose sensing and self-regulated insulin release at physiological pH. *Acs Nano*, *4*(8): 4831-4839.
18. Vinogradov, S.V., Batrakova, E.V. and Kabanov, A.V., 2004. Nanogels for oligonucleotide delivery to the brain. *Bioconjugate chemistry*, *15*(1): 50-60.
19. Aliyar, H.A., Hamilton, P.D., Remsen, E.E. and Ravi, N., 2005. Synthesis of polyacrylamide nanogels by intramolecular disulfide cross-linking. *Journal of bioactive and compatible polymers*, *20*(2): 169-181.
20. Lee, Y., Park, S.Y., Kim, C. and Park, T.G., 2009. Thermally triggered intracellular explosion of volume transition nanogels for necrotic cell death. *Journal of Controlled Release*, *135*(1): 89-95.