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REVIEW ARTICLE

Polymeric Nanogels for Theranostic Applications: A Mini-Review

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Abstract: Theranostics is a recently emerging area in nanomedicine. Nanoparticles which can combine both diagnostic and therapy in one single platform serve as theranostic agents. Some of the currently explored nanoparticles are metallic nanoparticles, mesoporous silica nanoparticles, carbon-based nanoparticles, and polymer nanogels. Polymeric nanogels are receiving considerable attention due to their high biocompatibility and functional performance. The present review article briefly summarizes the scopes and challenges of the state of art of using polymeric nanogels for theranostic applications. Among the different polymer nanogels, a special emphasis is given to polymeric nanogels with innate imaging potential.

Keywords: Theranostics, nanogel, fluorescence, imaging agent, therapeutic agent, nanoparticles.

1. INTRODUCTION

Polymeric biomaterials have been used for several years in various emerging technologies like tissue engineering, nanotechnology and drug delivery applications to repair, renew and support body tissues [1]. Polymers have a major representation in biomaterials due to their biocompatible, stimuli-responsive and mechanical properties [2]. These characteristics make them a favourable material for applications at different sites in the body. Some of the attractive properties of polymers such as the tunable degradation profiles, availability of versatile functional groups and loading capacity of biologically active molecules make them interesting for different applications in the field of medicine [3]. Nanotechnology is a constant contributor in the field of biomedical technology in terms of diagnostics and therapeutic applications. Nanoparticles can be conveniently prepared from polymers using different techniques such as single emulsion, double emulsion and organic precipitation.

Their physicochemical properties such as size, shape and surface functional groups can be tailored to augment stimuli-responsiveness which aids in focused and cumulative drug release [4, 5]. Further, apart from natural polymers, synthetic polymers like poly(ethylene glycol) (PEG), poly(lactic acid) (PLA) *etc*. have also been made use of tremendously in drug and gene delivery [5]. Recently, 'theranostics' as a research field has emerged from the fusion of molecular imaging and therapy for medical applications [6]. Merging diagnosis and therapy has been immensely useful especially in the case of cancer therapy [7]. Chemotherapy has several disadvantages; including non-specificity and toxicity to normal cells [8]. Polymer nanoparticles can be functionalized with targeting ligands and hence exhibit higher specificity. They may be loaded with various fluorophores or chromophores for imaging. Thus, polymer nanoparticles have applications in monitoring drug release and imaging; examples include targeted cancer therapies in various phases of development [6]. Polymer nanomaterials with responses toward exogenous and endogenous stimuli have been fabricated for use as drug delivery systems. Glucose-responsive polymeric nanomaterials have been studied for their applications in diabetic patients [9]. They also offer several advantages including extended half-life, increased efficacy, and imaging with magnetic resonance imaging (MRI). Polymeric nanomaterials have shown promising results and are expected to see sustained interest for theranostic utilization [10].

Nanogels are formed by cross-linked polymer networks with high water retention capacity contained within a nanoscale particle and have been employed for controlled release [11]. Nanogels are a subset of "smart materials" for stimuli-responsive drug delivery platforms [12]. Nanogels have been demonstrated for a variety of imaging purposes including MRI contrast agents, PET imaging, optical and multimodal imaging [13]. Nanogels can be synthesized *via* direct polymerization of monomers by heterogeneous free radical polymerization, or by hydrophilic copolymers which

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carry reactive functional groups with suitable cross-linkers [14, 15]. The degree of cross-linking was controlled using surfactants, however, these must be completely removed from the final product due to cytotoxicity concerns. As an alternative to surfactants, the development of "click chemistry" has proven successful through routes such as azide-alkyne reactions, nucleophilic and radical thiol-ene reactions for producing cross-linked nanogels [16].

Nanogels, thus, are extensively being explored for biomedical applications including drug delivery, tissue engineering, bioimaging, regenerative medicine, biosensors, orthopaedics and wound healing which are formed on the basis of the general characteristics of hydrogels [17, 18]. In one study, Au/PAm hybrid nanogels were manufactured by functionalization using methotrexate (MTX) which is an active targeting ligand and medicinal drug. This system was demonstrated to target cancer cells while minimizing macrophage cytotoxicity [19].

Polymer nanogels have been recently reviewed for theranostic applications [20]. One recent example is the use of NIR-fluorescent nanogels [21]. Further developments of fabricating polymeric nanogels using advanced methods such as radiation-induced cross-linking have also been reported [22]. Interpenetrating polymeric networks (IPNs) are sensitive to a number of parameters such as pH and salt and thus, have a similar structure with nanogels [23]. Researchers have, therefore, investigated the properties of IPNs to form nanogels. Polymers used in these studies are poly(vinyl pyrrolidone), poly (methacrylicacid), poly(acrylic acid) and poly(ethylene oxide) [24-26]. The scope of this review was to highlight some of the recent advancements in using polymer nanogels for theranostic applications. Special emphasis is given to the aspects of fluorescent nanogels which have been relatively unexplored.

2. ROLE OF POLYMER NANOGELS IN THERANOSTIC NANOMEDICINE

Polymer nanogels are extensively explored for theranostic applications. This is due to some of their attractive properties such as higher biocompatibility, higher drug loading potential and efficient incorporation of both diagnostics and therapeutic agents in a single domain [27, 28]. More importantly, owing to their excellent water retention capabilities, they can act as safe carriers for therapeutic applications. A theranostic nanogel system is comprised of an imaging component, a therapeutic agent and targeting ligand. The therapeutic agents are incorporated within the core of the nanogel by physical entrapment or chemical conjugation methods [29]. Usually, the diagnostic agents and targeting ligands will be conjugated in the outer corona of a theranostic nanogel [30]. The therapeutic components which are loaded inside the nanogels are mainly drugs, genes, or photosensitizers which, when judicially delivered with the help of nanogels, exert their therapeutic response on cancer cells without affecting the normal cells [31, 32]. In order to accomplish the imaging function, nanogels are loaded or conjugated with imaging agents such as quantum dots, organic dyes, radiolabels and magnetic nanoparticles. Theranostic nanogels mainly utilize imaging modalities such as fluorescence, radio, ultrasound and magnetic resonance imaging [33, 34]. The imaging agents are loaded along with the therapeutic agents in the nanogel for simultaneous diagnosis and treatment of diseases. One of the major challenges faced by the theranostic nanogels is the premature leakage of the imaging agent before reaching the target destination. This leads towards nonspecific tissue distribution and thereby generates potential toxicity [35]. Thus, theranostic nanogels with innate imaging potential do not require external imaging agents. In the present review, we categorize theranostic nanogels into two broad classes. Nanogels with external imaging agents and nanogels with innate imaging potential.

2.1. Theranostic Nanogels with External Imaging Agents

Nanogels can be easily tethered with external imaging agents such as quantum dots, organic dyes, radiolabels and MRI contrast agents. This is mainly achieved through physical entrapment or chemical conjugation methods. Chemical conjugation methods are highly preferred over physical entrapment for the imaging agents since they offer a more robust loading of the imaging agents with the nanogels. The presence of functional groups such as amino groups and carboxylic acid groups on the surface of the nanogel facilitates easy conjugation with external imaging agents.

Zhou *et al.* reported a polyglutamic acid-based theranostic nanogel which combines photothermal therapy (PTT) with photoacoustic imaging (PA) [36]. The nanogels were crosslinked with cystamine dichloride and subsequently loaded with polypyrrole. The developed nanogel, owing to its excellent near IR absorption capability, demonstrated both PTT and PA imaging capability. The theranostic potential of this construct tested in the mice model was found to be of great significance . Park *et al.* reported a sunflower type nanogel with good theranostic potential [37]. The designed nanogel was composed of a triblock polymer Pluronic F127 conjugated with a quantum dot (QD 655). The prepared nanogel was utilized for gene transfection and imaging of mesenchymal stem cells. The study has shown that the prepared nanogel has the potential to image the mesenchymal stem cells without causing any toxicity concerns. Nagahama *et al.* reported a theranostic nanogel based on curcumin-dextran conjugate [38]. The lack of sufficient water solubility is one of the major challenges associated with curcumin, thus, compromising the therapeutic efficacy of curcumin. The curcumin-dextran theranostic nanogel has successfully addressed this issue by improving the water solubility of curcumin; furthermore, this theranostic nanogel demonstrated selective uptake in cancer cells in comparison with the normal cells. In another work, Chiang *et al.* reported superparamagnetic hollow hybrid nanogels with theranostic potential [39]. Superparamagnetic iron oxide nanoparticles were loaded inside a poly-(ethylene glycol) and poly(N-isopropylacrylamide) backbones to prepare the theranostic constructs. The prepared nanogel demonstrated magnetic field controllable drug delivery with magnetic resonance imaging capabilities. By using an external magnetic field, the path of this nanogel can be controlled externally to ensure the site-specific release of the therapeutic components loaded inside the nanogels. Su *et al.* reported a system with iRGD coupled fluorescent theranostic nanogel [40]. The designed nanogel was composed of poly (N-isopropyl acrylamide-co-acrylic acid) conjugated with gold nanoclusters. The iRGD

Table 1. A summary of currently used theranostic nanogels with external imaging agents

Composition	Imaging Agent	Therapeutic Agent	Application	Ref No
Galactose	FITC	Iodoazomycinarabinofuranos	Treatment of Hypoxic Hepato carcinoma	[43]
Alginate	Gadolinium	Rhodamine	Cancer Cell Imaging and therapy	[44]
Chitosan	CdSe	Temozolomi	Cancer Cell Imaging and therapy	[45]
Dendritic Polyglycerol	Indocyanine (ICG)	Photodynamic therapy	Cancer Cell Imaging and therapy	[46]
Chitin	CdTe QD	Bovine serum Albumin	Cancer Cell Imaging and therapy	[47]
Polyethylene glycol	Curcumin	Curcumin	Cancer Cell Imaging and therapy	[48]
Polyvinyl Alcohol	Bi_2O_3 QD	Temozolomi	Cancer Cell Imaging and therapy	[49]

sequence was further conjugated to the surface of the nanogel for endowing targeting capability. The prepared nanogel demonstrated thermo and pH-responsive drug release characteristics. The stable red fluorescence of the gold nanoclusters present on the nanogel was used to track the particle location. Xing *et al.* reported a theranostic redox-sensitive polypeptide nanogel [41]. Disulfide linkages present over the surface of the nanogel confer it with redox-sensitive drug release behavior. A near infrared dye was conjugated over the surface of the nanogel to track the nanogel's location inside the cells in reducing environments. The *in vitro* cell experiments showed that the drug molecules loaded inside the nanogels migrated to the nucleus of the cancer cells, whereas, the nanogel remained in the cytoplasm. Wu *et al*. reported a core-shell hybrid theranostic nanogel [42]. The prepared nanogel was composed of poly(ethylene glycol-co-methacrylic acid) and Ni-Ag bimetallic nanoparticles as shell and core, respectively. The nanogel was responsive to both pH and magnetic field. It was found that the nanogel can overcome the cellular barriers and get internalized inside the mouse melanoma cells. Additional recently reported systems are summarized in Table **1**.

2.2. Theranostic Nanogels with Innate Imaging Potential

Recent interest in the area of theranostic nanogels is the development of nanogels which do not require any external imaging agents. There are no reviews of current progress in this area. Even though the chemical conjugation of imaging agents with the nanogel surface ensures safe loading of these imaging labels on the nanogel, there are still many concerns about the stability of these bonds in physiological conditions (enzyme and varying pH). Usually, the imaging agents chemically conjugated to the external functional groups present on the nanogel corona get the maximum exposure to the various enzymes and varying pH environments of the body. This can cause the premature leakage of the imaging agents before reaching the target destination and thereby affecting the functional performance of the nanogel. This leads to the quest for the development of polymeric nanogels with innate imaging potential.

Yang *et al*. for the first time developed a biodegradable fluorescent polymer (BPLP) based on diol, citric acid and amino acids [50]. This BPLP polymer has shown excitation wavelength-dependent fluorescence characteristics. The chemical reaction between citric acid and amino acid was found to be responsible for imparting fluorescence. On a subsequent study, they synthesized fluorescent nanogels and showed their imaging potential [51]. Even though this BPLP nanogel displayed innate imaging potential; it also displayed blue fluorescence characteristics which can significantly interfere with the autofluorescence of the body. It is well known that fluorescence at the near IR region (700-1000 nm) has the highest tissue penetration without any autofluorescence issues. Hence, it is imperative to develop fluorescent nanogels with innate near IR emissions, as they can be efficiently utilized for theranostic applications. In this regard, Vijayan *et al*. reported a photoluminescent comacromer with excitation wavelength-dependent fluorescence characteristics. This work for the first time explored the excitation wavelength-dependent fluorescence characteristics of PEG-based condensed polyesters [52]. It was found that the n-[]* interactions between the carbonyl groups and oxygen atoms of PEG were found to impart these interesting excitation dependent fluorescence characteristics. Nanogels were prepared to form the comacromer after crosslinking it with vinyl monomers such as acrylic acid and methacrylic acid. Monodisperse and stable nanogels were prepared from the comacomer (Fig. **1**). It was found that the nanogel exhibited good fluorescence imaging potential at the near IR region. The translational potential of biomaterials depends on their functional performance and biocompatibility. In this regard, the observed phenomenon of near IR fluorescence in FDA approved polymer like PEG can open up new possibilities of synthesizing biocompatible fluorescent biomaterials with versatile applications.

In a subsequent work, the authors designed a pH-responsive fluorescent nanogel from the comacromer [53].

Doxorubicin was loaded inside the nanogels and it has displayed good near IR imaging at both *in vitro* and *in vivo* studies (Fig. **2**). These theranostic nanogels also have shown the potential to migrate towards the lymph nodes which has suggested their promising future potential for applications in sentimental lymph node mapping in cancer biopsy. The specificity of a nanocarrier can greatly reduce the side effects associated with most of the anti-cancer drug formulations. In this regard, the stimuli-responsive characteristics observed for this type of fluorescent nanogels can be effectively utilized for imaging the drug release profile in cancer cells which will ensure the site-specific delivery of the cargo specifically to cancer cells.

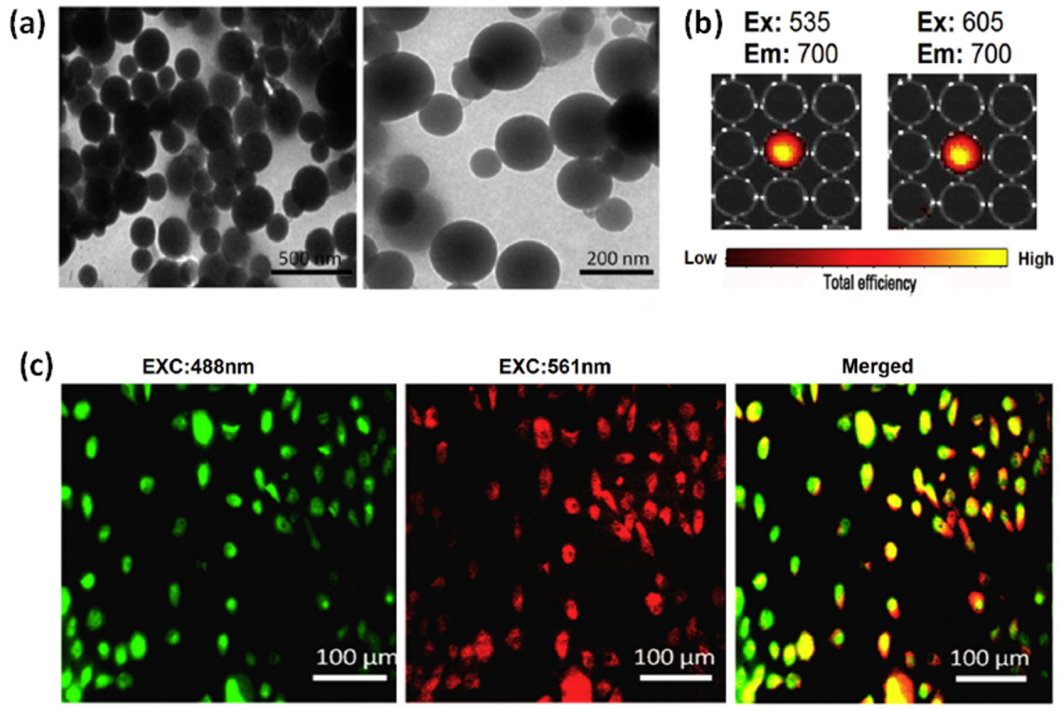

Fig (1). TEM images of the photoluminescent nanogels (a), Near IR fluorescence of the photoluminescent nanogels (b), The fluorescent cellular uptake images of the photoluminescent nanogels in cells (c) (Adapted from Vijayan *et al*. [Ref. 52] and reprinted with permission from Elsevier Copyright 2015.

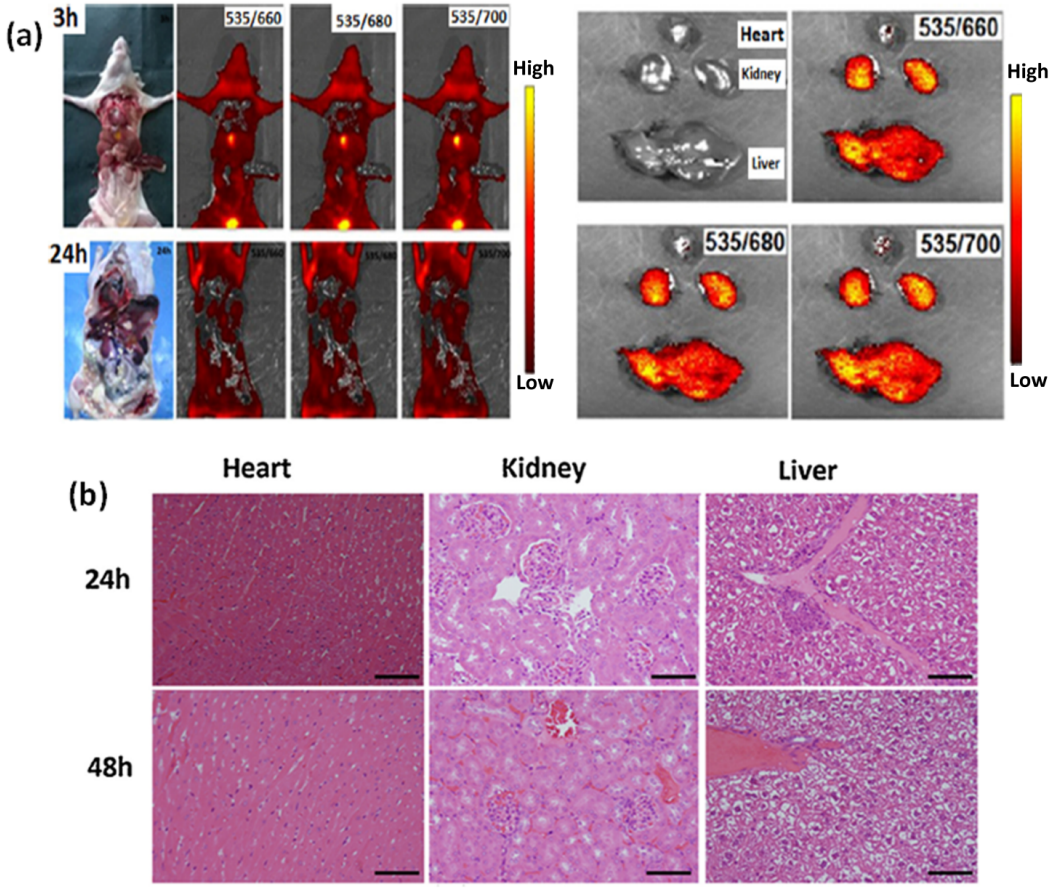

Fig. (2). *In vivo* Fluorescent bioimaging capability of the nanogel injected in mice (a), Histopathological analysis of the different organs of the nanogel injected mice (b) (Adapted from Vijayan et al. [Ref 53] and reprinted with permission from Elsevier Copyright (2016).

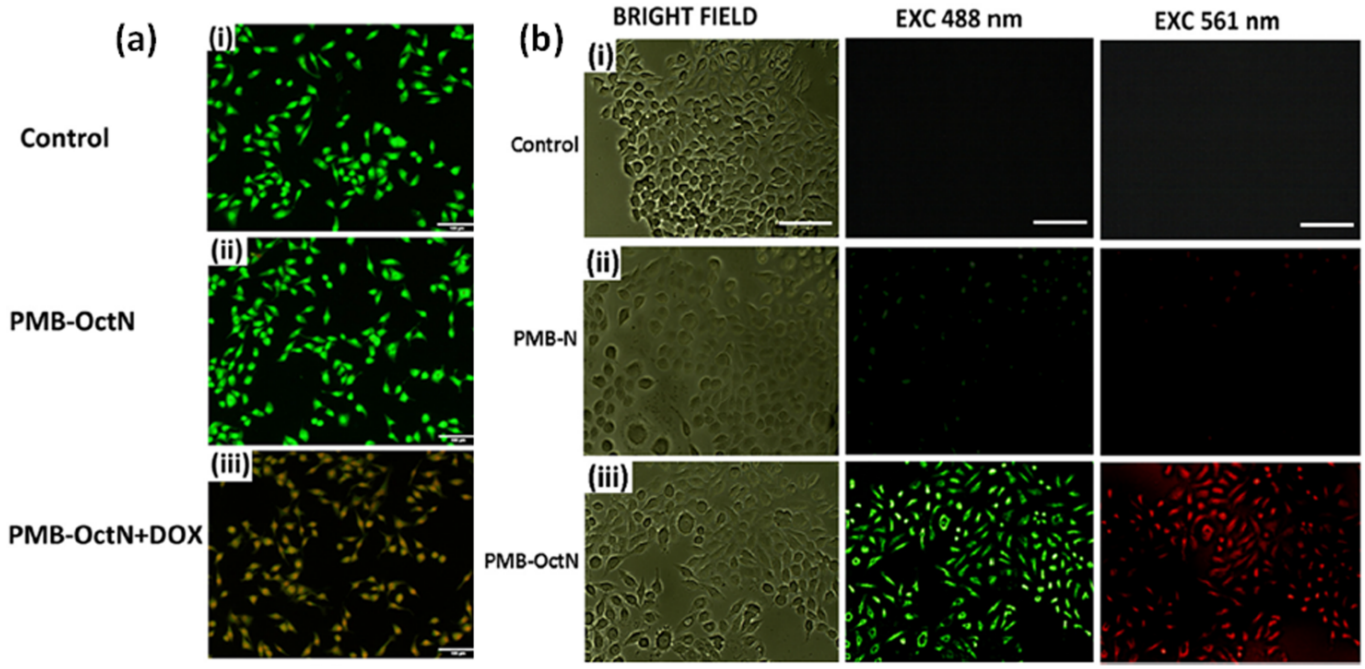

Fig (3). Live/dead assay of nanogel in Hela cells showing the therapeutical potential of the nanogel (a), Targeted imaging capability of the sandostatin conjugated nanogels in Hela cells (b) (Adapted from Vijayan *et al*. [Ref 21] and reprinted with permission from Elsevier Copyright (2017).

In another work, the same group developed a targeted near IR emitting nanogel for theranostic applications [21]. Sandostatin an octapeptide was conjugated over the surface of this self-fluorescent nanogel to ensure site-specific delivery of the anticancer drug doxorubicin. Usually, radiolabeling is the main strategy to label Sandostatin used for cancer therapy; this work explored a near IR fluorescence labeling strategy for Sandostatin. The nanogel has shown a sustainable release profile of the anticancer drug doxorubicin, suggesting its good therapeutic potential. The targeting capability of the nanogel was clearly visualized with Hela cells (Fig. **3**). This reported fluorescence labeling of the Sandostatin could potentially track the delivery of this formulation inside the body which gives a noninvasive method of determining the site-specific delivery of this widely used formulation.

CONCLUSION AND FUTURE DIRECTIONS

Nanogels have immensely contributed in the area of theranostic nanomedicine by improving the therapeutic outcome of the formulations used in diseases like cancer. They can simultaneously detect and treat diseased areas without affecting the normal healthy surrounding tissues. A number of imaging agents employing different imaging modalities can be conjugated over the surface of the nanogels for endowing them with the desired theranostic function. Even though they have good functional performance when used in combination with therapeutic agents, still there are concerns regarding the premature leakage of these imaging agents. Nanogels with innate imaging potential have greatly addressed this issue by avoiding external imaging agents. More specifically, fluorescent nanogels have contributed to this area; they exhibited good functional performance. They are endowed with innate near IR fluorescence emission which does not allow interference from the auto-fluorescence from the body, thus, they can efficiently image the diseased area.

There are many new developments taking place in this area. One prominent example is the utilization of techniques such as plasma treatment in the controlled deposition of smart therapeutic nanogels onto the surfaces of polymers [54]. The usage of plasma treatment can generate smart nanogel embedded polymer surfaces with a number of biomedical applications. Even though there are many important developments taking place, there is still a long way to go from the lab to clinical transition of these theranostic nanogels.

LIST OF ABBREVIATIONS

PEG	=	Poly(ethylene glycol)
PLA	=	Poly(lactic acid)
MRI	=	Magnetic Resonance Imaging
PET	=	Positron emission tomography
NIR	=	Near Infrared
IPNs	=	Interpenetrating polymeric networks
Au/Pam	=	Gold/Polyacrylamide
PTT	=	Photo thermal Therapy
PA	=	Photoacoustic imaging
QD	=	Quantum Dot
FITC	=	Fluorescein Isothiocyanate
CdSe	=	Cadmium Selenide
FDA	=	Food and Drug Administration

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Kulshrestha, A.S.; Mahapatro, A. *Polymers for biomedical applications*. American Chemical Society Washington, DC: 2008.

[2] Liechty, W.B.; Kryscio, D.R.; Slaughter, B.V.; Peppas, N.A. Polymers for drug delivery systems. *Ann. Rev. Chem. Biomol. Eng*., **2010**, *1*, 149-173.

[3] Oh, J.K. Polymers in drug delivery: Chemistry and applications. *Mol. Pharm*., **2017**, *14*(8), 2459-2459.

[4] Rao, J.P.; Geckeler, K.E. Polymer nanoparticles: Preparation techniques and size-control parameters. *Prog. Polym. Sci*., **2011**, *36*(7), 887-913.

[5] Vauthier, C.; Bouchemal, K. Methods for the preparation and manufacture of polymeric nanoparticles. *Pharm. Res*., **2009**, *26*(5), 1025-1058.

[6] Wang, Z.; Niu, G.; Chen, X. Polymeric materials for theranostic applications. *Pharm. Res*., **2014**, *31*(6), 1358-1376.

[7] Baetke, S.C.; Lammers, T.; Kiessling, F. Applications of nanoparticles for diagnosis and therapy of cancer. *Br. J. Radiol*., **2015**, *88*(1054), 20150207.

[8] Arruebo, M.; Vilaboa, N.; Sáez-Gutierrez, B.; Lambea, J.; Tres, A.; Valladares, M.; González-Fernández, Á. Assessment of the evolution of cancer treatment therapies. *Cancers*, **2011**, *3*(3), 3279-3330.

[9] Kim, H.; Kang, Y.J.; Kang, S.; Kim, K.T. Monosaccharide-responsive release of insulin from polymersomes of polyboroxole block copolymers at neutral pH. *J. Am. Chem. Soc*., **2012**, *134*(9), 4030-4033.

[10] Augustine, R.; John, J.V.; Kim, I. Nanoparticle-Homing Polymers as Platforms for Theranostic Applications. In: *Nanotechnology-Based Approaches for Targeting and Delivery of Drugs and Genes*, Mishra, V.; Kesharwani, P.; Amin, M.C.I.M.; Iyer, A, Eds. Elsevier Science B. V: Amsterdam, 2017; pp. 203-222.

[11] Parisi, O.I.; Scrivano, L.; Sinicropi, M.S.; Picci, N.; Puoci, F. Engineered polymer-based nanomaterials for diagnostic, therapeutic and theranostic applications. *Mini Rev. Med. Chem*., **2016**, *16*(9), 754-761.

[12] Liu, D.; Yang, F.; Xiong, F.; Gu, N. The smart drug delivery system and its clinical potential. *Theranostics*, **2016**, *6*(9), 1306-1323.

[13] Soni, K.S.; Desale, S.S.; Bronich, T.K. Nanogels: An overview of properties, biomedical applications and obstacles to clinical translation. *J. Control. Release*, **2016**, *240*, 109-126.

[14] Chacko, R.T.; Ventura, J.; Zhuang, J.; Thayumanavan, S. Polymer nanogels: A versatile nanoscopic drug delivery platform. *Adv. Drug Deliv. Rev*., **2012**, *64*(9), 836-851.

[15] Chambre, L.; Degirmenci, A.; Sanyal, R.; Sanyal, A. Multifunctional nanogels as theranostic platforms: exploiting reversible and nonreversible linkages for targeting, imaging, and drug delivery. *Bioconjug. Chem*., **2018**, *29*(6), 1885-1896.

[16] Khoee, S.; Asadi, H. Nanogels: Chemical approaches to preparation. In: *Encyclopedia of Biomedical Polymers and Polymeric Biomaterials, Mishra, M.; Ed.,* CRC Press, **2016**, 5266-5293.

[17] Vashist, A.; Kaushik, A. K.; Ahmad, S.; Nair, M., *Nanogels for Biomedical Applications*. Royal Society of Chemistry: 2017; Vol. 30.

[18] Vashist, A.; Vashist, A.; Gupta, Y.; Ahmad, S. Recent advances in hydrogel based drug delivery systems for the human body. *J. Mater. Chem. B,* **2014**, *2*(2), 147-166.

[19] Lu, S.; Neoh, K. G.; Huang, C.; Shi, Z.; Kang, E.-T., Polyacrylamide hybrid nanogels for targeted cancer chemotherapy *via* co-delivery of gold nanoparticles and MTX. *J. Colloid Interface Sci*., **2013**, *412*, 46-55.

[20] Vijayan, V.M.; Muthu, J. Polymeric nanocarriers for cancer theranostics. *Polym. Adv. Technol*., **2017**, *28*(12), 1572-1582.

[21] Vijayan, V.M.; Shenoy, S.J.; Muthu, J. Octreotide-conjugated fluorescent PEGylated polymeric nanogel for theranostic applications. *Mater. Sci. Eng. C*, **2017**, *76*, 490-500.

[22] Ghaffarlou, M.; Sütekin, S.D.; Güven, O. Preparation of nanogels by radiation-induced cross-linking of interpolymer complexes of poly (acrylic acid) with poly (vinyl pyrrolidone) in aqueous medium. *Radiat. Phys. Chem*., **2018**, *142*, 130-136.

[23] Khutoryanskiy, V.V.; Mun, G.A.; Nurkeeva, Z.S.; Dubolazov, A.V. pH and salt effects on interpolymer complexation *via* hydrogen bonding in aqueous solutions. *Polym. Int*., **2004**, *53*(9), 1382-1387.

[24] Li, Y.; Li, H.; Chen, X.; Zhu, F.; Yang, J.; Zhu, Y. Complexation of poly (acrylic acid) and poly (ethylene oxide) investigated by enhanced Rayleigh scattering method. *J. Polym. Sci. B Polym. Phys*., **2010**, *48*(16), 1847-1852.

[25] Pinteala, M.; Budtova, T.; Epure, V.; Belnikevich, N.; Harabagiu, V.; Simionescu, B.C. Interpolymer complexes between hydrophobically modified poly (methacrylic acid) and poly (N-vinylpyrrolidone). *Polymer*, **2005**, *46*(18), 7047-7054.

[26] Poe, G.D.; Jarrett, W.L.; Scales, C.W.; McCormick, C.L. Enhanced coil expansion and intrapolymer complex formation of linear poly (methacrylic acid) containing poly (ethylene glycol) grafts. *Macromolecules*, **2004**, *37*(7), 2603-2612.

[27] Kabanov, A.V.; Vinogradov, S.V. Nanogels as pharmaceutical carriers: Finite networks of infinite capabilities. *Angew. Chem. Int. Ed*., **2009**, *48*(30), 5418-5429.

[28] Vinogradov, S.V.; Bronich, T.K.; Kabanov, A.V. Nanosized cationic hydrogels for drug delivery: Preparation, properties and interactions with cells. *Adv. Drug Deliv. Rev*., **2002**, *54*(1), 135-147.

[29] Oh, J.K.; Drumright, R.; Siegwart, D.J.; Matyjaszewski, K. The development of microgels/nanogels for drug delivery applications. *Prog. Polym. Sci*., **2008**, *33*(4), 448-477.

[30] Vijayan, V.M.; Muthu, J. Polymeric nanocarriers for cancer theranostics: Nanocarriers for cancer theranostics. *Polym. Adv. Technol*., **2017**, *28*(12), 1572-1582.

[31] Zha, L.; Banik, B.; Alexis, F. Stimulus Responsive Nanogels for Drug Delivery. *Soft Matter*, **2011**, *7*(13), 5908-5916.

[32] Vinogradov, S.V. Nanogels in the race for drug delivery. *Nanomedicine*, **2010**, *5*(2), 165-168.

[33] Zan, M.; Li, J.; Luo, S.; Ge, Z. Dual pH-triggered multistage drug delivery systems based on host-guest interaction-associated polymeric nanogels. *Chem. Commun*., **2014**, *50*(58), 7824-7827.

[34] Wang, H.; Chen, Q.; Zhou, S. Carbon-based hybrid nanogels: A synergistic nanoplatform for combined biosensing, bioimaging, and responsive drug delivery. *Chem. Soc. Rev*., **2018**, *47*(11), 4198-4232.

[35] Li, F.; Liang, Z.; Ling, D. Smart organic-inorganic nanogels for activatable theranostics. *Curr. Med. Chem*., **2019**, *26*(8), 1366-1376.

[36] Zhou, Y.; Hu, Y.; Sun, W.; Lu, S.; Cai, C.; Peng, C.; Yu, J.; Popovtzer, R.; Shen, M.; Shi, X. Radiotherapy-sensitized tumor photothermal ablation using Γ-polyglutamic acid nanogels loaded with polypyrrole. *Biomacromolecules*, **2018**, *19*(6), 2034-2042.

[37] Park, J.S.; Yi, S.W.; Kim, H.J.; Kim, S.M.; Shim, S.H.; Park, K.-H. Sunflower-type nanogels carrying a quantum dot nanoprobe for both superior gene delivery efficacy and tracing of human mesenchymal stem cells. *Biomaterials*, **2016**, *77*, 14-25.

[38] Nagahama, K.; Sano, Y.; Kumano, T. Anticancer drug-based multifunctional nanogels through self-assembly of dextran–curcumin conjugates toward cancer theranostics. *Bioorg. Med. Chem. Lett*., **2015**, *25*(12), 2519-2522.

[39] Chiang, W.-H.; Ho, V.T.; Chen, H.-H.; Huang, W.-C.; Huang, Y.-F.; Lin, S.-C.; Chern, C.-S.; Chiu, H.-C. Superparamagnetic hollow

hybrid nanogels as a potential guidable vehicle system of stimuli-mediated MR imaging and multiple cancer therapeutics. *Langmuir*, **2013**, *29*(21), 6434–6443.

[40] Su, S.; Wang, H.; Liu, X.; Wu, Y.; Nie, G. iRGD-coupled responsive fluorescent nanogel for targeted drug delivery. *Biomaterials*, **2013**, *34*(13), 3523-3533.

[41] Xing, T.; Mao, C.; Lai, B.; Yan, L. Synthesis of disulfide-cross-linked polypeptide nanogel conjugated with a near-infrared fluorescence probe for direct imaging of reduction-induced drug release. *ACS Appl. Mater. Interfaces*, **2012**, *4*(10), 5662-5672.

[42] Wu, W.; Shen, J.; Gai, Z.; Hong, K.; Banerjee, P.; Zhou, S. Multifunctional core-shell hybrid nanogels for pH-dependent magnetic manipulation, fluorescent pH-sensing, and drug delivery. *Biomaterials*, **2011**, *32*(36), 9876-9887.

[43] Rejinold N,S.; Chennazhi, K.P.; Tamura, H.; Nair, S.V.; Rangasamy, J. Multifunctional chitin nanogels for simultaneous drug delivery, bioimaging, and biosensing. *ACS Appl. Mater. Interfaces*, **2011**, *3*(9), 3654-3665.

[44] Wu, W.; Shen, J.; Banerjee, P.; Zhou, S. Water-dispersible multifunctional hybrid nanogels for combined curcumin and photothermal therapy. *Biomaterials*, **2011**, *32*(2), 598-609.

[45] Zhu, H.; Li, Y.; Qiu, R.; Shi, L.; Wu, W.; Zhou, S. Responsive fluorescent Bi_2O_3@PVA hybrid nanogels for temperature-sensing, dual-modal imaging, and drug delivery. *Biomaterials*, **2012**, *33*(10), 3058-3069.

[46] Quan, S.; Wang, Y.; Zhou, A.; Kumar, P.; Narain, R. Galactose-based thermosensitive nanogels for targeted drug delivery of iodoazomycin arabinofuranoside (IAZA) for theranostic management of hypoxic hepatocellular carcinoma. *Biomacromolecules,* **2015**, *16*(7), 1978-1986.

[47] Podgórna, K.; Szczepanowicz, K.; Piotrowski, M.; Gajdošová, M.; Štěpánek, F.; Warszyński, P. Gadolinium alginate nanogels for theranostic applications. *Colloids Surf. B Biointerfaces*, **2017**, *153*, 183-189.

[48] Wu, W.; Shen, J.; Banerjee, P.; Zhou, S. Chitosan-based responsive hybrid nanogels for integration of optical pH-sensing, tumor cell imaging and controlled drug delivery. *Biomaterials*, **2010**, *31*(32), 8371-8381.

[49] Asadian-Birjand, M.; Bergueiro, J.; Wedepohl, S.; Calderón, M. Near infrared dye conjugated nanogels for combined photodynamic and photothermal therapies. *Macromol. Biosci.,* **2016**, *16*(10), 1432-1441.

[50] Yang, J.; Zhang, Y.; Gautam, S.; Liu, L.; Dey, J.; Chen, W.; Mason, R.P.; Serrano, C.A.; Schug, K.A.; Tang, L. Development of aliphatic biodegradable photoluminescent polymers. *Proc. Natl. Acad. Sci*., **2009**, *106*(25), 10086-10091.

[51] Gyawali, D.; Kim, J.P.; Yang, J. Highly photostable nanogels for fluorescence-based theranostics. *Bioact. Mater*., **2018**, *3*(1), 39-47.

[52] Vijayan, V.M.; Komeri, R.; Victor, S.P.; Muthu, J. Photoluminescent PEG Based Comacromers as Excitation Dependent fluorophores for biomedical applications. *Colloids Surf. B Biointerfaces*, **2015**, *135*, 243-252.

[53] Vijayan, V.M.; Shenoy, S.J.; Victor, S.P.; Muthu, J. Stimulus responsive nanogel with innate near IR fluorescent capability for drug delivery and bioimaging. *Colloids Surf. B Biointerfaces*, **2016**,146, 84-96.

[54] Štular, D.; Primc, G.; Mozetič, M.; Jerman, I.; Mihelčič, M.; Ruiz-Zepeda, F.; Tomšič, B.; Simončič, B.; Gorjanc, M. Influence of non-thermal plasma treatement on the adsorption of a stimuli-responsive nanogel onto polyethylene terephthalate fabric. *Prog. Org. Coat*., **2018**, *120*, 198-207.