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# NANOGELS: AN OVERVIEW OF PROPERTIES, CLASSIFICATIONS, DRUG TARGETING METHODS, EVALUATION PARAMETERS AND APPLICATIONS

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**Keywords:**

NGs, Release mechanism, Drug targeting, Cancer targeting, Marketed formulation, NGs application

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**ABSTRACT:** Nanogels (NGs) are advanced and innovative drug delivery systems that play an important role in remarking many issues that are associated with recent and trendy courses of treatment, such as non-specific effects and low stability. NGs could be well-defined as extremely cross-linked hydrogels (nano-sized) ranging from 20-200 nm. NGs are vigorous nanoparticles (NPs) used to deliver active drug complexes for the controlled delivery of drugs. This system is simpler and safer for both hydrophobic and hydrophilic drugs because of their chemical composition and formulations that are unsuitable for different formulations. Drugs are incorporated into NGs for many purposes, like gene targeting, organ targeting, diagnosis, and many more. NGs can be administered through different pulmonary, nasal, transdermal, intra-ocular, oral, and parenteral routes. Frequently, NGs are used to treat cancer, bone regeneration, inflammation, *etc*. This NGs system is a novel drug delivery system for hydrophobic and hydrophilic drugs. This review mainly focuses on providing general information on NGs, their properties, various classifications, drug targeting methodology, different types of drug delivery systems, evaluation methods and novel applications of NGs in detail.

**INTRODUCTION:** NGs are three-dimensional (3D) structures made up of physically or chemically cross-linked polymers with amphiphilic or hydrophilic molecular chains, as shown in **Fig. 1**. It maintains the structure intact because NGs are ready to swell by holding an excellent quantity of water with no dissolving.

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The good water content correlates with the fluid-like transport properties for the biologically active molecules that are considerably smaller than the gel pore size [1]. NPs have some advantages over conventional formulations, such as controlled drug release, resistance to degradation, delayed elimination, stimuli-responsive behaviour, and so on [2, 3, 4].

Moreover, NGs-based nanomedicines should fulfill all the desires of drug delivery systems to make sure maximum therapeutic impact with minimal side effects, stable covalent bonds or, less preferably, encapsulation of the active substance

must be guaranteed [3, 4, 5]. NGs are often administered with two basic methods, such as passive and active targeting. In passive targeting, NGs show drug release concerning the surface charge, size, swelling, and other physicochemical properties.

On the other hand, in active targeting, NGs conjugate with specific moieties that precisely identify and bind to several over-expressed receptors at the targets [3, 4, 6].

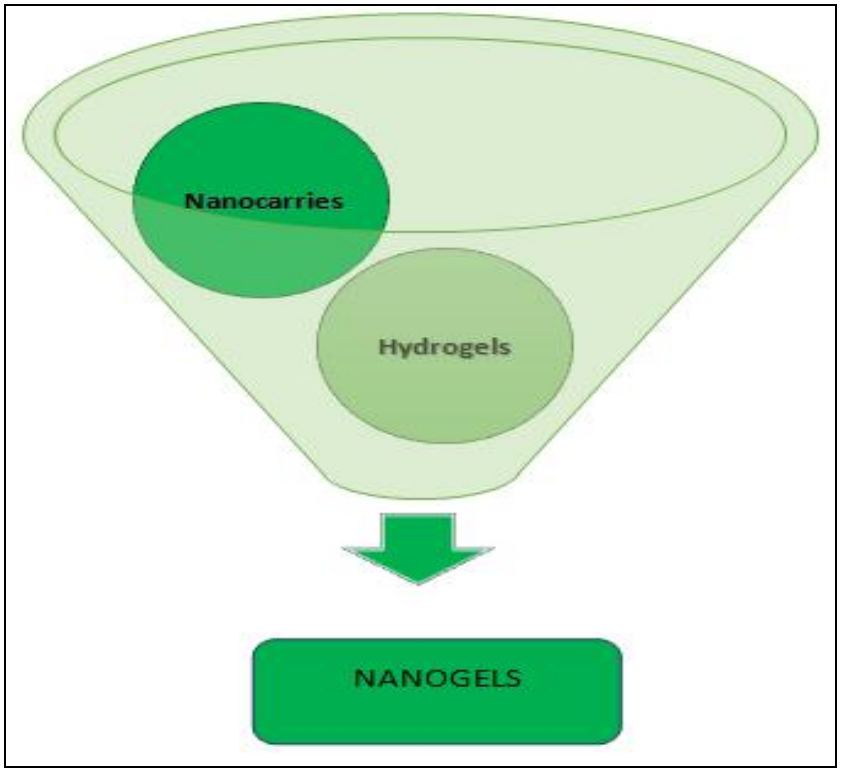


**FIG. 1: NANOGEL COMPOSITION**

**Advantages of Nanogels:**

- NGs occur with increasing biodegradability and biocompatibility in formulations. NGs are often precise for drugs sustained release from the formulation by the addition of a polymeric network.
- Enhanced bloodstream transport and tissue permeation properties because of their optimal nm size scale - Response to a wide variety of external stimuli (ionic strength, pH, temperature).
- Drug loading capacity is high. It will contain both hydrophobic and hydrophilic drugs.
- Improved ability to access areas that are not accessible by hydrogels upon intravenous administration.
- Release of drugs can be regulated in NGs by tuning cross-linking densities [4, 7, 8, 9, 10, 11].

**Limitations of Nanogels:**

- It is an exclusive way to get rid of the surfactant and, therefore, the solvent at the top of the preparation method, although the manufacturing process isn't very pricey.
- Adverse effects could occur if a trace of polymers or surfactants remains within the system.
- NGs have limited drug-loading efficiency and sub-optimal regulation of drug release.
- Tracing of the monomer or surfactant may also be left, which may be toxic [6, 7, 8, 11].

**Nanogels Classification:** NGs are frequently classified into many classes that support their behaviour to environmental stimuli, the presence of some linkage, supported polymers consistent with their structure, and supported preparation techniques, which are shown in **Fig. 2.**

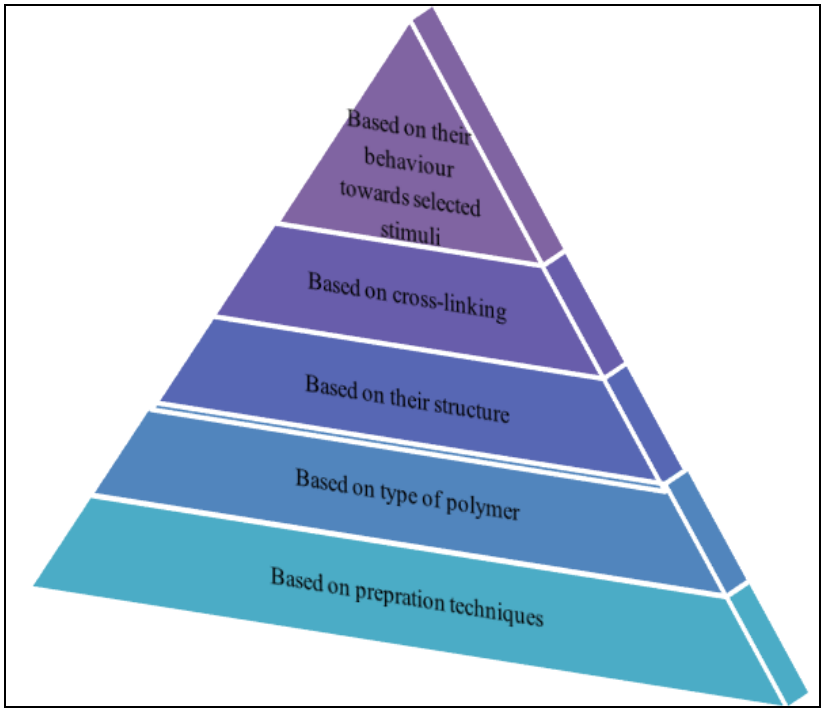


**FIG. 2: CLASSIFICATIONS OF NANOGELS**

**1. Based on their Behaviour towards Selected Stimuli:** Based on behaviour towards stimuli, they are of two types: non-responsive NGs and stimuli-responsive NGs. NGs that are non-responsive swell in the presence of water (due to water absorption), whereas stimuli-responsive NGs swell in response to a different environmental state.

- ✓ **Non-responsive Nanogels:** When non-responsive NGs are in contact with water, they absorb it, leading to swelling of the NGs.
- ✓ **Stimuli-responsive Nanogels:** Environmental conditions, like temperature, pH, magnetic flux, and ionic strength, control whether swelling will occur or not and, therefore the extent of swelling and de-swelling of NGs. Any changes in any of those environmental factors, which act as stimuli, will cause alteration in the behaviour of the NGs as a response, hence the term stimuli-responsive NGs [7, 12].

**Stimuli-responsive Nanogels are Many types:**

- pH-sensitive
- Temperature-dependent
- Light sensitive
- Field responsive
- Ionic strength sensitive

**2. Based on Cross-Linking:**

**I. Physical Cross-Linking:** Physically cross-linked gels involve weak bonds like hydrophobic bonds, venderwal forces, and hydrogen bonds. The formation of microgels and NGs takes a couple of minutes. Physical gels can also be formed by the aggregation and self-assembly of polymeric chains [2, 12, 13].

- ❖ **Liposome Modified Nanogels:** Liposome modified NGs are physically cross-linked, stimuli-responsive NGs currently being studied as transdermal drug delivery devices.
- ❖ These NGs involve the incorporation of poly [N-isopropyl-acryl amide] co-polymeric groups into the liposomes, leading to a high degree of responsiveness to temperature and ph. Additionally, succinate poly [glycidol] is infused into the liposomes under pH of 5 to make NGs that efficiently and expeditiously deliver calcein to the cytoplasm of target cells [7, 12].
- ❖ **Micellar:** Obtained by supra molecular self-assembly of amphiphilic block or graft copolymers in aqueous solutions. Drug molecules in the hydrophobic core are shielded from hydrolysis and enzymatic degradation.

- N-isopropyl acrylamide-based micelle systems, evaluated as drug delivery devices [1, 12].

- **Hybrid Nanogels:** Particles of NGs become dispersed in an inorganic or organic medium. It's referred to as a hybrid NGs. Self-assembly and aggregation of amphiphilic polymers, like pullulan-PNIPAM, hydrophobized Pullulan, and hydrophobized polysaccharides, were the procedures used in the formation of NGsin an aqueous medium [7, 12].

**3. Chemical Cross-Linking:** The chemically cross-linked NGs involve their networks' permanent and strong covalent bonds. The kinds of chemical bonds depend upon the sort of functional group present within the structure [2, 13].

- **Disulfide Cross-Linking:** Reacting groups: disulfide and thiol, at pH, gentle reaction conditions, simple further fictionalization-Self-cross linking amphiphilic random copolymers (PEG hydrophilic unit and pyridyl disulfide hydro-phobic and cross linkable unit).

- **Amide Cross-Linking:** Reacting groups: carboxylic and amino esters, iodides, no additives needed- Adjustable cross-linking degree.

- **Imine Cross-Linking:** Schiff-base reaction-amine or hydrazide and aldehyde-no catalyst-gentle reaction conditions.

- **Copper-free Click Chemistry Cross-Linking:** Reacting groups: alkyl units with amino groups immobilized to the particle shell *via* amidation of hydrophilic polymer micelles Counting on a slow or fast reaction, with or without a catalyst

- **Photo-induced Cross-Linking:** A technique that wants to stabilize polymers with functional groups which will polymerize -Reacting groups: alkene or coumarin-UV irradiation, photo initiator-extremely efficient, toxicity concern [1].

**4. Classification of Nanogels Consistent with their structure:**

1. **Simple Nanogels:** are self-assembled, cross-linked semi-interpenetrating polymer networks that are temperature and pH-responsive [5].
2. **Cross-shell Nanogels:** cross-linked stimulus-sensitive NGs made from polymers with different sensitivities and consisting of shell and core compartments [14].
3. **Hairy Nanogels:** cross-linked by RAFT aqueous dispersion polymerization. Hairy NGs consist of a twin structure having a shell and a core. These nanomaterials respond to various stimuli, including temperature, enzymes, and pH [14].
4. **Hollow Nanogels:** interpenetrating polymer networks Hollow NGs are fabricated by temperature-sensitive polymers with predominantly favourable constituents [14].
5. **Functionalized Nanogels:** three-step cross-linking. These are mostly used NGs; their formulation methods are complicated and require high purification at each step, including the inverse microemulsion or microemulsion methods [14].
6. **Multilayer Nanogels:** cross-linked, stimulus-responsive NGs that have many layers are referred to as multilayer NGs [14].

**Nanogels-Based Drug Release Mechanism:** There is more than one mechanism in which drug release or the bio-molecule is as well as simple diffusion, temperature, pH and the extent of transition of NGs as shown in **Fig. 3** [15].

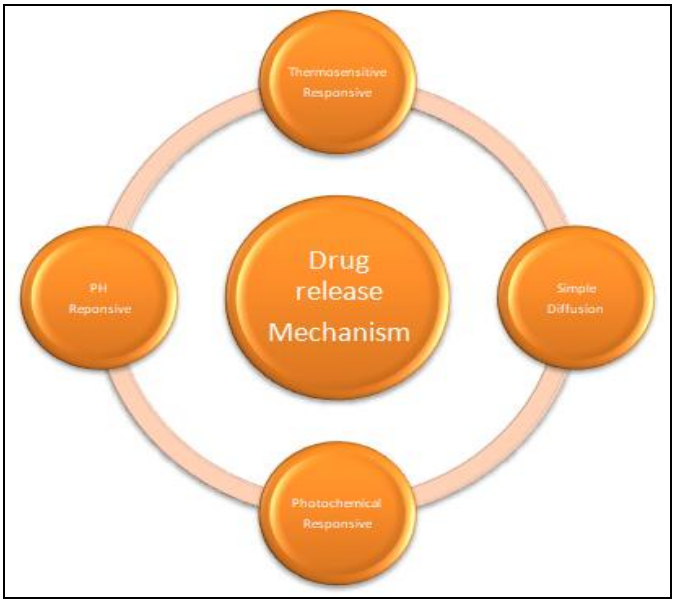


**FIG. 3: DRUG RELEASE MECHANISM**

1. **pH-Responsive:** Drug release in response to pH changes in the environment. In other words, drug release may happen in diverse physiological environments that obtain exclusive pH values. The maximum release will occur in the true pH region because the release is specifically executed in the targeted vicinity of a body with that pH 7 [12, 13, 16].

2. **Thermo Sensitive Responsive and Volume Transition:** Thermo sensitive NGs are developed by poly (N- isopropylacrylamide), which releases indomethacin because of temperature maintenance above the lower critical solution temperature (LCST), which results in unexpected shrinkage inside the volume of the gel. Thermo-responsive NGs was synthesized by changing polyethyleneimine with a pluronic group, which gave a decreased particle size and was efficiently used in gene transport systems. The volume transition function of NGs is a critical application in which NGs increase their volume when exposed to a change in pH, temperature, light, and so on. This quantity alternate triggers the drug launch from the NGs [6, 7, 12, 15, 16].

3. **Photochemical Responsive:** In this type of NGs, swelling and deswelling is controlled by using retaining photo controllable cross-linking between polymers. Photosensitizers loaded into NGs are animated. They produce species of oxygen (singlet and reactive) which may result in oxidation inside the cellular compartment walls that extremely influence the release of therapeutic marketers into the cytoplasm [6, 7, 12, 13, 16].

4. **Simple Diffusion:** Diffusion takes place while a drug or active agent passes via a polymer that forms a control release device. The diffusion may arise on a macroscopic scale, via pores inside the polymer matrix, or via passing among polymer chains on a molecular scale. The polymer and active agents have been blended to make a homogeneous system, which is mentioned as the matrix system. This type of system, the combination of polymer matrices and bioactive agents are chosen, permits the drug to diffuse through the pores or macromolecule's shape of the polymer upon introduction of the transport machine into the biological environment without consisting of any changes in the polymer itself. The timing of the release of a drug from the delivery system by using diffusion may be controlled by means of a number of factors:

- The binding strength of the drug in the micelle core (*e.g.,* hydrophobic binding in hydrophobic cores), that's characterized by way of the partitioning of drug among the micelle and external surroundings and
- The polymer chains bind to each other in a micelle structure and are characterized by means of cmc. Therefore mentioned elements show the 'thermodynamic' and 'kinetic stability' of the formulation, enabling them to link with the drug and micelles and manage the drug release [12, 15, 16].

**Drug Targeting *via* Nanogels:** NGs have been used for the most effective treatments for superficial acute diseases, but they have also entered the important class of deadly disease therapies. Nowadays, these transport systems are curing mental disorders, lung and liver disorders, cancer, skin diseases, joint disorders, ophthalmic disorders, wound restoration and vaccine delivery. In addition, corresponding NGs have additionally entered the field of diagnostic imaging. Many NGs formulations have been patented in several countries for diverse diseases. Hydrogel with a polymeric nanocarrier system has a very promising ability to improve the bioavailability of such poorly permeable tablets. In the field of brain shipping, NGs have been developed for numerous degenerative disorders in addition to brain cancer [17].

**Skin Disorders:** The NGs can be immediately carried out on the affected parts of the body. The drug's permeability enhancement is better by the drug's conversion into the size range of NPs. When compared to the existing gel, the zinc oxide NPs are incorporated into the gel to improve the antibacterial efficacy of the drug by using this method. Another study found high psoriatic activity by preparing methotrexate-loaded chitin NGs [2].

**Cancer:** Many anti-cancer drugs are repeatedly used in cancer treatment. However, they have

indicated shortcomings that offer hindrances to most cancers' effective remedy. Some of the shortcomings are poor permeability, much less bioavailability, less retention time, and quicker excretion of drugs.

To reduce these shortcomings, NGs loaded with anti-cancer drugs were prepared with N-hexylcarbamoyl-5-flurouracil-loaded NGs for brain cancer treatment and were found to have high retention time and accumulation in the brain [2].

**Healing of Wounds:** NGs are amongst the satisfactory carriers to incorporate when considering the topical application of drugs. Presently, it's thought that wounds with a wet environment show higher healing compared to dry dressing. NGs, which are gels, offer the best choice for wet dressing as the recovered tissue quality is best in wet (moist) dressing wounds. Furthermore, the hydrogel NPs (i.e., NGs) provides a cooling effect and help reduce swelling and erythema by reducing capillary circulation at the application site [6].

**Eye Disorders:** In treating eye disorders, NGs is very effective because of improved corneal bioavailability, much less formulation drainage from the corneal surface, and improved retention time compared to different carrier systems [2].

**Diagnosis:** From the diagnostic point of view, NGs with cell imaging play an important role in distinguishing cancer cells from ordinary cells to perform surgical procedures for removing cancerous cells without affecting normal cells. Many techniques presently exist for imaging tumours [2].

**Vaccine Delivery:** As a vaccine, NGs may also be active and can provide some advantages, like reduced inflammatory cytokines, induced toxicity, and enhanced immunity. Vaccination is specific to antigen immune response by using organic agents that can be weaker or kill microbes or resemble disorder causing microorganisms [6].

**The Anatomy of a Drug Delivery Vehicle:**

1. **Encapsulation Stability:** The molecules of a drug should be stably encapsulated such that they do not leak prematurely during circulation. This is important to ensure minimal side effects and maximal therapeutic efficacy.
2. **Response to Stimuli:** Encapsulation stability is desirable during circulation, and they should release the drug at a target site. Thus, responsiveness to stimuli is essential for drug-delivery vehicles.
3. **Passive Targeting:** The design of passive targeting is a key to targeting many diseases, especially, arthritis and cancer. This aspect of design, which is controlled by size, also determines the body's clearance times or circulation times.
4. **Active Targeting:** The strategy of active targeting is used to target a few specific disease phenotypes and so reduce the side effects.
5. **Toxicity:** The transport system should be non-toxic and, preferably, biodegradable with non-toxic degradation products [18, 19].

**Preparation Methods of Nanogels:**

- ❖ Photolithographic method
- ❖ Emulsion solvent diffusion method
- ❖ Coacervation polymerization method
- ❖ Emulsion cross-linking method
- ❖ Emulsion droplet coalescence method
- ❖ Emulsion polymerization method
- ❖ Ionic gelation method
- ❖ Desolvation method

**Photolithographic Method:** In this method, for drug delivery, the subsequent reaction and phytochemical reaction for activation have been discovered in an attempt to produce NGs and 3D hydrogel particles. To achieve the specific properties of the surface, replica molds and stamps are treated or released the incorporated agents by the molded gels allowed [2, 17].

**Emulsion Solvent Diffusion Method:** In this method for drug delivery, correctly weigh the polymer, drug and stabilizer, then dissolve in glycerol with continuous stirring.

On heating, the aqueous phase-gelling agent is dissolved in water with continuous stirring. Ultrasonicate the drug-containing phase and dropwise add the drug phase to the aqueous phase. It is converted into emulsion form by homogenization. Homogenizer at 5000-8000 rpm for 1 hour reduces emulsion in nanodroplets. After this, the O/W emulsion is formed, increasing the preparation efficiency, and the pH is adjusted [2, 19].

**Coacervation Polymerization Method:** This method employs the physicochemical characteristics of polymers involved in formulation. In alkaline solutions, chitosan becomes precipitated but insoluble in alkaline PH media. Particles are produced by blowing chitosan solution into coacervate droplets of NaOH-methanol using a compressed air nozzle into an alkaline solution such as sodium hydroxide (NaOH). A compressed nozzle spray controls the particle size of the polymer-containing drug. The separation of particles is carried by centrifugation or filtration and washed with cold and hot water. To control a drug's release, they used a cross-linking agent [2, 17, 20].

**Emulsion Cross-Linking Method:** The method is totally based on the cross-linking of polymers and cross-linking agents. The dispersion of the aqueous solution of polymer in the oil phase (w/o) emulsion is prepared. This method adds a surfactant and a cross-linking agent to stabilize the solution and harden the droplets. And then, the NGs are washed with organic solvents and dried [2].

**Emulsion-droplet Coalescence Method:** This method is obtained by a slight modification in the precipitation and emulsion cross-linking methods. By allowing the coalescence of polymer droplets, they become precipitated with the involvement of the cross-linking method. The aqueous polymer solution is emulsified by using suitable oil. In alkaline pH, the emulsion is prepared by using the same polymer-containing drug. Then both the emulsions are mixed by using high speed homogenization. Then the particles are separated by centrifugation, washed and dried [2, 17].

**The Emulsion Polymerization Method:** According to the type of continuous phase, emulsion polymerization can be divided into-

1. Aqueous continuous phase containing emulsion polymerization.

2. Organic continuous phase containing emulsion polymerization. Emulsion polymerization can be divided into three phases: nucleation, particle growth phase, and polymerization. The emulsification components are dispersion medium, hydrophobic monomer, surfactants and initiator. The type of emulsion polymerization technique includes surfactant-free emulsion polymerization, conventional emulsion polymerization, micro-emulsions, and mini-emulsion polymerization.

**Mini-emulsion Polymerization:** In mini-emulsion polymerization, the surfactant disperses oil in water. Sodium dodecyl sulphate (SDS) is used as a surfactant.

**Reverse Mini-emulsion Polymerization:** In reverse mini-emulsion polymerization, the surfactant disperses water-in-oil. Span 80 and sodium bis (2-ethylhexyl) sulfosuccinate are used as a surfactant [2].

**Ionic Gelation Method:** The interaction of an ionic polymer with an oppositely charged ion initiates cross-linking. Two methods are involved in generating the hydrogel beads through the Ionotropic gelation technique.

**External Ionotropic Gelation:** The position of the cross-linker ion is external.

**Internal Gelation / Emulsification:** In the inactive form, the cross-linker ion is incorporated within the polymer solution [17, 21].

**Desolvation Method:** In this method, gelatin is dissolved in double distilled water with heating and continuous stirring. After heating, the solution is allowed to stand at room temperature for 10 minutes. Ethanol is added for precipitation. After this, the aging geletin dissolves in double distilled water containing the drug. Then the solution is stirred at 500-1000 rpm for 8 hours. After stirring, the solution is centrifuged and the settled NPs are collected and washed. Other preparation methods include the Reverse micro emulsion polymerization method, the Inverse mini emulsion polymerization method, the Solvent emulsification method, the

Solvent Displacement method, and the Modified Pullulan method [2, 17, 20, 21].

**Nanogels Evaluation Parameters:**

**Swelling Studies/Pulsatile Swelling Studies:** It is the most important parameter of all NGs, and swelling is characterized by measuring their capacity to absorb water or an aqueous solution. To measure the weight with the swelling degree being calculated from the portion weight of the swollen NGs or the initial weight is the easy way to determine the kinetics and swelling equilibrium of NGs various factors, like the type and composition of the monomer, cross-link density, pH, temperature and ionic strength, influence the swelling of NGs. The pH-responsive behaviour of hydrogel beads was confirmed by a pulsatile swelling study [5, 22].

The degree of swelling was calculated by finding the weight of swollen NGs. The swelling behaviour of the NGs was studied at three different pH conditions. The swelling ratio is calculated by using the following formula after determining the dry and wet weight of the lyophilized, pelletized NGs after sufficient exposure to the corresponding pH solution. The swelling at each pH was studied in triplicate.

Swelling Ratio = final wt. of NGs after swelling- Initial wt. of NGs / Initial wt. of NGs ×100 [23, 24]

The swelling was highest at acidic pH compared to neutral, acidic and alkaline conditions [25].

***In-vitro* Drug Release of Nanogels:** To regulate the therapeutic effectiveness of the NGs formulation by *in-vivo* study. A dissolution tester is used to test the behaviour of the release rate of drug from the hydrogel. The study of the release of drugs was carried out in 900 ml of acidic medium (pH 1.2) and alkaline medium (pH 7.4 phosphate buffer) at 37.0 ± 0.5 C and 50 rpm speed. At different time intervals, 5 ml samples were withdrawn and replaced with the same volume of fresh solution.

The test samples were filtered by using a membrane filter, and the amount of released drug was analysed using a UV–visible spectrophotometer at the desired wavelength after suitable dilutions. The *in-vitro* drug release study was done at two pH values, physiological and acidic, since the skin pH as well as that at the tumour site is in the acidic range (4-5), the chitin NGs was shown to have higher swelling at acidic pH.

Release (%) = Released amount of drug / Total amount of drug × 100 [22, 23]

***In-vitro* Drug Permeation of Nanogels:** To evaluate transdermal absorption of NGs in-vitro skin permeation study performed by using Franz diffusion cell. Skin cuts into appropriate size and receptor solution filled in receptor chamber. Maintain the temperature at 32 ±1 °C using a circulating jacketed water bath. NGs formulation was applied on the donor chamber and collected samples collected and analyzed using High-performance liquid chromatography (HPLC) after a desired time period. Recovery of drug also calculated [24].

**Loading Efficiency of Nanogels:** The loading efficiency of NGs is calculated after determining the concentration of the unentrapped drug. The supernatant collected after an HPLC assay analyzed the centrifugation step to determine the concentration of the unentrapped drug.

The drug concentration in the sample is calculated against known standards via the area method under the absorption time curves. The loading efficiency is calculated by using the formula given below:

Loading Efficiency (%) = Weight of drug in NGs / Weight of drug taken initially × 100 [23]

**Entrapment Efficiency of Nanogels:** Entrapment efficiency is calculated based on the amount of drug in the NGs and the amount of drug used during drug loading.

Entrapment efficiency (%) = Total amount of drug in NGs/Total amount of drug × 100 [26]

**Cytotoxicity Studies of Nanogels:** A Cytotoxicity assay of NGs is performed and compared with the standard by cell viability testing. The percentage of cell viability was expressed by the equation as follows:

Cell Viability (%) = Absorbance of control cell/Absorbance of treated cell × 100 [24, 26]

## Applications of Nanogels:

**TABLE 1: THE LIST OF ANTI-CANCER DRUGS INCORPORATED INTO NANOGELS**

| Drug | Polymer | Type of cancer cells | Purpose | Method of Preparation | Route | Ref. |
|---|---|---|---|---|---|---|
| Doxorubicin | Chitosan-gellan gum | Acute lymphoblastic leukemia, breast carcinoma | Good entrapment efficacy and sustained release | In situ-cross linking | Topical/ transdermal | [26] |
| Doxorubicin | Chitin-PLA | Liver carcinoma | To overcome the cardiotoxicity of Dox and achieve better efficacy | Developed an intratumoral pH responsive Dox-chitin-PLA composite NGs(Dox-chitin-PLA CNGs) system | locally injectable | [27] |
| 5-Fluorouracil | Chitin | Skin cancer | Formed good, stable aqueous dispersion and showed pH responsive swelling and drug release. | Simple regeneration method without using any organic solvents. | Skin/topical | [28] |
| Heparin | Disulphide cross-linked heparin NGs | Melanoma cancer | Well-designed delivery carrier for controlled drug delivery applications | Cross-linked | Topical | [29] |
| Decitabine | NIPAM | Breast cancer | Inhibit cell proliferation via cell-cycle arrest and is effective in overcoming drug resistance, even in cancer cells that are resistant to DAC | Surfactant polymerization/ cross-link | Topical | [30] |
| Doxorubicin | Chitin | Prostate, breast and lung cancer | The doxorubicin loaded chitin NGs could be a better alternative for cancer therapeutic agent | Emulsion polymerization/ controlled regeneration method. | Topical | [31] |
| Paclitexal/ Lonadamine | PCL | Ovarian and breast cancer | Improved efficacy with combination therapy and active EGFR targeting. | Solvent displacement method | Topical | [32] |
| Curcumin | Dextrin | Colon, breast, prostate and lung cancer | Effective nanocarrier for the formulation of lipophilic curcumin | Interaction mechanism | Intravenous | [33] |
| Methotrexate | Poly (N-isopropylacrylamide-cobutylacrylate-co-N, N'-methylenebisacrylamide) | Breast cancer, lung cancer | NGs delivery system is potentially useful for the topical delivery | Surfactant-free emulsion polymerisation method. | Topical | [34] |
| Cisplastin | NIPAM | Breast cancer | The dual responsible NGs is a suitable CDDP delivery candidate | Emulsion polymerization | Topical | [35] |
| Fludarabine | PEI/PEG | Cancer | Efficient therapeutic activity but without elevated systemic toxicity | Emulsification–solvent evaporation method | Oral | [36] |
| Temozolomidine | Poly (acrylic acid-co-N, N'-methylenebisacrylamide) | Melanoma | Offer a pH-triggered sustained-release of the drug molecules in the gel | Polymerization | Topical | [37] |

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|---|---|---|---|---|---|---|
| | filled with hydroxypropyl cellulose | | | | | |
| Doxorubicin | PNA | Hyperthermia/ liver carcinoma | Reduce the toxic and side effect of anti-tumor drug, and improve tumor targeting delivery | Acid-cleavable hydrazone bonds | Topical | [38] |
| 5- Fluorouracil | Poly(N-vinylcaprolactum) | Solid tumors | Preventing the unwanted effects by specifically delivering the drug molecules to the target site. | Emulsion polymerisation | Topical | [39] |
| Doxorubicin | Poly (L-aspartic acid) | Ovarian carcinoma | Great potential for tumor therapy | Polymerization technique | Topical | [40] |
| Taxane | polyethylene glycol | Pancreatic and breast cancer | Improve the efficacy of drugs that have poor pharmacokinetics or dose-limiting toxicities | Chemical gradient method | Topical | [41] |
| Doxorubicin | Acetylated chondroitin sulphate | Cervical cancer | AC-CS self-organizing NGs may eventually prove useful in the development of effective anti-cancer drug carriers for chemotherapy. | Acetylation method | Topical | [42] |
| Curcumin | Chitin | Skin cancer | To achive effective treatment by transdermal route | Sonophoresis | Transdermal | [43] |
| Si-RNA anti EGFR | PNIMA | Ovarain cancer | Investigating the fundamental mechanisms of NGs endosomal release | Precipitation polymerization | Topical | [44] |
| Paclitaxel | Pluronic-F127/PEI | Tumor | Greater stability, increased solubility and better cellular uptake | Emulsification/ solvent evaporation method. | Topical | [45] |
| Doxorubicin | P9NIPAM-co-AAc) | Melanoma | Achieve environmental triggered drug release and targeted drug delivery and combine diagnostic and therapeutic functions in one nanostructure | Precipitation polymerization | Topical | [46] |
| Cisplastin | PEO-b-PMA | Ovarian cancer | Demonstrates fundamental possibility for targeted delivery of the NGs-based anti-cancer therapeutics | Conjugation | Topical | [47] |
| 5- Fluorouracil | PEG-Chitosan | Melanoma | Reduced toxicity in combined chemo-thermo treatments, | Physical interpenetration | Topical | [48] |
| 5- Fluorouracil | Poly (N-isopropylacrylamide-copolyethylenimine-co-N, N'-methylenebisacrylamide) | Mastocarcinoma therapy | Higher therapeutic efficacy and lower toxicity | Radical grafting copolymerization method | Topical | [49] |
| Doxorubicin | Cervical cancer | Self-assembly pullulan-based NGs with folic substituents | Overcoming the complications in the drug carrier design | A simple fabrication method | Topical | [50] |

**TABLE 2: THE LIST OF TRANSDERMAL DELIVERY DRUG INCORPORATED INTO NANOGELS**

| Drug | Polymer | Method of preparation | Purpose | Route | Ref. |
|---|---|---|---|---|---|
| Itraconazole | Euginol, labrasol, Carbopol | Emulsification followed by sonication | Sustain release profile and improved permeation of skin | Transdermal | [51] |
| Diclofenac sodium | carbopol 940, Eudragit S-100 | Emulsion solvent diffusion method | For improve bioavailability of drug and prolonged residence of | Transdermal | [52] |

| | | | | | |
|---|---|---|---|---|---|
| | | | drug in the skin | | |
| Ciclopirox | Tween 80, oleic acid, chitosan, Carbopol | Emulsification followed by gelation | Effective delivery by enahancing the penetration of CIC and retention time in skin layers | Topical | [53] |
| Methotrexate | Sodium 2,4-diaminopteroic acid, Tween 80 | Cross-linking | For improved arthritic joint mobility, repair and reduced inflammation | Transdermal | [54] |
| Chitin | Curcumin | Controlled regeneration | Excellent capacity for drug loading and release and good skin penetration and retention properties | Transdermal | [55] |
| Caffeine | PNIPAm-co-AA | Emulsion polymerization/ controlled regeneration method. | Excellent stability, reversible physical property change in response to a pH change | Topical | [56] |
| Tenoxicam | Poloxamer 188, Soybean lecithin | Emulsion/solvent evaporation method | Helps to design efficient dermatological bioequivalence assessment methods. | Topical | [57] |
| Acelofenac | Tween 80, ethyl acetate, Carbopol | Emulsification Diffusion | Significant improvement in the activity for the formulation in comparison with the conventional formulation | Topical | [58] |
| Diclofenac | Cholesterol, lecithin, chloroform and methanol | Thin-layer hydration method | More sustained and prolonged anti-inflammatory effect | Topical | [59] |
| Alcohol, soyabean oil polysorbate 80, Carbopol | Clinamycin and adapalene | Emulsification–High-pressure homogenization | Comparative efficacy and safety of a nano-emulsion gel | Topical | [60] |
| Chitin | 5-flurourazil | Controlled regeneration | Formed good, stable aqueous dispersion, pH-responsive swelling and drug release | Topical | [61] |

**TABLE 3: THE LIST OF PROTEIN AND PEPTIDE DRUG INCORPORATED INTO NANOGELS**

| Drug | Polymer | Method of preparation | Purpose | Route | Ref. |
|---|---|---|---|---|---|
| Clostridium botulinum type A neurotoxinBoHC/A | Cholesteryl group-bearing pullulan | Physically cross-linked NGs by self-assembly | A low risk of causing unfavourable and undesired biological reactions | Intranasal | [62] |
| Insulin | Cadmium chloride, Fe3O4 chitosan | Polymerization and controlled cross-linking | Prepared with different chitosan/QD/MNP ratios and under different processing parameters | Topical | [63] |
| Palmitoyl acylated extend in four peptides | Deoxycholic acid, chitosan | Hydrophobic modification self-assembly method | Fabricated self-assembled nanoparticles composed of deoxycholic acid-modified glycol chitosan (DOCA-GC) with incorporated palmitylacylated exendin-4 (Ex4-C16) | Pulmonary route | [64] |
| Vancomycin | PNIPAm, PMA, PEG | Photo-assisted polymerization | To improve their oral delivery relies on their association with colloidal carriers | Oral | [65] |

**TABLE 4: THE LIST OF OCULAR DRUG INCORPORATED INTO NANOGELS**

| Drug | Polymer | Method of preparation | Purpose | Route | References |
|---|---|---|---|---|---|
| Fluconazole | Chitin | Controlled regeneration chemistry and wet milling methods | Improve the bioavailability | Topical | [66] |

| | | | | | |
|---|---|---|---|---|---|
| Levofloxacin | PLGA, Chitosan | Nanoprecipitation technique | Improve precorneal residence time and ocular penetration | Ocular | [67] |
| Tacrolimus | N-isopropyl acrylamide, 2-hydroxy-methacrylate lactide–dextran | Solvent impregnation method | High drug-loading capacity and controlled release of the drug over a long time, better patient compliance | Topical / ocular | [68] |
| Timolol | Nano diamond, chitosan, poly (hydroxy ethyl methacrylate) matrix | Ultra-sonication | Improve matrix mechanical properties, produce a contact lens that releases TM in a controlled manner | Ocular | [69] |

**TABLE 5: THE LIST OF ANTI-INFLAMMATORY DRUG INCORPORATED INTO NANOGELS**

| Drug | Polymer | Method of preparation | Purpose | Route | Ref. |
|---|---|---|---|---|---|
| Methotrexate | PNIPAm-co-BA | Emulsion polymerization | Enhanced topical delivery and anti-inflammatory activity of methotrexate | Topical | [70] |
| Triclosan and flurbiprofen | Poly-ε-caprolactone (PCL), Chitosan | solvent displacement method | Provide dual action, anti-inflammatory and antimicrobial in periodontitis | Topical | [71] |
| Photosensitizer | Chitosan, Hyluronic acid | Ionic gelation | Targets of treatments aiming at their local destruction in inflammation sites. | Intraperitoneally injection | [72] |
| Sodium diclofenac | Isopropyl amine, d-limonene, lauric acid, HPMC | Microemulsion | For enhance the skin permeation of drug | Transdermal | [73] |
| Spantide 11 and ketoprofen | PLGA and chitosan | Emulsification solvent evaporation | Controlled and sustained release via modification of polymer composition and reducing irritation associated with direct contact of drug with skin | Topical | [74] |

**TABLE 6: THE LIST OF BRAIN DELIVERY OF DRUG INCORPORATED INTO NANOGELS**

| Drug | Polymer | Method of preparation | Purpose | Route | Ref. |
|---|---|---|---|---|---|
| Nucleoside reverse transcriptase inhibitors (NRTIs) | PEG and PEI | Emulsification-solvent evaporation | Increase antiviral activity against HIV infection in the brain | Intravenous | [75] |
| N-hexylcarbamoyl-5-fluorouracil | N-vinylpyrrolidone, N, N-methylenebisacrylamide, polysorbate 80 | Cross-linking and free radical mechanism | Increase the drug permeability into the brain | Intravenous | [76] |

**TABLE 7: THE LIST OF EYE DELIVERY OF DRUG INCORPORATED INTO NANOGELS**

| Drug | Polymer | Method of preparation | Purpose | Route | Ref. |
|---|---|---|---|---|---|
| Timolol maleate | Poly 2-hydroxyethyl methacrylate, polysaccharide, chitosan | Covalent conjugation | To develop a lysozyme-triggered drug delivery system capable of delivering a drug in a controlled fashion | Topical | [77] |
| Fluconazole | Chitin | Passive or ligand-mediated targeting mechanisms | For improve corneal bioavailability | Topical | [78] |

**TABLE 8: THE LIST OF VACCINE DELIVERY OF DRUG INCORPORATED INTO NANOGELS**

| Antigen used | Polymer | Method of preparation | Purpose | Route | Ref. |
|---|---|---|---|---|---|
| CHP-HER2, a cut protein(146HER2) complexed cholesterol pullulan (CHP) | Dimethylsulfoxide | Cr-release method | For humoral immunity | Subcutaneously injected | [79] |
| Pneumococcal surface protein A (PspA) | Cationic cholesteryl group- | Non-toxin-based | For respiratory Pneumococcal infection | Intranasal | [80] |

| | | | | | |
|---|---|---|---|---|---|
| | bearing pullulan | mucosal antigen carrier, gel filtration | | | |
| Ovalubumin (OVA) | Chitosan | Endosomal-based processes | Influence of surface decoration and amount of vaccine on targeting and activating dendritic cells | Topical route | [81] |
| A non-toxic subunit fragment of Clostridium botulinum type-A neurotoxinBoH/A | Cholesteryl-group-bearing pullulan | Physically cross-linked | For mucosal infection | Intranasal | [82] |

**TABLE 9: THE LIST OF ANAESTHETICS DRUG INCORPORATED INTO NANOGELS**

| Drug | Polymer | Method of preparation | Purpose | Route | Ref. |
|---|---|---|---|---|---|
| Lidocaine | Poly (e-caprolactone)–poly (ethylene glycol)–poly(e-carprolactone) | Tail flick latency tests | For prolong action of anaesthesia | Topical | [83] |
| Bupivacaine | N-isopropylacrylamide | Volume phase transition | Determine scavenging ability of NGs | Topical | [84] |
| Procaine HCL | Methacrylic acid–ethyl acrylate (MAA–EA) di-allyl phthalate (DAP) | Synthesized via emulsion polymerization | For determination of release kinetics | Topical | [85] |

**TABLE 10: MARKETED FORMULATION OF NANOGELS**

| Nanogels | Drug | Mfg. by | Uses |
|---|---|---|---|
| Zyclin Nanogel | Clindamycin | *Zydus candila* | Mild to moderate (Acne) |
| Zyflex Nanogel | Thiocolchicoside, methyl salicylate, methanol, alcohol | *Zydus candila* | Releaving pain |
| Silver nanogel | Nanocrystalline silver | Cipla ltd. | Pimples (Acne) |
| Adalene Nanogel | clindamycin, Adapalene | *Zydus candila* | Acne |
| Oxalgin Nanogel | Diclofenac, methyl salicylate and methanol | *Zydus candila* | Inflammation and pain |

**CONCLUSION:** In this review, we focused on the properties, classification, drug targeting or evaluation methods, and applications of NGs in detail. NGs can achieve an efficient drug delivery system. NGs are categorized according to their behaviour towards selected stimuli, cross-linking, and structure. Some preparation methods, such as photolithographic techniques, the Emulsion solvent diffusion method, coacervation/ precipitation / precipitation polymerization, *etc*., were also discussed.

NGs found excellent application for anti-cancer drug delivery, transdermal delivery, protein and peptide delivery, ocular delivery, brain delivery, vaccine delivery and anaesthesia drug delivery and made the treatment effective. Various evaluation parameters are also discussed.

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