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Short Communication

Nanogels Based Drug Delivery System: A Promising Therapeutic Strategy

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ABSTRACT

Through particular structural designs and unique preparation techniques, nanogels can encapsulate drugs within three-dimensional crosslinked polymeric networks. This allows for the controlled and sustained delivery of loaded drugs, improving patient compliance and therapeutic efficacy. Furthermore, compared to other nanocarriers, nanogels offer a better drug loading capacity and biocompatibility. The science of therapeutic biology has undergone a revolution with the use of nanoparticles in drug delivery. Drug nanocarriers are being used to extend the drug's circulation time, regulate its release and stability, and shield it from cell clearance or premature breakdown in order to increase medicinal efficacy. For more secure and reliable delivery to the intended locations, the hydrogel nanoparticle dispersions are crosslinked using a crosslinked polymeric framework. The last two decades have seen the development of nanogels as promising biomaterials with a broad range of uses. Drug accumulation in disease areas can be improved and active targeting can be accomplished with the modification of nanogels. They can be made to respond to both internal and external stimuli, including pH, temperature, light, and redox, allowing the loaded medicine to release gradually. On the other hand, there has been new research on the use of nanogels for purposes unrelated to biomedicine. Since nanogels can be used for a wide range of purposes, we have thoroughly examined the state of the art for all practical uses and production techniques of nanogels. The purpose of this note is to understand why and how nanogels are regarded as such a novel approach to drugs delivery.

INTRODUCTION

Nanotechnology has been widely used in the design and development of innovative drug delivery systems because it provides suitable methods for the time-controlled or time-specific delivery of bioactive substances. In particular, the nanoscale size can increase the rate at which poorly soluble drugs dissolve, increase the amount of drugs that accumulate in tumors, improve the stability of therapeutic agents against chemical or

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enzymatic degradation, and lessen the cytotoxic side effects of cancer therapy. Various nano-scaled delivery systems, including liposomes, polymeric micelles, sol-gel derived materials, and others, have been described to tackle these issues[1,2]. Drug stability and release can be improved with the use of nanomaterials, creating new opportunities for the treatment of disease [3]. In essence, nanoparticle-based gels serve as a drug delivery transporter scaffold; however, they can be artificially engineered to incorporate different ligands for precise drug release and transport [4]. Nanogels are highly crosslinked nano-hydrogel scaffolds made of either monomers that are ionic or nonionic or copolymerized [5]. The phrase "nanoparticle constituted gel" was used by Alexander and Serguei (2008) to characterize crosslinked bifunctional scaffolds that include a poly-ion for polynucleotide transport and a nonionic polymer [6].

Future drug delivery systems need to be carefully studied to gain a better understanding of how physical and chemical characteristics affect the bridging of biological barriers in a certain disease subtype and a particular patient population in order to develop a personalized drug delivery strategy[43]. Nanohydrogels have the benefit of having characteristics found in both hydrogels and nanoparticulate systems. They are described as a three-dimensional polymeric network made up of macromolecular chains that are cross-linked and range in diameter from 1 to 100 nm [7]. They are capable of retaining a significant amount of water [8]. The cross-linked network functions as a matrix to contain the absorbed liquid medium, while the absorbed liquid medium by the nanohydrogels serves as a filter media for the diffusion of solutes [9]. Nanogels range in size from 20 to 200 nanometers [10]. They can avoid renal clearance and have an extended half-life in the serum. They can absorb large amounts of water or physiological fluid thanks to their structure, which also keeps their three-dimensional hydrophilic networks intact. When it comes to delivery, there are several benefits to employing nanogels. They have good solubility, little viscosity, great thermodynamic stability, and can withstand intense sterilizing methods [11].

Numerous natural and manmade polymers were used to create nanoscale hydrogels. Polysaccharide nanogels are a promising drug delivery method because of their superior physicochemical and biological properties. Polysaccharide-based nanohydrogels in particular, as well as other nanohydrogels in general, work well for drug delivery and tumor targeting [12]. Kabanov et al. created the first nanogels by combining the polymers poly (ethylene glycol) (PEG) and polyethyleneimine (PEI) to produce a chemical crosslinking and using the nanogels for the transport of oligonucleotides. Regular reports describe a number of therapeutic applications for nanogels, such as sensor applications, drug-encapsulated hydrogels, burn therapy hydrogels, and skin substitutes. Hydrogels made of silver nanocomposite have been proven to have antibacterial properties. Consequently, total inhibition of bacterial and yeast growth by silver composite hydrogels may be advantageous for the development of new superabsorbent antimicrobial pharmaceutical products and the management of wound infections [13]. Polymeric nanogels' capacity to reverse surface characteristics, such as theranostics, is correlated with their ability to cross the blood-brain barrier [14, 15]. Consequently, extreme caution must be used while designing nanogels to maximize the special qualities of the constituent parts in order to provide a response to variations in pH, temperature, osmotic pressure, and diffusion coefficients. Nanoparticle-based gels have been used in numerous research trials to treat cancer. Dickerson and colleagues proposed employing nanoparticle-based gels to distribute siRNAs as a quality control tool to improve the

efficacy of chemotherapeutic medications [16, 17]. Nanogels are becoming more and more popular as potential transdermal drug delivery vehicles. Drug-loaded polymeric colloidal nanogels (DPCN) have garnered significant attention due to their potential application in releasing a variety of drugs for controlled or sustained drug delivery systems. Compared to intravenous or oral drug delivery methods, Transdermal Drug Delivery Systems (TDDS) have the advantage of easier medication administration [18]. For TDDS to be applied, the drug formulation must be able to accumulate sufficient amounts in the particular regions of interest. Critical properties for TDDS design are nanogels' substantial drug loading capacity, biocompatibility, and biodegradability [19].

2. Fabrication of Nanogels: Chemical crosslinking and physical self-assembly are the two categories into which the synthesis techniques for nanogels can be subdivided according to the various structures and constituent parts of nanogels. When compared to physical crosslinking caused by the covalent crosslinking of functional groups on polymer chains, the chemically crosslinked nanogel demonstrated a higher degree of stability. On the other hand, noncovalent interactions—which mostly involve hydrogen bonding, Van der Waals force, hydrophobic interaction, host-guest contact, electrostatic interaction, and so forth—are frequently responsible for the reversible connections of physically crosslinked nanogels[20]. Physical self-assembly is a more flexible and convenient method because it doesn't involve complicated processes, despite the fact that the interaction of physical noncovalent bonds is comparatively weaker than that of chemical covalent crosslinking[21].

2.1 Physical crosslinking: Surrounding polymer molecules created by noncovalent interactions, physically crosslinked nanogels are supramolecular particles. During the formation of nanogels, several environmental factors like temperature, pH, and ionic strength can affect the size of the gels as well as the concentration of the polymer. An insoluble molecule can be physically inserted into a network of crosslinked polymers using the semi-interpenetration method. The resulting nanogels can then expand the new properties of the incorporated molecule. Dendritic polyglycerol (dPG) cross-linked poly(N-isopropylacrylamide-co-N-isopropyl methacrylamide) nanogels (p(NIPAm-co-NIPMAm)) were formed by semi-interpenetration of poly-pyrrole (PPY) with photothermal convention, which could be used for photoacoustic (PA) imaging[22].

2.2 Chemical crosslinking: Chemical crosslinking is the most advanced and adaptable method for creating nanogels, exceeding physical crosslinking in its versatility. Polymerization by emulsion, click chemistry crosslinking, reversible addition-fragmentation chain transfer (RAFT), and photo-induced crosslinking are examples of chemical crosslinking techniques [23]. Biodegradable nanogels based on amino acids are frequently prepared via amino crosslinking [24]. Inverse emulsion polymerization is a polymerization reaction initiated by the continuous emulsification of water-in-oil emulsifiers in the oil phase. The sizes of nanogels can be regulated by many factors, such as the surfactant, feed ratio of the monomer and crosslinker, and pH[25]. Emergent hydrogels and nanogels have been linked to click chemistry in recent years because of its exceptional selectivity, high yield, and high reactivity[26].

3. Types of nanogels: Modern science developed so many kind of nanogels and those include, stimuli responsive nanogels, temperature responsive nanogels, pH responsive nanogels, magnetic field responsive nanogels, enzyme responsive nanogels, redox responsive nanogels,

antigen responsive nanogels, core-shell nanogels, functionalized nanogels, degradable nanogels, photo sensitive nanogels, ultrasound-responsive nanogels, micellar nanogels, liposome revised nanogels, hollow nanogels.

4. Properties of nanogels: Nanogels can swell and de-swell very rapidly. The advantages of water soluble nanogels are combined with the unique properties needed by their nanoscale size in water-soluble nanogels. Because they contain polymers with high-affinity functional groups, nanogels—like microgels—can regulate the administration of medications while simultaneously preserving them [27, 28]. It is possible to modify the nanogel's chemical composition to adjust its softness [29]. The surface charge of polymers inhibits the development of blood aggregations and the problems that accompany them. Elevating the zeta potential results in increased repulsive interactions between the particles, stabilizing the nanogels electrostatically and changing the surface charge. Another option is to employ surfactants, like polyethene glycol, which can generate a hydrostatic force as well as a steric effect, resulting in a reliable and stable nanosuspension [28]. Nanogels have become increasingly popular in the medication delivery industry in recent decades due to their special qualities [29]. Polymers, both synthetic and natural, can be used to create nanogels. Because they are biocompatible and biodegradable, they won't build up in the circulatory system. Nanogels can be made from chitosan, methylcellulose, sodium alginate, polyacrylic acid, and various polysaccharide-based polymers such as dextran, pullulan, and cyclodextrin. Nature has created these polymers to be nontoxic, biodegradable, hydrophilic, and stable[30].

Table 1: Properties of nanogel

Properties	References
Colloidal stability	31
Drug loading	32
Drug release	32
Swelling behavior	33
Shape control	34
Viscoelasticity	31

5. Nanogels' drug release mechanisms: Three types of drug release mechanisms can be distinguished in relation to nanogels: chemically controlled, swelling regulated, and diffusion-controlled. The pharmaceutical release mechanism is contingent upon the loading technique of the pharmaceuticals into the nanogels as well as the physicochemical characteristics of the drug molecule. The majority of the time, covalent and noncovalent interactions, as well as physical entrapment, are used to load drugs into nanogels. When there is a physical contact, the loaded cargo should come free of the nanogels as soon as they swell.

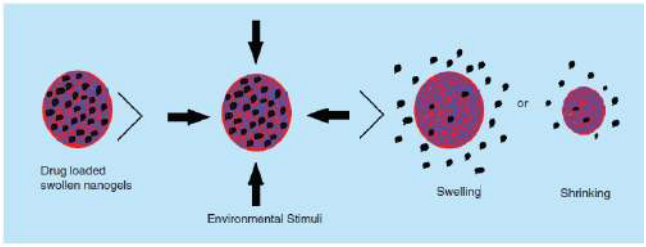

Figure 1: Drug release mechanism of nanogels, (Copyright from sultana et al, 2013) [35].

Given all of its benefits, nanogels are a better drug delivery technological advances than others. These include highly biocompatible and biodegradable nanogels, as well as recyclable preparation techniques.

Because nanogels are prepared by assembling a polymer system, which also regulates the preparation's particle size, they can also offer a more accurate sustained drug release. Moreover, the nanogels' freely flowing iridescent solution diffuses smoothly in a water solution [36]. The main benefit of nanogels is the decreased initial outflow of the drug from the solution[37].

6. Applications of nanogels: Nanogels can be applied parenterally, topically, intraocularly,

nasally, and by any combination of these modes of administration. A few examples include the encapsulation of curcumin for oral delivery in low density lipoprotein/pectin nanogels [38], the loading of acetazolamide intended for ocular delivery into nanogels made of surfactant-based nanovesicles [39], and the use of nanogel-based antigen-delivery system and bio-inspired pulmonary surfactant-modified nanogels (a promising siRNA delivery system) for pulmonary and nasal purposes, respectively [40, 41]. Nanogel based drug delivery systems used in autoimmune diseases drug delivery, anti-inflammatory drug delivery, vaccine delivery, antibacterial & antimicrobial drug delivery, diabetes drug delivery, gene delivery, bone drug delivery, topical drug delivery, enzyme based drug delivery and in cancer therapy.

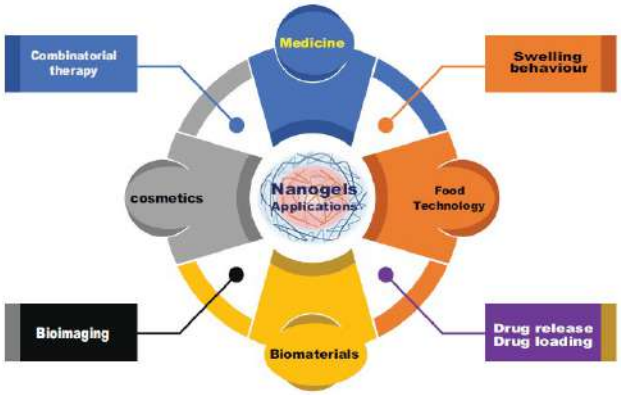

Figure 2: Diagrammatic illustration of nanogels and their application in the biomedical sector, (Copyright from Tariq et al. 2023) [42].

7. Nanogel formulation available in market: Commercially available formulations, including zyflex nanogels, are used as a muscle relaxant and to ease pain in the body. Knee discomfort, muscle soreness or pain, neck soreness or pain, back soreness or pain, and shoulder pain can all be relieved with Oxalgin nanogels, a diclofenac, menthol, and methyl salicylate combination medication. Certain nourishing gels, such aqua multi effect nanogels cream, function as antiwrinkle cream and thoroughly hydrate for a long time. An anti-wrinkle lotion called Revivagenix Pro Collagen Nanogel helps to fully hydrate the skin over an extended period of time. Similar to this, skin ideal brightening nanogel hydrates the skin deeply and enlivens it, while Augen nanogels eye care gel has subterranean penetration qualities. Some others marketed formulations are Zyclin nanogel, Adalene nanogel, Dextrin nanogel, NIPAM-co-BA nanogel, PEG-chitosan nanogel, PNIP/Aam nanogel etc.

8. Summary: Nanogel-based nanoplatforms have emerged as a very promising new medication delivery technology. This article provides a detailed analysis of the characteristics, characterization, synthesis, and biomedical uses of nanogels. Current advances in nanogel development have delivered a positive vision in the applications of nanogels, especially within the treatment of cancer, gastrointestinal complications and gene transfection, protein folding and enzymology. The use of nanogel formulations on market basis is the recent success of nanogel-based drug-delivery systems. Large-scale production of nanogels will require the development of cost-effectiveness strategies and the solution of technological issues. There are still a lot of pharmacokinetics and pharmacodynamics-related issues that need to be appropriately resolved.

Disclosure of conflict of interest

There is no conflict of interest regarding this paper.

Author contribution

All author contributed significantly to design and development of this work.

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