REVIEW PAPER

Nano-gels: A versatile nano -carrier platform for drug delivery systems: A review

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ABSTRACT

Nowadays the application of nanotechnology in different biomedical fields such as drug delivery is increasing due to its unique advantages. With this in mind, it is widely believed that nanogels as the nanometer-sized networked polymeric particles have a considerable impact on drug delivery systems as biocompatible nanocarriers resulted to their versatile characteristics like desirable absorption ability and sustainability. The nanogels have the three-dimensional constructions containing the hydrophilic or hydrophilic polymeric chains that they can physically or chemically trap the appropriate percentage of water and they never dissolve in water so that polymer structure is reversible as well as the capability of swelling. These nanomaterials are made using polymeric precursors and heterogeneous polymerization monomers, and recently some researchers have reported the networked nanogels based on optical processes. In this review, we will try to address methods to synthesize them also investigate their usages as nanocarriers systems with examples of pharmaceutical systems.

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INTRODUCTION

Nanotechnology is nowadays currently applied in various research tendencies as drug nanocarrier systems (DNS) [1], medical imaging [2], cancer therapy [3], diagnostic tests [4] and so on for the remedy of diversity cancers to improve medical diagnosis methods. Nanocarriers can control the drug release into the cell compared with the bulk drug delivery systems [5]. In addition, they can circulate within the blood circulation system after the injection as well as the ability to deliver the drug to target [6]. This aspect of nanomaterials is particularly useful in the cancertherapy so that accurate design of nanocarrier systems is a special factor in the targeted treatment of this disease according to the increased permeability and inhibition [7-8]. In the drug delivery systems (DDS), the patient's cells are attacked by the attachment of ligands or antibodies [9]. With this in mind, nanogel particles which are polymer-based material with adjusting properties are applied for various applications in the drug delivery [10]. Nanogels are the networked polymeric particles with a dimension less than 100 nm which they create the hydrophilic polymer similar to hydrogels [11]. The nanogels have been introduced as biocompatible nanocarriers in the biomedicine and biotechnology sciences to date [12]. On the other hand, nanogels are used in the various fields such as sensors [13], biomedicine [14], in vivo imaging detectors [15], water purification [16], catalyst [17], and bioactive scaffolds production [18], but they have the most effect on DNS because of their capability to carry drug and significant sustainability [19]. In the nanogels, the bioactive molecules can absorb a lot of water based on properties of their fluid

transfer which nanogel size is significantly less than the pore size of the bioactive molecules [20-22]. The hydrogel nanoparticles are chemically (covalently bonded) or physically bonded together [23] (without covalent bonding) and also they have a high capability to convert to the initial structure through the hydrogen, electrostatic, and hydrophobic interactions [24]. Chaco et.al synthesized the nano-gels from the chemical network of polyethylene glycol (PEG) so that they applied the polyethylene imine (PEI) ligand to release the oligo-nucleotide anesthetic drug [25]. In a conducted study by Akiyoshi et al [26] focus on the self- organized amphiphilic polymers, the physical networked nanogels were prepared by using polysaccharides containing the cholesterol in water as a nanocarrier for the DDS [26]. Undoubtedly, cancer is one of the challenging issues to study of nanogels. Although for a long time, these systems have been used to synthesis methods not only for DDS, but also for other systems such as quantum dots [27], MRI (Magnetic Resonance Imaging) contrast agents [28], and other diagnostic cases. The designing the different polymeric systems has been led to formulate nano-gels with unique physical and chemical characteristics (Fig. 1) [29]. Also in the Table 1, kinds of nanogels, properties and their applications are presented [78]. As a result, nowadays the researchers have focused on the design the nanogels as the effective

nanoplatforms to encapsulate the bioactive substances with specific chemical properties such as cytokines [30], nucleic acids [31] and so on for cancer treatments and autoimmune diseases [32].

SYNTHESIS METHODS OF NANO-GELS

In this section, preparation methods of nano-gels are divided into three procedures: 1) self-assembly of active amphiphilic polymers; [33] 2) emulsion; [34] and 3) Nano-template [35].

Self-assembly of active amphiphilic polymers

In this method, amphiphilic polymers are made so that the recognized active groups located on the base polymer structure. These polymers have the potency to surfactant self-assembly (micelle) in an aqueous medium so that the nanogels will be prepared after the process of networking as well as fixing of micelles. Generally, networking of micelles is done based on the chemical mechanism, which is related to the synthetic copolymer structure completely [36-38]. The construction of nano-gels in this pathway and also some examples related to the synthesis of nanogels according to the chemical method are presented following. For instance, in the polymerization process by adding a primer, the gelation process can be done with disulfide (S-S) bonds [39]. The synthesis of nanogels based on the replacement of the thiol with the lipoic acid-dextran structure is an example related to the mentioned method (Fig. 2)
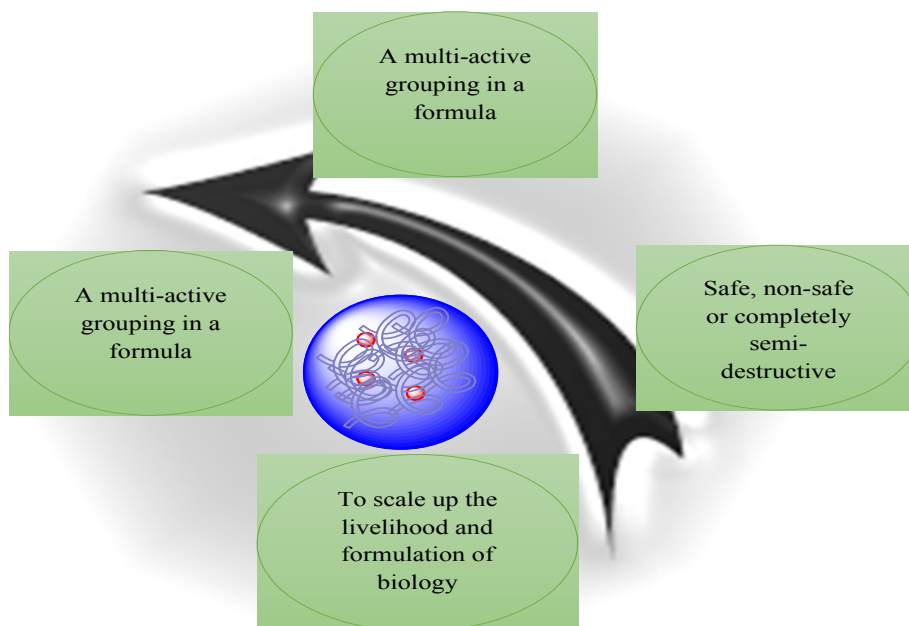

Fig. 1. advantages formulating of nanogels

Table 1. A summary of the types of nanogels, their characteristics and their applications.

Type	Schematic	Properties	Application
Simple		Reticular polymer semi-permeable self-assembled	Synthetic of 3D nanogels
Hollow		Permeation polymers	Nanogel responder / stimulant to sensitive (pH and temperature) nanogel of cholesterol synthesis
Core-shell		Networked	Chaperone synthesized by the enzymatic method of glycogen, nanogel responder/stimulant to sensitive
Capillary		Networked	Nanogel responder/stimulant to sensitive
Multilayer		Networked	Nanogel responder/stimulant to sensitive
Functionalized		Networked	Polyethylene glycol bonded to poly-meth acrylic acid with polyethylene glycol with aldehyde groups

[40]. In this process, lipoic acid is attached to dextran, which process of attaching occurs by self-assembly in the aqueous medium. Then, the drug is loaded within nanoparticles and the drug-loaded nanogels are formed by the user of the dithiothreitol (DTT) subsequently [40]. It is important to mention that in the current process, the degrading enzymes leads to break the S-S bond and resulting in the drug release occurs instantaneously (Fig. 3) [40]. Woolley et al have reported a variety of methods for the creation of nanogels using amine groups [41-43], activated esters [44], carboxylic acids [45], and isocyanates [46] related to the main structure of the copolymer. The formed zwitterion shell on networked polymers (nanogel)

via the copolymer precursor of 2-(dimethylamino) ethyl meta acrylate-2-tetrahydro pyranine meta acrylate (DMAEMA-THPMA) through 1,2-bis-(2-iodo ethoxy) ethane (BIEE) and tetra hydropyranile (THP) of hydrolysis has been reported by Armes et al [47]. Hawker et al, carried out the synthesis of gel nanostructures by creating cross-links based on click chemistry. In this method, the alkylated and azide groups there are in the principal structure so that they are fabricated using spontaneous assembly of copolymers and also the enhancing of networking agent [48]. They in their study also referred to cross-link based on an optic agent of coumarone and the formation of a nanogel [49].

Emulsion

In this synthesis process, the polymerization reaction of the monomers occurs in a heterogeneous phase and the nanogels creates. Generally, this method involves normal and reversible emulsions [50-51]. Few types of research have reported a method on the preparation of nano-gels by the process of water-oil (W/O) emulsion. in the other words, polymerization accomplishes between solvent monomers in water and monomers containing several functional groups to synthesis the networked nano-gels [50]. In a study, Peppas et.al produced a suspension of polyethylene glycol (PEG) nanoparticles of conjugated to the polymethacrylic acid (PMA) molecules by

employing UV for preparation of nanogels based on the reverse phase emulsion [52]. Recently, atom transfer radical polymerization (ATRP) reported by Matyjaszewski et.al. In this syudy, the nanogels produce through the network of polymerization. This procedure carried out by selecting sulfide bridges of dual-function monomers [53].

Nano template

The basis of this manner is the use of nanoparticles as a template that the most well-known of them are liposomes [54]. A liposome is microscopy of a vesicular structure consisting of two layers of phospholipid that has been enclosed a water space around it [55]. This method has
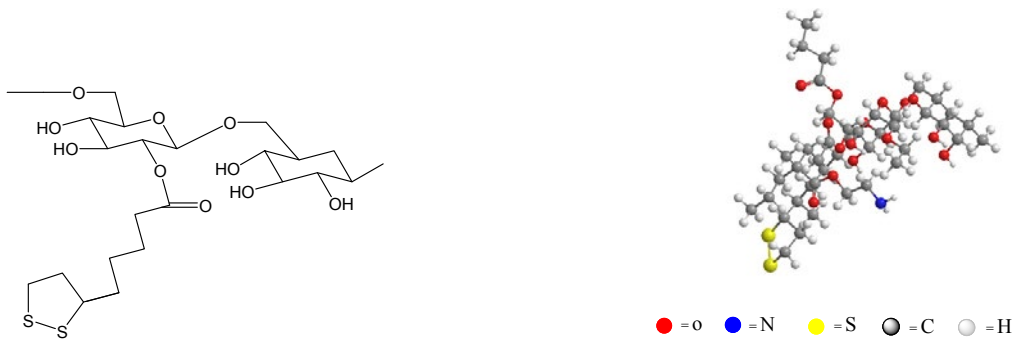

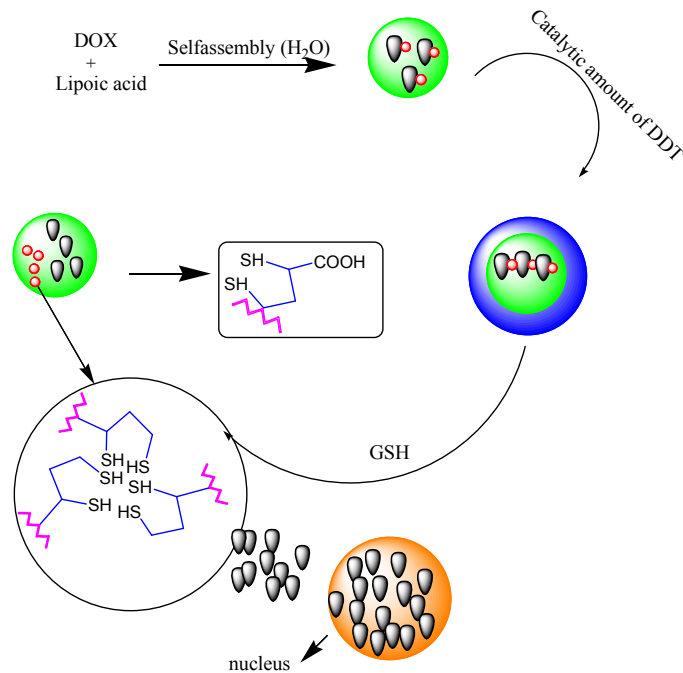Fig. 2. Pre-polymer structure of lipoic acid-dextran

Fig. 3. Stages of nanogel synthesis and the release of the drug in the target cell

been generally applied to synthesize the nano-gels due to its advantages such as non-toxicity [56] and biodegradability [56]. The aqueous core of these nanomaterials is a good location for the polymerization reaction, which eventually by removing the template, the nanogels are produced [57-58]. In a study by Sudhakar et.al by using the in situ polymerization process to synthesize the nano-gels, at the first, the designed liposome modified with poly (N-isopropylacrylamide-co-acrylamide) (P (NIPAM-co-AAM)) and resulting they were utilized in oeder to DNS applications [59]. Zoratto was carried out the hybrid cholesterol derivatives of nano-gel utilizing liposome template [60]. One of the unique advantages of this method is the synthesis of hollow nanogels. For example, by selecting nanoparticles of gold as the template, the polymer at their surface is turned to the hydrogel, and by removing the template by KCN, a product of the hollow nanogels has resulted that is illustrated in Fig. 4 [61]. In other research by Teng et.al, in an general process were developed the synthesis method of nanogels using precursors of glycol chitosan (GC) and poly (ethylene oxide) (PEO) [62]. Generally, this synthetic approach in the future will exhibit a clear vision for composing drug carrier nanogels.

NANOGELS IN DRUG DELIVERY

The novel biomedical nano-gels systems are considered as a DDS based on their important properties such as high capacity to encapsulate

drugs [63], capability to encapsulate the different drugs [64], uniformity [65], adjustable size [66], easy preparation [67], minimum toxicity [68], stability in blood serum [69], and external response capabilities [70]. Natural derived nano- gels for drug delivery purposes can be synthesized from natural polymers like collagen, albumin and etc. [25]. On the other hand, polymers like polylactic acid, poly-lactic-poly glycolic glycoproteins, polyacrylates (PC), poly-methacrylates (PMA) and poly (ε-caprolactone) are certain examples for preparation of polymers to the synthesis of nano-gels [25]. Although nano-gels are often spherical particles but recent advances related to synthesis of nanogels has been led to synthesize nanogels with different shapes such as the core-shell structures with at least one polymeric network layer with uniform structure [25]. Due to the highly hydrophilic and highly biocompatible properties of nano gels, they are suitable for placement of inorganic nanostructures, medications and biological molecules but without having direct effectiveness on their gel-like performance. The ability to encapsulate more than one biologically active materials with different physical properties is a particular advantage of these nanoparticles compared to some nanocarriers like mesoporous, metal organic framework (MOF), noisome, and quantum dot [26].

The nano-gel network prevents the in-vivo destruction and removal of encapsulated biological molecules and distributes them well in the target
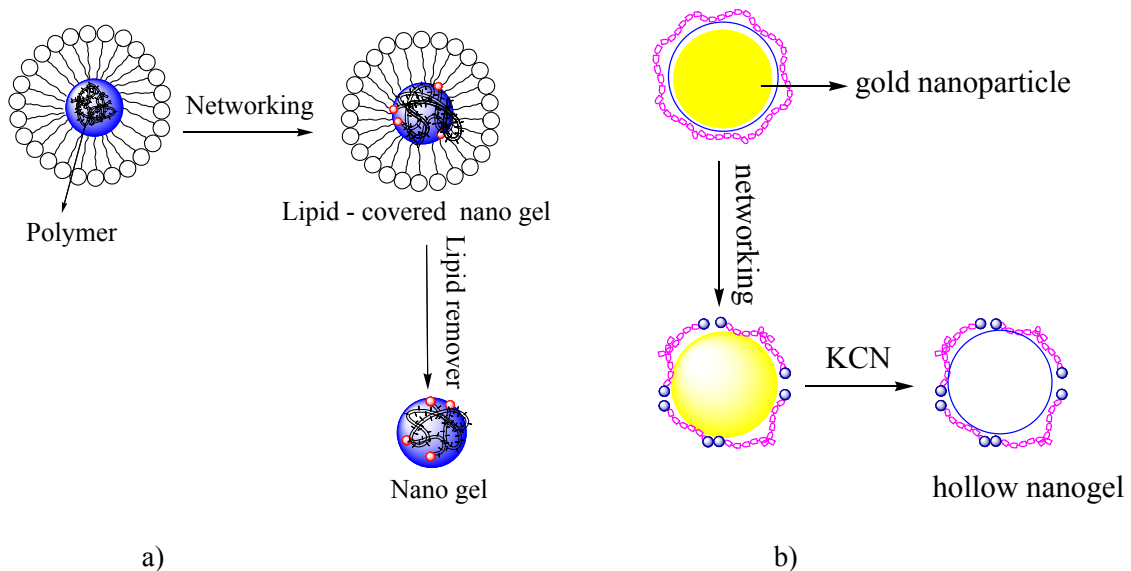

Fig. 4. Nano gel preparation using Nano template a) liposome, b) gold nanoparticle

position during the release process for fabrication a controlled response as a result their features of hydrogels such as swelling [71-72], compatibility into their stimulus [70], and their flexibility [73]. However, the conducted studies confirm the multiplicity of the nanogel applications and the diversity of their release systems. Du et al. a special nanogel were synthesized with different charges to absorb tumor cells and release doxorubicin. These nano-gels were generated through poly (2-aminoethyl methacrylate hydrochloride) (PAMAH) (Fig. 5).

The zeta potential related to this system was ranges from -17 mV to 0 mV within 35 minutes confirming with pH<7 media. Also, the release rate related to the loaded-doxorubicin PAMA-DMMA system indicated an increase as pH decreased [74]. In other words, the release of therapeutic molecules has been studied in order to the treatment of inflammatory disorders. In the treatment, this type of disorder based on the dynamic light, macrophage cells of the immune system are attacked. Schmit et al developed the hyaluronate (HL)-loaded nanogels based on chitosan to disport macrophages. Then, the nanogels were loaded with one of the different sensitizing light sources such as tetraphenyl porphyrin-tetrasulfonate (TPPS4), tetra-phenyl chloride-tetracarboxylate (TPCC4), and chlorin e6. They in their study found that nano-gels of TPPS4 and TPCC4 were safe when combinated to macrophages of RAW 264.7 for mice and the human THP-1 in the dark situation while nano-gels of Ce6 were toxic. As a result, further studies showed that they were uptaken by the target cells in less than 4 hours and accumulated in the cytoplasm and their organelles [75].

In recent years, study the anesthetic drugs

release has developed by using nanogels. In a conducted study by Yin et al, they reported the encapsulated- lidocaine biodegradable nano-gels with polymer precursor of poly (ε-caprolactone) – poly (ethylene glycol) - poly (ε-caprolactone) (PCL-PEG-PCL) nanoparticles. The results indicated that these nanocarriers drastically influenced the blood for long-term effects of these materials and are convenient for surgical therapy [76].

The synthesis of nano-gels with an useful drug absorption potential and controlled distribution has been introduced via Soni et.al by controlling different networking densities of polymers [77]. In addition, synthesis of anticancer nano-carrier as the nucleoside 5-triphosphate (NTP) were reported by Vinogradov et al.. The NTP forms the capsule made of polyethylene-imine (PEI) molecules and polyethylene glycol-polaronic within a polymer nanoparticle. This model can prevent DNA polymerase activity (RNA) in the proliferation of cancer cells [78]. However, like other nanoscale delivery systems, nanogels have limitations in terms of biodegradation optimization, degradation mechanism and toxicity of components. On the first problem, by increasing the component ratio can be overcome. The rapid disappearance of nano-gels from the bloodstream can be prevented by the absorption of macrophages. In this case, factors there are in the mechanism related to destroying nano-gel compounds that they can affect the toxicity of the drug that it is necessary to consider these factors. Hence, the choice of the precursor of the nano -gel should be done properly. In contrast, smoothness specifications of nano-gels have an impact effect on bioavailability and duability. In other words, the smaller adjustable size of nano-gel provides conditions to increase the circulation
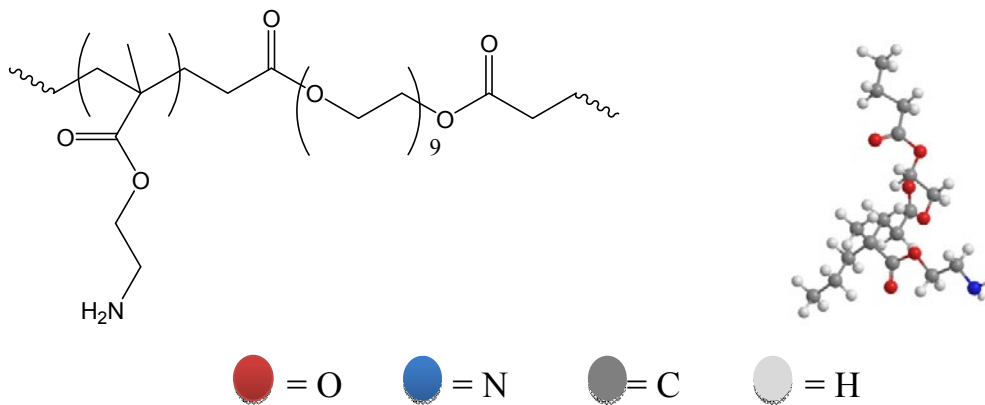

= O   = N   = C   = H

Fig. 5. Nano-gel structure of PAMA

time after applying nano-gels so that it can active or non-active the target [76-77]. Therefore, it is hoped that synthesis of nanogels with new structures and strong potential applications can help to design the DNS with high drug material absorption and high loading. Due to, the controlled encapsulation, distribution and release at a specified time period and resulting treatment of different diseases in the future.

CONCLUSION

In the current review, one try was made to introduce the nano-gels as the carrier nanoplatform for DNS. In the targeted DNS, the stability of the nanocarriers as well as the adjusted release of the drugs materials is a critical problem. Nano-gels are considered as a nanocarrier for targeted drug delivery due to their good stability. With proper design, they can be susceptible to pH, temperature, and release the drug instantaneously. Nanogels are synthesized in a variety of routes so that the synthesized method can affect the specifications of the nanogel product. The amount of the drug release is varied by changing the cross-links, which is not possible in nanoparticles such as micelle. This issue has led to develop the polymer nanoparticles with good capability in drug delivery system.

REFERENCES

1. Chen S, Li R, Li X, Xie J. Electrospinning: An enabling nanotechnology platform for drug delivery and regenerative medicine. Advanced Drug Delivery Reviews. 2018;132:188-213.

2. Cheheltani R, Kim J, Naha PC, Cormode DP. Nanoparticle Contrast Agents for Medical Imaging. Nanobiotechnology: CRC Press; 2018. p. 219-50.

3. Chaturvedi VK, Singh A, Singh VK, Singh MP. Cancer Nanotechnology: A New Revolution for Cancer Diagnosis and Therapy. Current Drug Metabolism. 2018;19.

4. Syedmoradi L, Daneshpour M, Alvandipour M, Gomez FA, Hajghassem H, Omidfar K. Point of care testing: The impact of nanotechnology. Biosensors and Bioelectronics. 2017;87:373-87.

5. Ricci-Junior E, de Oliveira de Siqueira LB, Rodrigues RAS, Sancenón F, Martínez-Máñez R, de Moraes JA, et al. Nanocarriers as phototherapeutic drug delivery system: Appraisal of three different nanosystems in an in vivo and in vitro exploratory study. Photodiagnosis and Photodynamic Therapy. 2018;21:43-9.

6. Guisasola E, Baeza A, Asín L, de la Fuente JM, Vallet-Regí M. Heating at the Nanoscale through Drug-Delivery Devices: Fabrication and Synergic Effects in Cancer Treatment with Nanoparticles. Small Methods. 2018;2(9):1800007.

7. LaVan DA, McGuire T, Langer R. Small-scale systems for in vivo drug delivery. Nature Biotechnology. 2003;21(10):1184-91.

8. Yin Win K, Feng S-S. Effects of particle size and surface coating on cellular uptake of polymeric nanoparticles for oral delivery of anticancer drugs. Biomaterials. 2005;26(15):2713-22.

9. Danhier F, Feron O, Préat V. To exploit the tumor microenvironment: Passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. Journal of Controlled Release. 2010;148(2):135-46.

10. Lanzalaco S, Sirés I, Sabatino MA, Dispenza C, Scialdone O, Galia A. Synthesis of polymer nanogels by electro-Fenton process: investigation of the effect of main operation parameters. Electrochimica Acta. 2017;246:812-22.

11. Oh JK, Drumright R, Siegwart DJ, Matyjaszewski K. The development of microgels/nanogels for drug delivery applications. Progress in Polymer Science. 2008;33(4):448-77.

12. Ramos J, Forcada J, Hidalgo-Alvarez R. Cationic Polymer Nanoparticles and Nanogels: From Synthesis to Biotechnological Applications. Chemical Reviews. 2013;114(1):367-428.

13. Wu W, Mitra N, Yan ECY, Zhou S. Multifunctional Hybrid Nanogel for Integration of Optical Glucose Sensing and Self-Regulated Insulin Release at Physiological pH. ACS Nano. 2010;4(8):4831-9.

14. Molina M, Asadian-Birjand M, Balach J, Bergueiro J, Miceli E, Calderón M. Stimuli-responsive nanogel composites and their application in nanomedicine. Chemical Society Reviews. 2015;44(17):6161-86.

15. Hasegawa U, Nomura S-iM, Kaul SC, Hirano T, Akiyoshi K. Nanogel-quantum dot hybrid nanoparticles for live cell imaging. Biochemical and Biophysical Research Communications. 2005;331(4):917-21.

16. Nakamura T, Tamura A, Murotani H, Oishi M, Jinji Y, Matsuishi K, et al. Large payloads of gold nanoparticles into the polyamine network core of stimuli-responsive PEGylated nanogels for selective and noninvasive cancer photothermal therapy. Nanoscale. 2010;2(5):739.

17. Xiao C, Chen S, Zhang L, Zhou S, Wu W. One-pot synthesis of responsive catalytic Au@PVP hybrid nanogels. Chemical Communications. 2012;48(96):11751.

18. Saez-Martinez V, Olalde B, Juan MJ, Jurado MJ, Garagorri N, Obieta I. Novel Bioactive Scaffolds Incorporating Nanogels as Potential Drug Eluting Devices. Journal of Nanoscience and Nanotechnology. 2010;10(4):2826-32.

19. Chen Y, Zheng X, Qian H, Mao Z, Ding D, Jiang X. Hollow Core–Porous Shell Structure Poly(acrylic acid) Nanogels with a Superhigh Capacity of Drug Loading. ACS Applied Materials & Interfaces. 2010;2(12):3532-8.

20. Raemdonck K, Demeester J, De Smedt S. Advanced nanogel engineering for drug delivery. Soft Matter. 2009;5(4):707-15.

21. Zhang H, Zhai Y, Wang J, Zhai G. New progress and prospects: The application of nanogel in drug delivery. Materials Science and Engineering: C. 2016;60:560-8.

22. Kousalová J., Etrych T., Polymeric nanogels as drug delivery systems. Physiol Res., 2018;67:305–17.

23. Pikabea A, Forcada J. Novel approaches for the preparation of magnetic nanogels via covalent bonding. Journal of Polymer Science Part A: Polymer Chemistry. 2017;55(21):3573-86.

24. Kabanov AV, Vinogradov SV. Nanogels as Pharmaceutical Carriers: Finite Networks of Infinite Capabilities. Angewandte Chemie International Edition. 2009;48(30):5418-29.

25. Chacko RT, Ventura J, Zhuang J, Thayumanavan S. Polymer

nanogels: A versatile nanoscopic drug delivery platform. Advanced Drug Delivery Reviews. 2012;64(9):836-51.

26. Rolland JP, Maynor BW, Euliss LE, Exner AE, Denison GM, DeSimone JM. Direct Fabrication and Harvesting of Monodisperse, Shape-Specific Nanobiomaterials. Journal of the American Chemical Society. 2005;127(28):10096-100.

27. Mishra A., Basu A., Maheshwari D., Gupta S., Saxena S., Sahoo A.K., et al., Study of Antibacterial Activity of Cu NPs and Fluorescent C-Dots Based Nano-gel. J Nanosci Nanoeng Appl., 2018;7:5–9.

28. Kersey FR, Merkel TJ, Perry JL, Napier ME, DeSimone JM. Effect of Aspect Ratio and Deformability on Nanoparticle Extravasation through Nanopores. Langmuir. 2012;28(23):8773-81.

29. Ly J, Li Y, Vu MN, Moffat BA, Jack KS, Quinn JF, et al. Nano-assemblies of cationic mPEG brush block copolymers with gadolinium polyoxotungstate [Gd(W5O18)2]9− form stable, high relaxivity MRI contrast agents. Nanoscale. 2018;10(15):7270-80.

30. Hashimoto Y, Mukai S-a, Sasaki Y, Akiyoshi K. Nanogel-Tectonic Materials: Nanogel Tectonics for Tissue Engineering: Protein Delivery Systems with Nanogel Chaperones (Adv. Healthcare Mater. 23/2018). Advanced Healthcare Materials. 2018;7(23):1870084.

31. Elkassih SA, Kos P, Xiong H, Siegwart DJ. Degradable redox-responsive disulfide-based nanogel drug carriers via dithiol oxidation polymerization. Biomaterials Science. 2019;7(2):607-17.

32. Song Q, Yin Y, Shang L, Wu T, Zhang D, Kong M, et al. Tumor Microenvironment Responsive Nanogel for the Combinatorial Antitumor Effect of Chemotherapy and Immunotherapy. Nano Letters. 2017;17(10):6366-75.

33. Oh JK. Polylactide (PLA)-based amphiphilic block copolymers: synthesis, self-assembly, and biomedical applications. Soft Matter. 2011;7(11):5096.

34. Spencer DS, Luu BC, Beckman DW, Peppas NA. Control of cationic nanogel PEGylation in heterogeneous ARGET ATRP emulsion polymerization with PEG macromonomers. Journal of Polymer Science Part A: Polymer Chemistry. 2018;56(14):1536-44.

35. Yan S, Sun Y, Chen A, Liu L, Zhang K, Li G, et al. Templated fabrication of pH-responsive poly(l-glutamic acid) based nanogels via surface-grafting and macromolecular crosslinking. RSC Advances. 2017;7(24):14888-901.

36. Alexandridis P., Lindman B., Amphiphilic block copolymers: self-assembly and applications. Elsevier, 2000.

37. Mai Y, Eisenberg A. Self-assembly of block copolymers. Chemical Society Reviews. 2012;41(18):5969.

38. Sasaki Y, Akiyoshi K. Nanogel engineering for new nanobiomaterials: from chaperoning engineering to biomedical applications. The Chemical Record. 2010:n/a-n/a.

39. Sun H, Guo B, Li X, Cheng R, Meng F, Liu H, et al. Shell-Sheddable Micelles Based on Dextran-SS-Poly(ε-caprolactone) Diblock Copolymer for Efficient Intracellular Release of Doxorubicin. Biomacromolecules. 2010;11(4):848-54.

40. Li Y-L, Zhu L, Liu Z, Cheng R, Meng F, Cui J-H, et al. Reversibly Stabilized Multifunctional Dextran Nanoparticles Efficiently Deliver Doxorubicin into the Nuclei of Cancer Cells. Angewandte Chemie. 2009;121(52):10098-102.

41. Sun H, Guo B, Li X, Cheng R, Meng F, Liu H, et al. Shell-Sheddable Micelles Based on Dextran-SS-

Poly(ε-caprolactone) Diblock Copolymer for Efficient Intracellular Release of Doxorubicin. Biomacromolecules. 2010;11(4):848-54.

42. Joralemon MJ, Smith NL, Holowka D, Baird B, Wooley KL. Antigen-Decorated Shell Cross-Linked Nanoparticles: Synthesis, Characterization, and Antibody Interactions. Bioconjugate Chemistry. 2005;16(5):1246-56.

43. Li Y, Du W, Sun G, Wooley KL. pH-Responsive Shell Cross-Linked Nanoparticles with Hydrolytically Labile Cross-Links. Macromolecules. 2008;41(18):6605-7.

44. Jiang G, Wang Y, Zhang R, Wang R, Wang X, Zhang M, et al. Preparation of Redox-Sensitive Shell Cross-Linked Nanoparticles for Controlled Release of Bioactive Agents. ACS Macro Letters. 2012;1(4):489-93.

45. Qiao Z-Y, Zhang R, Du F-S, Liang D-H, Li Z-C. Multi-responsive nanogels containing motifs of ortho ester, oligo(ethylene glycol) and disulfide linkage as carriers of hydrophobic anti-cancer drugs. Journal of Controlled Release. 2011;152(1):57-66.

46. Kim Y, Pourgholami MH, Morris DL, Stenzel MH. Triggering the fast release of drugs from crosslinked micelles in an acidic environment. Journal of Materials Chemistry. 2011;21(34):12777.

47. Kim Y, Pourgholami MH, Morris DL, Stenzel MH. Triggering the fast release of drugs from crosslinked micelles in an acidic environment. Journal of Materials Chemistry. 2011;21(34):12777.

48. Joralemon MJ, O'Reilly RK, Hawker CJ, Wooley KL. Shell Click-Crosslinked (SCC) Nanoparticles: A New Methodology for Synthesis and Orthogonal Functionalization. Journal of the American Chemical Society. 2005;127(48):16892-9.

49. He J, Yan B, Tremblay L, Zhao Y. Both Core- and Shell-Cross-Linked Nanogels: Photoinduced Size Change, Intraparticle LCST, and Interparticle UCST Thermal Behaviors. Langmuir. 2011;27(1):436-44.

50. Anton N, Benoit J-P, Saulnier P. Design and production of nanoparticles formulated from nano-emulsion templates—A review. Journal of Controlled Release. 2008;128(3):185-99.

51. Rao PS, Subrahmanya S, Sathyanarayana DN. Inverse emulsion polymerization: a new route for the synthesis of conducting polyaniline. Synthetic Metals. 2002;128(3):311-6.

52. Donini C, Robinson DN, Colombo P, Giordano F, Peppas NA. Preparation of poly(methacrylic acid-g-poly(ethylene glycol)) nanospheres from methacrylic monomers for pharmaceutical applications. International Journal of Pharmaceutics. 2002;245(1-2):83-91.

53. Averick SE, Magenau AJD, Simakova A, Woodman BF, Seong A, Mehl RA, et al. Covalently incorporated protein–nanogels using AGET ATRP in an inverse miniemulsion. Polymer Chemistry. 2011;2(7):1476.

54. Torchilin P.V., Torchilin V.P., Torchilin V., Weissig V., Liposomes: a practical approach. Oxford University Press, 2003.

55. Torchilin V.P., Papisov M.I., Bogdanov A.A., Trubetskoy V.S., Omelyanenko V.G., Molecular mechanism of liposome and immunoliposome steric protection with poly (ethylene glycol): theoretical and experimental proofs of the role of polymer chain flexibility. In: Stealth liposomes. CRC Press, 2018; 71–82.

56. Lian T, Ho RJY. Trends and Developments in Liposome

Drug Delivery Systems. Journal of Pharmaceutical Sciences. 2001;90(6):667-80.

57. Lian T, Ho RJY. Trends and Developments in Liposome Drug Delivery Systems. Journal of Pharmaceutical Sciences. 2001;90(6):667-80.

58. Zhao X, Deng L, Deng H, Dong A, Wang W, Zhang J. In Situ Template Polymerization to Prepare Liposome-Coated PDMAEMA Nanogels with Controlled Size, High Stability, Low Cytotoxicity, and Responsive Drug Release for Intracellular DOX Release. Macromolecular Chemistry and Physics. 2018;219(13):1800071.

59. Sudhakar K, Madhusudana Rao K, Subha MCS, Chowdoji Rao K, Sadiku ER. Temperature-responsive poly(N-vinylcaprolactam-co-hydroxyethyl methacrylate) nanogels for controlled release studies of curcumin. Designed Monomers and Polymers. 2015;18(8):705-13.

60. Zoratto N, Palmieri F, Cencetti C, Montanari E, Di Meo C, Manca M, et al. Design of Hybrid Gels Based on Gellan-Cholesterol Derivative and P90G Liposomes for Drug Depot Applications. Gels. 2017;3(2):18.

61. Singh N, Lyon LA. Au Nanoparticle Templated Synthesis of pNIPAm Nanogels. Chemistry of Materials. 2007;19(4):719-26.

62. Teng Y, Jin H, Nan D, Li M, Fan C, Liu Y, et al. In vivo evaluation of urokinase-loaded hollow nanogels for sonothrombolysis on suture embolization-induced acute ischemic stroke rat model. Bioactive Materials. 2018;3(1):102-9.

63. Gao X, Yang H, Wu M, Shi K, Zhou C, Peng J, et al. Targeting Delivery of Lidocaine and Cisplatin by Nanogel Enhances Chemotherapy and Alleviates Metastasis. ACS Applied Materials & Interfaces. 2018;10(30):25228-40.

64. Bai X, Gao M, Syed S, Zhuang J, Xu X, Zhang X-Q. Bioactive hydrogels for bone regeneration. Bioactive Materials. 2018;3(4):401-17.

65. Gundloori RVN, Singam A, Killi N. Nanobased Intravenous and Transdermal Drug Delivery Systems. Applications of Targeted Nano Drugs and Delivery Systems: Elsevier; 2019. p. 551-94.

66. Hildebrandt H, Paloheimo O, Mäntylä E, Willman S, Hakanen S, Albrecht K, et al. Reactive Self-Assembly and Specific Cellular Delivery of NCO-sP(EO-stat-PO)-Derived Nanogels. Macromolecular Bioscience. 2018;18(10):1800094.

67. Ahmed IN, Chang R, Tsai W-B. Poly(acrylic acid) nanogel as a substrate for cellulase immobilization for hydrolysis of cellulose. Colloids and Surfaces B: Biointerfaces. 2017;152:339-43.

68. Inamdar YM, Rane B, Jain A. Preparation and Evaluation of Beta sitosterol Nanogel: A Carrier Design for Targeted Drug Delivery system. Asian Journal of Pharmaceutical Research and Development. 2018;6(3):81-7.

69. Zhu X, Sun Y, Chen D, Li J, Dong X, Wang J, et al. Mastocarcinoma therapy synergistically promoted by lysosome dependent apoptosis specifically evoked by 5-Fu@ nanogel system with passive targeting and pH activatable dual function. Journal of Controlled Release. 2017;254:107-18.

70. Sakai T, Yoshida R. Self-Oscillating Nanogel Particles. Langmuir. 2004;20(4):1036-8.

71. Li J, Su Z, Xu H, Ma X, Yin J, Jiang X. Supramolecular Networks of Hyperbranched Poly(ether amine) (hPEA) Nanogel/Chitosan (CS) for the Selective Adsorption and Separation of Guest Molecules. Macromolecules. 2015;48(7):2022-9.

72. Milani AH, Saunders JM, Nguyen NT, Ratcliffe LPD, Adlam DJ, Freemont AJ, et al. Synthesis of polyacid nanogels: pH-responsive sub-100 nm particles for functionalisation and fluorescent hydrogel assembly. Soft Matter. 2017;13(8):1554-60.

73. Xu X, Wang J, Wang Y, Zhao L, Li Y, Liu C. Formation of graphene oxide-hybridized nanogels for combinative anticancer therapy. Nanomedicine: Nanotechnology, Biology and Medicine. 2018;14(7):2387-95.

74. Du J-Z, Sun T-M, Song W-J, Wu J, Wang J. A Tumor-Acidity-Activated Charge-Conversional Nanogel as an Intelligent Vehicle for Promoted Tumoral-Cell Uptake and Drug Delivery. Angewandte Chemie. 2010;122(21):3703-8.

75. Yin QQ, Wu L, Gou ML, Qian ZY, Zhang WS, Liu J. Long-lasting infiltration anaesthesia by lidocaine-loaded biodegradable nanoparticles in hydrogel in rats. Acta Anaesthesiologica Scandinavica. 2009;53(9):1207-13.

76. Toita S, Sawada S-i, Akiyoshi K. Polysaccharide nanogel gene delivery system with endosome-escaping function: Co-delivery of plasmid DNA and phospholipase A2. Journal of Controlled Release. 2011;155(1):54-9.

77. Soni G, Yadav KS. Nanogels as potential nanomedicine carrier for treatment of cancer: A mini review of the state of the art. Saudi Pharmaceutical Journal. 2016;24(2):133-9.

78. Sasaki Y, Akiyoshi K. Nanogel engineering for new nanobiomaterials: from chaperoning engineering to biomedical applications. The Chemical Record. 2010:n/a-n/a.