REVIEW ARTICLE

Nanogel: A versatile drug delivery system for the treatment of various diseases and their future perspective

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Abstract

Nanogel (NG) drug delivery systems have emerged as promising tools for targeted and controlled drug release, revolutionizing treatment approaches across various diseases. Their unique physicochemical properties, such as nano size, high surface area, biocompatibility, stability, and tunable drug release, make them ideal carriers for a wide range of therapeutic agents. Nanogels (NGs), characterized by their 3D network of crosslinked polymers, offer unique edges like high drug loading capacity, controlled release, and targeted delivery. Additionally, the diverse applications of NGs in medical therapeutics highlight their versatility and potential impact on improving patient outcomes. Their application spans cancer treatment, infectious diseases, and chronic conditions, allowing for precise drug delivery to specific tissues or cells, minimizing side effects, and enhancing therapeutic efficacy. Despite their potential, challenges such as scalability, manufacturing reproducibility, and regulatory hurdles must be addressed. Achieving clinical translation requires overcoming these obstacles to ensure therapeutic payloads' safe and efficient delivery. Strategies such as surface modification and incorporating stimuli-responsive elements enhanced NG performance and addressed specific therapeutic challenges. Advances in nanotechnology, biomaterials, and targeted drug design offer opportunities to improve the performance of NGs and address current limitations. Tailoring NGs for exploring combination therapies and integrating diagnostics for real-time monitoring represent promising avenues for future research. In conclusion, NG drug delivery systems have demonstrated tremendous potential in diverse disease applications. Overcoming challenges and leveraging emerging technologies will pave the way for their widespread clinical implementation, ushering in a new era of precision medicine and improved patient care.

Keywords Nanogel · Cancer · Anti-inflammatory · Gene therapy · Biomedical · Targeted drug delivery

Highlights

- Nanogels enable precise drug delivery to specific cells or tissues, minimizing side effects and enhancing therapeutic outcomes.
- A 3-D network of crosslinked polymeric nanogel allows efficient encapsulation of diverse drug types, promoting flexibility in treatment approaches for various diseases.
- Nanogels offer controlled release kinetics, ensuring a sustained and prolonged therapeutic effect, improving patient compliance, and reducing the need for frequent dosing.
- Nanogels are often biocompatible and can be engineered to be biodegradable, reducing potential toxicity concerns and allowing for safe elimination from the body.
- Nanogels enhance drug stability, protecting the encapsulated drugs from degradation, leading to improved shelf life and effectiveness in diverse medical applications.

Abbreviations

TDDS	Targeted drug delivery system
Dox	Doxorubicin
BBB	Blood-brain barrier
CDDS	Controlled drug delivery system
CNS	Central nerovous system
NG	Nenogel
NGs	Nenogels
CNGs	Composite NGs
HG	Hydrogel
HGs	Hydrogels
NP	Nanoparticle
NPs	Nanoparticles
MTX	Methotrexate

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Introduction

The nanoparticle (NP) technology is rapidly advancing, offering innovative and effective treatments for various medical conditions such as cancer, inflammation, cardiovascular diseases, psoriasis, diabetes, bone regeneration, gene therapy etc. These nanoparticles (NPs) are designed to overcome challenges like poor selectivity, known targeting sites, and side effects on various body tissues. They also address the limitations of micron-size particles, including surface area, site specificity, retention at the targeting site, swelling behaviour, drug loading, and release behaviour. Nanogels (NGs) type of NPs have garnered significant attention over the past 20 years due to their biocompatibility, biodegradability, versatility, and safety from leakage [1–5]. In addition to in-vitro and in-vivo tests, other methods like ex-vivo and in-silico testing are used to validate drug delivery systems [6]. With the wide range of nanosized materials involved in nanotechnology-developed drug delivery systems, each material exhibits unique properties dependent on its nano-size. These properties allow for enhanced intracellular drug delivery, subcellular targeting, and the capability to access previously inaccessible body areas [7].

NGs are typically 3-dimensional submicron-sized networks of hydrophilic polymers developed by chemical or physical cross-linking that exhibit the full range of characteristics of both NPs and hydrogels (HGs). Ionic interactions, hydrogen bonds, electrostatic interactions, and hydrophobic interactions are the main types of physical cross-linking [8, 9]. While some studies have shown that NGs as large as 1,000 nm are reasonable, others have found that those as small as 200 nm are ideal for use in the medical field [10]. NGs may absorb a considerable amount of water. NG cross-linking network may be used as a grid to contain the internal fluid system, while the absorbed water is used as a filtration medium for cargo diffusion. NGs with an unsuitable zeta potential help avoid immune phagocytosis and may resist the adsorption of negatively charged proteins [2, 11]. Considering their high-level performance in extending blood circulation and boosting healing effectiveness, several drug carriers, including liposomes, polymer vesicles, and micelles, have drawn broad interest in studying controlled drug delivery [12–14].

NGs have been extensively researched for integrating and releasing actions of bioactive substances such as proteins, vitamins, and drugs [15], DNA, antigens, oligonucleotides, genes, as well as inorganic molecules such as quantum dots, silver NPs, magnetic NPs [16]. NGs may be delivered using one of two methods: passive targeting or active targeting. In the case of passive targeting, the size, swelling, surface charge, and various physicochemical attributes of the NGs reveal drug release. Active targets involve conjugating NGs with particular scaffolds that selectively identify and bind with some over-expressed receptors at the target areas, like in tumours. This process causes conjugated NGs to accumulate at the target site [17], attaining more than 98% loading efficiency. Since NGs are HGs, their capacity to resemble tissue is another distinctive quality that distinguishes them because of the significant water content and the bio-compatible ingredients utilized. Such gel topically has a calming effect that is highly helpful in treating conditions like wounds [18].

Drug delivery system

Developing effective treatments and tackling disorders is a significant challenge for formulation nowadays. The existing drugs and active molecules are often effective mechanisms for treating specific disorders, but their efficacy is sometimes severely constrained by challenges in their delivery. To bring drugs and active molecules to the target sites where they will have the most incredible pharmacological effects, a process known as a drug delivery system has been developed [19]. One of these systems' significant benefits is the ability to regulate the rate, timing, and target site of a drug's delivery to a patient [20]. NPs are essential in drug delivery as well-synthesized nanocarriers can meet high drug-loading levels and regulate drug release [21]. Their nanostructures and functions may increase delivery processes such as selectivity, decreasing toxicity and side effects. Polymeric NPs are essential in this context since their structure provides good bio-compatibility and biodegradability and can be readily functionalized [22]. Furthermore, while dealing with suitably functionalized polymer chains, it is reasonable to modify factors such as mechanical qualities, composition, or degradation rate. In the interest of completeness, these formulations are expensive, restricting their use in clinical practice.

Controlled and targeted drug delivery system

Compared to traditional formulations, controlled and specifically designed drug delivery systems are intended to produce significant benefits. They are optimizing the drug release from the delivery system since the rate and duration of the procedure dramatically affect the therapy's efficacy [23]. Controlled drug delivery systems (CDDS) should avoid restrictions on drug concentration within the targeted therapeutic range. Actuality, the drug release profile of traditional drug delivery techniques, is characterized by a rapid decline below the lowest effective concentration, followed by an increase to a peak concentration over the maximum safe concentration. A correctly constructed CDDS ensures the drug's

blood concentration profile stays within these limits [24]. However, controlled drug release is not enough if it fails to take place in the tissues that we wish to address; a targeted drug delivery system (TDDS) is a different approach that can preferentially access a specific target area, emphasizing therapeutic benefits and minimizing undesirable effects produced by the drug's interaction with various body tissues [25]. TDDS and CDDS provide the potential to utilize a smaller dose of the drug compared to conventional therapies, and the carrier's structure may keep the drug in-vivo, preventing early deprivation or quick breakdown [26].

NGs

NGs are promising for therapeutics, diagnostics, macromolecules, and other applications. NGs, primarily hydrophilic and with a large capacity for guest molecules, are highly biocompatible and have significant benefits over other nanomaterials for biomedical applications. Due to their distinctive characteristics, including stimuli-responsive behaviour, softness, and swelling, NGs shield the cargo from deterioration and removal and actively engage in the delivery process to create a regulated, triggered reaction at the target region. [27]. NGs offered merits are as follows:

- High water content makes materials more bio-compatible, which causes them to behave like actual tissue and elicit favourable immune reactions.
- Nanocarriers are biodegradable, making them non-toxic.
- Drug loading capacity is high.
- Controlling drug release by adjusting crosslinking densities [28].

- Resist entrapment by the reticuloendothelial system quickly [29].
- Tiny size makes them better at permeating biological membranes.
- Drugs and charged solutes that are both hydrophilic and hydrophobic may be included (Fig. 1) [30].
- Superior transport qualities [31].

Limitations of NGs NGs provide many benefits but have specific vital points that sometimes prevent their application. The limits of NGs are listed below:

(a) The solvent and surfactants must be removed entirely using expensive methods.
(b) There may be residual residues of monomers or surfactants, which might be hazardous.
(c) Variation in manufacturing, whereby the usual qualities of NGs are only attainable within a specific range of dimensions [32].

Types of NGs A cross-linked HG particle with a polymer basis known as an NG is sub-micron-sized [2]. NGs are highly customizable in size, shape, surface functionalization, and degradation processes and may be natural, synthetic, or a combination [33]. Based on the kind of crosslinking, reactivity to external stimuli (including pH, temperature, light, ionic concentration, etc.), and production techniques, NGs may be classified into several types (Fig. 2).

Polymers used for NGs Hydrophilic polymers, which typically absorb abundant water within their crosslinked

Fig. 1 Macroscopic and microscopic view of NGs. The figure was developed using BioRender (www.biorender.com) (accessed 5 October 2023)
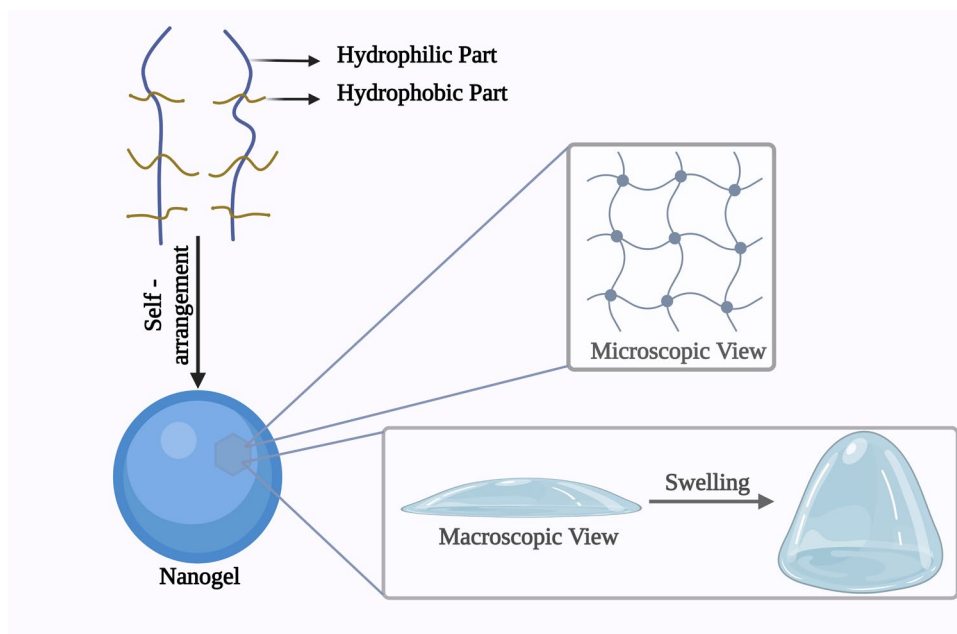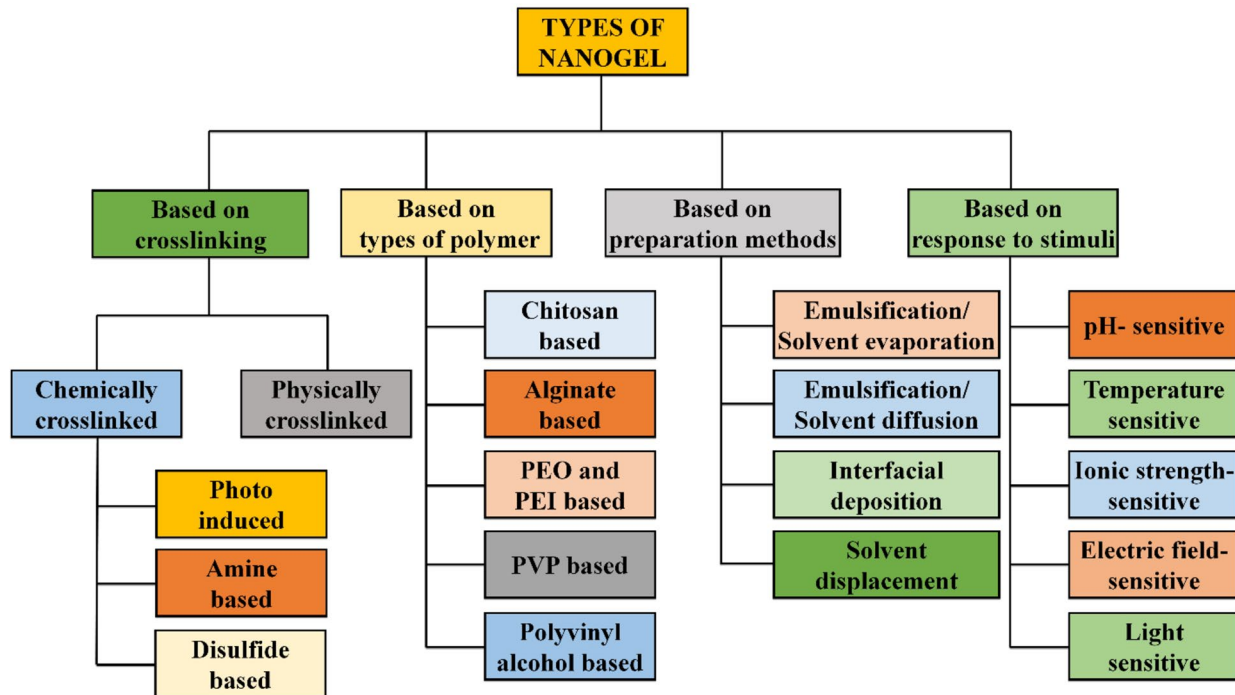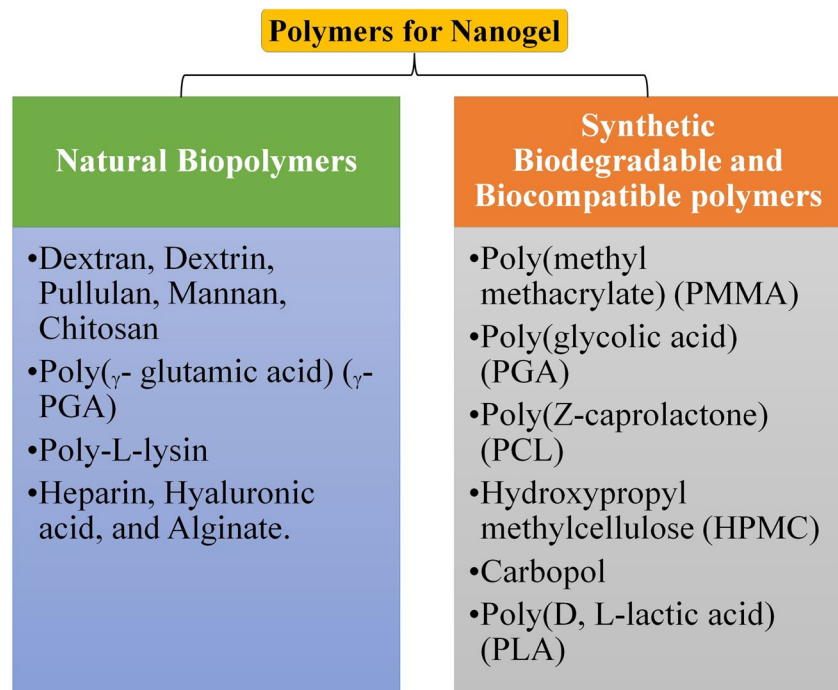
Fig. 2 Different types of NGs

frameworks, are the key components of NGs. These NGs are distinguished by their biological inertness and water sorption capabilities, which cause them to expand up to 1000 times in water, according to the 3D structure of the polymers utilized in their manufacturing (Fig. 3).

Surface functionalization of NGs for delivery of drugs Drug and biological molecule entrapment is possible using NGs. As a result, they may be used extensively in transporting genes and proteins. Both passive and active drug targeting are possible by adjusting the particle size and surface

Fig. 3 Different nature of polymers used to design to develop NGs

Polymers for Nanogel

Natural Biopolymers

- Dextran, Dextrin, Pullulan, Mannan, Chitosan
- Poly(γ- glutamic acid) (γ-PGA)
- Poly-L-lysin
- Heparin, Hyaluronic acid, and Alginate.

Synthetic Biodegradable and Biocompatible polymers

- Poly(methyl methacrylate) (PMMA)
- Poly(glycolic acid) (PGA)
- Poly(Z-caprolactone) (PCL)
- Hydroxypropyl methylcellulose (HPMC)
- Carbopol
- Poly(D, L-lactic acid) (PLA)

characteristics to prevent fast clearance by phagocytic cells. Controlled and prolonged drug is delivered at the desired site, increasing therapeutic effectiveness and minimizing side effects [34]. Due to their small volume, NPs can penetrate tissues, even the smallest capillaries, via paracellular or transcellular routes. NGs offer a significant drug-load capacity, a low floating density, and a high degree of stability during dispersion in aqueous mediums (Fig. 4). In comparison to other NPs, particularly in terms of drug loading, NGs show potential as suitable nanomedicine carriers [35].

NGs: Drug incorporation techniques Due to their incredible ability to target a wide variety of organs, NGs have been widely accepted in nanotechnology, resulting in dual nature: (a) As an HG system, which boosts their ability to load drugs, and (b) a system with nanoparticulate that enables them to reach deeper organs and tissues.

Incorporation of drugs inside the NGs may be achieved by numerous methods (Fig. 5), including-

- Biological agents can covalently conjugate either during or after the development of NGs. Develop nanosized HGs (Table 2), mutated enzymes can copolymerize using acrylamide for inverse micro-emulsion and diluted water-based solutions. [36, 37].
- Drug molecules are physically trapped inside NGs. Proteins have been included in cholesterol-modified pullulan NGs, and small interfering RNAs (siRNAs) have been incorporated into hyaluronic acid (HA) NGs using this approach [38, 39].

- Drug loading through passive/diffusion, for instance, NPs and dexamethasone, can be separately introduced within the dextran lysozyme NGs via diffusion, and the NGs are agitated in excessive drug or NP solutions. Generally, the drug loading produced by these methods is small, often less than 10% by weight [40–42].

Potential applications of NGs in the treatment of various diseases

NGs have gained significant attention from research groups worldwide. These structures have been developed to treat various pathologies, including cancer, spinal cord injury, ischemic stroke, cardiovascular diseases, wound healing, bone regeneration, psoriasis, inflammation, etc. They have also been used for delivering anaesthetic drugs. In the following sections, we will analyze the different pathologies in which NGs have been applied and tested. We will provide examples and references to highlight the importance of these formulations in nanomedicine.

NG in CNS-related diseases Numerous drugs are used to treat CNS-related diseases and other brain disorders. Still, their low bioavailability in such organs, owing to the inadequate permeability of the blood–brain barrier (BBB), has permanently restricted their capacity to enter the brain [43, 44]. A more effective nano-system might lead to better therapy for diseases associated with the brain (Table 1). However, many current methods of brain targeting in nanotechnology involve improving drug access to the brain. Drug bioavailability has
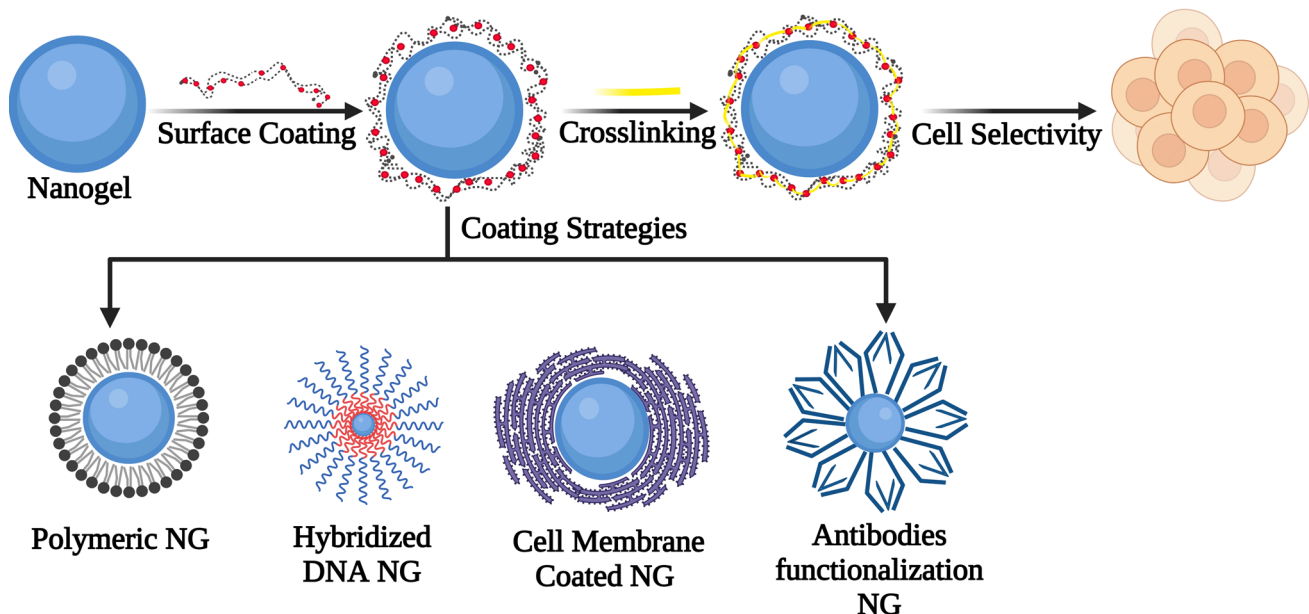
Fig. 4 Coating strategies of surface functionalization of NGs for selective targeting the cells. The figure was developed using BioRender (www.biorender.com) (accessed 14 October 2023)

Fig. 5 Various techniques used to prepare NGs

constantly been significantly enhanced by polymeric NPs, some of which can cross BBB [45]. The incorporation of NGs is an efficient nanoparticulate technology for effective brain-targeted therapy. Methotrexate (MTX), an anticancer drug, has been developed as a NG and is an extensively used chemotherapeutic drug with a vital role in malignancies and autoimmune disease treatment. MTX was added to the NG system to increase BBB permeability, and polysorbate was used to functionalize the surface [46, 47].

NG significantly boosted the capacity and efficiency of drug loading. The in-vitro experiments confirm the NPs' suitability for brain administration. A study found that even though the drug plasma concentration decreased due to intravenous administration, the drug crossed the BBB and safely entered the brain slowly and controlled. It demonstrates that the drug was absorbed gradually and without risks into the brain. Compared with free drugs, MTX concentrations in the brain were considerably more significant in both kinds of NGs (surface-modified and untreated NGs). Results indicated that using drug-loaded NGs increased MTX concentration in the brain by 10–15 times, presenting a promising future for NGs used for brain delivery. Oligonucleotides (ODN) have also been developed as NG to target CNS against neurodegenerative diseases. Research demonstrated that NG formulations with ODN successfully crossed the BBB. When transferrin or insulin is added to the NG's

surface, the effectiveness of the transport is significantly improved to the target. Compared to free ODN, the concentration of phosphorothioate ODN rose onefold inside the brain after 1 h of intravenous NG injection while decreasing twofold in the spleen and liver [48–50]. Another researcher developed cisplatin-loaded NGs coupled over monoclonal antibody conjugates to mark exceedingly expressed connexin 43 (Cx43), a tumour-specific membrane protein, and BSAT1, an anion transporter specific to the brain in human glioblastoma, the most aggressive and common brain disorder in the world. The cisplatin-loaded NG formulation for treating gliomas showed higher efficacy, and the survival rate of rats was increased for around 27 days compared to the control group [51].

NG in cancer Cancer is a chronic illness that includes around 277 forms of cancer pathology [52]. Several treatments have been available, including radiation, surgeries, and targeted therapies [53, 54]. Several teams of researchers are keen on NGs since they offer an opportunity for specific delivery of drugs for cancer therapy (Fig. 6). Specific formulations and surface functionalization using particular ligands may be helpful strategies to selectively target malignant cells within the body and give non-invasive treatments [55]. NGs have the potential to cure diseases such as breast cancer. In this work, the researchers produced dextrin NG encapsulated

Table 1 Potential applications of NG and their outcomes

Drug	Size	Polymer	Method	Drug use	Outcome	Refn(s)
MTX	118.56±15.93 nm	Chitosan	Ionic gelation process	Brain disorder	Surface-modified MTX-loaded NGs have excellent bio-properties to deliver into the CNS	[46]
MTX	113.43±7.06 nm	N-isopropyl acrylamide and butyl acrylate	Surfactant-free emulsion polymerization	Anti-inflammatory	Concentration gradient and flux-ins increased and reduced PGE2 production	[98]
Dox	90±20 & 270±20 nm	Chitin-PLA	-	Liver carcinoma	Dox-chitin-PLA-CNGs exhibit a significant cytotoxic effect against HEPG2 cells	[59]
Dox	60 nm at 37 °C	N-isopropylacrylamide-co-acrylic acid polymer PNA	-	Hyperthermia	The cellular uptake of Dox-PNA increased by approx. 43% at pH 6.8, but no change appears at pH 7.4 as temperature rises and pH decrease	[105]
Dox	125–375 nm	Poly (l-aspartic acid β-carboxy benzyl ester)	Oil-in-water emulsion method	Antitumor	Lysosomal enzyme leakage promoted tumour cell death, indicating cytotoxicity	[145]
Bleomycin	150 nm	Chitosan and Pluronic F-127	Ion gelation technique	Chemotherapy	Biodegradable chitosan NGs with a stimuli-sensitive nature release the anticancer drug's ability to treat skin cancer	[146]
siRNA	sub-100 nm range	Dendritic polyglycerol and poly ethylenimine	Thiol-Michael nanoprecipitation	Gene Therapy	siRNA, when introduce into cells, exhibits a similar transfection performance, leading to a significant significant reduction in cytotoxicity	[112]
Dox and rose Bengal	92.5±3.5 nm to 601.1±23.2 nm	PAA-b-PNIPAAm NGs	Polyelectrolyte complex method	Breast cancer	Dox loaded in NGs showed inhibition improvement by chemical therapeutic or photodynamic effect against MCF-7/ADR cancer cells	[147]
MTX	460 nm, PDI<0.30	Dextran NG	Polymerization precipitation	Chemotherapy	MTX-DEX NG significantly compromised HeLa cell viability due to effective cell internalization and release of MTX in the cytoplasm	[148]

Table 1 (continued)

Drug	Size	Polymer	Method	Drug use	Outcome	Refin(s)
5-fluorouracil	100 to 190 nm	N-isopropyl acrylamide and N-(hydroxymethyl) acrylamide NGs loaded with sodium copper chlorophyllin	Emulsion polymerization	Chemotherapy	Enhanced cell mortality to a maximal extent	[149]
Tacrolimus	110.5 nm	Poly (N-isopropyl acrylamide) with dendritic polyglycerol NG	N/A	Treatment of skin inflammation	Tacrolimus NG represents an alternative water-based formulation for topical delivery of high molecular weight drugs	[150]
Insulin	520 to 526 nm	2-(acryl amido) glucopyranose, 3-acrylamidophenylboronic acid, and boron dipyrromethene	Reversible addition-fragmentation chain transfer polymerization	Detection and treatment of diabetes	NGs with carbohydrate moieties bearing phenylboronic acid have shown a significant improvement in efficacy. These glucose-sensitive NGs are a reliable option for self-regulated insulin delivery system	[151]
Dox	90–230 nm	Poly (vinyl caprolactam)-based acid degradable NGs	Incubation	Anticancer	Dox-carrying NG showed showed more significant antiproliferative activity against tumour cells	[152]
Coumarin 102	82–153 nm	o-nitro benzyl acrylate-modified NGs	Hydrophobic effect	HeLa cervical cancer cells	Coumarin NG showed excellent cell viability at different concentrations (>91%), demonstrating photocleavage NG is more biocompatibility in a drug delivery system	[153]
Labeled insulin	236 nm	PEG and polycyclic phenylboronic ester	N/A	Hypoglycemic effect	Dual-sensitive NG shows glucose-responsive insulin release, promoting the release rate of incorporating glucose oxidase	[154]
Dox and indocyanine green	108.1–121.4 nm	Poly [poly (ethylene glycol) monomethyl ether methacrylate]	Encapsulation	Photothermal-chemotherapy	The synergistic effects of photothermal chemotherapy based on NIR light-triggered drug release at 805 nm showed superior tumor growth suppression	[155]

Table 1 (continued)

Drug	Size	Polymer	Method	Drug use	Outcome	Refin(s)
Purpurin 18 and 10- hydroxy camplothecin	66.95 ± 1.93 nm	90% Bis(2-hydroxyethyl) Disulfide	Iron ion gradient	Enhanced synergistic cancer therapy	A high concentration of Glutathione in the tumor activates the disulphide bond in developed NGs, thus releasing a loaded drug that shows antitumor effect	[156]
Spantide II and Ketoprofen	169 nm- 183 nm	Chitosan with poly-(lactide-co-glycolic acid)	Solvent evaporation	Anti-inflammatory	Translocating the NPs improved skin permeation for spantide II and ketoprofen, improving skin contact time and hydration	[157]
Saporin	162 nm	Dual-targeting, saporin-loaded HA	Inverse nanoprecipitation technique	Breast cancer	Dual-targeted EGFR and CD44 HA NGs offered more significant metastatic breast cancer activity	[158]
Ribonuclease A	488 nm- 518 nm	Poly (L–glutamic acid)–graft-poly (ethylene glycol) methyl ether (PLG-g-mPEG)	N/A	Breast cancer	Nano RNAse combined with vascular disrupting agent PLG-g-mPEG/combretastatinA4 (nano-CA4) results in TSR 91.7% These hypoxic–sensitive NGs provided excellent delivery of RNAse	[159]
Interleukin-12	20–30 nm	Cholesterol-bearing pullulan-based NGs	Incubation at room temperature method	Cancer	NPs offer newer therapeutic intervention technology and take advantage of bioactive cytokines, which results in the slow and sustained release of biocompatible NPs	[68]
Irinotecan	86.5 ± 7.4 nm	Irinotecan-loaded gelatin NGs	Double emulsion solvent evaporation method	Colorectal carcinoma	Platelets membranes (PTM)-gelatin NG-Irinotecan formed from the natural properties of its parent effectively accumulate at tumor sites due to the coated PTM's tumor-targeting capabilities	[76]

Table 1 (continued)

Drug	Size	Polymer	Method	Drug use	Outcome	Refn(s)
Rolipram	155 nm	PEG-PEI coated with amines	Emulsification-evaporation method	Spinal cord injury	Biodegradable NS-deliver Rolipram reduced the pro-inflammatory responses mediated by the activation of astrocytes	[78]
Paclitaxel, minocycline hydrochloride	50 to 220 nm	polylactic-co-glycolic acid	Directly inserted method	Spinal cord injury	The formulation offered a dual drug delivery system, showing reduced scar tissue and enhanced neuronal regeneration	[79]
Minocycline	N/A	Poly-ε-caprolactone-based NPs	-	Spinal cord injury	NPs potentially modulate resident microglial cells, reduce the pro-inflammatory responses, and maintain a pro-regenerative milieu	[80]
Minocycline	17.12 ± 0.27 to 18.97 ± 0.21 nm	PEG-polylactic-co-glycolic acid	Emulsion polymerization process	Spinal cord injury	Drug-loaded micelles decrease lesion cavity area, resulting in prolonged survival of axons and myelin sheaths from the injury	[81]
Urokinase	16.23 ± 1.62 cells/mm2	PEG-conjugated urokinase NGs	Crosslinking reaction method	Ischemic stroke	NGs reduced the severity of Ischemic stroke, improved ischemic brain tissues, protected BBB, inhibited apoptosis, and decreased neurotoxic behavior	[88]
Urokinase	200 nm	uPA-loaded hollow NGs	Ultrasonic spray method	Ischemic stroke	NGs prolonged the protein's circulation duration with better protection of BBB	[91]
AT1R-PspA	N/A	Cationic cholesteryl-group-bearing pullulan NG	-	Hypertension and Pneumococcal infection	Intranasal vaccination loaded with ATR-PspA prevents hypertension and provides protection against pneumococcal infections	[115]
Bosentan monohydrate	230–305 nm	Propyl Karaya gum NGs	Solvent evaporation method	Systemic hypertension	NGs exhibited pH-dependent swelling, released under simulated gastro-intestinal conditions preferentially with the excellent oral delivery system	[116]

Table 1 (continued)

| Drug	Size	Polymer	Method	Drug use	Outcome	Refn(s)
N, -L-rhamnopyranosyl vincosamide	35.25 ± 1.65 nM/g	N-Isopropylacrylamide-methacrylic acid NG	Magnetic HG method	Myocardial infarction	Biomarker expression levels decrease with an increase in drug conc. Treatment with Vincosamide raised glutathione and superoxide dismutase levels, decreasing malondialdehyde levels in cardiac tissues	[117]
Human cardiac stem cells	N/A	Poly (co-acrylic acid/N-isopropyl acryl amine)	Encapsulation	Myocardial infarction	NGs offer a hydrophilic environment required for cell proliferation and engraftment, enhancing cell activity and survival rate	[118]
Silver sulfadiazine	975-120 nm	Alginate-coated chitosan NG	Dissolution method	Wound healing	NGs showed excellent drug release profile with initial bursts followed by slow and sustained release	[123]
Chlorhexidine diacetate	120 nm	Chlorhexidine diacetate-loaded lysine-based HG	Enzyme degradation method	Wound healing	Formulation achieved hemostasis quickly, thus enhancing wound healing rate	[124]
Baicalin	~362 nm vs. ~530 nm	Gellan-cholesterol nanohydrogels	Phosphate buffer method	Wound healing	NGs serve as a moisturizer for the stratum corneum, leading to baicalin accumulation in the epidermis. They diffuse into the dermis, combating oxidative stress, controlling inflammation, and stimulating skin restoration	[125]
Interleukin-II	317 ± 195, 1201 ± 375, and 1007 ± 459 nm	Rh-IL-II-loaded chitosan	Ionic gelation method	Wound healing	NGs reduced malondialdehyde and elevated glutathione levels in injured tissues, resulting in an increased healing rate	[127]
bFGF and VEGF165 genes	70 nm-100 nm	Heparin-modified supramolecular NGs	Direct dissolution	Wound healing	NG complex is delivered to endothelial progenitor cells and promotes differentiation and neovascularization of cells in the ischemic limb model	[128]

Table 1 (continued)

Drug	Size	Polymer	Method	Drug use	Outcome	Refn(s)
Bone morphogenetic protein 2 (BMP2)	~30 nm	Cholesteryl and acryloyl bearing pullulan	Cross-linking method	Bone Regeneration	NGs efficiently stabilized BMP-2-dependent bone repairing and induced infiltration of osteoprogenitor cells	[131]
Mesoporous bioactive glass	N/A	P-(N-isopropyl acryl amide-co-butyl methyl acrylate)	Emulsion polymerization	Bone regeneration	NGs effectively delivered the drug content to the primary osteoblast, promoting tissue regeneration	[160]
Clobetasol	132 ± 14 nm	Chitin NG	Controlled regeneration method	Psoriasis	NGs were cytocompatibility against dermal fibroblast and demonstrated toxicity for monocytes and proliferation of HaCaT cell lines. NGs significantly inhibited COX-2 and LOX-5 and were associated with inflammation	[137]
MTX	196 ± 14 nm	Chitin NG	Magnetic stirring	Psoriasis	NGs showed toxicity towards tested cell lines, favored its efficiency to treat inflammation and cell proliferating psoriasis	[139]
miR-210 antisense	150–300 nmol/L	High-density lipoprotein	Dispersion method	Psoriasis	NGs remarkably decrease miR-210 expression in skin lesions and CD4+T cells from IMQ-induced psoriasis	[141]
Naproxen	311 ± 14.1 nm	Poly-N-isopropylacrylamide NG	surfactant-free emulsion polymerization	Skin inflammation	NGs activated as the drug entered the epidermis, and the steady-state flow rate increased by 2.8 folds, reducing COX-2 activity by 50%	[161]
Tannic acid	250 nm	Polymeric phenyl boronate-tannic acid NG	simply mixing method	Peritonitis	NGs demonstrated excellent reactive oxygen species (ROS) scavenging activity, leading to decreased macrophage inflammation caused by external (ROS)	[162]

Table 1 (continued)

Drug	Size	Polymer	Method	Drug use	Outcome	Refn(s)
Triclosan and flurbiprofen	100–330 nm and 150–400 nm	Poly-ε-caprolactone and chitosan-based NG	Directly loaded method	Periodontitis	NGs carried the drug in the amorphous state, leading to an increment in drug release. Treatment results showed considerable improvement, including inflammation and plaque reduction	[163]
Prednisolone	300–600 nm	Chondroitin sulfate – glycyl prednisolone conjugate NG	Solvent evaporation	Colitis	NGs' distribution and pharmacokinetic characteristics of GIT made them ideal for large intestinal administration. Results showed that NGs have a high potential to treat colitis	[164]
bupivacaine	<300 nm to >500 nm	Poly(N-isopropylacrylamide)-based NG	-	Local anesthetic	An increase in anionic charge density or a decrease in the size of NGs made an extended period of anesthetic release profile	[165]
Bupivacaine	198.4 ± 1.5 nm	Nanostructured lipid carriers + sodium alginate solution	Emulsification-ultrasonication method	Local anesthetic	NGs contain biodegradable excipients and do not require higher drug conc., making them a viable option for post-operative pain management	[166]
Deferoxamine	<10 nm	ROS-responsive polymeric NGs	Direct method	Hemochromatosis: Iron overload	NGs have high iron binding and exclusion abilities, resulting in lower serum ferritin levels and enhanced faecal elimination of iron-bound chelates	[167]
Isoniazid and Rifampin	60 to 130 nm	Genipin-crosslinked deacetylated chitosan NG	Immersion method	Tuberculosis	NGs demonstrated promising antitubercular activity due to prolonged release of drug content	[168]

Fig. 6 Fate of NGs to act on cancer using endocytosis. The figure was developed using BioRender (www.biorender.com) (accessed 1 November 2023)
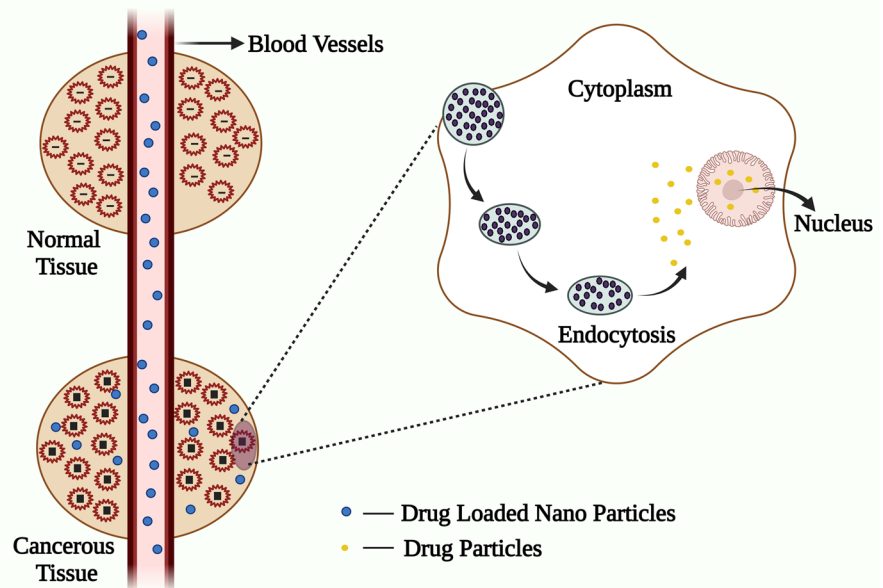
by Plerixafor and supplied with Dox (Table 1) [56–58]. They coupled with the PLG-g-m polyethene glycol (PEG)/combretatatinA4 nano-formulations using azobenzene and cyclodextrin attached to polyglutamic acid (PGA)-graft-PEG methyl ether NG revealed a tumour reduction rate of 68.7%, that was increased to 91.7%. NGs based on cholesterol are a significant and actively researched method for treating cancer. This study created IL-12-loaded pullulan (CHP)-based NGs that include cholesterol [59].

In-vivo experiments showed that this technique may slow down fibrosarcoma development. In separate research, vascular endothelial growth factor (VEGF)-specific siRNA was administered via cholesterol-endowed cycloamylose through spermine NG, and the ability to inhibit neo-vascularization and proliferation of renal cell carcinoma [60]. Hyaluronic acid is a significant polymer incorporated to produce NGs to treat cancer. Contesting it, researchers developed a cisplatin-crosslinked hyaluronic acid (HA) NG comprising Dox [61]. Dox and cisplatin had a synergistic effect, increasing the biological activity while decreasing toxicity, resulting in favourable outcomes during in-vivo tests. The identical polymer produced a zein NG, including curcumin, crosslinking using HA, which was efficient towards a CT26 tumour model (Table 1) [62]. As a result, the scenarios provided do not represent the formulae that may be employed. The reduction-responsive polypeptide NG containing Dox demonstrate encouraging in-vivo results due to its exceptional security and cancer-inhibitory properties [63]. Researchers also developed pullulan NGs featuring similar characteristics [64]. In this approach, two independent pullulan NGs for administering Dox were formed with two

distinct cross-linking agents, leading to tumour suppression (83.37%) in-vivo studies utilizing an ortho ester-modified Pluronic copolymer (acid-labile) as the crosslinking mediator. Another investigation looked into another NG composition [65]. Researchers developed a lactobionic acid-modified soy-protein NG to deliver Dox. In-vivo investigations demonstrated that this combination facilitated tumor targeting and treatment efficacy. The potential to alter the composition of NGs for selective drug release activities is an attractive feature. In this context, transferrin-modified poly-sulfamide NGs enabling Dox loading were developed [66]. In-vivo studies presented that the formulation had tumour-targeting attributes, which could improve cancer treatment. This investigation used a different approach. In this instance, they synthesize an irinotecan-loaded gelatin NG membrane with platelets embedded. The prepared NGs decrease in-vivo cancer cell growth, reducing side effects [67].

However, hepatic cancer (HCC) is thought to be the third leading cancer-related cause of death worldwide [68–72]. Among the most often used chemotherapeutic drugs for the treatment of liver carcinoma is doxorubicin (Dox), [73]. However, it requires an effective therapy potential because of its decreased effectiveness as a consequence of its severe toxicity. Additionally, Dox has a history of being rapidly metabolized into inactive derivatives, which further reduces its effectiveness. A composite biodegradable NG that are pH-sensitive for local injectable administration was synthesized to counteract the harmful effects of Dox, such as cardiotoxicity and the present issues with HCC [74]. The NG system target tumour tissues due to the enhanced permeability and retention (EPR) effects. It releases drugs through pH-controlled hydrolysis in endosomes and lysosomes

through the endocytic route (Table 1). This results in more precise drug delivery with fewer side effects and enhanced effectiveness in cancer treatment. Chitin-poly L-lactic acid composite NGs (CNGs) successfully included Dox, with 86% entrapment efficiency. At an acidic pH, chitin-PLA and Dox-chitin-PLA CNGs resulted in more enlargement and drug release. Additionally, these NGs demonstrated no haemolysis of RBCs, demonstrating the systemic route's safety. In-vitro tests have demonstrated improved cytotoxicity employing pH-sensitive NGs, which deliver the drug with low pH, specifically where the tumour occurs without producing adverse effects via systemic drug distribution [75].

Nano formulations with appropriate surface charge and size offer a vast opportunity for cytotoxic drugs to target specific regions owing to their superior biological membrane permeability. Concerning the topical distribution of drugs through small gels, NGs among contemporary Nano formulations are gaining attention. Chitin NG of 5-fluorouracil (5-FU) is a skin cancer drug thus far produced. The study's findings led to the effective loading of 90% of the drug in the NG, which had a higher capacity for swell and drug release at an acidic pH. Although introducing 5-FU to the NG didn't enhance its penetration for various reasons, it might increase the gel's retention period for the deepest layers of skin (up to 5 times) and is advantageous since the therapy's targets, melanocytes, are found in deeper layers [76].

Moreover, hyperthermia is an abnormal elevation in body temperature or overheating [77]. Whole-body hyperthermia (WBH) and hyperthermic perfusion treatments, such as hyperthermic isolated limb perfusion (HILP) and hyperthermic peritoneal perfusion (HPP), differ from local/interstitial and regional hyperthermia [78]. Clinical investigations on people with locally advanced malignancies supported the application of regional and local hyperthermia [79]. These studies found a remarkable association between administered doses and outcomes. In phase II investigations, regional and local hyperthermia were used in addition to chemotherapy and radio-chemotherapy. The findings suggest that hyperthermia has many therapeutic benefits [80]. The initial heat-activated formulation of a liposomal carrier for drugs to be used in human clinical trials is also thermosensitive liposomal Dox (Table 1) [81]. One of the most popular antineoplastic drugs used in the treatment of human cancer is Dox [82]. The study conducted by the researchers involved the synthesis of a dual pH and temperature-sensitive PNA NG, which was used to deliver drugs. Under normal conditions, the PNA NG was hydrophilic (Table 1).

However, upon heating through its LCST (lower critical solution temperature), the NG undergoes a phase transition influenced by pH value. Because of the pH difference across cancer and normal tissues, tumour cells could preferentially absorb Dox-PNA NGs. Consequently, such NGs might deliver chemotherapeutic drugs directly to tumour cells, increasing cellular internalization during region hyperthermia therapies. Dox was covalently linked to PNA through an acid-labile bond to form NGs. The association was robust at extracellular and physiological pH, but it cleaved to release the drug when it came into contact with moderately acidic conditions in tumour cell endosomes. The approach could lessen the adverse impacts of anti-cancer drugs while boosting their ability to target tumour cells. Dox-PNA NGs may significantly enhance the combination treatment of hyperthermia and chemotherapy [83].

NG in spinal cord injury A spinal cord injury (SCI) constitutes a devastating CNS disorder that can come from both traumatic and non-traumatic occurrences [84]. The 'primary injury' involves immediate neurological impairment to the spinal cord, and the 'secondary injury' is marked by a sequence of biochemical and inflammatory responses. In the present instance, the most essential aspect of the second stage is inflammation, which is intensively studied to develop an efficient therapeutic candidate for reducing it. The two polymer-based vehicles for drug delivery developed for the treatment of SCI are NGs and NPs. The capacity to penetrate the CNS's intrinsic barrier and selectively address its cells is essential in all conditions. In a recent study, rolipram (an anti-inflammatory drug) was put into a PEG and PEI-NGs coated with amines (Table 1) [85]. In-vivo studies indicated that formulations might specifically target the astrocytes and restore motor functions in animal models in the initial stages of spinal cord injuries despite lowering the pro-inflammatory events triggered by the activation of astrocytes.

Similarly, a researcher developed poly lactic-co-glycolic acid (PLGA) microspheres carrying paclitaxel and minocycline hydrochloride introduced to alginate HG [86]. In-vivo examinations on rats with dual-drug regimens demonstrated that it successfully decreased inflammatory responses after seven days of treatment, scar tissue development, and neuronal regeneration after four weeks. In a study, the researcher developed a new and significant approach involving polymeric NPs [87]. They employed poly-caprolactone-based NPs loaded with minocycline to target microglia in their investigation. By regulating specific microglial cells, the acute therapy of the NGs in a mouse model with SCI reduced the pro-inflammatory responses while maintaining pro-regenerative surroundings for up to 10 week's post-injury. SCI was also treated with minocycline. This study developed a sialic acid-PEG-PLGA co-polymer that specifically targets E-selectin and can assemble itself into micelle formation [88]. In-vivo experiments revealed that these micelles could be assembled in SCI sites in mice, lowering the extent of the lesions and enhancing axon and myelin survival. The scientist also used polymeric NPs carrying IRF5

siRNA, which were delivered into the wounds of SCI mice [89]. Introducing these NPs altered the anti-inflammatory reaction in the wound by minimizing M1 macrophages while boosting the amount of M2 macrophages. Many conditions, other than SCI, can influence the CNS. Thus, NGs can help treat them successfully. Brain tumours, such as glioblastoma, represent an excellent illustration, as they may be highly aggressive and threatening to human life [90]. NGs have the potential to deliver immunotherapy onto glioblastoma cells in an efficient manner. They can be done by consistently developing thermo-reversible PEG-chitosan HGs designed to release T-lymphocytes [91]. These HGs have a solid capability to kill glioblastoma cells and are an essential tool for targeted immunotherapy [92].

NG in ischemic stroke Ischemic stroke can be treated through thrombolytic treatment, which includes drugs including streptokinase, urokinase, anistreplase, and tissue plasminogen activator [93, 94]. Respondent NGs, such as pH-sensitive NGs, may be beneficial for developing urokinase delivery and are considered a practical approach in stroke management. In one instance, researchers developed pH-sensitive PEG-urokinase NGs (Table 1) [95]. When the pH drops owing to microcirculatory clots, which typically cause an oxygen deficit in this sickness, the NG releases urokinase. In-vivo studies found that urokinase was introduced one hour after cerebral artery congestion, minimizing ischemia damage by preserving the BBB, strengthening ischaemic brain tissues, suppressing apoptosis, and minimizing neurotoxicity. Another investigation [96] discovered that using the same formulation outside the conventional thrombolysis interval produced encouraging outcomes for in-vivo assessment in a second study. In this research, the loaded NGs protected the BBB and decreased stimulate-neurotoxicity among rats with chronic middle cerebral occlusion. Another study developed a hollow NG carrying urokinase (made by combining chitosan glycol and aldehyde-capped PEG) for delivering urokinase under ultrasonic diagnosis conditions [97]. In-vivo investigations revealed that this formulation might prolong urokinase circulation time. The formulation provided urokinase more rapidly, increasing clot thrombolysis, and was responsive to diagnostic ultrasonography. The present study suggested by in-vivo tests that similar urokinase-loaded hollow NGs might mitigate severe ischemic stroke by enhancing urokinase's thrombolysis consequences, maintaining the BBB's integrity, preventing adverse brain haemorrhage and death of animals after one week of administration [98].

NG in inflammation MTX was initially developed as a folic acid antagonist in the 1940s. This drug primarily inhibits malignant cell proliferation by inhibiting the de novo production of purines and pyrimidines. Because high doses of folinic acid and folic acid may counteract MTX's antiproliferative effects, it is clear that MTX is an antifolate drug. Cells take up MTX via a folate carrier and convert it to polyglutamate [99, 100]. MTX is a potent drug used for cancer [101], anti-inflammatory, and immunosuppressant treatments [102]. It has long-lasting metabolites called MTX polyglutamate that retain the parent compound's antifolate actions while altering the potency of inhibiting specific folate-dependent enzymes [103, 104]. A further investigation examined how sodium carbonate (Na_2CO_3) affected the transport of MTX within a NG in vitro and the modification of prostaglandin E2 (PGE2) synthesis in skin ex vivo. A NG containing MTX was administered to resected porcine epidermal membranes. The introduction of saturated aqueous Na_2CO_3 boosted MTX flow while decreasing PGE2 synthesis (Table 1). The findings suggest a unique mechanism in which temperature changes caused de-swelling and ejection of MTX in situ. At the same time, the addition of Na_2CO_3 resulted in more solubilization and MTX release, lowering PGE2 production [105].

NG in gene therapy Gene therapy is a legitimate therapeutic option nowadays. However, the initial clinical trials were discontinued due to serious adverse effects [106]. Two out of ten patients who underwent retroviral gene therapy for X-linked severe combination immunodeficiency (X-SCID) developed T-cell leukaemia [107]. Indeed, among the most promising areas of gene therapy is RNA interference (RNAi), which employs siRNAs [108]. Antisense RNA (asRNA) was initially utilized for gene silencing in rats, and this work found that long dsRNA triggered selective mRNA degradation in C. elegans. The sense and antisense strands within dsRNA produced up to tenfold quieter than either strand alone, resulting in Post Transcriptional Gene Silencing (PTGS). After RNAi was discovered in lower eukaryotes, biomedical researchers found it also occurs in mammalian cells [109–111]. A new method for delivering siRNA into cells has been developed using a platform called cationic dendritic polyglycerol (dPG-PEI) NG (Table 1). This platform has demonstrated a similar transfection performance to the conventional 25 kDa branched polyethyleneimine (PEI), significantly reducing cytotoxicity. The NG synthesis method employs a thiol-Michael nano-precipitation approach, allowing sensitive contents to be added directly during the NG synthesis. pH-sensitive benzacetal linkages in the NG network help to release the content. The cationic NG platform represents a ready-for-use transfection solution that may be administered directly to cells without requiring complex polyplex production techniques. The new platform ensures that polyplexes and their exact sizes are specified irrespective of the preparation technique [112].

NG in cardiovascular diseases These are the significant causes of death globally [113]. It covers a variety of diseases, including cerebrovascular, venous thromboembolism, peripheral artery, congenital and coronary heart disease [114]. Various factors, like genetics, hypertension, diabetes, and obesity, can cause cardiovascular diseases. Several researchers are exploring using NGs to deliver drugs to treat these diseases (Fig. 7). Multiple approaches are available to treat hypertension. Still, a novel therapy option has been found that can also treat pneumococcal pneumonia. The technique employs drug nanocarriers to provide an intranasal vaccine (Table 1) [115]. The novel therapy involves cationic-charged cholesteryl-pullulan NG bearing Pneumococcal surface-protein A (PspA) and Angiotensin 1 Receptor (AT1R) from the pneumococcal surface. AT1R antagonists efficiently decrease blood pressure, excluding side effects in rat models. PspA can trigger immunity against Streptococcus pneumoniae. This novel therapy has the potential to alter the treatment of hypertension and pneumococcal pneumonia. In-vivo studies have shown that immunization effectively avoids lethal pneumococcal infections by lowering blood pressure. Another study presents a distinct approach to treating hypertension using NG compositions [116]. The researchers developed NG of amphiphilic Karaya gum with a 3.24 propyl group substitution to distribute Bosentan monohydrate inside the colon selectively. In-vivo studies demonstrated that the NG could effectively lower blood pressure for up to 10 h following delivery, with the most significant decrease occurring after 8 h, reducing by approximately 31%. Besides hypertension, other potential cardiovascular disease treatments use NG-based drug delivery systems. This study developed an N-isopropylacrylamide-methyl methacrylate NGs to administer N, L-rhamnopyranosyl vincosamide and determine cardioprotective attributes. The study revealed that these NGs have intriguing cardioprotective capabilities [117]. In-vivo studies demonstrated that these structures could significantly reduce heart damage in the Dox-induced toxicity model. In further studies, researchers developed temperature-sensitive poly (N-isopropyl amine-co-acrylic acid) NGs containing cardiac stem cells of humans to treat myocardial infarction. These NGs were in-vivo against mouse and pig models, proving their capability to decrease scar size and maintain heart function without causing systemic inflammation [118].

NG in wound healing The wound healing process consists of four phases: inflammation, proliferation, production of the extracellular matrix components, and remodelling [119, 120]. This biological process involves various elements, including keratinocytes, platelets, immunological cells, fibroblasts, and microvascular cells [121]. Historically, various compounds, especially those derived from plants with medicinal properties, have been utilized to accelerate wound healing [122]. Nanocarrier-based techniques, like NGs, have been extensively researched to enhance treatment effectiveness and targeted delivery of active substances. During the process of wound healing, there is a possibility of infection. Researchers have developed chitosan-based NGs packed with an antibacterial drug called silver sulfadiazine to tackle this issue. These NGs were then compared to commercial formulations containing the same chemical (Table 1) [123]. The results of in-vivo experiments have shown that the NGs are an effective treatment for burn wounds. The concentration of silver sulfadiazine necessary to accomplish this effect

Fig. 7 Schematic representation of treatment of cardiovascular disease (myocardial infection) using NGs. The figure was developed using BioRender (www.biorender.com) (accessed 7 November 2023)
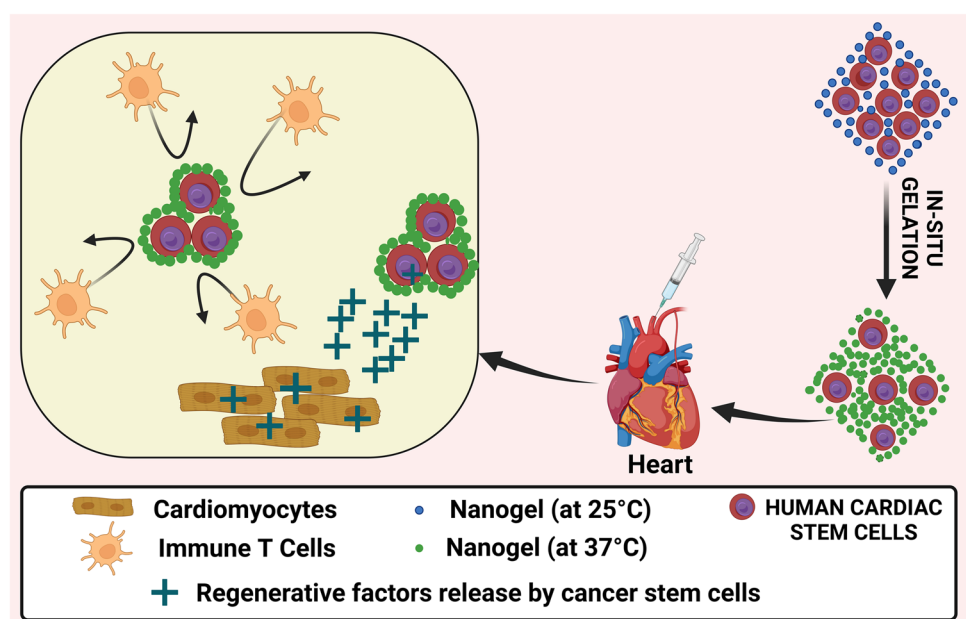
is lesser than that of commercial formulations [124]. Their research created a lysine-based NG with the antiseptic/disinfectant chemical chlorhexidine diacetate. The loaded NGs were combined with HGs containing methacrylate methoxy PEG and aminoethyl methacrylate HA. In-vivo studies have shown that HGs containing loaded NGs possess strong antibacterial capabilities, as no bacterial biofilm was detected.

Additionally, these HGs were observed to have a quick hemostasis outcome, hastening the healing process. Researchers have also explored alternative methods of controlling inflammation during wound healing. Scientists synthesized gellan-cholesterol NGs carrying baicalin, a flavone often used to treat inflammatory conditions [125]. In-vivo studies demonstrated that these NGs suppressed several inflammatory markers, such as TNF- and myeloperoxidase, more efficiently than marketed formulations and baicalin in phosphate buffer solution. Natural compounds, like curcumin, have demonstrated remarkable wound-healing properties. In another study, researchers created NGs containing fish-scale collagen-HPMC to treat related diseases [126]. In-vivo, studies have shown that combining collagen with curcumin improves wound tightening and reduces irritation symptoms compared to alternative curcumin preparations. IL-2 is a different significant molecule in the healing process because of its positive effect on T-lymphocyte formation. The researchers designed a chitosan-based NG containing IL-2 [127], which provided exciting in-vivo results revealing a reduction in malondialdehyde, a lipid peroxidation biological indicator, and a rise in glutathione concentration. This renowned antioxidant had positive results towards wound recovery applications. In a different study, researchers developed heparin-modified pluronic NGs containing the VEGF195 and BFGF genes, stimulating wound site neovascularization [128]. In-vivo studies revealed that this composition effectively increased endothelial differentiation of cells and neovascularization.

NG in bone regeneration Bone diseases constitute one of the most prevalent causes of disability globally. Fractures, osteoporosis, and tumours are among the pathologies that cause bone diseases (Table 1) [129]. When bones are healthy, they may reestablish themselves without forming tissue with scars [130]. Fortunately, specialized treatments are frequently needed, like the application of bone alternatives with osteoconductive and osteoinductive properties, as well as the utilization of cells such as mesenchymal stem cells (human), growth factors including bone morphogenic proteins (BMP), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelets-derived growth factor (PDGF) [129]. In this instance, scientists

have developed pullulan NGs containing cholesteryl and acryloyl [131]. Recombinant human FGF18, which is used to enhance the activity of low BMP2 doses, and recombinant human BMP2 were produced using these frameworks to generate fast degradable HGs. In in-vivo studies, these formulations induced bone regeneration more efficiently than free BMP2 or a mixture of independent BMP2 and FGF18. The study showed an alternative method for using BMP2 to induce bone healing [132]. To deliver BMP2, the investigators combined polycaprolactone (PCL) with redox-sensitive c-6A PEG-PCL NG (Table 1). This combination yields nanofibers with a core–shell configuration. In-vivo investigations revealed that the NGs controlled distribution of BMP2 might promote bone defect repair.

Similarly, in a different research p-(N-isopropylacrylamide-co-butyl methylacrylate), NGs were designed to develop moieties that function as carriers for delivering mesoporous bioactive surface. The findings (in-vivo) indicate that the bioactive glass-loaded NG-based framework may aid in the repair of femur deformity in osteoporotic animals. The W9-peptide, a TNF-α and receptor activator of kappa beta antagonist, is a potent molecule that has the potential to accelerate bone regeneration. Scientists developed a CHP NG that delivers the W9 peptide [133]. Their research concluded that this framework might prevent the loss of bone in bone resorption models in-vivo. PGE2, a nonpeptide anabolic molecule, may also help with bone rebuilding. The substance's high dosage and short half-life lead to adverse effects. Researchers produced a CHP NG for PGE2 to address these issues [134]. In in-vivo assessments, PGE2 encouraged new bone development when paired with an HG sphere that cross-linked NGs.

NG in psoriasis Psoriasis is a persistent, inflammatory skin disorder that affects 1–3% of the global population [135]. Because T cells in the epidermis and dermis are activated, it is an immunologically mediated illness [136]. Traditionally, various dosage forms of MTX, retinoids, and cyclosporin are used to treat psoriasis. Various NG preparations have been developed to distribute this type of medication effectively. In this work, scientists proposed a vital method to address this issue [137]. They formulate chitin-based NGs containing clobetasol (CLCNG) for skin application (Table 1). In their study, they compared the effectiveness of prepared NGs to commercial costate cream, and results suggested that CLC NG attained equal anti-psoriatic properties with reduced skin irritation, which made it a suitable choice for skin application.

Moreover, the same team developed an MTX-loaded chitin NG for topical use (Table 1) [138]. They achieved

an overall Psoriatic Area and Severity Index (PASI) reduction of 73.11–89.22% (depending on drug dose) using these NG formulations, which was greater than the ideal reduced percentage (73–75%) for taking into account them clinically valuable, demonstrating anti-psoriatic property. They also compared their simplicity for use with a commercial MTX gel, which showed a lower PASI drop and no adverse induction. In a second experiment, they discovered that their MC NG outperformed traditional MTX oral tablets because of their lower toxicity induction [139]. Babchi oil, a naturally existing essential oil with fewer adverse effects than other produced medications, is another helpful constituent in psoriasis treatment. Cyclodextrin-based NGs carrying Babchi oil for application on the skin were developed to test their efficacy for psoriasis therapy by comparing their effectiveness to the native Babchi oil gel [140]. Their in-vivo investigations revealed that these NG were effective against psoriasis without producing visible skin irritation, inflammation, or erythema. Earlier studies indicated that MiRNA-210 plays a crucial role in this type of disease. A high-density lipoprotein NG carrying miR-210 antisense was developed, and its efficiency in reducing inflammation comparable to psoriasis in mice was demonstrated in the study, indicating its potential use in topical treatments [141].

NG in diabetes MIT and Boston Children's Hospital researchers are developing a self-operating insulin delivery system utilizing a unique nanotech technique comprising just one NG injection stabilizing blood glucose levels for up to 10 days. Due to its glucose sensitivity, the NG can monitor glucose levels and release insulin as necessary. The MIT method uses NG of a combination of oppositely charged dextran NPs, which are attracted to one another electrostatically and help the gel maintain its mechanical consistency. The inner core of the NPs comprises glucose oxidase, modified dextran, and insulin. When exposed to high blood glucose levels, the enzyme transforms glucose into gluconic acid. The dextran spheres are broken down by the gluconic acid that has thus been generated, which also releases insulin, bringing the blood glucose level back to normal. Due to biocompatibility, Dextran and gluconic acid eventually disintegrate in the body [142, 143]. In recent years, a poly (4-vinylphenylboronic acid-co-2-(dimethylamino) ethyl acrylate) [p(VPBADMAEA)] silver NP NG with insulin loading has been developed (Table 1). In the research, the polymer-bound Ag NPs were given the glucose-sensitive p(VPBADMAEA) shell, which caused the Ag NPs to react to glucose. The glucose-responsive polymer, p(VPBADMAEA), detects any variation in the concentration of glucose in the blood throughout a therapeutically meaningful range (0–30 mM) and converts this variation into an optical signal that is recognized by the optically responsive silver core (10 ± 3 nm) [144].

Challenges and future perspective

NG drug delivery systems represent a promising frontier in medical science, addressing challenges in conventional drug administration. NG offers a unique platform for controlled drug release, enhancing therapeutic efficacy while minimizing side effects. However, their widespread application faces several challenges. One primary obstacle is the intricate design required to optimize drug encapsulation and release kinetics. Achieving a balance between stability and responsiveness is critical to ensuring the NGs effectively deliver drugs to target sites.

Moreover, the potential toxicity of nanomaterials and their long-term effects on the body demand a thorough investigation and regulatory scrutiny. Another challenge involves the scalability of NG production. Developing cost-effective manufacturing processes that maintain consistent quality poses a hurdle in translating these innovations from the lab to large-scale clinical applications. Despite these challenges, the future perspective of NG drug delivery is highly promising. The versatility of NGs allows for tailored solutions to treat various diseases. In oncology, for instance, NGs can enhance the specificity of chemotherapy, redutreatcing damage to healthy tissues. Neurological diseases may benefit from targeted drug delivery across the BBB, improving treatment outcomes. Moreover, the advent of smart NGs, responsive to specific physiological cues, further amplifies their therapeutic potential [169, 170].

As research progresses, addressing challenges and refining NG technologies will propel them into mainstream medical practice, revolutionizing drug delivery and significantly improving patient outcomes across a spectrum of diseases. The collaboration between researchers, clinicians, and regulatory bodies will be instrumental in realizing the full potential of NG drug delivery systems in the future of medicine [83, 171–175].

NG: Status of patents for treatment of various diseases and their marketed products

The status of NG contain therapeutic agents used for treatment of various diseases and marketed products are showed in Table 2 and 3 respectively.

Table 2 Patents on NG used for treatment of various diseases

Patent No	Date of publication	Description/ outcome	Refn(s)
US2015/0250899A1	Sep. 10, 2015	The invention aims to overcome cancer treatment resistance, enhance therapeutic efficacy, and minimize toxicity to healthy tissues	[176]
US2007/0224164 A1	Sep. 27, 2007	The present invention indicates degradable NG DDS. NG is made of PEG. This invention shows that a polymer complex with the cancer drug cisplatin forms core shell-type gels with sizes from 1 to 2000 nm	[177]
US10206885B2	Sep. 1, 2016	NG was formed to compress one or more tumour cells by encapsulating one or more epigenetic drugs into NG base	[178]
US10,829,672B2	Nov.10, 2020	The water-dispersible or compatible NG are used as reactive additives in monomer and resin systems and 3D microgel polymer precursors in monomer-free water-based applications	[179]
US10,709,664 B2	Jul. 14, 2020	Nanolipogel is used as the core–shell of NPs, with a core polymer matrix that can contain host molecules within a liposomal shell that may be unilamellar or bilamellar, optionally cross-linked	[180]
US8242165B2	Aug. 14,2012	The invention relates to a pharmaceutical composition with NPs, such as glyceryl mono fatty acid ester, chitosan, and an anticancer drug	[181]
US 9.433,682 B2	Sep. 6, 2016	This invention delivers pharmaceutical composition to a cell using TPCG HG	[182]
US11,261,226 B2	Mar. 1, 2022	A technique for effective and stable coupling of NPs to a T-cell surface while minimizing cellular internalization and enabling the extracellular drug delivery of cytokines and small compounds for various biological applications, including targeted immunotherapy	[183]
US10,434,192 B2	Oct. 8, 2019	The innovative formulations consist of several nano-sized solid particles and a gel-forming mechanism	[184]
US 9,694,085 B2	Jul. 4, 2017	Polysaccharide NPs have been cross-linked to poloxamers, polysaccharides, and poloxamer nano-colloids. NPs may be manufactured using various methods, like inverse mini-emulsion polymerization technologies, which generate NGs with the correct shape, size, and consistency for controlled therapeutic drug administration, imaging, and theragnostic activities	[185]
EP 2 906 617 B1	Aug. 19, 2015	The current invention addresses some disadvantages by developing a HG that may be employed as a transporter for carrier-linked prodrugs, allowing the controlled and prolonged release of more giant drug molecules	[186]
US 9,763,968 B2	Sep. 19, 2017	Doxycycline or minocycline are cross-linkable polymer formulations that generate non-toxic and biocompatible HGs in situ. Methods for applying HGs to the skin tissues of mammals that have encountered vesicant chemicals such as sulfur mustard (SM), nitrogen mustard (NM), or half mustard (2-chloroethyl ethyl sulfide (CEES)) are also given	[187]
AU2016305087B2	Aug. 3, 2018	The disclosed invention pertains to techniques and formulations, including cells with a non-internalizing receptor and NP surfaces treated with a ligand that binds to the non-internalizing receptor	[188]
US2013/0131008A1	May 23, 2013	Lipophilic monophosphorylated analogues of gemcitabine are available, among other things. Additional NP compositions containing lipophilic monophosphorylated derivatives of gemcitabine, pharmaceutical compositions thereof, and a method of treating cancer or viral infection in a subject in need, including administering a pharmaceutical composition, are also disclosed	[189]
US 9,364,545 B2	Jun. 14, 2016	The innovation generated thermosensitive injectable HGs made with HA, a polyethene oxide copolymer, and polypropylene oxide, with a gel formation temperature ranging from 30 to 37 °C. The invention's thermosensitive injectable HGs offer a possible medication delivery method to improve the medicine's therapeutic effectiveness	[190]
US10,729,659 B2	Aug. 4, 2020	Methods for inhibiting the proliferation of one or more tumour cells include contacting them with a composition containing one or more epigenetic drugs that inhibit one or more epigenetic mechanisms associated with the tumour cells, where one or more epigenetic drugs are encapsulated in NGs	[191]
US 9,642.925 B2	May 9, 2017	The invention describes methods for producing derivatized and usable magnetic NP and ways for employing such NPs	[192]
US11,029,539 B2	Jun 8, 2021	The copolymer's leading polymer chains are hydrophilic and have polymerization degrees ranging from 10 to 10,000. This invention's water-soluble, crosslinked copolymers do not contain terminal substrate-associating segments. The copolymers can be integrated into the formulation used to make the article or come into contact with it after it has been formed	[193]

Table 2 (continued)

Patent No	Date of publication	Description/ outcome	Refn(s)
US10,502,867 B2	Dec. 10, 2019	The linear substrate associative segment links the block copolymer to a surface with at least one hydrophobic site, including silicone HG. The polymers can be integrated into the formulation that produces the silicone HG or come into contact with it after it has formed	[194]
US2020/0030244 A1	Jan. 30, 2020	Intravesical therapeutic drug delivery includes attaching a photoactive NG to the bladder's mucosal surfaces and administering cell-penetrating peptides. Photoactive NGs can combine when exposed to UV light, in-vitro and in-vivo, allowing for the regulated or extended release of drugs like antibiotics	[195]

Table 3 Marketed products of NG used for treatment of various diseases and their brand name

Brand name	Drugs	Use	Cost (Quantity)	Manufacturer	Refn(s)
Oxalgin NG	Diclofenac, Methyl Salicylate	Analgesic, anti-inflammatory	139 Rs (30 g)	Zydus Healthcare Ltd	[196]
Adlalene NG	Adapalene, Clindamycin	Anti-acne, prevent from infection, prevent from blackheads on the skin	273 Rs (15 g)	Zydus Healthcare Ltd	[197]
Zeldinac NG	Diclofenac, Linseed oil, Methyl salicylate	Reduced inflammation	58 Rs (30 g)	Leeford Healthcare Limited	[198]
Acnesol A NG	Adapalene, Clindamycin	Reduced oil production, anti-inflammatory, anti-microbial, prevent from infection	175 Rs (15 g)	Systopic Laboratories Pvt	[199]
Zeldinac NG	Clindamycin	Antibiotic	204 Rs (15 g)	Zydus Healthcare Ltd	[200]
S-Shield NG SPF 30+	Ethyl hexylmethoxy cinnamate, Butyl methoxydibenzoylmethane, Benzophenone-3	Reduction of oils from the skin, refreshing skin feel	604 Rs (50 g)	Skinska Pharmaceutica Pvt Ltd	[201]
D F O NG	Oleumlini, Diclofenac diethyl ammonium	Anti-inflammatory, analgesic	119 Rs (30 g)	Ozone Pharmaceuticals Ltd	[202]
Silvercure NG	Nanocrystalline silver	Wounds and burns	213 Rs (50 g)	Cipla Pharmaceuticals Ltd	[203]
Uv-Aid NG Spf 30+	Green tea extracts, Allantoin, Vitamin E, Glycerin	Protect from UV rays effects	280 Rs (50 g)	Arlak Biotech Pvt Ltd	[204]
Warflam NG	Diclofenac, Capsaicin, Methyl salicylate, Methanol, Linseed oil	Analgesic	109 Rs (30 g)	Biosortia Healthcare Pvt Ltd	[205]
Turnup NG	Diclofenac diethylamine, Linseed oil, Methyl salicylate, Menthol	Analgesic	120 Rs (30 g)	Nasa Pharmaceutical	[206]
Fasiclo 4X NG	Diclofenac diethylamine	Analgesic	101 Rs (30 g)	Fascin Pharmaceuticals	[207]
Acgel NG	Clarithromycin	Antibacterial	87 Rs (15 g)	Rapross Pharmaceuticals Pvt Ltd	[208]
Skinlite Ever NG	Hydroquinone, Tretinoin, Allantoin	Prevent from melasma	141 Rs (20 g)	Zydus Cadila	[209]
Nanomac Gel	Nanocrystalline silvers	Wound healing	51 Rs (10 g)	Macleods Pharmaceuticals Pvt Ltd	[210]
Mega NG	Silver nano particles	Prevent from infection	807 Rs (200 g)	Zuventus Healthcare Ltd	[211]
Aveil with Heat Shield Gel SPF 50	Thermus themophilus ferment phenylbenzimidazole sulfonic acid	Prevent from UVA and UVB rays	742 Rs (50 ml)	Shivoham Dermatology Pvt Ltd	[212]
Nan Cola 0.002% Gel	Silver NP	Prevent from infection	489 Rs (10 g)	DD Pharmaceuticals Pvt. Ltd	[213]
Instaplus Gel	Silver NP	Prevent from infection	187 Rs (50 g)	Lupin Ltd	[214]
S Gel	Nanocrystalline silvers	Wounds and burns and surgical wounds	129 Rs (25 g)	Hetero Drugs Ltd	[215]

Conclusion

NGs, versatile nanoscale structures, exhibit immense potential in revolutionizing medical treatments across various diseases. Their unique properties, such as high surface area and tunable drug release kinetics, make them promising candidates for targeted drug delivery. In oncology, NGs have shown remarkable efficacy by delivering chemotherapeutic agents directly to cancer cells, minimizing collateral damage to healthy tissues. The application of NGs extends beyond oncology; they have successfully treated inflammatory diseases, tumours, liver disease, SCI, infections, cardiovascular diseases, hyperthermia, diabetes, and neurological diseases, and also in the biomedical field. Their adaptability allows customization to suit specific therapeutic needs, heralding a new era in precision medicine. However, the journey from the laboratory to clinical implementation is fraught with challenges. One significant hurdle is ensuring the biocompatibility and safety of NGs. Ethical concerns surrounding the long-term impact of NGs on the human body necessitate thorough investigation.

Moreover, scalability and cost-effectiveness are addressed to make these innovations accessible on a global scale. The ongoing clinical trials involving NGs are crucial milestones to determining their real-world viability. Researchers are diligently evaluating their performance, side effects, and therapeutic impact. Looking ahead, the future of NGs appears bright. Continued research and advancements in nanotechnology promise to overcome current challenges, fostering widespread adoption of NG-based therapies. NGs may be pivotal in this paradigm shift, offering precise and efficient strategies for many medical conditions.

In conclusion, NGs represent a groundbreaking innovation with far-reaching implications for medical science. While challenges persist, ongoing clinical trials and a commitment to rigorous research pave the way for a future where NGs become indispensable tools in the fight against various diseases, offering hope for more effective, targeted, and controlled treatments.

Author's contributions GS: Data curation, Writing, Language, Figures, Tables. **JG:** Original draft, Figures, Data curation, Software, Reviewing, editing, and conceptualization.

Data availability statement Data will be available on request.

Declarations

Ethics approval It's a review article. So, no ethical approval and no consent from participants is required.

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