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The Functional Nanogel: An Exalted Carrier System

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ABSTRACT

Nanotechnology is widely growing field nowadays. Under these vast variety of carriers are available through which the drugs can be delivered to the affected organ. Nanogels are one of the most effective carrier systems for targeting the drugs directly to the diseased tissues with their highly adaptive properties. Nanogel can be defined as nanoparticles incorporated in hydrogel. These systems are very efficient in embodying drugs of diverse nature and also in enhancing their delivery and retention to the targeting organ. Due to their targeting properties they reduce the dose of drug required in free form and also reduces the side effects produced by accumulation of drugs to any other organ. This review highlights various types of nanogels, their advantages, most commonly used preparation techniques, biomedical applications, drug targeting through nanogels, drug loading and release through the nanogels. The review has also incorporated the recent patents related to the topic. However, there is an urgent need for relevant clinical data from nanogels so as to allow translation of the nanogel concept into a viable therapeutic application for the treatment of cancer.

Keywords: Nanogels, Polymers, Drug targeting, Hydrogel, Diagnosis.

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INTRODUCTION

In the current era of drastic improvements in diagnosis and therapy of diseases, Nanotechnology is a newly introduced field of drug delivery. Nanotechnology is also completely involved in imaging and diagnostic tests, hormone therapy, bone replacement, and in prescriptions of almost all kinds of illness. Under nanotechnology polymer based materials, nanogels are getting great consideration due to their magical potentials.[1,2]

Nanogels are basically nanoparticles incorporated in hydrogel system. Fig. 1 shows the basic composition of nanogels. These are the advanced delivery systems which possess the properties of both nanoparticles and hydrogels. These formulations are also known as nanohydrogels, nanogels or hydrogel nanoparticles. Nanoparticle have many advantages over the traditional formulations such as a controlled drug release, protection from degradation, delayed elimination, stimuli responsive behavior etc. [3,4]

The hydrogel delivery systems consist of three dimensional cross linked structures of polymers attached with non-covalent bonds. This structure is suitable for loading and release of drugs specially of natural origin. They have a large capacity of imbibing water inside their structure and swell to a greater extent. The imbibed water maintains the fluid like consistency. Their water absorbing capacity is an indication of their hydrophilic functional groups such as –OH, -COOH, -CONH2, - CONH- etc. The nanoparticle size ranges from 20 to 200 nm. The nanogel delivery systems are more advantageous than the original hydrogels because the former can be injected directly to the target site and can release the drugs for both local and systemic action. Ligands can be added by chemical modification for facilitating the targeting action. These nanogels systems also incorporate noticeable thermodynamic stability, enhanced solubilization capacity, low viscosity and higher capacity to withstand the sterilization procedures. These properties improve the release characteristics.[5]

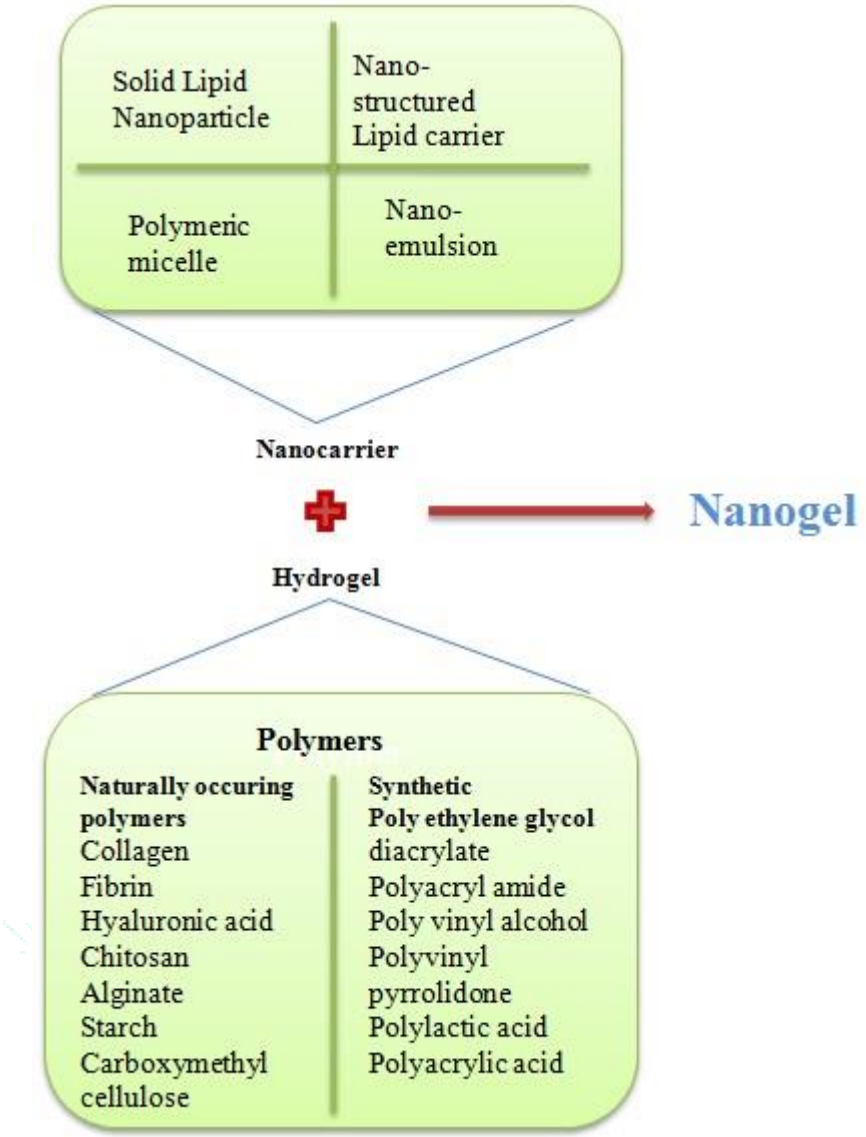

Figure 1; Basic Composition of Nanogel

Nanogel term was first time reported by Vinogradov et al., 1999 in the scientific paper. They prepared it as a hydrophilic polymer network by chemically crosslinking poly(ethylene glycol). Whereas, Akiyoshi described the first physically cross-linked nanogels using self-assembly of cholesterol-bearing polysaccharides in water.[6]

Fig. 2 compiles all the benefits of nanogel carrier system. Nanogels are highly biocompatible as they are made up of either natural or synthetic polymers. This biocompatible and biodegradable nature avoids its accumulation in the organs. The common natural polymers utilized for this purpose are collagen, fibrin, albumin, polysaccharide based polymers like chitosan, ethyl cellulose, hyaluronic acid, chondritin sulphate, heparin, dextrane, pullulan etc. These polymers provide swelling properties to the nanogels which helps in controlled drug release from the system. Poly(lactic acid), poly(lactic)–poly(glycolic) copolymers, polyacrylates and polymethacrylates, poly(e-caprolactone), are some typically synthetic polymers for nanogel preparation. Nanogels can incorporate any kind of drug inside them. Therefore these are advanced media for the delivery of poorly soluble drugs. [7]

These polymers based drug delivery systems are of particular advantage in targeting the drug to the required site with lesser side effects in case of fatal diseases like cancer.

Nanogels can be administered by variety of routes, including oral, pulmonary, nasal, parenteral, intra- ocular and topical. These systems are formulated in a specific manner with a diameter of 20-200 nm, which is sufficiently small to permeate blood brain barrier and at the same time can avoid clearance. They have the ability to respond to environmental changes such as pH and temperature. Nanogels have high loading capacity for guest molecules ranging from inorganic nanoparticles to drugs, bio-macromolecules like proteins and DNA, with appropriate adaptation of their structure, but without affecting the gel-like performances.

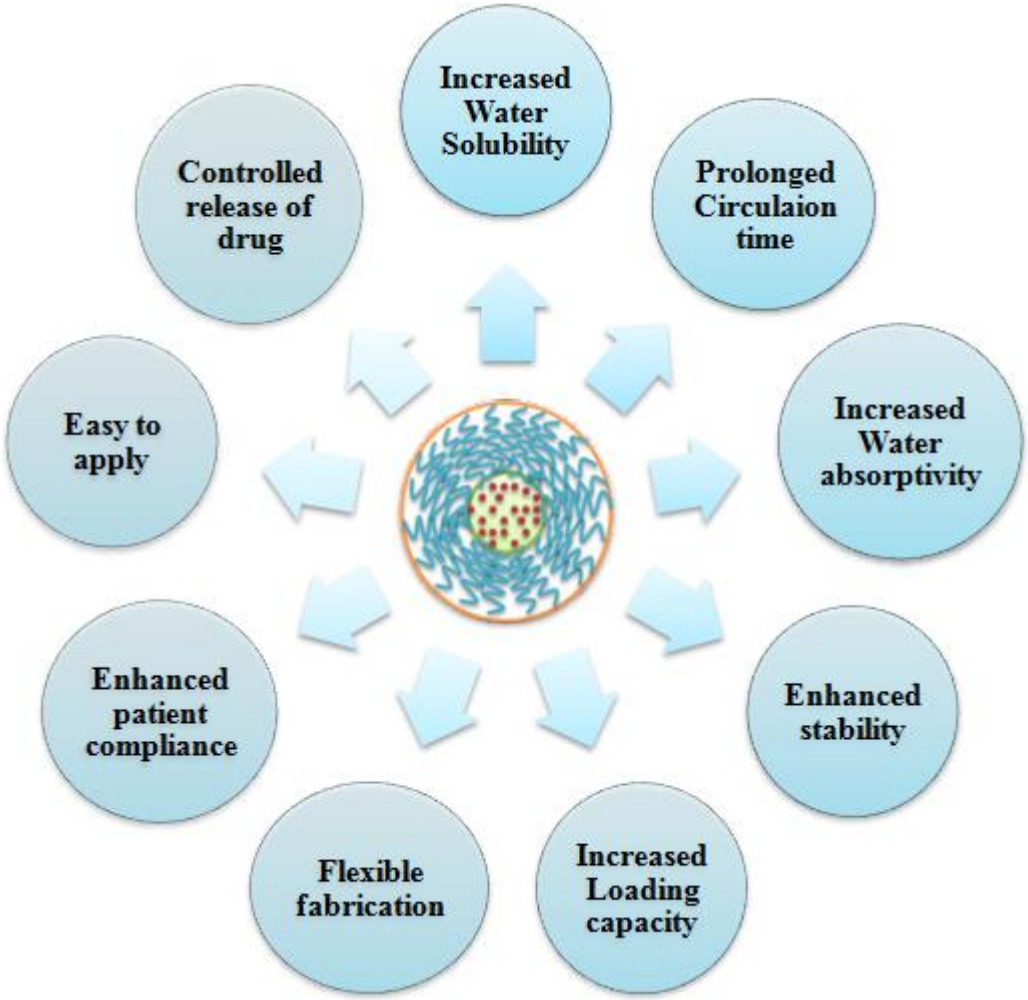

Figure 2: Benefits of Nanogel

Swelling of nanogels in water is governed by several factors like cross- linker concentration and environmental parameters like pH, temperature, ionic concentration etc. [8]

CLASSIFICATION

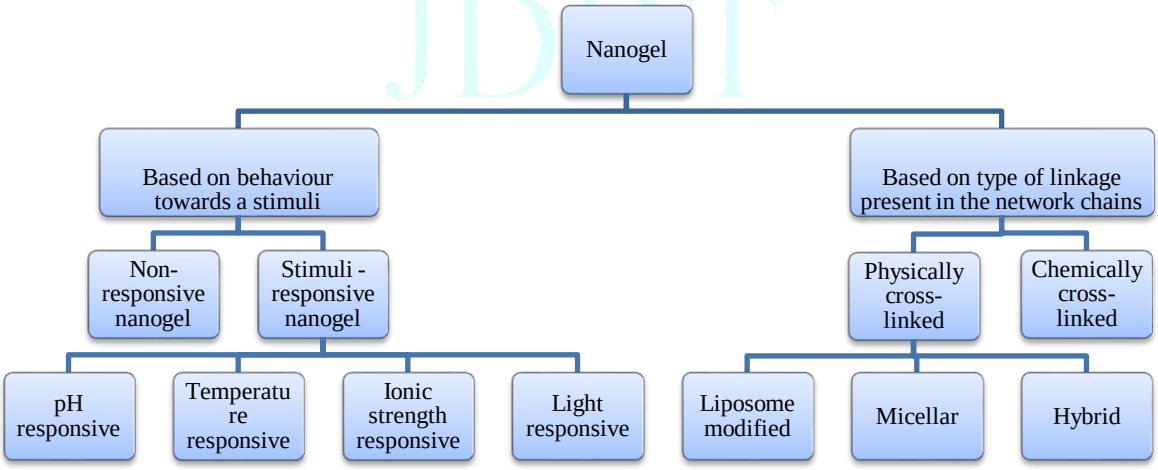

Figure 3: Classification of nanogels on different basis

Nanogels can be classified into various classes based on their behavior towards environmental stimuli, the type of linkage present etc. Fig. 3 describes the classification. The swelling of stimuli responsive nanogels is affected by various environmental factors such as light, pH, ionic strength, temperature and magnetic field, but, the same for non-responsive nanogels is unaffected by these factors. It just absorbs water and swells. In another classification physically cross linked gels involve weaker bonds like hydrophobic bonds, vanderwaal forces, and hydrogen bonds. In this case the formation of microgels and nanogels takes only a few minutes. Physical gels can also be formed by the aggregation and/or self-assembly of polymeric chains. The chemically cross linked nanogels involve strong and permanent covalent bonds in their networks. The types of covalent bond depend on type of functional group present in the structure. [9]

Preparation of Nanogels:

Fig. 4 and fig. 5 decribe the broad classification and general preparation techniques of nanogels.

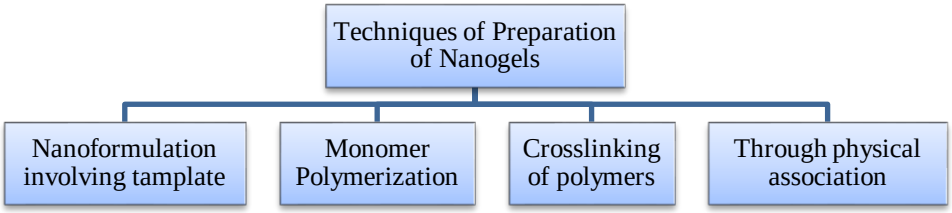

Figure 4: Broad Classification of Preparation of Nanogels

Most Commonly Used Methods (10):

1. Ionic gelation method
2. Emulsion polymerization
3. Solvent emulsification/ evaporation method / Emulsion solvent evaporation technique
4. Solvent Displacement method/ nano-precipitation method
5. Emulsion solvent diffusion method
6. Coacervation/Precipitation/ Precipitation polymerization
7. Emulsion cross- linking
8. Emulsion droplet coalescence method
9. Desolvation method
10. Micro-emulsion template method

1. **Ionic gelation method**-Using ionic gelation method, there are two techniques by which hydrogel beads (also called as gelispheres) can be prepared. The basis of classification of the techniques is the source of cross linking ion

(a) **External Ionic gelation**-In this method, the position of cross linker ion is outside the polymer solution.

(b) **Internal Ionic gelation/Emulsification-**In the second method, the polymer solution embodies the cross-linker ion in inactive form. [10]

Amongst these two methods the first method is most extensively used because of formation of thin films with smoother surface, greater matrix strength, stiffness, permeability than internally cross-linked films and also have greater drug encapsulation efficiency and slower drug release rate.

In the external ionic gelation method, a drug polymer solution is prepared and then it is added dropwise into the aqueous counter ion solution which leads to the diffusion of drug loaded polymeric drop and cations of counter ion solution, forming a three dimensional lattice of ionically crosslinked moiety called gelispheres. [11]

2. Emulsion polymerization method

On the basis of the type of the continuous phase, emulsion polymerization can be classified into-(a) Aqueous continuous phase containing emulsion polymerization

(b) Organic continuous phase containing emulsion polymerization.

The major emulsion polymerization techniques involve conventional emulsion polymerization, surfactant-free emulsion polymerization, as well as mini- (or nanoemulsions) and microemulsions polymerizations. This method can be divided into three phase nucleation, particle growth phase and polymerization. The process involves hydrophobic monomer, dispersion media, initiator and surfactant as the main component for emulsification. When monomer is emulsified in water and the concentration of surfactant exceeds the critical micellar concentration (CMC), formation of micelles occur, which causes reduction of surface tension at the surface and entry of monomers inside the micelles. Then the initiator is added and the micelle act as as reaction site of monomer and free radical. The step of polymerization starts and the micelle grows by continuously adding monomers. [12]

3. Solvent emulsification/ evaporation method /Emulsion solvent evaporation technique

In this method, a drug and polymeric solution is prepared in an organic solvent and then it is added to an aqueous continuous phase containing stabilizer with continuous magnetic stirring at room temperature or under reduced pressure which leads to the formation of emulsions. After the formation of nanoemulsion, it is converted to nanoparticle suspension due to the evaporation of solvent from water-air interface until saturation is achieved leading to the diffusion of solvent from an inner droplet of emulsion to the external continuous phase.It results in the formation of solidified nanosized particles which is collected by ultra-centrifugation and finally lyophilized. [12,13]

4. Nano- Precipitation

This method is basically based on the interfacial deposition of polymers following the displacement of a semi-polar solvent miscible with water from a lipophilic solution. It is mainly preferred for hydrophobic drugs. It requires two miscible organic and aqueous solvents. For the preparation of nanoparticle by this method the drug is mixed with polymer in a specific ratio. The nanoparticle formation requires three phases: nucleation, growth and aggregation. Supersaturation is the most important step for determination of nucleation rate. The difference between the surface tensions of two of the liquids plays an important role in the formation of nanoparticles. [13, 14] This difference between surface tensions of the aqueous and the oil phase causes interfacial turbulence and thermal inequalities in the system. This leads to the continuous formation of vortices of solvent at the interface of both liquids. The organic solvent diffuses from regions of low surface tension which causes gradual precipitation of the polymer on the oil surface and formsb nanocapsules. The prepared nanoparticles are then dispersed in gel using a magnetic stirrer. Penetration enhancers, humectants and pH modifiers are added. [14]

5. Emulsion solvent diffusion method:

In this method, weighed amount drug, polymer and stabilizer are dissolved in glycerol with continuous stirring. For aqueous phase a gelling agent is dissolved in water with continuous stirring and heat. The drug containing phase is ultrasonicated. After that the drug phase is added dropwise to the aqueous phase with homogenization to form emulsion.

Further the emulsion is reduced to nanodroplets by homogeniger at 5000- 8000 rpm for 1 hour. The prepared emulsion is O/W emulsion. Penetration enhancer is used for increasing the efficiency of the preparation and pH is adjusted. [15]

6. Coacervation/Precipitation/ Precipitation Polymerization

This method utilizes the physicochemical properties of polymers involved. As with chitosan, its insolubility in alkaline solution is utilized. This polymer is insoluble at alkaline pH and when comes in contact, it precipitates. A compressed nozzle spray is used to control the particle size of polymer containg drug. The particles are then separated using centrifugation and washed with hot and cold water. [16]

7. Emulsion Cross-Linking

This method is based on cross-linking of reactive functional groups of polymer and cross- linking agent. In this method an emulsion (w/o) is prepared by dispersing the aqueous solution of polymer in the oil phase. A suitable surfactant and cross-linking agents are added to stabilize the solution and harden the droplets respectively. The obtained nanospheres are then washed with organic solvents and dried. [16]

8. Emulsion-droplet coalescence method

This method involves the concepts of both the emulsion cross-linking and precipitation method with slight modification. In contrast to the cross-linking method, it induces the precipitation by allowing coalescence of polymer droplets. In the first step aqueous polymer solution is emulsified with a suitable oil. Then another emulsion of the same polymer containing drug is prepared with the alkaline pH. Both the emulsions are then mixed with high speed homogenization. The droplets collide and coalescence, which results in precipitation of small particles. The particles are separated by centrifugation, washed and dried. [16,17]

9. Desolvation method

In this method generally high molecular weight polymers are used such as gelatin and it is dissolved in double distilled water under heating and continuous stirring. The prepared aquous phase is allowed to stand at room temperature for 10 minutes and the a calculated amount of desolvating agent (i.e. ethanol) is added immediately to precipitate the high molecular weight polymer. The supernatant liquid is discarded & the high molecular weight polymer is again dissolved in double distilled water containing drug. The The prepared solution is then stirred under 500-1000 rpm for 8 hours at a constant temperature. pH is adjusted. In the second desolvation step, In-situ nanoparticle is formed by adding desolvating agent drop-wise with constant stirring. When turbidity is observed in the solution the solution is allowed to stand for 10 minutes and a crosslinking agent is added and further stirred at 500- 1000 rpm for 8 hours. The resulting solution is centrifuged, the settled nanoparticle are collected and washed whereas the supernatant is discarded. [17]

10. Tempelate Method

Photolithography is used to formulate 3 dimensional hydrogel particles and nanogels for drug delivery. This method involves the use of replica molds for molding gels. It requires the development of treatment methods of molds for easy release of molded gels from replica. This method consists of five basic steps

(a) UV cross linkable polymer is taken as a substrate on pre- baked photo resist coated water.
(b) Molding of polymer into predetermined patterns by pressingthe quartz template on to the polymer. Then it is exposed to high wavelength UV light.
(c) Thin film layer is uncovered by removing the quartz template.
(d) Oxidation of this layer.
(e) Collection of fabricatedparticles by dissolution of substrate.[18]

Figure 5: General Preparation Techniques of Nanogel

Table 1: Biomedical Applications of Nanogels

S.No	Author name	Description	Benefits	Ref
CANCER				
1.	Vinogradov, S.V., Kohli, E. and Zeman, A.D.	Nanogel carrier made up of amphipilic polymers and cationic polyethylenamine was prepared to deliver and encapsulate cytotoxic nucleoside analogs 5′-triphosphates (NTP) for the treatement of cancer.	Nanogel made up of Pluronic® F68 and P123 with improved delivery and advance therapeutic potential for NTP analogs in comparison to NG(PEG) was prepared for the treatment of cancer with chemotherapy.	19
2.	Shi, B., Huang, K., Ding, J., Xu, W., Yang, Y., Liu, H., Yan, L. and Chen, X	They formulated a pH and reduction dual-responsive polypepetide nanogel which was loaded with doxorubicin, with the help of sequential dispersion and dialysis technique. Certain tumor suppression activities were confirmed by histopathological and immunohistochemical analysis of NC/DOX.	It can be concluded that the developed doxorubicin nanogel had excellent in vitro & in vivo properties, improved on-demand intracellular delivery of antitumor drug, high drug loading capacity and also respond according to different environmental stimuli in comparison to free DOX.HCl.	20
3.	Reeves, A., Vinogradov, S.V., Morrissey, P., Chernin, M. and Ahmed, M.M.	In their work,curcumin being a potent anticancer compound was formulated into nanogel using NG127 amphiphilic Poloxamer-cationic network for its encapsulation which was found helpful in the treatment of breast cancer.	They developed curcumin nanogel had enhanced aqueous solubility and bioavailability, which ultimately enhanced its therapeutic activity with increased potential to specific tumor targeting, by using antibodies against surface receptors specific to breast cancer cells in comparison to carcumin alone.	21
4	Ashwanikumar, N., Kumar, N.A., Nair, S.A. and Kumar, G.V.	They prepared a 5-Fluorouracil nanogel using Methacrylic acid and 2-ethyl hexyl acrylate copolymer which effectively treated colon cancer.	With the help of cell proliferation assay of a human colon tumor colon cancer cell line (HCT-116),the study concluded that 5-FU-loaded MAEHA nanogels were considerably cytotoxic in comparison with free 5-FU.	22
5	Yang, W.J., Zhou, P., Liang, L., Cao, Y., Qiao, J., Li, X., Teng, Z. and Wang, L.	A nanogel-incorporated injectable hydrogel was prepared which was loaded with combretastatin-A4 phosphate (CA4P) and doxorubicin (DOX) to produce a synergistic effect for the treatment of cancer.	The prepared dual drug injectable hydrogel with embedded nanogel was found to more therapeutically active and also showed reduced drawbacks like drug resistance, high dose and is universally acceptable drug carrier for local delivery of dual drug in treatment of cancer.	23
6.	Ohya, Y., Takahashi, A. and Kuzuya, A	They prepared a dextrane(Dex) nanogel having a disulphide bond linked oligolactide chain(OLA) along with galactose(Gal)and tetraethylenepentamine(EI_4) to enhance drug delivery by controlling intracellular traffic.	The developed EI_4/Gal-Dex-g-SS-OLA (nanogel) was found to have highly effective drug delivery system by collapsing in cytosol under reductive condition as in the case of cancer chemotherapy.	24
7.	Hoelzer, D., Leiske, M.N., Hartlieb, M., Bus, T., Pretzel, D., Hoeppener, S., Kempe, K., Thierbach, R. and Schubert, U.S	The synthesis of a new nanogel drug carrier system loaded with the anti-cancer drug doxorubicin (DOX) is presented. Poly(2-oxazoline) (POx) based nanogels from block copolymer micelles were cross-linked and covalently loaded with DOX using pH sensitive Schiff' base chemistry.	The POx based nanogel system revealed a therapeutic efficiency despite the low DOX concentrations and could be a promising strategy to control tumor growth with fewer side effects.	25
8.	Neshastehriz, A., Khateri, M., Ghaznavi, H. and Shakeri-Zadeh, A.	They developed an alginate nanogel co-loaded with AuNPs and cisplatin (ACA) and studied its chemo-radiotherapeutic effects on U87-MG human glioblastoma cells for treatment of brain tumor	The developed alginate nanogel co-loaded with gold nanoparticles and cisplatin was found to have enhanced therapeutic ratio of human glioblastoma radiation therapy.	26
9	Azadi, A., Hamidi, M., Khoshayand, M.R., Amini, M. and Rouini, M.R.	They prepared a chitosan and sodium tripolyphosphate nanogels loaded with methotrexate (MTX) by ionic gelation process for the treatment of brain disorders.	The developed nanogel was found to be highly effective for certain brain disorders.	27
10.	Shi, B., Huang, K., Ding, J., Xu, W., Yang, Y., Liu, H., Yan, L. and Chen, X.	They formulated a pH and reduction dual-responsive polypepetide nanogel which was loaded with doxorubicin, with the help of sequential dispersion and dialysis technique. Certain tumor suppression activities were confirmed by	It can be concluded that the developed doxorubicin nanogel had excellent in vitro & in vivo properties,improved on-demand intracellular delivery of antitumor drug, high drug loading capacity and also respond according to different environmental	28

		histopathological and immunohistochemical analysis of NC/DOX.	stimuli in comparison to free DOX.HCl.	
SKIN DISEASE				
11	Avasatthi, V., Pawar, H., Dora, C.P., Bansod, P., Gill, M.S. and Suresh, S.	They developed nanostructured lipid carriers of methotrexate and incorporated it into nanogel. Along with this they evaluated its efficacy in imiquimod-induced psoriasis model.	The prepared nanogels shown sustained and optimized release of methotrexate. They reduced the signs and symptoms of the disease significantly and proved better formulation than the existing one.	29
12	Mujahid, M., Ahmad, L. and Ahmad, M.	They developed Zinc oxide nanoparticle incorporated in the gel which enhanced the surface volume ratio and shown more efficiency than the existing gels that are prepared from traditional methods for the treatment of superficial skin microbial infection.	Preparation of Zinc oxide nanogel showed maximum antibacterial activity as nanoparticles present in it helped to kill biofilms present on the infected skins by increasing UV activity as compared to conventional ZnO gels.	30
13	Panonnummal, R., Jayakumar, R., Anjaneyan, G. and Sabitha, M.	They prepared a chitin nanogel loaded with methotrexate for treatment of psoriasis.	The prepared methotrexate loaded chitin nanogel was found to have high psoriatic activity with high serum and tissue level of methotrexate without systemic toxicity in comparison to methotrexate tablets.	31
INFLAMMATION				
14	Singka, G.S.L., Samah, N.A., Zulfakar, M.H., Yurdasiper, A. and Heard, C.M.	They prepared a methothrexate loaded nanogel co-polymerised with *N*-isopropylacrylamide (NIPAM) and butylacrylate (BA) and examined the effect of sodium carbonate on topical application of nanogel for treatment of inflammation.	The prepared nanogel with sodium bicarbonate was found to have a more methotrexate release in comparison to other conventional preparations.	32
15	Talele, S., Nikam, P., Ghosh, B., Deore, C., Jaybhave, A. and Jadhav, A.	They enhance the bioavailability and anti-inflammatory effect of Diclofenac sodium by developing nanogel.	The drug release was enhanced by using carbopol 940 as gelling agent, propylene glycol as permeation enhancer and Eudragit S-100 as comapared to plane nanogel with HPMC and MC.	33
16	Pawar, S. and Pande, V.	They developed a biodegradable, surface decorated zaltoprofen nanogel using gelatin as a base and its texture characteristics were also evaluated.	The developed zaltoprofen nanogel was found to give better patient compliance,sustained analgesic activity and more stability as compared to marketed nanogel due to its acceptable texture characteristics and bio-adhesive properties and three months stability.	34
MICROBIAL INFECTION				
17	Kłodzińska, S.N., Molchanova, N., Franzyk, H., Hansen, P.R., Damborg, P. and Nielsen, H.M.	They developed a lysine-based α-peptide/β-peptoid hybrid biopolymer nanogel incorporating octenyl succinic anhydride-modified hyaluronic acid along with anti-bacterial peptidomimetic for the treatment of pseudomonas aeruginosa caused infection.	It can be concluded that the antibacterial peptidomimetic nanogel prepared was found to have reduced cytoxicity, more cell selective, high efficacy of encapsulation and also enhanced bacteria killing kinetics in comparison to simple peptidomimetics for treating pseudomonas aeruginosa caused infections.	35
18	Malik, T., Chauhan, G., Rath, G., Kesarkar, R.N., Chowdhary, A.S. and Goyal, A.K.	They prepared a thermosensitive nanogel in which Efaverinz (EFV) and gold nanoparticles(GNPs) combination neosomes were dispersed for completely inhibiting Human Immunodeficiency Virus-1(HIV-1).	The prepared nanogel formulation of combined niosomes was found to be more effective inhibitor of HIV-1 by exploiting protein-carbohydrate interaction of HIV in comparison to other preparations.	36
19	El-Feky, G.S., El-Banna, S.T., El-Bahy, G.S., Abdelrazek, E.M. and Kamal, M.	A silver sulphadiazine nanogel was prepared using sodium alginate as polymer which could be used topically for healing burns by its controlled release anti-microbial activity.	The prepared nanogel formulation of silver sulfadiazine was found to be more therapeutically effective in vivo in comparison to other marketed products.	37
ANASTHETICS				
20	Khongkhunthian, S., Sastraruji, T., Klayraung, S. and Okonogi, S.	They prepared two modified rice nanogels, one loaded with 5% lidocaine hydrochloride and other with 20% prilocaine hydrochloride for use as local anaesthetics in the buccal cavity.	After evaluation, it was found that prepared modified rice nanogels was more effective in reducing pain in buccal cavity on needel insertion and hence were more clinically effective local anaesthetic in comparison to other market products.	38
21	Hoare, T., Young, S., Lawlor, M.W. and	They prepared a poly(n-isopropylacrylamide based nanogel loaded	The prepared nanogel was found to have a prolonged duration of action in comparison	39

	Kohane, D.S.	with bupivacaine for use as local anaesthetics.	to other local anaesthetics.	
EYES				
22	Moya-Ortega, M.D., Alves, T.F., Alvarez-Lorenzo, C., Concheiro, A., Stefánsson, E.	They prepared a Ɣ-cyclodextrin based nanogel loaded with Dexamethasone to treat ophthalmic inflammation.	The prepared nanogel was found to be more efficient with no side effects in comparison to commercially available product Maxidex	40
23	Ilka, R., Mohseni, M., Kianirad, M., Naseripour, M., Ashtari, K. and Mehravi, B.	They prepared chitosan-alginate biopolymers nanogel loaded with Timolol Maleate for effective treatment of glaucoma through cornea.	The developed nanogel formulation was found to have a higher cornea penetration rate and also sustained drug release in comparison to other marketed formulations.	41
FROST BITE				
24	Shen, C.Y., Xu, P.H., Shen, B.D., Min, H.Y., Li, X.R., Han, J. and Yuan, H.L.	A more therapeutically effective and stable nanogel formulation of *Ganoderma lucidum*(GLT) was developed which was highly effective for topical application in the treatment of frostbite.	Poorly soluble drug GLT was formulated into suitable nanomedicine which was found to be more effective for its dermal delivery as compared to GLT–carbopol gel in the treatment of frostbite.	42
NARCOTICS				
25	Asadi, H., Rostamizadeh, K., Salari, D. and Hamidi, M., 2011	A more therapeutically effective and stable nanogel formulation of *Ganoderma lucidum*(GLT) was developed which was highly effective for topical application in treatment of frostbite.	Poorly soluble drug GLT was formulated into suitable nanomedicine which was found to be more effective for its dermal delivery as compared to GLT–carbopol gel in the treatment of frostbite.	43
LUNGS DISEASE				
26	Hoelzer, D., Leiske, M.N., Hartlieb, M., Bus, T., Pretzel, D., Hoeppener, S., Kempe, K., Thierbach, R. and Schubert	They prepared a degradable nanogel carrier to which imidazoquinoline TLR 7/8 agonist is covalently linked which plays an important of adjuvant for respiratory syncytial virus.	The study provided strong in-vitro and in-vivo evidences to choose nanogel carriers of imidazoquinoline in comparison to soluble polymers of the same for vaccination against syncytial virus.	44
JOINT DISORDER				
27	Schmitt, F., Lagopoulos, L., Käuper, P., Rossi, N., Busso, N., Barge, J., Wagnières, G., Laue, C., Wandrey, C. and Juillerat-Jeanneret, L.	They prepared a chitosan nanogel in which hyaluronate was surface decorated and photosensitizers were encapsulated for effectively targeting inflammation inducing macrophage in the treatment of rheumatoid arthritis.	The prepared hyaluronate nanogel was found to have more therapeutic index and increased retention time in comparison to free photosensitizers.	45

Table 2: Other Applications of Nanogels

S.N.	Author name	Description	Benefits	Ref
OTHERS				
1	Beloqui, A., Kobitski, A.Y., Nienhaus, G.U. and Delaittre, G.	They prepared a single-enzyme nanogel in which a hydrophilic and polymeric crosslinked nanostructure was used for embedding enzyme molecule.	They developed an enzyme nanogel with preserved enzyme chemistry which was found to have high catalytic activity similar to that of free enzyme in the body.	46
2	Drude, N., Winz, O.H., Mottaghy, F.M., Roller, M., Königs, H., Möller, M., Singh, S. and Morgenroth, A.	They reduced glutathione level by inhibiting GSH synthesis with the help of buthionin sulfoximin for efficient in-vitro and in-vivo behavior of redox sensitive nanogels having disulphide linked nanoparticles.	The data obtained after decreasing GSH level showed enhanced circulation half life, decreased nanogel distribution and increased biodistribution when compared with data obtained from nanogel without any change in GSH level.	47
3	Carr, A.C., Piunova, V.A., Maarof, H., Rice, J.E. and Swope, W.C.	They studied effect of various organic solvents (dichloromethane, diethyl ether, toluene, methanol, dimethyl sulfoxide, and tetrahydrofuran) on drug loading capacity of nanogels star polymeric nanoparticle.	Their work suggested that dichloromethane, tetrahydrofuran, and toluene showed maximum drug loading capacity in comparison to methanol, while diethyl ether could not be used as a solvent for drug loading.	48
4	Bai, X., Xu, S. and Wang, L.	They prepared a nanogel for effective recognition of hydrogen sulphide which plays a key role in various pathological and physiological actions in body.The prepared nanogel was suffused with gold nanoclusters(AuNCs) using glycol-chitosan (GC) polymer matrix.	The prepared AuNCs@GC nanogel showed increased quantum yield to 6-folds, enhanced selectivity and sensitivity to aqueous hydrogen sulphide and also very good biocompatibility and super fluorescence stability across the full pH range which leads to improved intracellular sulphide imaging.	49

Drug loading and drug release in Nanogels:

The nanogel systems are very flexible Nanomedicine carriers as compared to other systems in respect of drug loading. As the drug loading in these systems can be done during or after the formulation. Additionally the drug loading is higher and spontaneous in case of nanogels. The drug loading process in nanogels can involve either covalent conjugation, or physical entrapment or self assembly process. Out of these three processes, self assembly process is more beneficial as compared to the other two processes as it is a cost effective and versatile process. It is an independent organization of monomers into well defined polymeric structures. [50, 51]

And the drug is released from these nanogels by

(a) Simple diffusion

(b) Complete degradation of nanogel

(c) pH change

(d) Counter-ions present in the environment

(e) Other external intermediary energy sources

Specific polymers are added in composition for imparting temperature and photosensitivity in the formulation. Upon alteration of temperature, expansion of polymer chain occurs which results in release of drug load. Similarly, in case of photosensitive polymers cross-linking densities alter which affect selling and deswelling of polymers. Finally, change of volume control the release of drug from the nanogel. In case of pH responsive release, polymers containing weakly acidic and basic groups in their structures are chosen. The extent of ionization of polymer molecule then governs the swelling and deswelling, which controls the drug release from the nanogel. For more efficient release control combination of these approaches are used. [50, 51]

Drug Targeting Through Nanogels

Nanogels are gaining importance day by day as they have dramatic advantages for targeting any drug in a vast number of diseases. They posses both the hydrogel and Nanocarrier's properties. Table No. 1 and 2 provides a list of nanogels, that have already been developed for various diseases.

Nanogels have utilized not only for superficial acute diseases, but also entered the critical fatal disease therapies. These delivery systems are now curing the brain disorders, lung and liver disorders, cancers, skin diseases, joint disorders, ophthalmic, wound healing and vaccine delivery. In parallel nanogels have also entered the field of diagnostic imaging. (52) Many nanogels have also been patented in various countries for various diseases. Table no. 3 summarizes the recent patents related to nanogels.

The brain delivery of various drugs is strictly limited by the blood brain barrier and suffers poor bioavailability problems. The polymeric nanocarriers with hydrogel system have very promising potential to improve the bioavailability of such poorly permeable drugs. In the field of brain delivery nanogels have been developed for several degenerative disorders as well as for brain cancer. For the neurodegenerative disorder several oligoneucleotides have been formulated as nanogel which successfully crossed the BBB. [52]

Skin Diseases- The nanogels can be directly applied to the affected area topically. The permeability of drug is enhanced by its conversion to the nanoparticle size range. Mohammad M. et al prepared nanoparticles of zinc oxide and incorporated in the gel and they proved that the antibacterial efficiency of drug is improved by this method as compared to the existing gels.(30) In another study Panonnummal R. et al prepared methotrexate loaded chitin nanogel and found it to have high psoriatic activity. [31]

Inflammation and Joint Disorder- Nanogel plays a key role in treatment of certain join disorders due to its effective targeting towards the inflammation causing macrophages. Amongst various joint inflammatory disorders, rheumatoid arthritis is the most common disorder. A nanogel has shown increased therapeutic index and decreases vascular and tissue permeability as compared to conventional system and was found to be effective in treatment of certain joint disorders. [52, 53] Schmitt et al prepared hyaluronate nanogel having more therapeutic index and less retention time in comparison to free photosensitizers.[27]

Wound Healing- Nanogel provides many advantages over conventional therapy for healing of wounds due to its high consonant ability, greater retention time on the applied surface (keshavraj and kaffashi 2013) and also enhanced healing ability due to its moisturizing nature. [55]

Kobayashi et al. prepared a cholestrol bearing pollulan(CHP) nanogel loaded with prostaglandin(PGE1) which when tested on induced wound animal model, was found to have greater wound size reduction ability in comparison to mere cholestrol bearing pollulan(CHP). [56]

Cancer- Many anti-cancer drugs are frequently used for the treatement of cancer but they have shows certain shortcomings which provide hinderence in the effective treatment of cancer.Some of the shortcomings are poor permeability, less bioavailability,less retention time and faster excretion of drugs .To overcome these shortcomings nanogels loaded with anti-cancer drugs were prepared. [57, 58] Soni et al prepared a N-hexylcarbamoyl-5-flurouracil loaded nanogel for treatment of brain tumour and was found to have increased retention time and accumulation in brain. [59] Shi et al prepared a pH sensitive biodegradable nanogel loaded with Doxirubicine and the result evident enhanced permeability and retention time (EPR) of drug for the treatment of hepatic carcinoma.[60] Sabita et al prepared a chitin nanogel loaded with 5-Flourouracil for the treatment of skin carcinoma and the results showed enhanced drug loading capacity,enhanced drug release and improved retention time. [61]

Eye Disorder- Nanogel are found to be highly effective in treatment of eye disorders due to its improved corneal bioavailability,less drainage of the formulation from the corneal surface and also increased retention time in comparison to other carrier system.Moya-Ortega et al.,2012 prepared a nanogel loaded with dexamethasone in combination with gama-cyclodextrine which leads to prolonged retention time of drug on the corneal surface. [62]

Diagnosis- From diagnostic point of view ,nanogel play an important role in cell imaging to differentiate cancer cells from normal cells to carry out surgeries for removal of cancerous cells without effecting normal cells. Hesegawa et al. prepared a hybrid nanogel($CHPNH_2$-QD) by simply mixing nanogel quantum-dots (QDs) and amino acid modified nanogel of cholesterol bearing pullulan($CHPNH_2$), which gave long term imaging with greater potential in comparison to a single one($CHPNH_2$) when tested on certain cancerous cell lines. [63]

Immunity:Vaccine- Nanogels can also be employed as vaccines and can provide certain advantages like enhanced immunity and reduced inflammatory cytokines induced

toxicity.Nochi et al prepared a nanogel loaded with non-toxic fragment of Clostridium botulinium for treatment of mucosal infection disease by intranasal route. [64]

Diabetes- In the treatment of diabetes many glucose sensitive nanogels have been prepared with encapsulated insulin which releases in response to the level of glucose.Wu et al. prepared a silver nanoparticle nanogel of 4-vinylphenylboronic acid-co-2-(dimethylamino)ethyl acrylate) [p(VPBV-DMAEA)] loaded with insulin in which an increase in blood glucose level generates optical signals with the help of polymer p(VPBV-DMAEA) in nanogel and silver core detects optical signals resulting in release of insulin. [65]

Table 3: Review of Patents on Nanogels

S. No.	Inventors	Date	Patent Number	Description
1.	Se-hoon K.,Chang-geun L.,Huh,Jung-Yun,Su J.K.	30/01/2018	KR101823490B1 South Korea grant	The invention includes a method of preparation of polyamine based polymer nanogel, a method for diagnosis of inflammatory diseases and the ultrasonic composition including the contrast medium for diagonising the disease. [66]
2.	Young J.K.	10/10/2017	KR101780772B1 South Korea grant	The invention describes a process for the ceramide preparation for stabilizing the cosmetic composition and multilayered nanogel emulsion. [67]
3.	Kabanov, A.V. and Vinogradov, S.V.	24/02/2004	US6696089B2 US grant	This invention is related to nanogel networks having at least one cross-linked polyionic polymer fragment and at least one nonionic water-soluble polymer fragment, and compositions thereof, having at least one suitable biological agent. [68]
4.	Mittal, R., Roy, S.B., Kothari, J.S.	02/05/2017	US9636353B2 US grant	This invention describe a method for treating, reducing or preventing acne. They also described the method for reducing incidence, number and severity of acnelesions and incidences and severity of adverse events resulting from topical application of anti-acne agents resulting in improvement of skin tone. It also includes the composition and administration of a novel antiacne formulation. [69]
5.	Jie Y,Lingling Z,Dongwei Z,Jingxia,Yajuan Z,Rui W,Hongze L.	16/10/2018	CN104758945B China grant	They invented preparation method and applications for thrombolytic drug carrying nanogel for effective delivery of protein or peptide drug with synergistic activity. [70]
6.	Caihua N,Liping Z,Gang S.,2017.	13/05/2015	CN104817660B China grant	They developed a method for nano-carboxymethyl chitosan nanogel with increased pH and reducing sensitivity of drug nanoparticles. [71]
7.	Wei L.	30/11/2017	CN107811966A China grant	The method describes the method of preparation of musarin nanogel. The nanoparticles are obtained by emulsified solvent evaporation method and then dispersed in gel phase so as to obtain musarin nanogel.The prepared nanogel showed high drug loading capacity, high stability, possessed core shell structure and passes all the crieterias for nanogel preparations. The method provided a basis for application of musarin. [72]
8.	Xiaowen S,Jianwei Z., Hongbing D,Yumin D.	13/06/2017	CN107141494A China grant	This invention described in detail a preparation method of chitin nanogel. The prepared nanogel possessed all the ideal characteristics of a nanogel with diameter of 20nm. The preferred method was easy and simple to convert into large scale production. [73]
9.	Quanchen X,Zhiguo W,Xiaoyan X,Changquing Y,Qiuxia J,Xiulei C,Yujin Y.	29/05/2018	CN104958251A China grant	They invented a method of preparation for hyaluronic acid nanogel for the treatment of oral ulcer with enhanced clinical treatment efficacy. [74]
10.	Fahmy T.M.,Look M.,Craft J.	05/02/2019	US10195144B2 United States grant	They described the composition and methods for preparation of sustained release nanolipogel for treating or reducing the symptoms of inflammatory and autoimmune disease.The composition embodies hydrogel core surrounded with lipid bilayer optionally including active molecule as like cyclodextrin or ion-exchange resin in which one of the agent is immunosuppresant. [75]

11	Thayumanavan S.,Ramireddy R.R.	16/01/2018	US9868821B2 U S grant	They invented method of preparation and uses of biodegradable polymeric nanogel as nano-carriers and can be utilized for diagnostic and drug delivery purposes. [76]
12	Mashimo K.,Kitamura S.,Shojo K.,Akiyosha I.,Sawada S.	15/02/2017	JP6082633B2 Japan grant	They prepared a polysaccharide nanogel with excellent wound healing tendency and enhanced safety. [77]
13	Heller D.A., SHAMAY Y.	22/08/2017	US9737614B2 U S grant	In the present invention,p-selectin targeted polymeric drug carrying nanogel for the treatment of cancer and other P-selectin targeted disease was developed which was having enhanced tumor targeting and reduced toxicity. [78]
14	Han-su P,Muhammad K.,Knoppad U.	29/04/2016	KR101616400B1 South Korea grant	The prepared an upgraded anti-fungal nanogel with enhanced anti-pathogenic activity specially for the treatment of Candida which is an infectious anti-fungal disease. [79]
15	Tao W.,Xuemei T.,Junyan H.,Yuzhang Z.,Min X.,Wenzhong C.	24/08/2016	CN104371066B China grant	They invented a preparation method for smart nanogel with improved pH and temperature sensitivity. [80]

CONCLUSION

From the review about nanogel it can be concluded that the nanogels are the versatile carriers exhibiting properties of both the nanoparticles and hydrogel. The combination of properties of these two systems provides nanogel its uniqueness amongst other carriers available. Hydrogel system allows them to accommodate any kind and size of a therapeutic molecule inside them. And the nanoparticles allow deeper penetration, and enhanced retention of the drug molecule. With these advancements nanogels can be delivered to variety of organ through various routes of administration. The review shows that the nanogel is covering vast number of diseases ranging from topical application for acute irritation and pain to parenteral delivery of drug for brain cancer. The studies shown that the nanogels even work for the very fatal diseases where other treatments cannot work because of their severe side effects. The nanogels as nanogels have been proved more effective therapies. Nanogels are fluently internalizedin target cells, and doesnot show accumulation in non- target tissues thereby enhace the bioavailability, reduces therapeutic dose, and minimizes harmful side effects. One future goal for research in this area should be experiments for reduction of toxic effects due to surfactants present as well as more clinical trails for launching this flexible and effecient carrier system for each and every disease.

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