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## **Advancement in Nanogel formulations provides controlled drug release**

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### **Abstract**

Nanogels are currently considered as promising nanosized drug delivery carriers. Nanogels are made of a crosslinked polymeric network which could encapsulate both hydrophilic and hydrophobic drugs due to their tunable nature. The ability of nanogels to control drug release is vastly described in the literature and researchers are consistently improving the control of drug release from nanogel by designing new polymers having specific sensitivity to a chemical or physical stimulus. In this review, we briefly discuss the definition of nanogels, their release profiles, their specific gel-based characteristics and the pathways of drug release from nanogels, we have focused on the stimuli responsive nanogels and their release profile. This compilation opens the window for understanding the influence of chemical composition and design of various nanogel on their release in the presence and absence of corresponding stimuli such as temperature, pH, enzymes and others. The uniqueness of this review is that it highlights the data of release profiles in terms of the different nanogel composition and triggers. It also points the high potential of nanogels in the list of candidates for drug delivery systems, thanks to their properties regarding drug encapsulation and release, combined advantages of nano-size and swelling characteristics of hydrogel.

**Keywords:** Nanogel, Hydrogel, Controlled release, Triggered release, Crosslinked polymeric network, Drug delivery systems

## 1. Introduction

Hydrogels are three-dimensional networks of cross-linked hydrophilic polymers endowed with prevalingly elastic behavior. The polymer matrix is insoluble, composed of macromolecules which form non-covalent binding complexes such as inter-polymer or intra-polymer complexes. Polymer complexes can be classified as stereo-complexes, polyelectrolyte complexes, and hydrogen bonded complexes (Krigbaum and Flory, 1953; Lowman and Peppas, 1997). Hydrogel are largely used for biomedical applications, especially for tissue engineering scaffolds (Mantha et al., 2019; Peppas et al., 2000). Moreover, their ability to retain and release a therapeutic molecule is exploited for several applications in pharmaceutical sciences. Controlling their swelling ratio is a crucial step in order to develop hydrogel based pharmaceutical dosage forms with controlled release properties (Bettini et al., 1994; Lin et al., 2014; Narayanaswamy and Torchilin, 2019; Rizwan et al., 2017).

Hydrogels are usually classified according to the nature of the polymer crosslinking: i) reversible physical hydrogels which are formed via physical processes of entanglements. Physical crosslinks are feeble interactions within gel networks like van der Waals, electrostatic interactions or hydrogen bonding (Eckmann et al., 2014), ii) permanent chemical hydrogels in which crosslinking is formed by covalent bonds between different functional groups present on the polymer chains, iii) dual-network hydrogel which formed by the combination of physical and chemical processes (Ullah et al., 2015). In addition, crosslinking may take place during the preparation of hydrogel or at a precise location in tissues after the administration (in situ), thanks to specific physiological conditions such as temperature (Yu and Ding, 2008).

Several triggered responsive hydrogels are discussed in the literature, for example, hydrogel with different release properties such as pH sensitive hydrogel. The advances in polymer chemistry leads to the development of smart hydrogels which have swelling properties dependent on external stimuli and multiple combined properties. Smart hydrogels may change their dimension or/and structure according to different environmental conditions (Lowman and Peppas, 1997; Peppas et al., 2006; Tibbitt and Anseth, 2009). Innovative design of smart hydrogels have been conceived for specific purposes, including wound dressings, tissue repair and pharmaceutical formulations with controlled drug release delivery (Ferreira et al., 2018; Li and Su, 2018; Sood et al., 2016). Hydrogels containing liposomes, nanocrystals or nanoparticles, are also described in the literature. These promising

formulations offers more stability and sustained release of encapsulated drug (Bamrungsap et al., 2012; Bobo et al., 2016; Gao et al., 2014; Grijalvo et al., 2016; Lin et al., 2014; Shimoda et al., 2012).

Hydrogels are macroscopic networks which can be designed as micro or nano sized colloidal particles, called microgel or nanogel depending on their size as shown in Figure 1. These colloidal particles present a promising approach for the development of drug delivery systems offering controlled drug release. Micro and nanogel combine the properties of hydrogel and those of micro/nanoparticles. They are characterized in terms of cross-link density and swelling ratio, like macroscopic hydrogel, and also in terms of mean average size, size distribution and colloidal stability, like micro/nanoparticles (Pelton, 2000).

The transition of hydrogel to nanogel was the major breakthrough in the drug delivery field. This opened the possibility of gel interaction at the cellular level and the feasibility of systemic administration. Nanogels formation improved the stability and stimuli responsive characteristics, while restricting the swelling ability (Vashist et al., 2017; Verma et al., 2016).

The term ‘Nanogel’ was first proposed by Vinogradov et al. in 1999 to describe a new drug carrier designed for the delivery of antisense oligonucleotides, it was made of cross-linked networks of water-soluble nonionic polymer (PEG) and cationic polymer, polyethyleneimine (PEI) (Vinogradov et al., 1999). The term nanogel was then used to describe hydrogel particles, composed of crosslinked polymers and able to swell in an aqueous environment, in the nanoscale size. According to the European commission ‘The material is a nanomaterial if 50% or more of the constituent particles (by number) have one or more external dimensions in the size range of 1-100 nm. A material is also considered as nanomaterial if its volume-specific surface area is larger than  $60 \text{ m}^2/\text{cm}^3$ ) (Rauscher et al., 2012).

Nanogels can be formed with various structures such as core shell nanoparticles, hollow nanogels, double walled and yolk shell structure (Liu et al., 2015; Sahu et al., 2017; Shoueir et al., 2017; Xing et al., 2011). Nanogels can be prepared by using different cross-linking methods such as ionic cross-linking, crystallization, cross-linking polymerization, radiation cross-linking and functional group cross-linking (Yallapu et al., 2011). A wide variety of natural and synthetic polymer can be used to formulate nanogels. Their composition can be tuned to ensure the biocompatibility and the biodegradability of nanogels (Kabanov and Vinogradov, 2009; Sharma et al., 2016).

Nanogels present a high potential as advanced drug delivery systems, thanks to their multifunctionality and stability in biological fluids (Soni et al., 2016). Thanks to their

nanosized, they can reach alternative tissues as regard to larger hydrogels. Nanogels can offer a high drug loading capacity and encapsulation efficiency due to their swelling capacity. Moreover, this capacity of nanogels to encapsulate higher amount of drug as regard to other nanoparticles is accompanied with sustained release of entrapped molecules (Shah et al., 2020). Small therapeutic molecules, biological molecules and even nanoparticles can be loaded into nanogels. Like for any other nanoparticles, loading can be achieved by i) physical entrapment, through electrostatic, van der Waals and/or hydrophobic interactions or, ii) covalent attachment or iii) controlled self-assembly (Kabanov and Vinogradov, 2009; Soni et al., 2016). A customized design could offer triggered drug release ability which could be controlled by several stimuli like temperature, pH, ion-exchange, light and others (Jing Yang et al., 2018; Verma et al., 2016; Xiong et al., 2012; Zha et al., 2011).

This review is basically focusing on the potential of nanosized hydrogel in terms of controlling the release of entrapped therapeutic molecules. The aim of this review article is to provide a general idea about drug release from different types of nanogels according to their specific compositions, based on the factful data gathered from several literatures. Primarily, in this review we discussed the mechanisms of drug release from nanogels, then summarize trigger-responsive nanogels and referenced them in tables to provide a complete overview for the readers, then we comment and propose a general scheme for the release profiles of nanogels provided by the different examples of nanogels reported in the literatures.

## **2. Drug Release Mechanism for Nanogels**

Drug delivery systems, aiming to enhance the drug concentration at the pathological site, are usually designed to carry drug and to provide its controlled release. To achieve an optimal therapeutic effect, the factors affecting drug release should be considered during the design stages. These factors are related to i) drug-material interactions which are determined by several features including hydrophilicity/hydrophobicity of drug and carrier, and ii) biodegradability mechanisms and clearance time of the carrier (Felice et al., 2014). Regulating the rate of both drug release profile and biodegradation along with stability in systemic circulation is rather challenging. In addition, a burst release phenomenon, which is an initial large bolus release of drug after the administration of the drug delivery system, or its placement in release medium, is observed for many drug delivery systems (Felice et al., 2014; Huang and Brazel, 2001). The nanogels have the tendency to release the drug quickly in the form of burst release as shown in Figure 2. This leads to the loss of hydrophilic and

hydrophobic drugs in the circulation just after the administration. A small amount of drug remain intact within the nanogel and is able to reach the target site (Soni and Yadav, 2016). To control the release of the drug, a combination of polymer or modified polymers should be used to slow the release from the nanogel, preferably in a controlled manner. The various mechanisms governing drug release have been well reviewed by Siepmann et al. (Siepmann and Siepmann, 2008). From nanogels, the release of the drug can be due to the aqueous phase at the surface of the nanogel, aqueous penetration, drug dissolution, change of excipient transition phase, excipient degradation, change in microenvironment, or simple diffusion.

Trigger is the way to control the release. Nanogels with responsive behavior and triggered drug release are reported in the literature and termed as Smart nanogels as shown in Figure 3. Chemical or physical triggers lead to a change in their swelling behavior or cause the degradation of polymeric network and structure which influence the drug release profile. The main physical triggers reported are temperature, pressure, electrical and magnetically fields, whereas chemical triggers are pH, ionic change, enzymes and chemical agents, that changes the polymer-solvent interactions (Luckanagul et al., 2018; Ullah et al., 2015; Zhu et al., 2019). Three main release mechanisms have been reported including simple diffusion, chemical and physical triggers: i) drug release by diffusion is governed by Fick's law (Fick, 1995). The polymer chain retards the solute release by reducing the average free volume available to the solute, acting as physical obstructions. Therefore, the density of polymer chain is a means to control drug release by diffusion (Amsden, 1998). ii) Physical triggers such as temperature, irradiation and others can also cause swelling or degradation of polymeric network to control the release, which influences drug diffusion. The kinetics of release is controlled by the increase of matrix area that exposed to the dissolution medium produced by the triggering phenomenon (Bettini et al., 1994). iii) Chemically release mechanism of drug is based on the degradation of the polymeric chain, inducing hydrolysis of the gel network, leading to surface erosion and drug diffusion (Lin and Metters, 2006).

### **3. Nanogels with Trigger Responsive Behavior**

#### **3.1. Thermo-Sensitive Triggered Release**

Temperature triggered hydrogels have the capability to swell and de-swell with temperature variation thanks to their composition based on thermosensitive polymers (Klouda and Mikos, 2008). The temperature triggered hydrogels can be classified into two systems, positive responsive system and negative responsive system according to their low critical solution

temperature (LCST), (i) Positive temperature hydrogels shrinks at temperature lower than LCST and swells at temperature higher than LCST, (ii) Negative temperature hydrogels shows swelling property at temperature lower than LCST and shrinks at temperature higher than LCST (Sood et al., 2016). The temperature can change the volume of nanogels, which is called volume phase transition temperature (VPTT). The variation in volume is usually exploited to enhance the encapsulation and to control the release of drug (Bergueiro and Calderón, 2015; Lu et al., 2011). The thermosensitive nanogels release depend upon one of the three mechanism which are simple diffusion, swelling mechanism and degradation mechanism. Release can be with or without burst release depending upon the compositions of the nanogels.

Examples of temperature sensitive nanogels are summarized in Table 1. Poly(N-isopropylacrylamide) namely PNIPAM also termed as pNIPAAm is a commonly used thermosensitive polymer which was reported in several nanogel formulations. PNIPAM shrinks at temperature higher than LCST due to the exclusion of water from the vicinity of the PNIPAM chains, this property makes it a polymer of choice for designing controlled release gel-based formulation. Lu et al, in 2013, designed a microgel composed of PNIPAM and lipids (termed it as lipogel) and evaluated its temperature-triggered drug release behavior using calcein as drug model. The results showed a release of calcein up to 20% at 22°C in 8 hours, and reached 80% in 8 hours at 37°C (Lu et al., 2013). PNIPAM was also used in combination with (PNIPAM-co-AA) by Bardajee et al, in order to prepare nanogels based on salep (polysaccharide) modified graphene oxide. Nanogels were loaded with Doxorubicin (DOX) or Diclofenac sodium (DS) and results showed a faster release of both drugs at 42°C than 37°C. DS release was faster than DOX as DOX showed strong interaction with the polymeric chain of nanogel (Bardajee and Hooshyar, 2017). Later on, Bardajee and Hooshyar proposed another PNIPAM nanogel carrier for anti-cancer therapy based on PNIPAM grafted on sodium alginate modified graphene oxide nanogel. Doxorubicin loaded nanogel subjected to 37 °C and 42 °C buffer solution at pH 5.0 showed 45% at 37 °C and 75% release at 42°C (Bardajee and Hooshyar, 2018). Lou et al prepared a dual sensitive nanogel, thermo- sensitive and redox-sensitive, composed of poly (2-lactobionamidoethyl methacrylamide), poly (sulfobetaine methacrylate) and PNIPAM. In this study, the release rate of DOX was significantly enhanced in the presence of Glutathione (GSH), since after 24h, DOX release was 20% at 30°C without GSH, whereas around 50% at 40°C without GSH and 90% drug release at 40°C in the presence of GSH. The release was affected by temperature as well as

redox conditions (Lou et al., 2017). Other examples of thermo-sensitive nanogels are given in Table 2.

### 3.2. pH Sensitive Release

The pH value varies in different human tissues including dysregulated cellular microenvironments, such as inflammation or cancer. Therefore, pH triggered release systems have a great potential to achieve a specific drug release at the pathological site. pH-sensitive nanogels are composed of crosslinked polyelectrolytes with weak acidic or basic groups or the combination of both (Zha et al., 2011). The ionization degree of the polyelectrolyte chain changes according to the variation of the environmental pH value. The deprotonation leads to a rise in osmotic pressure, swelling and porosity of the polymer which causes the release of electrostatically bound molecules (Tan et al., 2010).

The pH sensitive nanogels and their release profile are listed in Table 2. Zhang et al. designed self-assembled crosslinked hyaluronic acid (HA) nanogels loaded with cisplatin and doxorubicin as a controlled drug delivery system for osteosarcoma. This nanogel was found to be stable at physiological pH, while its sizes, and swelling properties were modified at pH 6.8 and 5.5. It swelled from 56 to 386 nm within 24h at pH 6.8 and dissociate. This destruction was even faster at pH 5.5, where the gel swelled from 57 nm to 473 nm in 12 h. Its drug release profile showed an increase in doxorubicin release with decrease of pH (Zhang et al., 2018). Likewise, Yang et al. in 2017 proposed pH-triggered chitosan nanogels via an ortho ester-based cross-linker for efficient drug- loading. Methacrylated succinyl-chitosan was polymerized with ortho-ester diacrylamide to form chitosan nanogel with pH sensitive properties. The release of doxorubicin from nanogel was measured at various pH. At pH 7.4, 6.0 and 5.0 the doxorubicin release was 8.2%, 64.9% and 86.0%, respectively, in 7 days (Yang et al., 2017). Xue et al. proposed sodium alginate nanogels for sustained drug release thanks to electrostatic interactions between the drug and sodium alginate. The *in vitro* release was carried out at pH 5.0 and 7.4 to comprehend the dissociation of drug and nanogel due to disintegration of  $\text{Ca}^{2+}$  induced network. The results showed a complete release of DOX at low pH in 60 hours while the release was limited to 68% at pH 7.4 (Xue et al., 2015). Other examples of pH-sensitive nanogels are given in Table 2.

### 3.3. Redox-Responsive Release

Reports of redox responsive release systems are increasing due to the presence of redox-active stimuli in human tissues and cells. Glutathione (GSH) is the most reported stimulus for

drug release and several GSH-responsive nanovehicles were developed for targeted intracellular drug delivery. GSH is indeed present in abundance inside the intracellular fluid (about 2–10 mM) and extracellular fluid (about 2–20  $\mu$ M) (Cheng et al., 2011).

In 2017, Zhang et al. designed a bio-reducible cross-linked dextrin nanogels coated with Plerixafor, a CXCR4 antagonist, for targeting metastatic breast cancer. The proposed redox responsive nanogel was loaded with Doxorubicin, which was released upon reduction of the disulfide bonds of the dextrin derivative. The release profile indicated that in non-reducing conditions at pH 7.4 and 5.0, the release of Dox from the nanogel was similar and around 30%, however in reducing conditions in the presence of 10mM GSH at pH 5.0, Dox release from the nanogel reached 70% (Zhang et al., 2017). Another nanogel model for anti-tumor therapy was proposed by Huang et al. The nanogel was composed of copolymer Methoxy poly(ethylene glycol)–poly(L-phenylalanine-co-L-cystine) and encapsulated Doxorubicin. The Dox release profile showed a responsive release under reducing environment at 10 mM GSH (Huang et al., 2015).

A new formulation of injectable hydrogel containing nanogel for combination therapy by local delivery of the anti-angiogenic combretastatin-A4 Phosphate (CA4P) and the anticancer drug doxorubicin was proposed by Jing Yang and his coworkers. Nanogel of poly (acrylic acid-co-4-vinylphenylboronic acid) was loaded with Dox and incorporated into a hydrogel containing CA4P in order to release CA4P and DOX sequentially. DOX release profiles from the nanogel showed a release of 66% without GSH and 84% with GSH at pH 7.4 in 14 days. The release of Dox was due to redox stimuli-responsive properties related to the presence of disulfide linkages on the polymer (Jing Yang et al., 2018). Another example of redox-responsive nanogel was described by Lee et al. who designed a thiol conjugated hyaluronic acid. The release profile confirmed that in the presence of GSH a faster release of siRNA was measured, an increase of released percentage is observed with increasing the concentration of GSH in release medium (Lee et al., 2007). A list of nanogel formulation with redox responsive release are listed in Table 3.

### **3.4. Photo-Sensitive Release**

Light sensitive nanogels are composed of polymers bearing photoactive groups like azobenzene, spirobenzopyran or cinnamonyl. When these polymers are subjected to light exposure, their double bonds undergo a transition from trans to cis inducing a change in the shape and size of the nanogel (Alvarez-Lorenzo et al., 2009; Jiang et al., 2006). Another

category of light sensitive nanogels is the hybrid nanogels which combines polymer and noble metals. In this case, metals convert light energy to heat which causes the transition in the polymer structure (Timko et al., 2010). Photo-sensitive nanogels have the ability of cis-trans isomerization, and upon exposure to specific radiations, nanogels can swell or shrink due to alteration in temperature, which triggers the release of drugs (Molina et al., 2015). For instance, azo-dextran nanogels encapsulating aspirin showed an improvement of aspirin release by light exposure, which can be explained by the fact that light exposure induced a photo-isomerization of azobenzene, which led to faster release in case of Z-isomers than E-isomers. (Patnaik et al., 2007). A core-shell hybrid nanogel, made by coating the Ag-Au bimetallic NP core with a thermo-responsive nonlinear poly(ethylene glycol) based hyaluronic acid hydrogel have been reported in the literature by Wu et al. The release of Temozolomide from this nanogel was achieved faster in the presence of near infra-red light than without NIR light. This was explained by the fact that Ag-Au nanoparticles absorb light and convert it to heat, causing the disruption of the polymer chain (Wu et al., 2010). Later on, Qin et al. designed amphiphilic chitosan derivatives coated single-wall carbon nanotubes encapsulated in thermo/pH sensitive nanogel. This nanogel showed photosensitive properties as the release of Doxorubicin was 27% without NIR irradiation and up to 45% with irradiation at pH 7.4, at 25 °C (Qin et al., 2015). Similarly, another very promising design of photo sensitive graphene oxide containing hyaluronic acid based nanogel was presented by Fiorica et al. This nanogel encapsulates irinotecan and its release was controlled by NIR. The release was faster in the presence of NIR up to 100% in just 4 hours. Whereas, in the absence of NIR the release slows down up to 40% in 10 hours (Fiorica et al., 2017). Examples of photo responsive release nanogels are listed in Table 4.

### **3.5. Enzymatic Responsive Release**

Enzyme sensitive nanogel systems are an inspiring approach taking benefit of the enzyme present in the body. Made with polymers sensitive to enzymatic hydrolysis, these nanogels change physically and chemically upon exposure to enzymes. This approach is more sensitive and specific than the other approaches of triggered sensitive nanogel. The more common polymers are sensitive to proteases, lipases, phosphatases and endonucleases hydrolysis (Hu et al., 2012). An enzyme responsive nanogel loaded with Doxorubicin was proposed by Yang et al. in 2015, methacrylated hyaluronic acid was copolymerized with di(ethylene glycol) diacrylate to formulate a nanogel with enzymatic responsive release. The

release profile could be adjusted at various pH, at 37 °C, in presence of various enzymes (Table 5) (C. Yang et al., 2015). A lipase responsive nanogel was developed by Xiong in 2012. The nanostructure composed of a triple layered nanogel (Polyethylene shell, poly( $\epsilon$ -caprolactone) fence and polyphosphoester core) showed a release of vancomycin dependent on the presence and the concentration of pseudomonas lipase in the release medium. In addition, the percentage of released drug was increased to 86% by adding alkaline phosphatase (ALP) in the release medium, authors explained this result as following: the degradation of the poly( $\epsilon$ -caprolactone) fence by Pseudomonas lipase which facilitated the degradation of the poly- phospho-ester core by ALP (Xiong et al., 2012). Sun et al. proposed the dual sensitive alginate-keratin nanogel which is responsive towards both redox and enzymatic conditions. The encapsulated doxorubicin showed the highest release (around 80%) in presence of GSH and trypsin (Sun et al., 2017). The detailed release profile of enzyme sensitive nanogels are listed in Table 5.

### **3.6. Magnetic field responsive nanogels**

The nanogels specially designed to be responsive to magnetic field are composed of polymer and iron oxide nanoparticles. Ferro and ferrimagnetic nanoparticles are most commonly used in drug delivery as they possess superparamagnetism properties (Medeiros et al., 2011; Zha et al., 2011). Non-toxic biocompatible iron oxides nanoparticles are suitably use for drug delivery as they can be entrapped into nanogels by using emulsion polymerization techniques. The magnetic field responsive nanogels have the ability to remotely control the drug delivery (Medeiros et al., 2011; Murakami and Maeda, 2005; Satarkar et al., 2010). Wang et al designed a thermosensitive nanogel with bifunctional iron dots embedded in the shell and iron oxide nano particles clustered in the core of poly(N-isopropylacrylamide-co-acrylamide) [poly(NIPAM-AAm)]-based nanogel. Both the NIR and magnetic field was applied to alter the temperature indirectly and to control the release remotely. Magnetic field was provided at various time periods (0.5, 5, 60 and 92 h) for 30 min each. After each exposure, a drastic increase in the release of Curcumin from nanogel was obtained as compared to the release without magnetic field exposure. Magnetic field could be another means of controlling the release as turning off the magnetic field stopped the release (Wang et al., 2014).

Another type of magnetic responsive nanogel was introduced by the copolymerization of N-isopropylacrylamide (NIPAM) and (2-dimethylamino)ethyl methacrylate (DMA) which was

embedded into graft copolymerization of poly(2-dimethylamino)ethyl methacrylate (PDMA) onto salep (PDMA-g-salep) and Fe<sub>3</sub>O<sub>4</sub> nanoparticles (NPs). The release profile was carried on the basis of swelling and deswelling of nanogel which lead to release of drug. Doxorubicin release from the nanogel enhanced in the presence of the magnetic field. This result is attributed to electrostatic repulsions between amine groups in their polymeric structure and Fe<sub>3</sub>O<sub>4</sub> NPs, which disrupt polymeric structure and favors the drug release from the polymer structure (Somayeh Ghavami et al., 2019).

Another multi-responsive nanogel was designed based on three different triggers: temperature, pH and magnetic field. The nanogel was composed of (2-dimethylaminoethyl) methacrylate, N-isopropylacrylamide grafted onto sodium alginate. Doxorubicin release was slower in the presence of the magnetic field due to the impact of the magnetic field on the iron oxide incorporated within the gel. The reduced distance of iron oxide nanoparticles under the magnetic field produced an hindrance delaying the drug release (Hayati et al., 2020). The detailed release profile of magnetic field responsive nanogels are listed in Table 6.

#### **4. Conclusive prospects**

Nanogels present interesting properties, combining the advantages of hydrogels and nanoparticles, meaning high loading capacity and large surface area. The main advantage is probably the fact that these nanogels are designed in order to be stimuli responsive, responsive to an external trigger or an internal environmental change. The responsive nature of the nanogel as regard to their structure can be summarized in the Figure 4. Basically, there are two types of nanogels, the one formed via physical cross-links of lower energy binding and the one resulting from chemical cross-links forming covalent bonds. The first ones can either release their content via simple diffusion upon gel swelling, or via a stimulus. These stimuli can be the pH change from the environment or application of increased temperature both resulting in swelling, increased porosity and then drug diffusion or the application of light also leading to structural change within the polymeric matrix. The second ones need a bond degradation to be able to release the drug, such as a reductive environment or/and an enzymatic hydrolysis.

The stimuli responsive nanogels offers the advantage of a better control of the release of their content and that is obviously what researchers are trying to reach through the reviewed studies. This is not yet achieved in terms of clinical application, however, from the examples described above, we can see that advances have been made. Noteworthy, some triggers might

be more reliable than others, such as temperature or light deposition which are applied in clinic for thermal therapy or photodynamic therapy respectively. Environmental stimuli are less reliable as they are highly dependent on the patient conditions. Moreover, another point to pay attention to is that the chemical degradation required for chemical cross-linked nanogels might lead to the release of toxic monomers from the matrix. These points, together with the preparation process should be thought upfront in order to apply these formulations to the patient.

Finally, one has to select the type of drug which can be benefit from nanogels. Most of the polymeric matrix are made of hydrophilic polymers, therefore highly soluble drug might mostly be entrapped. The limit of drug aqueous solubility might indeed be a limit for the drug release (Siepmann et al., 2019). Among the hydrophilic drug which definitely require delivery systems, are naturally the biotherapeutics. Biomolecules such as proteins or nucleic acids are the more prone to biodegradation and do not cross cell membranes. Due to their size, they are also poorly released from drug delivery systems. Therefore, nanogels which are capable to high loading and cell internalization could be a very attractive system. Combining this transport with a stimulus to release the large biomolecules would also be of high interest. This topic has been lately reviewed by the group of Wim Hennink (Li et al., 2017).

Obviously, scientific advancement in the drug formulation should be the primary step for developing and marketing new pharmaceutical dosage forms based on smart nanogels. In this field, lipids and polymers remains are best companions to apprehend new formulations (Siepmann et al., 2019). New chemically modified lipids and polymers, hybrid systems and auto-assembled mixed systems remain challenging formulations to control and characterize. Advances in new preparation process and characterization methods will undoubtedly benefit to novel nanogels formulations (Ahmed et al., 2019; Hayati et al., 2020; Yang et al., 2017; Zhang et al., 2013), together with novel mathematical models to define control release (Costa and Sousa Lobo, 2001; Grassi and Grassi, 2005; Siepmann and Siepmann, 2008).

Overall, the data collected from the literature and presented in this review showed the growing interest in the topic of nanogel and highlighted their potential to address challenges in the treatment of severe diseases.

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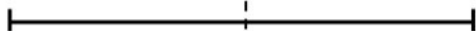
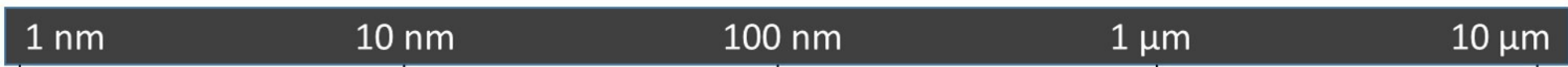
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Hydrogel



10-50 nm

50-500 nm

1-10 μm



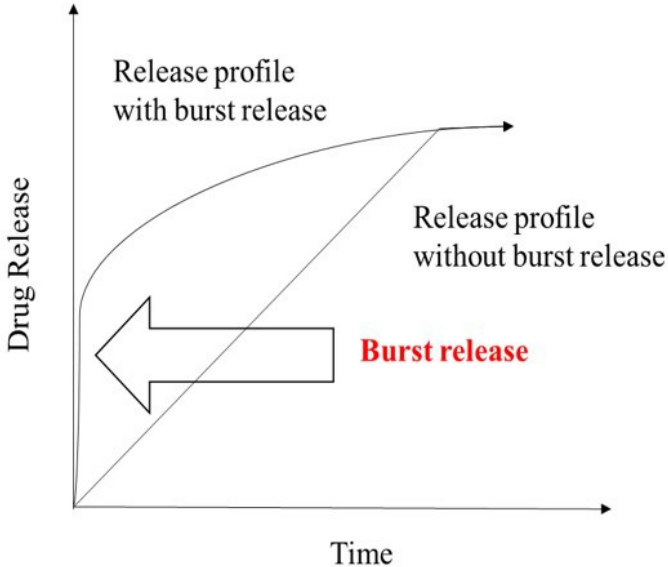
Micelles



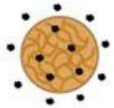
Nanogel



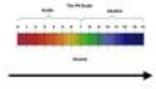
Microgel



a



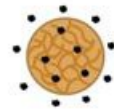
b



c



d



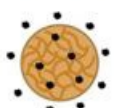
e



f



g



Physical cross-link

Chemical cross-link

Non stimuli responsive

Stimuli responsive

- Swelling
- Diffusion

- pH
- Light
- Temperature

- Reductive environment
- Enzyme
- pH

Uncontrolled release

Controlled release

## Tables

Table 1: Examples of thermo-sensitive nanogels with their drug component, release percent, temperature and time of experiment.

Composition/ Carrier	Drug/Loaded component	Release %	Temp	Time	Reference
Poly(N-isopropylacrylamide) microgel	Calcein	20% 80%	22°C 37°C	8 h	(Lu et al., 2013)
N-isopropylacrylamide graft-copolymerization onto salep modified graphene oxide	Doxorubicin + Graphene oxide	30% 50%	37 °C 42 °C	8 h	(Bardajee and Hooshyar, 2017)
	Doxorubicin - Graphene oxide	45% 70%	37 °C 42 °C	3 h	
	Diclofenac Na + Graphene oxide	60% 75%	37 °C 42 °C	8 h	
	Diclofenac Na – Graphene oxide	90% 100%	37 °C 42 °C	3 h	
Poly(N-isopropylacrylamide) grafted onto sodium alginate-modified graphene oxide	Doxorubicin	45% 75 %	37°C 42 °C	16 h	(Bardajee and Hooshyar, 2018)
Poly (2-lactobionamidoethyl methacrylamide) poly (sulfobetaine methacrylate) poly(N-isopropylacrylamide)	Doxorubicin	90% + GSH 40% - GSH	40°C	24 h	(Lou et al., 2017)
Thermo-sensitive fibrinogen- <i>graft</i> -poly (N-isopropyl acrylamide) nanogels	5-FU/Megestrol acetate	45 % 70%	25°C 37 °C	72 h	(Rejinold et al., 2014)
Arginine–glycine–aspartic acid containing peptide and transferrin conjugated to poly (N-isopropylacrylamide- <i>co</i> -propyl acrylic acid) nanogel	Peptides	35% 80%	27 °C 37 °C	71 h	(Quan et al., 2009)
N-isopropylacrylamide and acrylic acid in the presence of β-cyclodextrin	Doxorubicin	82% 85% 90%	25°C 37°C 42 °C	10 h	(Yi et al., 2017)
PEG-Based ether- anhydride triblock copolymer	Doxorubicin	60% 80% 90%	25°C 37°C 45°C	48 h	(Zhao et al., 2010)

Table 2: Examples of pH-sensitive nanogels with their drug component, release percent, pH and time of experiment.

Composition/ Carrier	Drug/Loaded component	Release %	pH	Time	Reference
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Cisplatin crosslinked hyaluronic acid (HA) nanogel	Doxorubicin + cisplatin	86.0% 60.1% 38.5%	5.5 6.8 7.4	72 h	(Zhang et al., 2018)
Hyaluronic acid nanogels	Doxorubicin	9.3% 88.4%	7.4 5.0	168 h	(Yang et al., 2017)
Sodium alginate pH responsive nanogel	Doxorubicin	100% 40%	5 7.4	6 h	(Xue et al., 2015)
Chitosan-based hydrogel conjugated with tetrakis(4-aminophenyl)porphyrin (NH <sub>2</sub> -TPP) and 2,4,6-tris(p-formylphenoxy)-1,3,5-triazine	Porphyrin	22% 7% 1%	5 6.8 7.4	12 days	(Belali et al., 2018)
Egg yolk /polysaccharide nanogels	Curcumin	Uncross linked nanogel 75% Crosslinked nanogel 80%	2.4 7.5	2 h 6 h	(Zhou et al., 2018)
Dextrin <i>N, N'</i> -methylene bi sacrylamide	Doxorubicin	60% 35%	5.5 7.4	76 h	(Das et al., 2017)
Metotraxate Carbopol gel (MCG) Methotrexate Loaded Chitin Nanogel (MCNG)	Methotrexate	MCG 100% MCNG 92%	5.5 5.5	3 days 5 days	(Panonnumma I and Sabitha, 2018)
Poly (PEGMEMA- <i>co</i> -FuMaMA- <i>co</i> -HEMA nanogels	Doxorubicin	17.6% 5.8%	5.4 7.4	30 days	(Chambre et al., 2018)
Aldehyde dextran nanogel	Doxorubicin	66% 28% 9%	2.0 5.0 7.4	72 h	(Su et al., 2018)
Methacrylated succinyl chitosan (MASCS) polymerized with ortho ester-based linkage	Doxorubicin	8.2% 64.9% 86.0%	7.4 6.0 5.0	168 h	(Yang et al., 2017)
Bleomycin-Chitosan	Bleomycin	50% 85% 85% 35%	4.0 5.0 6.0 7.0	96 h	(Sahu et al., 2017)
Poly (vinyl alcohol) based nanogel	Paclitaxel	21.2% 90%	7.4 5.0	30 h	(Chen et al., 2017a)
Dendritic polyglycerols Nanogels	Doxorubicin	15% 60%	7.4 5.0	96 h	(Zhang et al., 2014)
Fish gelatin methacryloyl	Doxorubicin	11% 4%	4.5 7.4	72 h	(Kang et al., 2019)
Chitosan/Sodium triphosphate nanogel Magnetic nanoparticle / Chitosan / Sodium triphosphate nanogel	Doxorubicin	55 65 60 75	7.4 5.3 7.4 5.3	96 h	(Sadighian et al., 2017)

Table 3: Examples of redox responsive nanogels with their drug component, release percent, reducing agent and time of experiment.

Composition/ Carrier	Drug/Loaded component	Release %	Reducing condition	Time	Reference
Dox loaded Dextrin nanogel coated with AMD3100	Doxorubicin	70%	5.0 pH 10 mM GSH	24 h	(Zhang et al., 2017)
		29.2%	5.0 and 7.4 pH 10 $\mu$ M GSH		
Methoxy poly (ethylene glycol) poly(L-phenylalanine-co-L-cystine) nanogel	Doxorubicin	28.1%	37 °C	3 days	(Huang et al., 2015)
		74.7%	0 mM GSH 10 mM GSH		
Poly (acrylic acid-co-4-vinylphenylboronic acid) nanohydrogels	Doxorubicin	15.8%	pH 6.5 - GSH	14 days	(Jing Yang et al., 2018)
		22.9%	pH 6.5 + GSH		
		66%	pH 7.4 - GSH		
		83.9%	pH 7.4 + GSH		
Thiol-conjugated hyaluronic acid HA nanogel	siRNA	5.8%	GSH	2 h	(Lee et al., 2007)
		17%	0 mM	2 h	
		55%	0.1 mM	2 h	
		70%	1 mM	2 h	
		100%	5 mM	1 h	
i) Poly (ethylene glycol)-b-poly(2-(hydroxyethyl) methacrylate-co-acryloyl carbonate) (PEG-P(HEMA-co-AC)) nanogel ii) 1,4 butadiamine (non-reducing nanogel)	Protein	i) 96 %	10 mM DTT	22 h	(Chen et al., 2013)
		i) 30 %	0 mM DTT		
		ii) 30 %	10 mM DTT		
Cyclo(Arg-Gly-Asp) peptide (crgd) decorated disulfide (SS) containing poly(vinyl alcohol) nanogels (crgd-SS-ngs)	Doxorubicin	$\approx$ 20%	GSH	2 days	(Chen et al., 2017b)
		61%	0 mM, 7.4 pH		
		65%	10 mM, 7.4 pH		
		$\approx$ 78%	0 mM, 5.5 pH 10 mM, 5.5pH+ 7.4pH After 4 h		
Disulfide-cross-linked polypeptide nanogel with near-infrared fluorescence property	Doxorubicin	68%	PBS	10 h	(Xing et al., 2012)
		88%	GSH 10 mM		
Poly(oligo(ethylene glycol) methacrylates-ss-acrylic acid) (P(oegmas-ss-AA)) nanogels	Doxorubicin	35%	0 mM GSH	100 h	(H. Yang et al., 2015)
		25%	pH 4.5		
		23%	pH 6.5		
		32%	pH 7.4		
		22%	2 $\mu$ M GSH		
		20%	pH 4.5		
		65%	pH 6.5		
		62%	pH 7.4		
60%	10 mM GSH				
Disulfide cross-linked dextrin	siRNA	0%	PBS +pH7.4	12 h	(Li et al., 2018)
		70%	DTT + pH 7.4		

Fluorescent carbon nanogel	Paclitaxel	3% 37% 65% 100%	0 mM GSH 3 mM GSH 6 mM GSH 10 mM GSH	24 h	(Choi et al., 2019)
Di-thio-di-propionic acid in tri-polyphosphoric acid cross-linked poly(ethylenimine) nanogel. Nanogel ratio i) (2:1:0), ii) (2:1:0.05) and iii) (2:1:0.1)	Carboxylic fluorescein	i) 8.2, 8.1, 8.5, and 8.3% ii) 7.17, 49.6, 50.0, and 51.9% iii) 9.39, 41.1, 49.9, and 54.9%	Dithiothreitol 0 mM, 2 mM, 5 mM, 10 mM	24 h	(Guo and Kim, 2017)

Table 4: Examples of photo-sensitive nanogels with their drug component, release percent, irradiation and time of experiment.

Composition/ Carrier	Drug/Loaded component	Release %	Irradiation	Time	Reference
Chitosan-modified chemically reduced graphene oxide (CRGO) Incorporated in NIPAM nanogel (DOX- CGN)	Doxorubicin	5 % - NIR 18.81% + NIR	3 min irradiation of in Near infra-red	3 h	(Wang et al., 2013)
Adamantine (AD)-conjugated copolymer, poly [poly (ethylene glycol) monomethyl ether methacrylate]-co-poly(N-(2-hydroxypropyl)- methacrylamide)-co-poly(N-adamantan-1-yl-2-methacrylamide) (PPEGMA-co-PHPMA-co-PADMA), and $\beta$ -cyclodextrin ( $\beta$ -CD)-functionalized poly(amidoamine) Nanogel	Doxorubicin or Indocyanine green (ICG)	20% - NIR 90% + NIR	3 min irradiation of in Near infra-red	16 h	(Zan et al., 2015)
Ag–Au core PEG–Hyaluronic hybrid shell nanogels (nanogels coded as PSG 1, PSG 2, PSG 3)	Temozolomide	PSG 1 50% PSG 2 58% PSG 3 75%	5 min irradiation Near infra-red	24 h	(Wu et al., 2010)
Azo-Dextran nanogel	Rhodamine, aspirin	N/A	UV irradiation	6 h	(Patnaik et al., 2007)
Chitosan coated carbon nanotubes encapsulated PNIPAAm	Doxorubicin	27% - NIR 45% + NIR	Near infra-red	2 days	(Qin et al., 2015)
Poly(NIPAM-Aam) nanogel	Curcumin	47% - NIR 70% + NIR	Near infra-red	3 days	(Wang et al., 2014)
Hyaluronic acid/polyaspartamide-based double-network nanogels poly(N-phenylglycine) – PEG hydrogel	Irinotecan Cisplatin	40% - NIR 100% + NIR 07% - NIR 33% + NIR	Near infra-red Near infra-red-II	10 h 04 h -- 4 cycles each for 5 mins	(Fiorica et al., 2017) (Ruan et al., 2019, p.)
Perylene diimide zwitterionic polymer (PDS) and Ascorbic acid (Vc)-	Doxorubicin / Photo-thermal	30% - NIR 70% + NIR	Near infra-red	36 h	(Sun et al., 2020)

Table 5: Examples of enzyme sensitive nanogels with their drug component, release percent, enzyme and time of experiment.

Composition/ Carrier	Drug/Loaded component	Release %	Enzyme	Time	Reference
Methacrylated Hyaluronic acid nanogels	Doxorubicin	28%	No enzyme pH 7.4	120 h	(H. Yang et al., 2015)
		60%	No enzyme pH 5.0		
		57%	HAase pH 7.4		
		63%	HAase pH 5.0		
		53%	Lipase pH 7.4		
		64%	Lipase pH 5.0		
		62%	Multi-enzyme pH 7.4		
74%	Multi-enzyme pH 5.0				
lipase-sensitive polymeric triple-layered nanogel	Vancomycin	10 ± 1%	Without P. Lipase	48 h	(Xiong et al., 2012)
		40%	0.5 mg/mL P.Lipase		
		70%	1 mg/mL P.Lipase		
		86 ± 3%	1 mg/mL P. Lipase + ALP		
Alginate-Keratin composite nanogel	Doxorubicin	11%	PBS	48 h	(Sun et al., 2017)
		14%	10 µM GSH		
		27%	10 mM GSH		
		70%	0.04mM Trypsin		
		80%	10mM GSH+0.04mM Trypsin		

Table 6: Examples of magnetic-responsive nanogels with their drug component, release percent, magnetic field and time of experiment.

Composition/ Carrier	Drug/Loaded component	Release %	Magnetic field (MF)	Time	Reference
Bifunctional nanoparticles fluorescent carbon dots embedded in the porous carbon shell and superparamagnetic iron oxide nanocrystals clustered in the core of poly(N-isopropylacrylamide-co-acrylamide) [poly(NIPAM-AAm)]-based nanogel	Curcumin	~ 45% - MF	100 V, 0.8 A, 50 Hz For 30 min	92 h	(Wang et al., 2014)
		~ 75% + MF			
Copolymerization of N-isopropylacrylamide and (2-dimethylamino)ethyl methacrylate embedded into graft copolymerization of poly(2-dimethylamino)ethyl methacrylate onto salep and Fe <sub>3</sub> O <sub>4</sub> nanoparticles.	Doxorubicin	~ 75% - MF	---	10days	(Somayeh Ghavami et al., 2019)
		~ 100% + MF			
(2-dimethylaminoethyl) methacrylate and N-	Doxorubicin	~ 85% - MF	---	12 h	(Hayati et al., 2020)

isopropylacrylamide grafted onto sodium alginate entrapped Iron oxide nanoparticle and doxorubicin		~ 70% + MF			
magnetic chitosan-g-PNVCL (MCP) polymeric nanogel	Doxorubicin	~ 12% - MF ~ 73% + MF	MF + pH 7.4	300 min 40min	(Indulekha et al., 2017)
Oligo(ethylene glycol) methacrylate based nanogels with maghemite	Doxorubicin	~ 24% - MF ~ 47% + MF	335 kHz, 9 mT, 12.0 kA.m <sup>-1</sup> , 30 min. at pH 7.5	4 h	(Cazares-Cortes et al., 2017)

