Available online on 15.08.2024 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research



*Open Access Full Text Article*

Review Article

# Review on Nanogel as a Novel Platform for Smart Drug Delivery System

Ms. Rupali A. Mendake , Ms. Pooja R. Hatwar *, Dr. Ravindrakumar L. Bakal , Mr. Shriyog V. Amalkar

*Department of Pharmaceutics, Shri Swami Samarth Institute of Pharmacy, At Parsodi, Dhamangoan Rly, Dist -Amravati (444709) Maharashtra, India.*

Article Info:

Article History:

Received 20 May 2024
Reviewed 03 July 2024
Accepted 19 July 2024
Published 15 August 2024

Cite this article as:

Mendake RA, Hatwar PR, Bakal RL, Amalkar SV, Review on Nanogel as a Novel Platform for Smart Drug Delivery System, Journal of Drug Delivery and Therapeutics. 2024; 14(8):161-174

*DOI: http://dx.doi.org/10.22270/jddt.v14i8.6704*

*Address for Correspondence:

Ms. Pooja R. Hatwar, Department of Pharmaceutics, Shri Swami Samarth Institute of Pharmacy, At Parsodi, Dhamangoan Rly, Dist -Amravati (444709) Maharashtra, India.

## Abstract

One of the most popular applications of nanotechnology in both topical and internal medicine administration to the body is nanogel technology. The materials comprising the nanoparticulate frameworks are less than 100 nm in a single measurement. The goal of this review paper is to provide a concise overview of the most recent developments in the nanogel medicine delivery framework with regard to drug loading and swelling. It categorises according to links (chemical and physical) and responding behaviour. This article is to give a broad overview of nanogels, their innovative use in many contexts, and current synthesis techniques. NGs use drugs for a variety of reasons, including diagnostics, gene targeting, organ targeting, and many more. Different pulmonary, nasal, transdermal, intra-ocular, oral, and parenteral routes can be used to give NGs. The primary goals of this review are to present broad details on NGs, their characteristics, multiple categories, medication targeting strategies, kinds of drug delivery systems, assessment techniques, and cutting-edge uses for NGs in depth.

**Keywords:** Nanogel, DLS, CD, mechanism of drug release, classification, application

## Introduction:

The use of nanogels as frameworks for redox-responsive DDSs is growing in popularity [1]. Since novel biomaterials may be created with noticeably better qualities, the advent of nanogels was a breakthrough advance in the detection and treatment of illnesses [2]. The term "nanogel" was initially used to refer to bifunctional cross-linked networks that use a nonionic polymer and a polyion to transfer polynucleotides [3]. Nanogels in a range of 100–200 nm in diameter [4]. Nanogels, also referred to as hydrogel nanoparticles or comprised of nanoparticles Gels are three-dimensional, nanoscale, chemically or physically cross-linked polymer networks [5]. In addition to having the potential benefits of nanoscale formulations, nanogels are appealing drug delivery vehicles because they have the alluring qualities of a hydrogel, such as high hydrophilicity, high loading capacity, and the potential for biocompatibility and regulated dispensation [6]. As a new and promising medication delivery technology, nanogel exhibits opportunities in the biomedical industry because of its high drug loading capacity, stimuli reactivity, and outstanding biocompatibility. Biodegradability and little toxicity [7]. The drug release is possible due to the breakdown of the diffusion gradient and the drug's supporting structure, swelling behaviour, or affinity-based processes [8]. Due to this notable variation in GSH levels, redox-responsive nanogels present a highly appealing platform for targeted drug delivery. Nanogels are widely employed in situations where a burst release in reaction to the redox environment is necessary, as well as in the transportation and delivery of substances to specified locations at certain times [9]. Making advantage of Natural polymers with functionalized properties, like hyaluronic acid, polypeptides, alginate, pullulan, and dextran, are still a crucial decision to make nanogels biocompatible and biodegradable. Complimentary to the chemical Physical crosslinking, or crosslinking, is particularly fascinating because of its reversible nature [10]. This analysis offers a provides a broad review of nanogels and lists their primary applications [11]. The nanogels can be employed as a delivery mechanism for various medication combinations for different types of cancer and other immunological diseases. The system was created to contain bioactive materials with various chemical and functional characteristics, such as cytokine delivery, vaccinations, In the future, nasal vaccinations and nucleic acid may offer novel treatments for autoimmune diseases and possibly cancer [12]. They can be administered orally, through the eyes, sublingually, topically, or by any other route [13]. This kind of Particularly for those exhibiting behaviour sensitive to various stimuli, nanogels are of great interest because of the manillnesses (such as cancer, degenerative processes, diabetes, etc.) that alter the body's pH or temperature tissue [14]. Its good self-degradability property facilitates easy removal of the leftover nanogel formulation and helps with drug release [15]. Nanogels have reduced the likelihood of toxicity and increased drug loading; however, these carrier systems work better with hydrophilic medicines [16].

## Routes of Administration of Nanogels: [17-19]

- Oral
- Pulmonary
- Nasal
- Parenteral
- Intra-Ocular
- Topical

## Advantages of Nanogels: [20- 30]

- Highly biocompatible, eliciting immune reactions because of its high water content and ability to function like genuine tissue. Because these nanocarriers are biodegradable, they are not harmful.
- Quickly escape reticuloendothelial system entrapment.
- It is possible to control drug release by adjusting crosslinking densities.
- Better penetration across biological membranes because of the minuscule size.
- Has the ability to combine charged solutes with both hydrophilic and hydrophobic medications.
- Outstanding features for transportation.
- Capacity to enter the tissues either by penetrating the tissues or by reaching the tiniest capillary veins. Via the transcellular or paracellular routes.
- Adaptability in style.
- Flexibility in the loading and release of drugs.
- High water absorptivity: Due to their nanoscale size, nanogels may absorb a significant quantity of water when they are swelled and unloaded.
- Rapid responsiveness to external stimuli: Extended and accelerated circulation time: This increases their likelihood of concentrating on the desired location.
- Particle size reduction and surface characterization may be used to prevent the absorption of phagocytic cells. Should allow for both active and passive medication targeting in order to prevent rapid removal.
- Avoid excluding the kidney abruptly. Renal clearance evasion causes a longer serum half-life.
- The main benefit of using nanogels is that there is less chance of the medication escaping the solution too soon.
- Nanogels will include macromolecular medicinal specialties such as proteins, siRNA, amides, and DNA.

## Disadvantages of Nanogels: [21-23, 25, 26, 28-31]

- Expensive method to fully eliminate the solvents and surfactants at the conclusion of the preparation process; residues of surfactant or monomer may still be present and may have negative consequence.
- A portion of the particles have a micrometers size.
- Because of average weight and size, scaling up is difficult. Nanogels' efficacy in loading drugs is limited, and inadequate control over the discharge of drugs.
- The polymerization processes used to create the nanogels are quite severe.

## Characterization of Nanogels: [31-33]

Efficient production of nanogels is necessary to obtain a consistent product. Nanogels have a number of noteworthy physical characteristics that have particular attributes. For instance, visible light is finely scattered by nanogels, giving them a white appearance. Refraction is the cause of the multiple scatterings of light. Mechanism brought about by the increased refractive index of the nanogel particles. The little photon bundles that are passing through the nanogels and scattering the particles many times before leaving the nanogel because there is insufficient optical absorption. In addition to having cross-linked hydrophobic pockets, the nanometric dimensions of the nanogels give them a higher surface area-to-volume aspect ratio, which improves the solubility of hydrophobic medications. Several more characterization criteria also show the numerous unique characteristics of the nanogel drug delivery technology, which are covered in the sections that follow.

### 1) Dynamic light scattering:

One method for figuring out the size distribution profile of nanoparticles in liquids is dynamic light scattering (DLS). Light scattering is measured and recorded in a microsecond time frame. Measurements of the cross linker's impact and potential charge of the effective hydrodynamic particle radius polymer chains based on the nanogel's size. Additionally, DLS may be used to gauge how much a nanogel is swelling in various media. It is important to note that the DLS data shouldn't be interpreted as more accurate than the DLS readings in ignoring the smaller polymer particle population. Often, a variety of analytical techniques are required to completely comprehend the properties of nanogels.

### 2) Scanning electron microscopy:

One may ascertain the size and surface of a particle using electron microscopy. Nanogel morphological properties and particle sizes between 50 and 80 nm can be ascertained with scanning electron microscopy (SEM). It gives the nanogel particles' three-dimensional picture. The final picture is further examined using top-notch software, such as a Leica imaging system, to get automatically generated analysis findings. Of the nanogel particles' form and surface morphology.

### 3) Circular dichroism:

CD, or circular dichroism, is used to measure the final product's optical activity. This approach works especially well for finding chiral compounds that have been added to nanogels. Their existence results in spiral-based macromolecular formations that have chiral centres and are detectable by CD.

### 4) Size-exclusion chromatography:

The technique known as size-exclusion chromatography (SEC) separates the material based on its size. The distribution of the nanogel molar mass and the molar mass of particular fractions are the most frequent uses for it. Atomic force microscopy (AFM), TEM, Zeta-size analyzer, and SEM may all be used to examine particle size.

### 5) Field-flow fractionation:

A solution or suspension is pushed through a long, narrow channel, and cross-flow is applied as part of the field-flow fractionation (FFF) separation procedure. This cross-flow's direction is perpendicular to the flow direction. Compared to other separation methods, FFF is unusual in that it can separate polymer material throughout a large colloidal size range while maintaining high resolution. Typically, FFF relies on the smooth movement of particles inside a solution. Sample components flow at different speeds because of their mass and size, which causes separation since the components move at different speeds.

### 6) Nanoparticle tracking analysis:

NTA, or nanoparticle tracking analysis, is a method for measuring particles with sizes ranging from around 30 to 1,000 nm. This method makes it possible to see and record nanoparticles in a solution by fusing charge-coupled device microscopy with laser light scattering microscopy. When a single nanoparticle moves in a Brownian motion, NTA can detect it, monitor it, and correlate its movement with particle size. It measures both specific size and concentration.

**7) Swelling studies of nanogels:**

The most significant characteristic of nanogels is swelling, which is determined by how effectively they can absorb water or another aqueous solution. The weight component of the swelled nanogel and the beginning weight are used to quantify the degree of swelling, making weight measurement the simplest method for determining the kinetics and swelling equilibrium. The type and content of the monomer, cross-link density, pH, temperature, and ionic strength all affect how much the nanogel swells.

## Ideal characteristics of drug for Nanogel: [34, 35]

• The medication should have a low-weight unit.
• The medication should work well with the polymers used to make nanogels.
• A drug's charge density should be less than
• Drugs that are hydrophilic or hydrophobic will be added to nanogel.

## Benefits of Nanogels: [35, 19]

- They act like genuine tissue because of their high-water content, making them highly biocompatible; Because of the biodegradable carrier, they are safe.
- Their loading capacity is great.
- Via tuning, crosslinking densities may be changed. Because of its tiny size, it may penetrate biological membranes more easily. It also makes it easy to combine medications with charged solutes of both the hydrophilic and hydrophobic types.
- Drugs may penetrate even the tiniest capillaries and enter tissues by transcellular absorption due to their minuscule volume. Or channels paracellular.
- By using a polymeric network in the formulation, the medication can be delivered gradually over time. Why the iridescent solution that "nanogels" freely flow in aquatic settings can spread quickly.
- Parenteral and mucosal administration.
- It protects against the body's innate propensity to degrade prescription drugs.
- It is simple to alter and maintain the physical properties of nanogels, such as size, to make them compatible with certain delivery molecules.
- Merely a tiny amount of the drug is required, requiring fewer doses.
- Reduces toxicity while increasing the absorption of medications.
- Transdermal application of drug-loaded nanogels allows for internal body penetration without adverse or side effects.
- These can pass across blood-brain barriers and other physiological barriers like the skin.

## Properties of Nanogels:

It is believed that the use of gels and nanoparticles together represents a significant advancement in the realm of medication delivery [36].

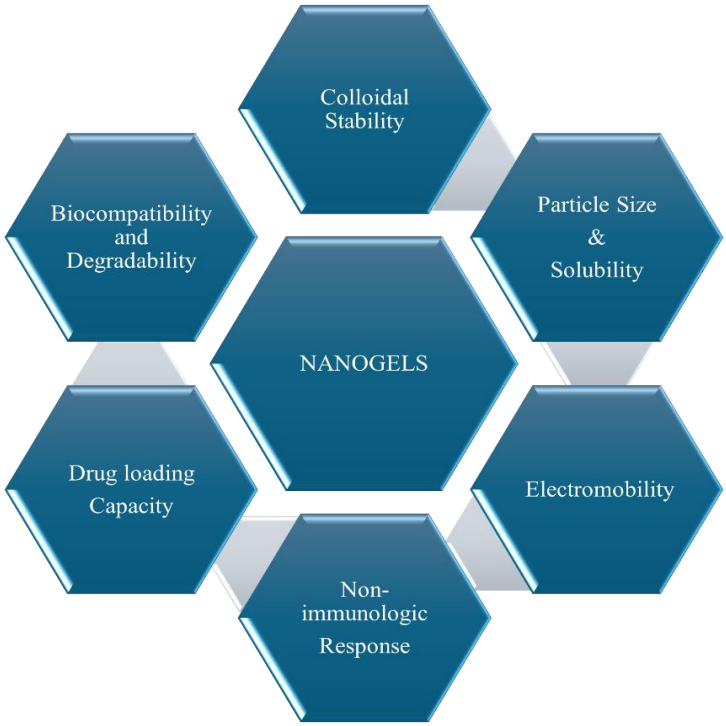


Figure 1: Properties of Nanogels [31]

**Biocompatibility and Degradability:**

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 [37].

**Swelling Property in Aqueous Media:**

As a result of solvent penetration, the polymeric framework grows, increasing the volume of the system. External stimuli like pH, temperature, or certain molecules can change the swelling or de-swelling capabilities. Structural factors like the cross-linking degree or the presence of a functional group can also regulate these features [38].

**Higher Drug Loading Capacity:**

The presence of a functional group within the polymeric unit determines the features of nanogels with increased drug-loading capacities. A handful of these functional groups have the ability to combine with medicines or antibodies for targeted applications. These functional groups have a significant impact on drug-carrying and drug-releasing capabilities [39].

**Particle Size:**

Since nanogels are tiny enough to evade reticuloendothelial system absorption while still being efficient in preventing rapid renal exclusion, their usual size ranges from 20 nm to 200 nm, or India metre. Excellent permeability because of its extremely tiny size. It has the ability to pass across the blood-brain barrier (BBB)[39].

**Solubility:**

Hydrophobic medications and diagnostic chemicals can be dissolved into nanogels' gel networks or cores [39]. Furthermore, several nanogels have lipophilic domains that can solubilize lyophilic compounds. The solubility of prostaglandin E2 was found to be pollulan nanogel modified with cholesterol. Additionally, doxorubicin was placed in amphiphilic cross-linked nanogels made of poly [oligo (ethylene oxide)-methyl methacrylate] or Pluronic F127. Interestingly, in the majority of cases where hydrophobic interactions alone are the cause of loading, the resulting loading capacities are rather modest [23].

**Electro mobility:**

In order to create nanogels, which are essential for encasing biomacromolecules, gentle conditions and energy sources such as homogenization or sonication are used [23].

**Colloidal Stability:**

Compared with surfactant micelles, polymeric micellar nanogel systems, or nanogels, exhibit greater stability, with slower rates of dissociation, lower critical micelle concentrations, and extended drug retention. Colloidal nanogels are platforms that are sensitive to environmental changes [39]. That two are intended for the delivery of drugs, targeting, and imaging and diagnostics. Applications involving physicochemical mechanisms like hydrophobic interactions and ionic or hydrogen bonding [40].

**Non-immunologic Response:**

Immune reactions or effects are often nonexistent with nanogel-based drug delivery methods [23].

**Viscoelasticity:**

Since nanogels frequently have highly solvated structures, they typically have viscous and elastic properties that ensure flow through the extracellular matrix and needles [41].

**Others:**

Drugs of both kinds charged solutes and hydrophobic and hydrophilic drugs are frequently administered using nanogels. Temperature, the existence of hydrophilic or hydrophobic groups in the polymeric networks, the gels' cross-linking density, the concentration of surfactants, and the kind of cross-links in the networks all have a major impact on these characteristics of nanogels [39].

## Classification of Nanogels:

Nanogels are generally classified into three major groups namely the linkage type, the responsive type as well as structural Type [42].

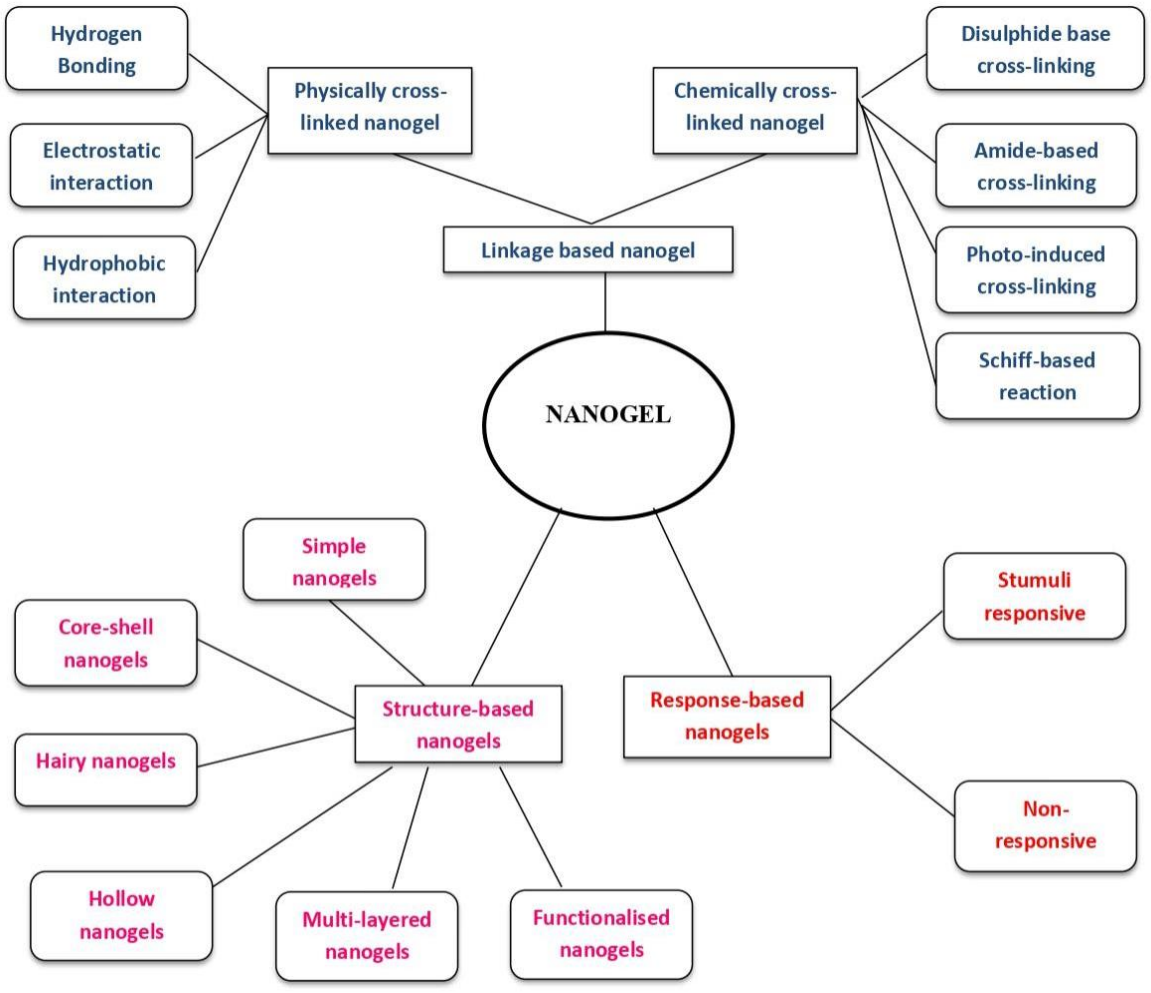


Figure 2: Classification of Nanogels [42]

**On the basis of responsive behavior:** [22]

Nanogels can react to stimuli in one of two ways:

• Nonresponsive gels simply swell up when introduced in an aqueous medium; stimuli-responsive nanogels swell or deswell in response to environmental stimuli such as temperature, magnetic field, pH, and ionic strength [43].

• Multiresponsive nanogels readily swell due to water absorption and can swell or deswell in response to many environmental changes.

**Stimuli-responsive nanogels:**

Active drugs are included in stimulus-sensitive nanogels, and when the volume changes or is stimulated externally, the medicine is released. Biological cues, such as specific pH and temperature variations, cause the medication to be released from nanogels in a regulated way at the site of action, improving therapeutic efficacy. Blood and healthy tissues have a pH of around 7.4, but tumours and inflammatory tissues have a lower pH. Furthermore, as the carriers first enter the endosome, which has a pH of roughly 6, and subsequently the lysosome, which has a pH of 4, a pH gradient is seen during cellular absorption [21]. Temperature is one of the environmental stimuli that is studied the most. Certain nanogels are engineered to undergo a sol-to-gel transition at body temperature, which is 37 °C. Nanogels are in a sol form below 37 ◦ C. The viscosity of nanogels increases to produce a semisolid gel at 37 °C [44]. The estimated location affectability for glucose change is ±0.1 mM, and the reaction pace is accounted for as happening within 100 ns of the request [24].

**Thermo-responsive nanogels:**

Among the most appealing intelligently responsive DDSs are thermoresponsive nanogels. Thermoresponsive nanogels exhibit shrinkage-swelling behaviour in response to changes in ambient temperature, allowing the medicine within to release at a regulated rate. Additionally, induced particle size reduction may lead to accumulation in the disease-related microenvironment and enhanced intracellular absorption efficiency, which would enhance therapeutic results [45]. The temperature-responsiveness of nanogels with water-based network architectures makes them suitable for use in biological applications [20].

**PH-responsive nanogels:**

Cross-linked nanoparticles with basic or acidic groups that display swelling-deswelling behaviour based on pH are known as pH-sensitive nanogels. Of particular relevance are nanogels having a volume-phase transition pH (VPTpH) in the medically relevant range. At pH levels higher than the pKa, cationic nanogels are compressed; however, when the pH falls below the pKa, these nanogels inflate because of the network being protonated and the electrostatic repulsion between positively charged groups [21]. It has also been shown that pH-responsive nanogels are effective in deeply penetrating tumours. With a cross-linked polyelectrolyte core made of poly (N-isopropylacrylamide) and N-lysinal-N'-succinyl chitosan, a nanogel was created as is well known, the pH of plasma is 7.4. In contrast, the pH of intracellular organelles like lysosomes and the milieu around tumours are 6.5 and 4-5, respectively [46, 47].

**Light-responsive nanogels:**

In order to achieve a regulated release of active molecules, light is employed as an external trigger. To achieve the intended therapeutic effect in vivo, variables including exposure time, light intensity, and wavelength are adjusted. Two types of light-responsive nanogels are distinguished: (i) nanogels made of light-responsive polymers, and (ii) hybrid systems that incorporate noble metals like silver or gold [21]. among the most promising external stimuli for DDSs is near-infrared (NIR) light, which has a wavelength between 750 and 1300 nm. NIR light has advantages over other forms of light, such as high tissue penetration and less damage [44].

**Magnetic nanogels:**

Magnetic nanoparticles (MNPs) can induce hyperthermia in the presence of an alternate magnetic field (AMF), in addition to their ability to cause magnetic targeting in the presence of an additional magnetic field. Thus, temperature-sensitive nanogels and MNPs were combined to form hybrid nanogels, which were subsequently loaded with the chemical drug DOX (DOX-MagNanoGels). Due to their three-dimensional network structure, nanogels enable the co-encapsulation of chemical medications and MNPs. Furthermore, the shrinking-swelling property of nanogels ensures the stimuli-drug release when AMF is applied [45]. Innovative nanogels could be made with MNPs' intrinsic magnetic properties and biocompatibility in biomaterials [48].

**Targeted nanogels:**

An additional viable method for precisely targeting the sick region is the attachment of active targeting ligands to nanosized delivery carriers. These targeting ligands, which bind to cell surface receptors, might be anything from tiny compounds to big antibodies. Since surface-functionalized ligands are readily recognised by cell surface receptors, they are often chosen for attachment to specific delivery systems [49].

**Redox-responsive nanogel:**

The concept of redox sensitivity is founded on the variation in GSH concentrations found in extracellular fluid (2–20 μM) and inside cells (2–10 mM) [50]. Reversibly crosslinking it with disulfide bonds, which are redox-responsive and cleave when exposed to reducing chemicals like glutathione (GSH) or dithiothreitol, is an alternate method for creating stimuli-responsive nanogel particles. Usually, the post-polymerization modification incorporates the disulfide moiety to provide the polymers with redox responsiveness. Developing amphiphilic copolymer nanoassemblies adorned with redox responsiveness while preserving their biodegradability and biocompatibility takes a lot of work [49].

**Structure-based:** [22]

These nanogels are classified according to the source of their structure. There are many different kinds of nanogels, including hollow nanogels composed of pH- or temperature-sensitive nanogels, Hairy, multilayer, functionalized, and simple nanogels (artificial chaperons) cross-linked core-shell nanogels and cross-linked nanogels that are also utilized to produce nanogels that respond to stimulation.

**On the basis of linkages:**

Physically Cross-Linked Nanogels:

Self-assembling (supramolecular) interactions between identical or dissimilar polymer chains cause physically cross-linked nanogels to form. These reversible interactions include hydrophobic, electrostatic, van der Waals, and hydrogen bonding interactions [51]. Therefore, as will be discussed in the next sections, physically crosslinked nanogels must be carefully developed to survive the stress under physiological settings [52].

**Hybrid Nanogels:**

A hybrid nanogel is a nanogel that has been mixed with different polymers or inorganic nanoparticles, such as plasmonic, magnetic, carbonaceous, and so on. This section covers the noteworthy stimuli-responsive hybrid nanogels that

have been created for a range of medical and diagnostic uses. Wu et al., for example, created a multifunctional hybrid nanogel (< 200 nm) with an Ag nanocore shielded by a copolymer gel shell for insulin administration and biosensing at physiological pH [53]. These are made by the self-assembly of two hydrophobically modified polymers: a copolymer of N-isopropylacrylamide (NIPAM) and a cholesterol-bearing pullulan (CHP) [21]. The main idea behind hybrid nanogels is the deliberate blending of polymers with other substances to create multipurpose nanogels [54].

**Micellar nanogels:**

Polymeric micelles are nanoscale particles with a standard core-shell structure, in which the corona stabilises the interface between the core and the external medium and the core is capable of solubilizing the hydrophobic medication [55]. The stable core-shell structure surrounding the micelles is the consequence of the hydrogen bond formed, and the hydrophilic section is essential to this process. These core-shell micellar nanogels are very stable and exhibit a stimuli response [31].

**Liposome-Modified Nanogels:**

Liposomes are a type of small, tiny vesicles that have an aqueous volume completely surrounded by a membrane made of lipid molecules. They have a lipid-bilayer structure. Liposomes are made up of several different substances, the primary ones being cholesterol and phospholipid [55]. When applied transdermally, liposome-tailored nanogels made of poly (N iso-propylacrylamide) polymeric molecules demonstrate a thermoresponsive-triggered mechanism of drug release [31].

**Chemically Cross-Linked Gels:**

Generally, water-soluble polymers, such as polysaccharides that have been modified with reactive groups, including vinyl and thiol groups undergo a cross-linking process to create chemically cross-linked nanogels under diluted circumstances. Moreover, NGs may be created by joining polymer chains together via covalent chemical interactions [56]. Because these relationships are stronger and largely irreversible, they are more stable than physical contacts. Some methods of chemical crosslinking are photo-induced crosslinking, reversible addition-fragmentation chain transfer (RAFT), click chemistry crosslinking, and polymerization by emulsion [51,57]. A wide range of chemical cross-linking techniques, including "click" chemistry, photo-cross-linking, and quaternization of amino groups, have been documented in the literature [58]. Amino acid crosslinking can be used to create biodegradable nanogels based on amino acids [46].

**Disulfide Cross-Linking:**

Reacting groups: thiol and disulfide, under mild reaction conditions and pH, with straightforward additional fictionalisation-Amphiphilic random copolymers that self-cross link (pyridyl disulfide, a hydrophobic and cross-linkable unit, and PEG, a hydrophilic unit) [59].

**Amide cross-linking:**

Iodides, carboxylic and amino esters, reacting groups; no other ingredients are required; degree of cross-linking is adjustable [59].

**Imine Cross-Linking:**

Mild reaction conditions, no catalyst, Schiff-base reaction between amine or hydrazide and aldehyde [59].

**Copper-free Click Chemistry Cross-Linking:**

Alkyl units with amino groups immobilised to the particle shell by amidation of hydrophilic polymer micelles are the reacting groups. Depending on whether a catalyst is used or not, on a quick or gradual reaction [59].

**Photo-induced Cross-Linking:**

An exceptionally effective method for stabilizing polymers containing reactive groups such as alkenes or coumarins by UV irradiation, photo initiators that are highly efficient, and concerns about toxicity [59].

## Features of Nanogel: [60]

**Targeting Delivery:**

Because of their surface reliance and attention to local conditions, nanogel carriers are often administered at specific places via binding to them or by other "passive" strategies, including retention inside physiological regions.

**Low Level of Toxicity:**

Biofriendly and non-toxic nanogels that break down quickly into non-toxic compounds that the body may quickly remove from it are also required.

**Controlled and Sustained Medication Delivery:**

Drugs should be delivered at the designated location in order to guarantee that each therapy is used as efficiently as possible and with the least amount of side effects. High drug loading is necessary to achieve therapeutic objectives.

**High Stability of Encapsulation:**

The greatest therapeutic benefit and lowest level of toxicity or side effects are offered by embedded drug molecules; however, they must not be overused or leak before their time.

**Size Control:**

Physicochemical techniques are frequently used to modify the size and surface characteristics of nanogels in order to reduce somatic cell clearance and alter the targeting of either active or passive cells. Nanogels should be small enough to allow them to enter tissues and capillaries by transcellular or paracellular routes.

## Synthesis techniques of Nanogels:

Many methods for creating nanogels have lately been condensed into a number of outstanding evaluations [61]. Provides a synopsis of the methods along with citations to further in-depth information. Nanogels have historically been divided into two categories: physically crosslinked nanogels and chemically (covalently) crosslinked nanogels [62].

**Polymerization of Monomers in a Homogeneous Phase or in a Microscale or Nanoscale Heterogeneous Environment:**

A drawback of self-assembled nanogels is their propensity to become unstable during blood circulation; however, covalent polymerization yields nanogels that are more diverse and have higher biological stability. Reverse (water or oil) and conventional heterogeneous polymerization are the two techniques for creating nanogels. (Oil/water) mixtures. Hydrogel preparation using micro- and nanoparticles has been the subject of several investigations. Amounts by emulsion polymerization. Typically, emulsion-based polymerization reactions consist of the following basic ingredients: oil, water, monomer solution, polymerization initiators, and surfactant acting as a stabilizer [63]. In general, chemical synthesis in heterogeneous colloidal settings might offer chances to change the nanogel's structure and characteristics [64]. First, controlled polymerization may be used to create synthetic polymers with the required function, fine-tuning their composition, molecular weight, functional groups, and architecture. Alginate, pullulan, chitosan, dextran, hyaluronic acid, polypeptides, and other

functionalized natural polymers help to increase the biocompatibility and biodegradability of nanogels [61].

**Cross-Linking of Preformed Polymers:**

This method creates large-sized NGs by emulsifying oil in water and then removing the solvent. Using the oxidation procedure, branched PEG (thiol-functionalized) and dimethyl sulfoxide-containing DNA are combined to create cross-linked NGs with DNA. This approach yields NGs that are toroidal, spherical, and rod-shaped. This technique works well for regulating the NGs' surface characteristics, composition, size, and form, among other factors [65].

**Novel Photochemical Approach:**

A novel photochemical approach is used to produce NGs in a 150 mL interlayer quartz flask with a nitrogen gas input and a stirrer. 60 milliliters of deionized water containing 186 milligrams of monomer are mixed with a predetermined amount of nanoparticles, usually 10 mg. After agitating the mixture for ten minutes, 0.8 milliliters of a one-weight percent cross-linker are added. Additionally, it is subjected to 25 minutes of ultraviolet (UV) light. Throughout the preparation process, N2 is effervescent. To be used again, the NGs are gathered, repeatedly cleaned in distilled water, and then redispersed in the same water. Utilising N-(2-aminoethyl) methyl acrylamide and N, N′-methylene-bis-acrylamide, this technique was utilised to create amino-functionalized magnetic nanogels (NGs) of coated ferric oxide nanoparticles for use as MSI contrast agents. The same UV light with a wavelength of 365 nm was used to create DNA-loaded diacrylated Pluronic and glycidyl methyacrylated chito-oligosaccharide NGs. A photoinitiator was also used. Injectable deposition strategies for gene therapy were improved with the use of these NGs, leading to increased native transgene expression at the injection locations [65].

**Inverse emulsion polymerization:**

One popular synthetic methodology for creating pH-responsive nanogels is the inverse emulsion method. There is no complicated equipment required for this procedure, and it is easy to manage the size range of the nanogel that is created. The monomer or precursor polymer solution is continuously emulsified in an apolar phase during the first step. For this, an appropriate oil-soluble surfactant is utilised. The precursor polymer, which is included in the emulsion droplets, is chemically crosslinked in the next stage. Direct polymerization of the monomers is another option. To accomplish crosslinking, a functional group of the polymer chain or an appropriate crosslinker may react [66]. By adding an aqueous polymeric solution to a water-miscible non-solvent, NG is prepared by inverse nanoprecipitation. This process creates nano-sized polymer clusters when the solvent and non-solvent are mixed and then crosslinked [67].

**Novel Pullulan Chemistry Modification:**

This technique involves the chemical alteration of pullulan. A mixture of cholesterol in DMSO and pyridine is used to create cholesterol-based pullulan (CHP) NGs. To modify, substitute 1.4 cholesterol moieties for every 100 glucoside units. The formulations made using this method require freeze-drying. Protein NG formulations function as an effective carrier when using the CHP-based approach. By using a Michael addition reaction to substitute PEG for the acrylate and thiol groups, the CHP technique may also be modified. A pullulan that is appropriate for targeting folate receptors is created when 1.6 units of glucose are used to modify it. After conjugating pullulan and the photosensitizer with carbodiimide and dialysis, NGs are produced. These NGs work well in the treatment of cancer [65].

## Drugs loading technique in nanogels:

Nanogels are frequently employed in the transportation of therapeutic substances. More medications should be able to be delivered by a nanodelivery system by reducing the number of carriers required. Three techniques might be used to include medications in nanogels: self-assembly, physical trapping, and covalent conjugation [19].

**Covalent Conjugation:**

Drug distribution is more convenient with the use of nanosystems. This is the outcome of its natural functional groups influencing how nanoparticles behave in terms of structure and characteristics. The medication is covalently conjugated to the cross-linked nanogel, which gives the encapsulated drug more stability. Ester bonds are established 1 between the hydroxyl groups in polysaccharides and the groups of carboxyls in the medication, resulting in hydroxyl groups that are easily interacting with one another. Here, the medicine will be released early because enzymes like esterases will cleave the functional groups [29].

**Physical Entrapment:**

Proteins are integrated into pullulan nanogels that have been modified with cholesterol, and siRNA is physically trapped in HA nanogels. Furthermore, the nonpolar area formed by nanogels containing hydrophobic chains might include hydrophobic materials. Hydrophobic interactions between the drug molecules and the nanogel were frequently the means by which loading was achieved, resulting in relatively low loading levels (no greater than 10%) [19].

**Self-Assembly:**

The self-assembly process is the autonomous grouping of components into distinct aggregates. It's easy, flexible, and reasonably priced, among many other good qualities. The system's thermodynamic minima cause this process, which results in stable and dependable structures [19]. Due to 1 the dynamic and reversible nature of the non-covalent contacts, physical cross-linked nanogels exhibit unique activities and have the ability to perform, recycle, and fix oneself when compared to chemically cross-linked nanogels [7]. Since the circumstances for crosslinking and self-assembly during the nanogel's creation are rather benign, this technique might be used to include delicate bioactive substances like proteins in the nanogels. A suitable polymer concentration and/or environmental factors, for example, pH and temperature and ionic strength, can be used to adjust the formed nanogels' size [68].

## Mechanism of drug release from nanogels:

The two drug releases from nanogels work as follows: Biological agents can be included into nanogels via the following methods: 1) physical trapping 2) covalent conjugation; 3) directed self-assembly or Biochemical One can also release compounds from nanogels: 1) basic diffusion; 2) The nanogel degradation 1) displacement by environmental counterions; 2) pH change; 3) nanogel; 4) or 5) changes brought about by a source of outside energy [69].

It has been noted that both the network mesh size of the nanogels and the drug's affinity for the polymer affect how readily pharmaceuticals are released from them. In the former scenario, on the other hand, interactions between the medication and polymer may play a major role in managing and controlling the drug's release [42].

**Diffusion Mechanism:**

When a medication is physically enclosed in the nanogel, a very basic drug release mechanism is anticipated. The steric

interactions between the encased pharmaceuticals and the nanogel polymer network are regulated by the sizes of the open gaps (meshes) between the networks, which in turn affect how the medications diffuse through material [42]. When a medication or other active ingredient diffuses through a polymer that creates a controlled release mechanism, diffusion takes place. Diffusion can happen at the molecular level by passing between polymer chains or at the macroscopic level through pores in the polymer matrix. There are two ways to regulate when a medicine releases by diffusion from the delivery system: (1) The degree to which the drug binds to the micelle core (e.g., hydrophobic binding in hydrophobic cores), as indicated by the drug's partitioning between the micelle and the surrounding environment; and (2) The degree to which polymer chains bind to one another within the micelle structure, as indicated by cmc [26].

The use of the diffusion process to transport therapeutic compounds has drawbacks, such as blood components interfering with the production of micelles and making it difficult to correlate the stability profiles of in vivo and in vitro features. Additionally, measurements of the compounds with continuous release produced from micelles are needed for assessment [70].

**Nanogel Degradation:**

Another method for the release of medications trapped in the polymer network is the breakdown of nanogels. Drugs diffuse out of the material as a result of the degradation's rise in nanogel mesh size. The polymer backbone of the cross-links may undergo nanogel breakdown, which is often mediated by hydrolysis or enzyme activity [42]. It has been demonstrated that the breakdown of these nanogels causes the release of encapsulated substances, such as the fluorescent dye rhodamine 6G and the anticancer medication doxorubicin, and also makes it easier to remove empty vehicles [17]. Improved drug release characteristics are a benefit of using this technique, as it makes use of the nanoparticles' pH responsiveness [70].

**Displacement by Ions Present in the Environment:**

Displacement with counter ions is a different method of drug release [71]. There is an increased interest in developing nanogels that can release biological agents in response to environmental cues at the targeted site of action. For example, disulfide cross-linked POEOMA nanogels biodegraded into water-soluble polymers in the presence of a glutathione tripeptide, which is commonly found in cells. Negatively charged substances released from cell membranes it was also suggested that drugs from complexes with cationic nanogels could account for the cellular build-up of an NTP drug delivered via nanogels [17].

**PH Responsive Mechanism:**

This process explains how variations in pH induce nanogels with weakly basic or acidic groups in their structure to swell or de-swell. The method, then, makes use of the body's pH fluctuations to produce a targeted reaction in particular cellular compartment [42]. Their nanogels were made up of ovalbumin nanospheres, with a portion of the chitosan chains creating the shell of the nanogel and the remainder being inserted throughout the structure. The hydrodynamic radius of the 100 nm-sized, pH-sensitive nanogels increased in the pH range of 5-5.3, increased in the pH range of 4.3-5.8, and increased considerably in the pH range of 5.3-5.8. They also mentioned a shift in pH-related hydrophobicity and hydrophilicity. At neutral and acidic pH, they are hydrophilic, whereas at alkaline pHs, they are hydrophobic. Because of their pH-dependent characteristics, the nanogels they created may find application in medication delivery [20]. It was found that this nanogel was stable at physiological pH, but that its swelling properties and size altered at pH 6.8 and 5.5. It dissociated at pH 6.8 after growing from 56 to 386 nm in less than a day [72].

**Photochemical Internalization and Photoisomerisation:**

Exposing a restricted rotation bond to light results in a variety of conformational changes throughout the photoisomerization process. One example would be molecules that are covalently bonded, which frequently isomerize from a Trans orientation to a cis orientation when exposed to light [25]. Photoexcitation of nanogels laden with photosensitizers produces reactive oxygen species and singlet oxygen, which oxidise cellular compartment barriers such as endosomal barrier walls and cause the release of medications into the cytoplasm[17]. Aspirin was used as a model medication in which Azo dextran-loaded nanogels presented an azo group in the Z-configuration, which has less release compared with the E-configuration at 365 nm radiation. The trans-cis was then able to see this using photoregulation in the isomerization of azoben-Zene [28].

## Preparation Techniques of Nanogels:

Various methods have been developed over the years to create nano-gels, depending on the excipients that are employed. Stepwise or contemporaneous polymerization-cross-linking processes can be used to create nanogels [73]. There are several methods for creating nanogels, some of which are listed here. Four types exist for the preparation of nanogels: [27].

1. Preparation by monomer polymerization
2. Preformed polymer cross-linking
3. Polymers physically interact through pressures
4. Nanofabrication with help from templates

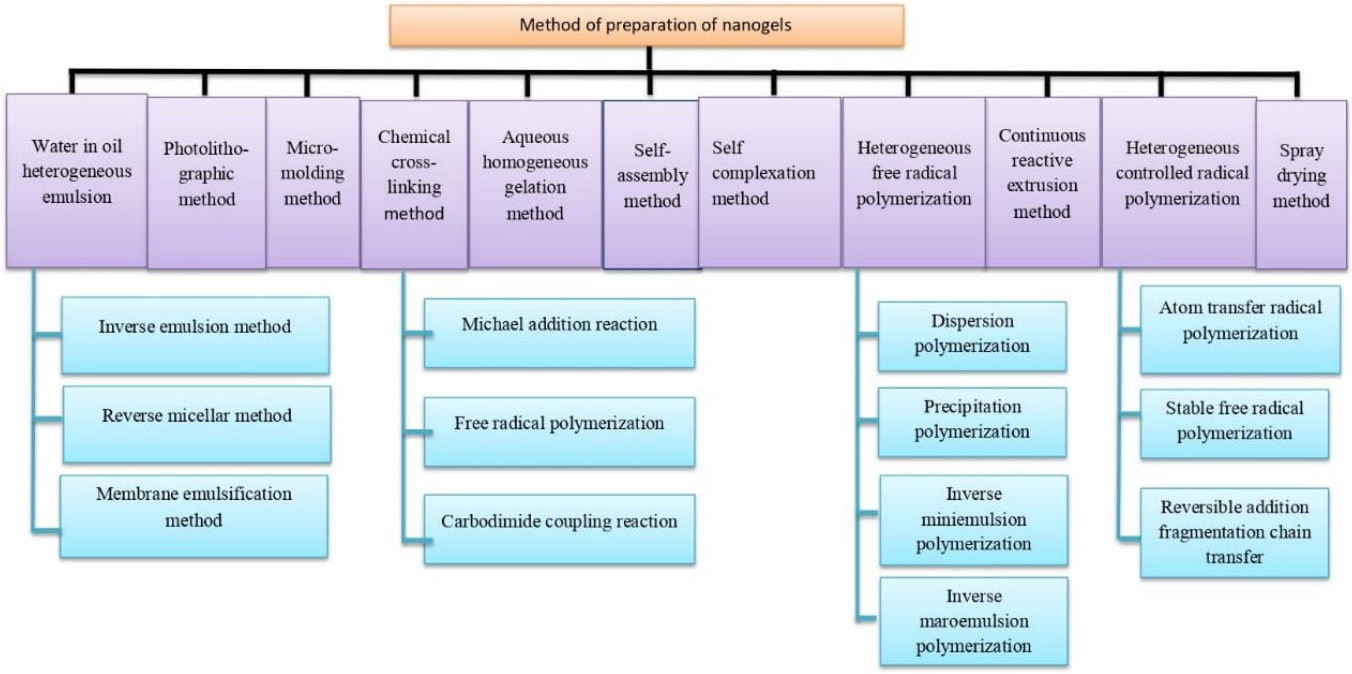


Figure 3: Method of preparation of Nanogels [49].

## Evaluation of Nanogels: [19, 34]

**Appearance:**

Visual examination was conducted to determine the clarity, color, and presence of any particles in the ready gel bases.

**Homogeniety:**

Visual inspection was used to verify the homogeneity of each generated gel once it was placed within the instrumentality.

**Particle size and polydispersity index (PDI):**

The findings of measuring the average size of the nanogels using the Zeta sizer and Malvern MasterSizer 2000 MS were reported.

**PH measurement:**

The pH of the nanogel formulation was measured using the Electrolab® digital pH metre. One beaker with a certain volume of filtered water contained a small amount of the formulation. After dipping the electrode into the formulation, the pH of the mixture was determined.

**Drug content:**

The level of medicines in the formulation was ascertained by both high-performance liquid chromatography and scanning using UV spectrophotometers.

**Spreadability:**

Mutimer's recommended equipment determines spreadability. Spreadability was determined by applying the formula S=M. L/T, where

S=spreadability, L=Length of glass slide, M=weight

tied to higher slide, T=Time taken to separate the slides.

**Infra-red spectroscopy:**

The infrared spectra of nanogels in the 4000-400 cm1 IR region were acquired using an FT-IR spectrophotometer.

**Viscosity:**

Using the Brookfield rheometer at 10 rpm and spindle number 64, the viscosity of the nanogel formulation was determined. A water bath with a thermostat-controlled temperature of 25°C was connected to the assembly. A thermostatic jacket was placed over the beaker, and the viscosity was computed and applied. After letting the spindle go through the nanogel, the values were noted.

**In-vitro drug release study:**

The Franz diffusion cell device was used to study the formulation's in vitro drug release. The formulation was distributed on a dialysis membrane in the donor-receptor chamber centre of the Franz diffusion cell. The 30-degree Celsius temperature was maintained. This assembly was magnetically stirred and continuously agitated using a magnetic field. It was computed how much medicine was released from the nanogel formulation.

**Stability study:**

The ICH guidelines were followed in performing the accelerated stability of nanogel. A three-month stability study at 25 °C and 60% relative humidity was carried out in an environmental stability chamber in order to assess the stability of topical nanogel. The liquid was filled into glass vials with caps that were amber in colour and stored in the chamber of stability. After three months, the medication's composition, consistency, and in vitro drug release were evaluated.

**Scanning electron microscopy (SEM):**

The surface morphology of a nanogel formulation was examined using scanning electron microscopy at magnifications of X30, X500, X1000, and X3000 using a 20 kV electron beam. A droplet of the nanoparticulate dispersion was applied to an aluminium metal plate during sample preparation, and the plate was vacuum-dried to create a dry film visible under a scanning electron microscope.

## Application of Nanogels:

Particularly because of their encapsulation stability, water solubility, and biocompatibility, nanogels have great potential as delivery methods. Drug delivery for cancer is only one of the many applications for these nanocarriers [74].

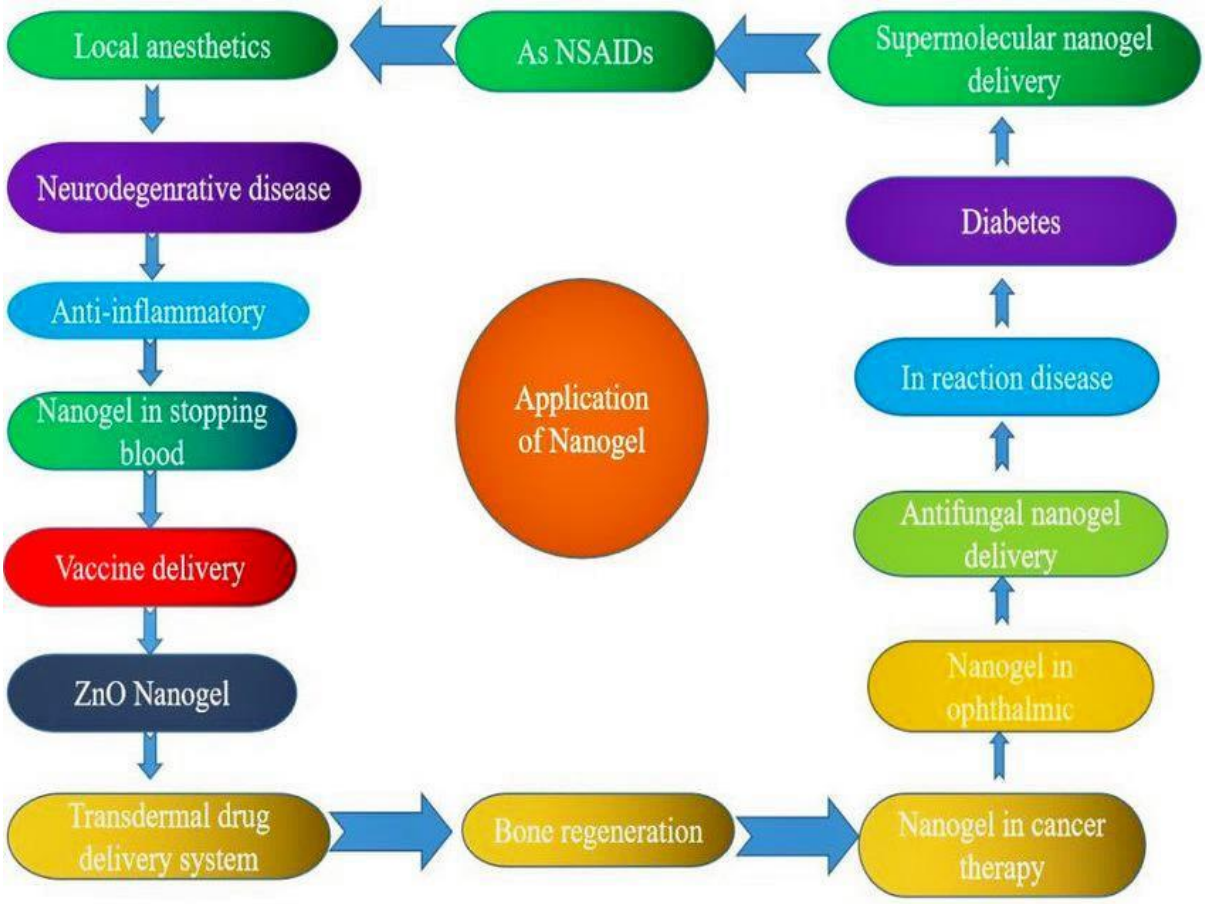


Figure 4: Application of Nanogels [34]

**Anticancer Therapy:**

During surgery, one possible use for nanogels would be to remove some of the tumour tissue, then implant the nanogel, which would solidify and offer a layer of protection or fill the void left by the tumour removal. To further prevent the tumour in the foreseeable future, nanogels might also be loaded with many therapeutic medicines [44].

**Autoimmune Disease:**

The use of nanogels in the treatment of autoimmune diseases has enormous promise. Immunosuppressive therapy, which completely shuts down the human immune system, is the mainstay of care for many autoimmune illnesses. Since autoimmune illnesses have the potential to cause inflammatory affections, it is important to maximise therapy efficacy. A medication delivery vehicle based on nanogels was created to provide the immunosuppressant mycophenolic acid (MPA) [75].

After being exposed to UV radiation, which causes the PEG oligomers to photopolymerize, the loading liposomes containing mycophenolic acid, oligomers of lactic acid-poly (ethylene glycol) that were ended with an acrylate end group, and the Irgacure 2959 photo initiator were readily dissolved by cyclodextrin [25].

**For Local Anaesthesia:**

One of the main goals of therapeutics in dental care is pain management. By adding local anaesthetics to medication delivery devices, the regional administration of these drugs might be improved. In research to design and assess a medication delivery method for periodontal anaesthesia using thermo-reversible in situ gelling, Pluronic gel was discovered to be a viable carrier for the efficient release of mepivacaine hydrochloride throughout the dental operation. Given their longer blood circulation duration and reduced discomfort following injection, nanogels are likely one of the best options [55].

**Stopping Bleeding:**

Solution-dissolved protein molecules, which have been utilised to create nanogels, may halt bleeding even in severe cuts. A biodegradable gel is produced by the proteins' nanoscale self-assembly process.

**Anti-Inflammatory Action:**

The primary therapy for several inflammatory illnesses involves the prescription of anti-inflammatory medications, such as nonsteroidal anti-inflammatory medicines, or NSAIDs. Oral NSAID medication might result in anemia when used chronically since it can induce gastrointestinal bleeding and ulcers. The medicine can be delivered transdermally to prevent these adverse effects. Transdermal delivery improves patient compliance, avoids first-pass metabolism, and sustains drug levels in the plasma for extended periods of time. Because of these characteristics, nanogels may be able to increase the penetration and transdermal permeation of active ingredients [75].

**Ocular Problems:**

Owing to the unique anatomical and physiological characteristics of the eye, ocular medication delivery continues to be a significant issue for pharmaceutical researchers. The cornea, retina, and sclera of the eye continue to enclose the solitary organ that is the eye within the eye socket. The main defence against foreign objects getting into the eye is these layers themselves. Administering therapeutic drugs becomes

more challenging due to the absence of blood flow to the cornea and crystalline lens. Further limiting the ocular availability of the delivered medications might be the presence of an efflux pump that actively transports out the drug candidate. Further issues with ocular medication administration include protein-drug binding, drainage due to lachrymal fluid, lysosomal enzyme degradation of the active component, and drug loss via regular blinking behaviour. When combined, these variables lead to a ten-fold decrease in the administered drug's concentration, a five- to six-minute residence period, and a one- to three-percent drug penetration. It is observed that ophthalmic drugs have a longer residence duration in nanogel systems that use muco-adhesive polymers like durasite and chitosan. Functionalized polymer-based nanogels are a good option for ocular delivery because they enable surface modification to regulate the release kinetics of loaded drugs, boost bioavailability, improve corneal penetration, target particular anatomical sites in the eye, etc. By preventing repeated medication administration, the longer residence period provided by nanogel improves patient compliance [76].

**Neurodegenerative Diseases:**

An effective method for delivering ODN to the brain is nanogel. Systemic transport of ODN to the central nervous system is necessary for the therapy of neurodegenerative disorders. Higher-molecular-weight injections into the bloodstream are quickly removed from circulation because they are unable to pass across the blood-brain barrier. Nanogels are included in when combined with a negatively charged ODN, it produces polyelectrolyte complexes. (A stable aqueous dispersion) capable of effectively crossing the BBB with particle sizes less than 100 nm. The. When insulin or transferrin modify the nanogel surface, the efficiency of transport is significantly increased [22,77].

**Diabetics:**

A novel nanotech approach, involving a single injection of a nanogel that can stabilise blood glucose levels for up to 10 days, is being used by researchers at the Massachusetts Institute of Technology (MIT) and Boston Children's Hospital to create a self-operating insulin delivery system. Because the nanogel is glucose-sensitive, it can measure blood glucose levels and produce insulin in response. An oppositely charged combination of dextran nanoparticles, which are attracted to one another by electrostatic forces and give the gel mechanical consistency, is the basis of the MIT method's nanogel. Modified dextran, glucose oxidase enzymes, and insulin make up the nanoparticles' inner core. Gluconic acid is produced when the enzyme reacts with the elevated blood glucose levels. By dissolving the dextran spheres and releasing insulin, the gluconic acid that is so produced brings the blood's glucose level back to normal. The body eventually dissolves both dextran and glutamic acid since they are biocompatible [27].

**Nasal Drug Delivery:**

One of the most appealing immunization techniques is intranasal vaccination, which delivers vaccine antigens straight to the mucosa in order to stimulate a protective immune response. The world has made needle-free vaccines a top goal in order to lessen the possibility of needle-related mishaps, such as the transmission of infections by reusing or disposing of needles incorrectly, and to prevent the discomfort or anxiety that comes with needle usage. A novel needle-free mucosal vaccination has the benefit of simultaneously inducing mucosal immunity, particularly in the aerodigestive and reproductive systems, and eliciting antigen-specific systemic humoral and cellular immune responses. Using type-A neurotoxin subunit antigen Hc (BoHc/A), a recombinant non-toxic receptor-binding fraction of Clostridium botulinum, an intranasal vaccination utilising the CHP-NH2 nanogel was shown [78].

**Vaginal Drug Delivery:**

Different vaginal infections have been treated with antibacterial drug-loaded vaginal nanogels. Applying them can also help relieve other sexual difficulties and reduce vaginal discomfort and discharge. One of its disadvantages is that vaginal nanogels should not be used if a woman is pregnant or during her period. According to research, women's risk of HIV infection may be lowered by a small amount of vaginal nanogels containing antiretroviral medications [22]. Tenofovir vaginal gels can be used to prevent HIV. Tenofovir gelatin nanoparticles may be made using a two-step desolvation process. Both a gelling agent and a bioadhesive polymer were employed with HPMC K15M [21].

**Nanogel in vaccine delivery:**

Vaccination is one method of generating active immunity, which is the immune system's stimulation to generate cellular immunity (T-cell immunity) and a humoral immunological response (IgG antibodies) with specificity for certain antigens. The primary benefit of vaccinations utilising live, attenuated microbe particles is a strong T-cell response; nonetheless, these vaccines may pose a risk. Since protein- and peptide-based vaccines contain adjuvants such as aluminium salts, this benefit is not relevant to them. Consequently, it's imperative to create better, safer, and more effective vaccinations that don't include attenuated germs or cause inflammation from aluminium salts. Targeted drug delivery Nanosystems are one avenue of study being pursued to develop a new generation of vaccinations. For the purpose of preventing or treating infections, cancer, allergies, and/or autoimmune illnesses, nanogels can be designed to either upregulate or downregulate the immune response [75].

**Targeted drug delivery:**

Nanogels' nano-particulate dimension offers them limitless opportunities for precise medication delivery. Medication delivery targeting improves optimum medication concentration in specific areas and decreases drug losses inside physiological voids [54]. Targeted drug delivery is particularly important for treating diseases like cancer [79-82]. Targeted drug administration also lessens unpleasant drug responses, which might result in non-adherence to prescribed medicine. Created nanogels that are intended to administer curcumin specifically to colon cancer patients. They created tailored medication delivery with potential future applications by combining several materials in multiple ways [54].

**Controlled drug delivery:**

The wide range of materials and nano-sizes of nanogels utilised in formulations result in solutions that are adaptable and can be adjusted for precise drug delivery. The production of a promising nanogel for the "on-demand" and regulated administration of camptothecin to tumour locations was reported by Qu et al. in 2019[54].

## Future Perspective:

The primary focus of nanogels' future needs to be on their therapeutic use. A number of nanogel components require further optimization and refinement prior to clinical use. It is necessary to do more thorough research on the pharmacokinetics and pharmacodynamics of nanogels. Research that focuses on the specifics of how nanogels achieve therapeutic effectiveness as well as their physicochemical properties will pave the way for the creation of various biomedical applications [76]. Drug release control based on stimulus responses is the main focus of upcoming nanogel drug

delivery technologies. The term "smart" refers to the ability of these nanogels to perceive changes in their environment and adjust the medication release profile accordingly. The development of such systems might have a wide range of uses, particularly for medications with strong side effects or limited indexes. When signals from certain environmental stimuli are identified, smart nanogels ought to be able to respond appropriately and provide immediate feedback. Research has already shown that, in comparison to traditional hydrogel particles, nanogels often exhibit a quick reaction [83]. Furthermore, one unique property of nanogels is their capacity to absorb large volumes of water or biological fluids without losing their structural integrity. This allows nanogels to introduce swelling behaviour, which is a feature shared by macroscopic hydrogel systems [84]. Numerous stimuli, including pH, redox, temperature, light, and others, have been created for use in targeting drug delivery systems; nevertheless, a significant problem remains in effectively integrating these stimuli together to maximize their synergistic effects [85].

## Conclusion

In this study, we paid close attention to the characteristics, categorization, drug targeting or assessment techniques, and uses of NGs. NGs can develop a medication delivery mechanism that works well. NGs are classified based on how they behave in response to particular stimuli, how they cross-link, and how they are structured. The treatment of ocular issues, nasal medication administration, vaginal drug delivery, and other uses for nanogel have become clearer with the recent advancements in nanogel and nanotechnology. Given the progress made with nanogels, we think that more studies and trials are necessary. There is more possibility for evaluating nanogels with smart qualities based on controlled physico-chemical characteristics of the apparatus.

## Contribution of Authors

All authors contributed to the Writing as well as critically reviewed and approved the final manuscript.

## Acknowledgement

None

## Conflicts of Interest

The authors declares that there are no Conflicts of Interest

## Funding source

None

## References

1. Abed HF, Abuwatfa WH, & Husseini GA, "Redox-Responsive Drug Delivery Systems: A Chemical Perspective" Nanomaterials (Basel, Switzerland), 2022; 12(18), 3183. https://doi.org/10.3390/nano12183183.
2. Neamtu I, Chiriac AP, Nita LE, Diaconu A, Rusu AG. "Nanogels containing polysaccharides for bioapplications" Polymeric Nanomaterials in Nanotherapeutics, 2018; pp.387-420. https://doi.org/10.1016/B978-0-12-813932-5.00011-X
3. Akotkhane M, Mahaparale S, Ahire S, Kanade R, Wanere S, & Dhanuka T. "Development and Evaluation of Herbal Nanogel for the Treatment of Oral Candidiasis" Journal of Coastal Life Medicine, 2023; 11(2), 813–838. https://www.jclmm.com/index.php/journal/article/view/1091
4. Sujeevan O, "Comprehensive review on nano drug delivery systems bioanalysis" GSC Advanced Research and Reviews, 2023;14(01): 127–140. https://doi.org/10.30574/gscarr.2023.14.1.0022
5. Siafaka PI, Özcan Bülbül E, Okur ME, Karantas ID, & Üstündağ Okur N. "The Application of Nanogels as Efficient Drug Delivery Platforms for Dermal/Transdermal Delivery"Gels (Basel, Switzerland),2023; 9(9),753. https://doi.org/10.3390/gels9090753
6. Arnfast L, Madsen C G, Jorgensen L, & Baldursdottir S, "Design and processing of nanogels as delivery systems for peptides and proteins", Therapeutic delivery, 2014; 5(6): 691–708. https://doi.org/10.4155/tde.14.38
7. Du X, Gao Y, Kang Q and Xing J, "Design and Applications of Tumor Microenvironment-Responsive Nanogels as Drug Carriers" Front. Bioeng. Biotechnol, 2021; 9:771851. doi: https://doi.org/10.3389/fbioe.2021.771851
8. Pinelli F, Perale G, & Rossi F, "Coating and Functionalization Strategies for Nanogels and Nanoparticles for Selective Drug Delivery" Gels (Basel, Switzerland), 2020; 6(1): 6. https://doi.org/10.3390/gels6010006
9. Kumar P, Liu B, & Behl G, "A Comprehensive Outlook of Synthetic Strategies and Applications of Redox-Responsive Nanogels in Drug Delivery", Macromolecular bioscience, 2019; 19(8): 1900071(1-28). https://doi.org/10.1002/mabi.201900071
10. Liu G and An Z, "Frontiers in the design and synthesis of advanced nanogels for nanomedicine" Polym. Chem., 2014; 5, 1559 DOI: https://doi.org/10.1039/c3py01502e
11. Kubeil M, Suzuki Y, Casulli M A, Kamal R, Hashimoto T, Bachmann M, Hayashita T, & Stephan H. "Exploring the Potential of Nanogels: From Drug Carriers to Radiopharmaceutical Agents" Advanced healthcare materials, 2023; e2301404. https://doi.org/10.1002/adhm.202301404
12. Iordana N, Alina GR, Alina D, Loredana EN & Chiriac AP "Basic concepts and recent advances in nanogels as carriers for medical applications" Drug Delivery, 2017; 24:1, 539-557, DOI: https://doi.org/10.1080/10717544.2016.1276232
13. Mali R, Patil J. "Nanoparticles: A Novel Antifungal Drug Delivery System" Materials Proceedings, 2023; 14(1):61. https://doi.org/10.3390/IOCN2023-14513
14. Demirel GB, & von Klitzing R. "A new multiresponsive drug delivery system using smart nanogels. Chemphyschem" a European journal of chemical physics and physical chemistry, 2013; 14(12), 2833–2840. https://doi.org/10.1002/cphc.201300149
15. Kumar A, Roy S, Srivastava A, Naikwade MM, Purohit B, Mahato K, Naidu VGM, Chandra P. "Nanotherapeutics: A Novel and Powerful Approach in Modern Healthcare System" Nanotechnology in Modern Animal Biotechnology: Concepts and Applications, 2019; pp.149-161 https://doi.org/10.1016/B978-0-12-818823-1.00010-7
16. Mishra E, Goyal AK, Rath G. "Recent advances in drug delivery systems in antiviral therapy" Pharmaspire,2018; 10(3):98-106.
17. Sultana F, Manirujjaman, Imran UH, & Arafat M, & Sharmin S "An overview of nanogel drug delivery system" Journal of Applied Pharmaceutical Science, 2013; 3. S95 S105. 10.7324/JAPS.2013.38.S15.
18. jadhao P, Harsulakar A.A., "A Review on: Herbal Nanogel" IAJPS, 2022; 09 (02), 19-27, https://doi.org/10.5281/zenodo.5996324
19. Mahaparale S, Akotkhane M, "A Review on : Nanogels" Latin American Journal of Pharmacy, 2023;42 (3)
20. Maya S, Sarmento B, Nair A, Rejinold NS, Nair SV & Jayakumar R. "Smart stimuli sensitive nanogels in cancer drug delivery and imaging: a review" Current pharmaceutical design, 2013; 19(41), 7203–7218. https://doi.org/10.2174/13816128194113121912414 2
21. Kendre P & Satav T. "Current trends and concepts in the design and development of nanogel carrier systems" Polymer Bulletin, 2019; 76. https://doi.org/10.1007/s00289-018-2430-y .
22. Agrawal RD, Tatode AA, Rarokar NR, Umekar MJ, Polymeric micelle as a nanocarrier for delivery of therapeutic agents: A comprehensive review, Journal of Drug Delivery and Therapeutics, 2020;10(1-s)191-195 https://doi.org/10.22270/jddt.v10i1-s.3850

23. Chandel D, Uppal S, Mehta SK, Shukla G, Preparation and characterization of celecoxib entrapped guar gum nanoparticles targeted for oral drug delivery against colon cancer: an in-vitro study, Journal of Drug Delivery and Therapeutics, 2020;10(2-s):14-21 https://doi.org/10.22270/jddt.v10i2-s.3951

24. Anooj ES, Charumathy M, Sharma Vipin, Vibala B.V. Gopukumar S.T., Jainab S.I. Beema, Vallinayagam Sugumari "Nanogels: An overview of properties, biomedical applications, future research trends and developments" Journal of Molecular Structure 2021;130446. https://doi.org/10.1016/j.molstruc.2021.130446

25. Chaudhary K, Parihar S, Sharma D, A critical review on nanoscience advancement: in treatment of viral infection, Journal of Drug Delivery and Therapeutics, 2021;11(6):225-237 https://doi.org/10.22270/jddt.v11i6.5030

26. Sharma A, Garg T, Aman A, Panchal K, Sharma R, Kumar S, & Markandeywar T. "Nanogel an advanced drug delivery tool: Current and future" Artificial cells, nanomedicine, and biotechnology, 2016; 44(1), 165–177. https://doi.org/10.3109/21691401.2014.930745

27. Parajapati SK, Maurya SD, Das MK, Tilak VK, Verma KK, Dhakar RC, Potential application of dendrimers in drug delivery: A concise review and update, Journal of Drug Delivery and Therapeutics, 2016;6(2):71-88 https://doi.org/10.22270/jddt.v6i2.1195

28. Fadhel AY, Rajab NA. "Advance Nanogels of Drug Delivery System: A Review" International Journal of Drug Delivery Technology, 2021; 11(4):1507-1512. DOI: https://doi.org/10.25258/ijddt.11.4.67

29. Chaudhari PM and Paithankar AV, "Herbal Nanogel Formulation: A Novel Approch", Journal of Science and Technology, 2020; 5(5), DOI: https://doi.org/10.46243/jst.2020.v5.i5.pp149-153

30. Singh N, Nisha, Gill V & Gill P, "Nanogel Based Artificial Chaperone Technology: an Overview" American Journal of Advanced Drug Delivery, 2013; 1, 271-276.

31. Sahu P, Das D, Kashaw V, Iyer AK, Kashaw SK, Nanogels: A New Dawn in Antimicrobial Chemotherapy, Antimicrobial Nanoarchitectonics: From Synthesis to Applications, 2017.https://doi.org/10.1016/B978-0-323-52733-0.00005-7

32. Kousalová J, and T Etrych. "Polymeric nanogels as drug delivery systems." Physiological research, 2018; 67(2), S305-S317. doi: https://doi.org/10.33549/physiolres.933979

33. Shah S, Rangaraj N, Laxmikeshav K, & Sampathi S. "Nanogels as drug carriers - Introduction, chemical aspects, release mechanisms and potential applications" International journal of pharmaceutics, 2020; 581, 119268. https://doi.org/10.1016/j.ijpharm.2020.119268

34. Chouhan C, Rajput RPS, Sahu R, Verma P, Sahu S, "An Updated Review on Nanoparticle Based Approach for Nanogel Drug Delivery System" Journal of Drug Delivery and Therapeutics, 2020; 10(5-s):254-266 http://dx.doi.org/10.22270/jddt.v10i5-s.4465

35. Muthal AD, Kshirsagar SJ, Bhambere DS, Patil MP, Ahhirao SS, Vishwakarma RP,"A Brief Overview of Nanogel" World Journal of Pharmaceutical Research, 2022; 11(4), 1922-1942, DOI: https://doi.org/10.20959/wjpr20224-23678

36. Wu Y, Tao Q, Xie J, Lu L, Xie X, Zhang Y, & Jin Y. "Advances in Nanogels for Topical Drug Delivery in Ocular Diseases" Gels (Basel, Switzerland), 2023;9(4),292. https://doi.org/10.3390/gels9040292

37. Tariq L, Arafah A, Ali S, Beigh S, Dar M A, Dar T U H, Dar A I, Alsaffar R M, Masoodi M H, & Rehman M U. "Nanogel-based Transdermal Drug Delivery System: A Therapeutic Strategy with Under Discussed Potential" Current topics in medicinal chemistry, 2023; 23(1): 44–61. https://doi.org/10.2174/1568026622666220818112728

38. Pinelli F, Ortolà Ó F, Makvandi P, Perale G, & Rossi F. "In vivo drug delivery applications of nanogels: a review" Nanomedicine (London, England), 2020; 15(27): 2707–2727. https://doi.org/10.2217/nnm-2020-0274

39. Gupta S, Sharma S, "Potential of Nanogel for Dental Disorder: A Comprehensive Review" Journal of Natural Product and Plant Resources, 2021; 11 (5): 1-10

40. Mogoşanu G & Grumezescu A, Bejenaru L, Bejenaru C. "Natural and synthetic polymers for drug delivery and targeting" Nanobiomaterials in Drug Delivery, 2016; DOI: https://doi.org/10.1016/B978-0-323-42866-8.000083 .

41. Filippo P, Marjan S, Ehsan N Z, Pooyan M, Maurizio M, Alessandro S & Filippo R. "A perspective on the applications of functionalized nanogels: promises and challenges" International Materials Reviews, 2023; 68:1, 1-25. DOI: https://doi.org/10.1080/09506608.2022.2026864

42. Botha N & Mushonga P & Onani M, "Review on nanogels and their applications on dermal therapy" Polymers and Polymer Composites, 2023;31. https://doi.org/10.1177/09673911231192816 .

43. Balladka S, Bailore N. & Pushparekha, "Emerging Trends in the Synthesis, Properties and Applications of Nanogels Derived from Pullulan" Collagen and Gelatin, 2021; https://doi.org/10.1007/978-981-15-7138-1_3 .

44. Stawicki B, Schacher T, Cho H. "Nanogels as a Versatile Drug Delivery System for Brain Cancer" Gels, 2021; 7, 63. https://doi.org/10.3390/gels7020063

45. Yin Y, Hu B, Yuan X, Cai L, Gao H, & Yang Q. "Nanogel: A Versatile Nano-Delivery System for Biomedical Applications" Pharmaceutics, 2020;12(3), 290. https://doi.org/10.3390/pharmaceutics12030290

46. Iyer S, & Das A, "Responsive nanogels for anti-cancer therapy" Materials Today: Proceedings, 2021; 44. https://doi.org/10.1016/j.matpr.2020.12.415 .

47. Garcia MC, Cuggino JC. "Stimulus-responsive nanogels for drug delivery" Stimuli Responsive Polymeric Nanocarriers for Drug Delivery Applications, 2018; 1, https://doi.org/10.1016/B978-0-08-101997-9.00016-3

48. Qureshi M, Khatoon F, "Different Types of Smart Nanogel for Targeted Delivery" Journal of Science: Advanced Materials and Devices, 2019; 4. https://doi.org/10.1016/j.jsamd.2019.04.004 .

49. Kumari L & Badwaik H, "Polysaccharide-based nanogels for drug and gene delivery" Advance and Challenges in Pharmaceutical Technology, 2019; https://doi.org/10.1016/B978-0-08-102553-6.00018-0 .

50. Korzhikov-Vlakh V, & Tennikova T, "Nanogels Capable of Triggered Release" Advances in biochemical engineering/biotechnology, 2021; 178, 99–146. https://doi.org/10.1007/10_2021_163

51. López-Iglesias C, & Klinger D, "Rational Design and Development of Polymeric Nanogels as Protein Carriers" Macromolecular bioscience, 2023; e2300256. https://doi.org/10.1002/mabi.202300256

52. Grimaudo MA, Concheiro A, Alvarez-Lorenzo C, "Nanogels for regenerative medicine" Journal of Controlled Release, 2019. doi: https://doi.org/10.1016/j.jconrel.2019.09.015

53. Preman NK, Barki RR, Vijayan A, Sanjeeva SG, Johnson RP, "Recent developments in stimuli-responsive polymer nanogels for drug delivery and diagnostics: A Review" European Journal of Pharmaceutics and Biopharmaceutics, 2020. doi: https://doi.org/10.1016/j.ejpb.2020.10.009

54. Attama AA, Nnamani PO, Onokala OB, Ugwu AA and Onugwu AL, "Nanogels as target drug delivery systems in cancer therapy: A review of the last decade" Front. Pharmacol, 2022; 13:874510. https://doi.org/10.3389/fphar.2022.874510 .

55. Zarekar NS, Lingayat VJ, and Pande VV, "Nanogel as a Novel Platform for Smart Drug Delivery System." Nanoscience and Nanotechnology Research, 2017; 4(1), 25-31. https://doi.org/10.12691/nnr-4-1-4 .

56. Sasaki Y, & Akiyoshi K. "Nanogel engineering for new nanobiomaterials: from chaperoning engineering to biomedical

applications" Chemical record (New York, N.Y.), 2010; 10(6), 366–376. https://doi.org/10.1002/tcr.201000008

57. Hoque M, Saha SN, Akram T, "Nanogels Based Drug Delivery System: A Promising Therapeutic Strategy" Int. J. in Pharm. Sci., 2023; 1(11): 103-111. https://doi.org/10.5281/zenodo.10070862

58. Zhang H, Zhai Y, Wang J, & Zhai G "New progress and prospects: The application of nanogel in drug delivery" Materials science & engineering. C, Materials for biological applications, 2016; 60, 560–568. https://doi.org/10.1016/j.msec.2015.11.041

59. Arti and Archna KM., "Nanogels: An overview of properties, classifications, drug targeting methods, evaluation parameters and applications" International Journal of Pharmaceutical Sciences and Research,2022;13(11):4385-4400. DOI: https://doi.org/10.13040/IJPSR.0975-8232.13(11).4385-00

60. Sindhu RK, Gupta R, Wadhera G, Kumar P. "Modern Herbal Nanogels: Formulation, Delivery Methods, and Applications" Gels, 2022; 8, 97. https://doi.org/10.3390/gels8020097

61. Keskin D, Zu G, Forson A M, Tromp L, Sjollema J, & van Rijn, P, "Nanogels: A novel approach in antimicrobial delivery systems and antimicrobial coatings" Bioactive materials, 2021;6(10), 3634–3657. https://doi.org/10.1016/j.bioactmat.2021.03.004

62. Soni KS, Desale S S, & Bronich TK, "Nanogels: An overview of properties, biomedical applications and obstacles to clinical translation" Journal of controlled release: official journal of the Controlled Release Society, 2016; 240, 109–126. https://doi.org/10.1016/j.jconrel.2015.11.009

63. Hajebi S, Rabiee N, Bagherzadeh M, Ahmadi S, Rabiee M, Roghani-Mamaqani H, Tahriri M, Tayebi L, & Hamblin MR,"Stimulus-responsive polymeric nanogels as smart drug delivery systems" Acta biomaterialia, 2019; 92, 1–18. https://doi.org/10.1016/j.actbio.2019.05.018

64. Kabanov AV, & Vinogradov SV, "Nanogels as pharmaceutical carriers: finite networks of infinite capabilities" Angewandte Chemie (International ed. in English), 2009; 48(30), 5418–5429. https://doi.org/10.1002/anie.200900441

65. Fakhara S, Muhammad IA, Maimoona Q, Iqra A, Muhammad J D, Kifayat U S, Alam Z, Gul MK, Naveed A, Fakhar-ud D, "Polymeric Nanogels as Versatile Nanoplatforms for Biomedical Applications", Journal of Nanomaterials, 2019. https://doi.org/10.1155/2019/1526186

66. Jha A, Rama A, Ladani B, Verma N, Kannan S, Naha A. "Temperature and pH-responsive nanogels as intelligent drug delivery systems: A comprehensive review" J Appl Pharm Sci 2021; 11(12):001- 016.

67. Narayanan KB, Bhaskar R, Han SS, "Recent Advances in the Biomedical Applications of Functionalized Nanogels" Pharmaceutics, 2022; 14(12):2832. https://doi.org/10.3390/pharmaceutics14122832

68. Li C, Obireddy SR, & Lai WF, "Preparation and use of nanogels as carriers of drugs" Drug delivery, 2021; 28(1), 1594–1602. https://doi.org/10.1080/10717544.2021.1955042

69. Sepideh K, Hamed A. "Nanogels: Chemical Approaches to Preparation. In Encyclopedia of Biomedical Polymers and Polymeric Biomaterials" Taylor and Francis: New York, Published online: 2016; 5266-5293. http://dx.doi.org/10.1081/E-EBPP-120050693

70. Manimaran V, Nivetha RP, Tamilanban T, Narayanan J, Vetriselvan S, Fuloria NK, Chinni SV, Sekar M, Fuloria S, Wong LS, Biswas A, Ramachawolran G and Selvaraj S,"Nanogels as novel drug nanocarriers for CNS drug delivery" Front. Mol. Biosci, 2023; 10:1232109. doi: https://doi.org/10.3389/fmolb.2023.1232109

71. Altuntaş E, Özkan B, Güngör S, & Özsoy Y, "Biopolymer-Based Nanogel Approach in Drug Delivery: Basic Concept and Current Developments" Pharmaceutics, 2023;15(6), 1644. https://doi.org/10.3390/pharmaceutics15061644

72. Ahmed S, Alhareth K, Mignet N, "Advancement in Nanogel formulations provides controlled drug release" International Journal of Pharmaceutics, 2020. doi: https://doi.org/10.1016/j.ijpharm.2020.119435

73. Alotaibi G, Alharthi S, Basu B, Ash D, Dutta S, Singh S, Prajapati B G, Bhattacharya S, Chidrawar V R, & Chitme H "Nano-Gels: Recent Advancement in Fabrication Methods for Mitigation of Skin Cancer" Gels (Basel, Switzerland), 2023; 9(4), 331. https://doi.org/10.3390/gels9040331

74. Chacko RT, Ventura J, Zhuang J & Thayumanavan S, "Polymer nanogels: a versatile nanoscopic drug delivery platform" Advanced drug delivery reviews, 2012; 64(9), 836–851. https://doi.org/10.1016/j.addr.2012.02.002

75. Misu M, Cristina H, Angela C, & Ramona-Daniela P, "Nanocellulose and Nanogels as Modern Drug Delivery Systems" Wiley, 2017; 209-269. https://doi.org/10.1002/9783527803835.ch9 .

76. Sivaram AJ, Rajitha P, Maya S, Jayakumar R, & Sabitha M. "Nanogels for delivery, imaging and therapy" Wiley interdisciplinary reviews. Nanomedicine and nanobiotechnology, 2015; 7(4), 509–533. https://doi.org/10.1002/wnan.1328

77. Mendake RA, Hatwar PR, Bakal RL, Hiwe KA and Barewar SS. "Advance and opportunities in nanoparticle drug delivery for central nervous system disorders: A review of current advances". GSC Biological and Pharmaceutical Sciences, 2024; 27(03): 044–058. https://doi.org/10.30574/gscbps.2024.27.3.0222

78. Tahara Y, Akiyoshi K, "Current advances in self-assembled nanogel delivery systems for immunotherapy" Adv. Drug Deliv. Rev., 2015. http://dx.doi.org/10.1016/j.addr.2015.10.004

79. Shaikh MSH, Hatwar PR, Bakal RL and Kohale NB. A comprehensive review on Liposomes: As a novel drug delivery system. GSC Biological and Phamaceutical Sciences, 2024; 27(01): 199-210. https://doi.org/10.30574/gscbps.2024.27.1.0121

80. Pakade ID, Barewar SS, Hatwar PR, Bakal RL, Shelke PG. Targated Drug Therapy. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(5): 1642-1656. https://doi.org/10.20959/wjpps20245-27299

81. Bagmar NA, Hatwar PR and Bakal RL, A Review on targeted drug delivery system. World Journal of Pharmaceutical Research. 2023; 12(19), 288-298.

82. Hatwar PR, Bakal RL, Dumare AA, Dere MD, Hage PD, Targeted Drug Delivery System for the treatment of Cancer. World Journal of Pharmaceutical Research. 2023; 12(12), 808-816.

83. Aminu N & Toh SM. "Applicability of nanoparticles-hydrogel composite in treating periodontal diseases and beyond" Asian Journal of Pharmaceutical and Clinical Research, 2017. 10. 65-70. https://doi.org/10.22159/ajpcr.2017.v10i2.15709 .

84. Mauri E, Perale G, Rossi F, "Nanogel Functionalization: A Versatile Approach To Meet the Challenges of Drug and Gene Delivery" ACS Appl. Nano Mater. 2018, 1, 6525–6541. DOI: https://doi.org/10.1021/acsanm.8b01686

85. Wu, HQ, & Wang C C, "Biodegradable Smart Nanogels: A New Platform for Targeting Drug Delivery and Biomedical Diagnostics" Langmuir: the ACS journal of surfaces and colloids, 2016; 32(25), 6211–6225. https://doi.org/10.1021/acs.langmuir.6b00842