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A COMPREHENSIVE REVIEW OF RECENT AND FUTURE PROSPECTS OF NANOGELS

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ABSTRACT: A hydrogel with strongly cross-linked hydrophilic polymer chains makes up the majority of nanogels, which are essentially nanoparticles. Several hydrophilic functional groups in hydrophilic polymers enable nanogels to absorb large amounts of water. Incredibly stable, adaptable, and responsive to sensory influences, nanogels have the potential to be a safe and effective medication delivery vehicle for biological products. Peptides, hormones, DNA, vaccines, chemotherapeutic treatments, and a wide range of pharmaceutical goods can all be delivered using these devices. There are several varieties of nanogel-based drug delivery systems, varied techniques of production, processes of drug release, and commercially available formulations. The presentation emphasizes the various types of nanogel based drug delivery systems, preparation methods, drug release mechanisms, marketed preparations, and their various applications in the medical field.

INTRODUCTION: Nanotechnology has been extensively used in the construction of innovative drug delivery systems because it provides acceptable strategies for the time-specific or time-controlled administration of bioactive substances. Because of the nanoscale size's capacity to improve drug dispersion, increase tumor accumulation, increase stability against chemical and enzymatic degradation and reduce cytotoxic side effects during cancer treatment, the nanoscale size can be advantageous in drug delivery [1]. Aqueous dispersions of hydrogel particles generated by physically or chemically cross-linked polymer networks at nanoscale scales are commonly referred to as "nanogels. This phrase refers to chemically cross-linked networks of cationic and neutral polymers that are swollen and engineered for the transport of antisense oligonucleotides, such as branching polyethylene mine (PEI) and poly (ethylene glycol) (PEG) (PEG-clPEI) [2]. It is possible to attach hydrophilic and hydrophobic payloads around the outside of the micellar nets and join nanoscopic micelles scattered in an aqueous solution to generate nanogels.

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Hydrogels, three-dimensional polymeric networks that develop in response to environmental cues, such as pH and temperature and the presence of ions or enzymes, are known to be created [3]. Polymers can be linked together chemically or physically (typically reversibly) to create gels. A physical gel comprises a network of polymers

linked together by hydrogen bonds, ionic interactions, hydrophobic associations, or agglomerations. For example, agarose is a copolymer altering *O*-3-linked β- D-galactopyranosyl and *O*-4-linked 3,6-anhydro-α-L-galactopyranosyl residues [4]. In nanogel production, chemical cross-linking and actual self are two of the main approaches. Then anogel created by chemical cross-linking was more stable than the nanogel formed by covalent linking among ligands on polymer chains [5]. Biodegradable (frequently biodegradable) soft polymers that resemble soft tissues are called hydrogels. Hydrogels' unique characteristics and likeness to real tissues opened the door to biomedical uses [6]. In order to maximize the usefulness of nanoparticles and hydrogels, there has recently been an increase in interest in the creation of "nano-in-hydrogels (known as nanogels)". As a result of cross-linking polymer networks of nanoscopic size, hydrogels are referred to as "nanogels" [2]. The ability to regulate the pace, timing, and location of a drug's absorption in the body are all significant advantages of these systems [7]. In the realm of drug delivery, nanotechnology and nanoparticles play a critical role; well-designed nanocarriers can assure maximum drug loading and regulated drug release [8]. Using their nanostructures and functions, the delivery procedure may be more selective, which reduces toxicity and adverse effects. When it comes to biocompatibility, biodegradability and functionalization, polymeric nanoparticles play a critical role [9]. When dealing with suitably functionalized polymer chains, adjusting factors like mechanical properties, composition, or degradation rate is feasible. To be thorough, it's worth mentioning that these formulations are expensive, which limits their applicability in clinical settings [10].

Mechanism of the Drug Release from Nanogels: Cross-linking and actual self are the two main strategies for making nanogels, based on their differing architectures. The nanogel created by chemical cross-linking was more stable than the nanogel formed by covalent linking among molecules on polymer chains. Noncovalent interactions, such as hydrogen bonding, Vander Waals force, hydrophobic interaction, host-guest contact, electrostatic interaction, and so on, play a major role in the reversible connections of physically cross-linked nanogels [11]. Physical self-assembly is more versatile and convenient than chemical covalent cross-linking, even though physical noncovalent linkages are weaker than covalent cross-links.

Physical Crosslinking: Noncovalent interactions between polymer molecules create physically cross-linked nanogels, supramolecular particles. Polymer concentration and ambient factors, such as temperature, pH, and ionic strength during nanogel formation, can affect the nanogel size **Fig. 1** [12].

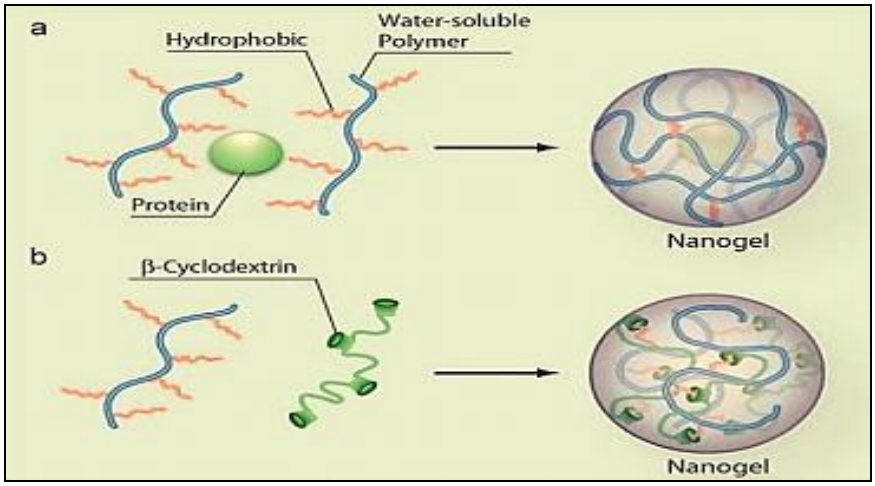

FIG. 1: IN AQUEOUS MEDIA, NANOGELS SELF-ASSEMBLE PHYSICALLY. AS A RESULT OF THE INSULIN-INDUCED AGGREGATE FORMATION OF THE HYDROPHOBIC POLYMER CHOLESTEROL-PULULAN, NANOGELS CONTAINING PROTEIN ARE FORMED

Chemical Crosslinking: Chemical modification is the most advanced and adaptable approach for nanogel creation beyond physical cross-linking. RAFT (reversible addition-fragmentation chain

transfer) polymerization, click chemical cross-linking, and photo-induced cross-linking are examples of chemical cross-linking processes. Nanogels cantered on amino acids can be prepared by amino cross-linking [13, 14].

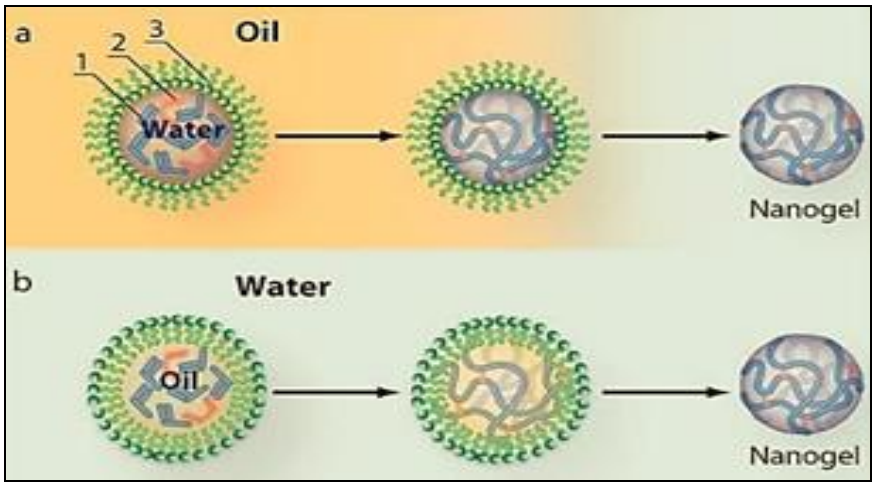

FIG. 2: COPOLYMERIZATION IN COLLOIDAL CONDITIONS IS USED TO SYNTHESIZE NANOGELS. AFTER THE SURFACTANTS AND ORGANIC SOLVENT HAVE BEEN REMOVED, NANOGELS MAY BE TRANSPORTED INTO AQUEOUS MEDIA BY COPOLYMERIZATION OF MONOMERS (1) AND BIFUNCTIONAL CROSS-LINKERS (2) IN MICROEMULSIONS STABILIZED BY SURFACTANTS (3). B) IN O/W EMULSIONS STABILIZED BY SURFACTANTS, COPOLYMERIZATION PROCESSES CAN ALSO BE CARRIEDOUT

Inverse Emulsion Polymerization: When water-in-oil micelles in the oil phase are continuously emulsified, the polymerization process is triggered. Penetration enhancer, feed ratio of monomer and cross-linking agent, and pH all influence nanogel size [15]. For example, zwitterionic poly (AA-BA-EGDMA) nanogels were created by combining ethylene glycol dimethacrylate (EGDMA) with butyl and acrylic acids as well monomers. When Peres and coworkers created poly (l-AGA) and poly (l- AGA+co-BIS) hydrogels using N, N'methylenebis (acrylamide) (BIS), they found that the degree of hydrogel expansion increased as the pH of the solution varied [11, 16].

Reversible Addition-Fragmentation Chain Transfer (RAFT) Polymerization: These processes include reversible adduct addition, adduct decomposition, and chain transfer reactions that govern polymer molecular weight during free radical polymerization, which is achieved using RAFT. The length, configuration, and characteristics of amphiphilic polymers may be altered using RAFT technology, which in turn alters the micelle structure. Poly (N-vinylcaprolactam) (PVCL), a biocompatible and temperature-sensitive polymer, has emerged as an intriguing material [17].

Click Chemistry Crosslinking Polymerization: In recent decades, click chemistry has related to emerging hydrogels and nanogels because of their high reactivity, high yield and excellent selectivity. It has become the most promising technique for the creation of nanogels, which comprises the copper(I)-catalyzed azide-alkyne (CuAAC) click reaction, the copper-free click reaction, and pseudo-click chemistry. A pH-responsive nanogel was created via thiol-ene click chemistry, an effective approach for nanogel creation without byproducts, using polymerization with methoxy polyethylene glycol acrylate (mPEGA), pentaerythritol tetra (3-mercaptopropionate) (PT) and orthoester diacrylamide (OA) (OEAM) [18, 19].

Photo-Induced Crosslinking Polymerization: It is becoming increasingly common for nanogels to be prepared using irradiation because of their bacteriostatic properties, additive-free nature, multifunctional existence, customizable particle diameter, and capacity to induce cross-linking. Intermolecular cross-linking stimulates the formation of nanogels by irradiating water molecules, which decomposes into hydroxyl radicals and hydrogen atoms. Laser wavelength or energy can be used to control the density of cross-linking [20, 21].

Stimuli-Responsive Nanogels: For medication delivery, the tumor microenvironment's low pH, high temperature, and high glutathione (GSH) concentrations have become increasingly important factors in the development of stimuli-responsive systems [22]. These methods reduce medication dosage and systemic toxicity and lessen toxicity to normal tissues. This is accomplished by using stimuli-responsive systems [23]. They have long been employed as stimuli-responsive systems because of their high drug loading capacity, simplicity of manufacture, and versatility in modification. Because of their distinct 3D network topologies, nanogels are more sensitive to mutative conditions than conventional DDSs and may therefore better regulate drug release [24].

Thermo-Responsive Nanogels: Among intelligently responding DDSs, thermo-responsive nanogels are particularly appealing. It is possible to adjust the release rate of medicine inside a thermo-responsive nanogel by changing the environment's temperature. To further enhance treatment efficacy, reduced particle size might be accomplished by stimulating the build-up of the disease-related microenvironment and enhancing intracellular absorption efficiency [25–27]. It is common in biomedicine to use NIPAm, a typical thermosensitive derivative. Aqueous imprinting precipitation was used to introduce this thermo-sensitive nanogel for protein loading. It's crucial to note that template protein lysozyme showed imprint-release characteristics when combined with the temperature-dependent shrinking and swelling of nanogel, indicating potential controlled delivery [28].

pH-Responsive Nanogels: Ionizing groups, which may ionize or deionize in response to pH changes, are responsible for the nanogel system's pH-dependent swelling-shrinking action. According to certain scientific studies, acidic microenvironments (pH6.5–7.2) have been found in tumor tissues and tumor cells, contrasted to the typical pH of 7.4 in the blood circulation and normal tissues. MAA and MA, sensitive to pH, have been shown to polymerize nanogels, which preserved a swollen form in basic pH conditions of extreme permeability. Nanogels would shrink, trapping the hydrophobic fluorescent signaling oligothiophene (TF) and the hydrophilic drug when deionization of MAA and MA was combined with lowering pH values. It is possible that the additional shrinking of pH-sensitive nanogels and the trivalent of the drug are to blame for the greater drug release seen at pH 5.5 [29].

Magnetic-Responsive Nanogels: Magnetic nanoparticles (MNPs) can also achieve hyperthermia in the presence of an alternate magnetic field (AMF). Thus, MNPs and temperature-sensitive nanogels were used to create the hybrid nanogels, which were then loaded with a chemical agent. The 3D network structure of nanogels allows for the co-encapsulation of MNPs and chemical medicines [15, 30].

Ultrasound-Responsive Nanogels: Ultrasound (US)-mediated medication delivery devices are widely employed in transdermal administration and treatment of central nervous system (CNS) illness. The benefits of the depth of penetration of acoustic waves also led to the developing of an anticancer treatment delivery system in the United States. Because perfluorohexane (PFH) evaporation occurred when US was administered, it enhanced the release of triggered drugs [31].

Multi Stimuli-Responsive Nanogels: Dual or multi-stimuli responsive nanogels have received extensive attention because they can better control medication release. Researchers have made significant progress in studying pH–temperature dual-sensitivity combinations. Nanogel polymerized from NIPAm, MAA, and PEGMA that responds to temperature and pH was invented by Peng and associates. For hydrophilic model pharmaceuticals of various molecular weights, the cross-linked p(NIPAm-MAA-PEGMA) nanogels demonstrated good drug loading and release behavior [32].

Modification of Nanogels for Active Targeting: For example, nanogels can be given with both passive and active targeting abilities, enhancing the accumulation of medications in diseased regions, exactly like other forms of nanoparticles.

The interaction between ligands and cellular or subcellular receptors is one way to accomplish active targeting. NPs were also coated with biological ligands, including such proteins,

peptides, and polysaccharides, as well as tiny compounds [33].

Small-Molecule Onjugation: Anti-tumor-targeted treatments have recently shown that folic acid (FA) can interact with cells overexpressing folate receptors (FRs). Human tumor tissues, particularly ovarian cancer tissues, are overexpressed in FRs, although FRs are seldom generated in normal tissues. Ovarian cancer and other tumor tissues express FR differently, making them intriguing biomarkers for tumor detection and therapy [34].

Peptide Conjugation: Some peptide ligands have recently been widely studied for treatment and imaging purposes. Using nanoparticles with the tumor-homing peptide LyP-1, which was found to have an affinity for binding to the p32 protein in various tumor cells, for example, might help improve tumor targeting. Additionally, photo thermotherapy, photochemotherapy, and photoimmunotherapy saw increased therapeutic effects after using these modified nanoparticles [35].

Antibody Conjugation: These modified nanogels have a greater affinity for binding sites compared to tumor cell receptors on the surface. As a result, antibodies are frequently utilized as ligands in the modification of nanogels. Cancer treatment can benefit from antibody-dependent cell-mediated cytotoxicity (ADCC), which has been shown to block cellular signaling pathways linked to tumor development and inception and the ligands [36, 37].

Biomembrane Camouflaged: When nanoparticles are exposed to a living environment, they get coated with a protein corona. In several investigations, the ability of tumor-targeting ligands to evade protein corona has been reduced. The targeting ability of compounds can be partially preserved following *in-vivo* corona formation, according to some recent research as well. However, it's still not obvious how the protein corona generated on the cyclin nanoparticle affects the targeting capacity [5, 38].

Characteristics of Nanogels:

Biocompatibility & Degradability: Natural or synthetic polymers can be used to make nanogels. As a result, nanogels avoid organ build-up since they are biocompatible and biodegradable. For the production of nanogels, cellulose, methylcellulose, chitosan, and a variety of polysaccharide-based polymers such as dextran and dextrin can all be employed. Glycosidic linkages bind the repeating units of monosaccharides in carbohydrate-based polymers, making them polysaccharides. Hydrophilic, nontoxic, stable, and biodegradable characterize each of these polymers in nature [39]. It is the process by which a material is broken down into its constituent parts by the activity of microorganisms, such as bacteria, in a biochemical reaction [40]. Biodeterioration, bio fragmentation, and assimilation are the three primary steps of the biodegradation mechanism [41].

Biological degradation affects just the material's surface and does not affect its mechanical, physical, or chemical qualities. In other words, when the chemical is exposed to abiotic elements in the atmosphere, it becomes vulnerable to further deterioration. Several abiotic elements, including temperature, light, compression (mechanical), and chemicals in the environment, play a role in these early alterations [41]. The initial stage of biodegradation, biodeterioration, is traditionally thought of as the first stage of bio fragmentation, however, this is not always the case [42]. The lytic mechanism by which polymer bonds are broken to produce oligomers and monomers is known as bio fragmentation of a polymer. Additionally, the amount of time it takes to divide these components depends on the amount of oxygen present in the system. Aerobic digestion occurs when bacteria are present, while anaerobic digestion occurs when microbes are not present. Anaerobic reactions yield methane, whereas aerobic reactions do not (although water, carbon dioxide, residues of certain types, and new biomass is produced by the reactions of both) [4].

Swelling Characteristics in Water: One of the most important aspects of nanogels is their rapid swelling and deflation [43]. When it comes to polyelectrolyte gels, swelling is controlled by the concentration, cross-linking strength, ionic strength, pH, the type of LMW ions in the polymer chains, and the concentration and other environmental elements such as the charge and pH of the polyelectrolyte gels. It's well-known that the osmotic pressure and polymer elasticity work in concert to regulate the physical dimensions of hydrogel particles.

Drug Loading Capability: The functional groups in the polymeric substance are responsible for the increased drug loading capacity of nanogels. These functional groups have an excellent influence on drug transport and drug release properties, and some functional groups may be coupled with drugs/antibodies for site-specific applications.

This pendulous substituent of polymeric chains facilitates hydrogen bond formation or van der Waals forces of contact in the gel linkage. Maximum loading can also be caused by the presence of functional groups at the boundaries of drug or protein molecules [43].

Particle size Effectiveness: As a result of their tiny particle size, nanogels can evade rapid renal clearance while remaining small enough to avoid being absorbed by the reticuloendothelial system. Small sizes are also related to strong permeation capacities, allowing it to pass the blood–brain barrier, as demonstrated (BBB). Biological variables such as organ dispersion, tissue extravasation, hepatic filtration, and excretion *via* the kidneys influence the distribution of long-circulating nanoparticles [44].

Solubilization Behavior: Soluble hydrophobic medicines and diagnostic substances can be dissolved in the gel's shell or through the gel's links [37].

Nanogels with accessible hydrophobic regions can also solubilize hydrophobic compounds. Amphiphilic cross-linked nanogels derived from Pluronic F127 or poly [oligo (ethylene oxide)-methyl methacrylate] have been used to encapsulate doxorubicin, while prostaglandin E2 has been solubilized in cholesterol-modified pullulan nanogels. Loading that relies solely on hydrophobic connections has limited loading capacities, to say the least [44].

Colloidal Stability & Electro Mobility: When compared to surfactant micelles, polymeric micellar nanogel nanostructures or nanogels have superiorim mobility and stability, with lower critical micelle concentrations, a softer dissociation rate, and better drug stability maintenance. There are several ways to make nanogels without wasting energy or putting delicate biomolecules at risks, such as homogenization or sonication [43].

Nonimmunologic Response: This medication delivery technology seldom elicits an immune response.

Other Characteristics: Because nanogels may carry both hydrophilic and hydrophobic medicinal molecules as well as charged solutes, this is a significant benefit. The presence of hydrophilic/hydrophobic groups in polymeric networks, temperature, cross-linked gel density, surfactant concentration, and the kind and number of cross-links present in the polymeric system all influence these nanogel properties [1].

Applications of Nanogels:

Nanogels in Cancer Therapy: Drug delivery technologies, including liposomes and nanoparticles have been studied to address the limitations of traditional chemotherapy, such as limited therapeutic window, low solubility, and damage to normal tissues. These low-molecular-weight medications were carried by nanogels, including doxorubicin, cisplatin, 5-fluorouracil, temozolomide, neocarzinostatin and others. Polymers based on maleic acid poly (N- isopropyl acrylamide) are commonly used in treating cancer as pH and temperature-sensitive nanogels containing doxorubicin. In response to a minor drop in pH or a temperature rise, doxorubicin is generated from these nanogels. The prostate, breast, lung, and liver cancer therapy was also examined with a chitin-based doxorubicin-bearing nanogel.

Nanogels for Delivery of Protein and Peptide: Proteins and peptides can also be transported to the target spot using nanogels. Artificial nanogels can be utilized to transport a wide range of proteins thanks to their small size. There are a variety of nanogels that may be employed for protein and peptide delivery.

Nanogels for Gene and Antisense Delivery: Progress in gene and antisense treatment has led to the adoption of safe and effective medication delivery technologies. Oligonucleotides can be delivered using a variety of viral and non-viral vectors.

Non-viral vectors, on the other hand, have received substantial attention because of the limits of viral vectors (immune response and toxicity). As a

result, a great deal of work was put into developing polymeric nanogels smaller than 200 nm that could form monodisperse complexes with DNA or oligonucleotides while also considering the limitations of standard non-viral vectors, notably accurate size attainment and poor durability. Oligonucleotide stability was increased, and targeted distribution of the oligonucleotide was enabled by the nanogel-oligonucleotide combination, which was demonstrated. McAllister et al. synthesized monodisperse and non-toxic cationic nanogels and shown to form stable complexes with oligonucleotides [45].

Nanogels as Vaccine Delivery Systems: The objective of immune treatment for cancer is to induce a particular immune response against cancer cells. Tissue-specific and humoral immune responses can be stimulated by hydrophobic polysaccharide nanogel vaccines that include shortened oncoprotein complexes. Dendritic cells such as bone marrow-derived APC were able to stimulate the proliferation of CD4+ and CD8+ T cells after treatment to the cholesterol-bearing pullulan-HER2 nanogel combination.

Nanogels for Therapy of Alzheimer's disease: Amyloid beta-role proteins in the pathogenesis of Alzheimer's disease is widely acknowledged. Amyloid-protein aggregation inhibition is a viable therapeutic strategy. An artificial absorption of amyloid proteins, cholesterol-bearing pullulan nanogels can be utilised to limit the production of amyloid -protein (1-42) fibrils with substantial anti-amyloidogenic action. These nanogels have a polysaccharide backbone and hydrophobic cholesterol moieties. One amyloid -protein-(1-42) molecule can be integrated into 6-8 other amyloid -proteins. With positive charges under physiological conditions, nanogels composed of amino group modification of cholesterol-bearing pullulan showed an improved inhibitive action over pullulan without modification, possibly due to electrostatic interactions between the amino group modification nanogel and amyloid -protein, which may be important in the inhibition of fibril formation. In addition, the amyloid-protein toxicity of PY12 cells can be reduced by using these nanogels [45].

Nanogels for Autoimmune Diseases: The delivery mechanism must be able to inhibit the immune cells that play a part in the course of the illness by modulating the immune system. Nanogels loaded with immunosuppressant medications have been researched to treat autoimmune illnesses due to their capacity to target cells contributing to autoimmune diseases and enable systemic accumulation of the loaded drug. They have shown promise [1].

Nanogels for Bone Regeneration: Slow and local release of lithium and other medications can help regenerate bone. Using polyacrylic acid micro-emulsion polymerization and a biodegradable polyhydroxy butyrate matrix, lithium nanogels have been created for controlled release into bone tissue. For the administration of antibiotics and antimicrobials, Infections are getting more difficult to treat in the present 'post antibiotic' age due to the resistance of traditional antibiotics.

Nanogel systems may be useful in overcoming this issue, since they may administer the antimicrobial agent in a targeted and localized manner with quick-release characteristics. The dextran cross-linked polyacrylamide nanogels loaded with zinc (in the form of ions) were made using the mini-emulsion technique (i.e., polysaccharide based nanogels). As a cross-linking agent, methylated hyaluronic acid was utilized. To combat methicillin-resistant Staphylococcus aureus, this nanogel was created.

Nanogels for Diabetes Treatment: Given the prevalence of diabetes, several insulin delivery systems have been developed to combat the condition. One such system has been developed that responds to fluctuations in blood glucose levels by releasing a predetermined quantity of insulin.

As a result of the gel matrix's ability to bind and respond to pH changes, the nanogel system is also accompanied by electrically charged particles in the opposite direction. The nanogel system will transport insulin and other enzymes necessary to convert glucose into gluconic acid using dextran.

Hyperglycemia causes glucose molecules to permeate across the nanogel network, causing the medium's pH to drop as gluconic acid is formed. As a result, insulin production will increase. To be used in human trials, the nanogel diabetes

management system still need some further research to be fully developed and tested in lab [46].

Nanogels in Combinational Therapy: Accordingly, even though nanogels have been used to encapsulate a wide range of drugs in previous studies, the results have been unsatisfactory, which can be blamed on several drawbacks, including poor chemotherapeutic drug selectivity with side effects and the development of resistance. Furthermore, because cancer growth and incidence are so intricate, the impact of a single anticancer drug may be minimal.

This has led to a boom in combination treatments, particularly nano carrier-based code livery systems like micelles and liposomal delivery systems like polymeric nucleic acid (PNA) and inorganic NPs. The unique qualities of nanogels, such as their high biocompatibility, outstanding stability, large loading capacity and controlled drug release in response to environmental stimulation, make them ideal candidates for drug administration [5].

Marketed Formulations of Nanogels: Nanogels are employed in everyday life in several ways. For example, Zyflex nanogels can be used to relax muscles and alleviate pain in the body. To alleviate symptoms such as knee pain, muscular pain or soreness, cervical pain or swelling, back pain or tenderness, and shoulder discomfort, doctors prescribe Oxalgin nanogels (a diclofenac-menthol-methyl salicylate combination). Antiwrinkle cream and long-lasting hydration are both features of some nourishing gels, such as aqua multi effect nanogels cream. Anti-wrinkle cream Revivagenix pro collagen nanogel aids to the skin's total hydration for a lengthy period. Nanogels for the eyes and skin are two examples of products that can penetrate the skin's outer layer and deliver broad-spectrum hydration, as is the case with augen's nanogels eye- care gel. The skin is cared for, toned and protected [1].

Nanogels in Bleeding Blockage: Nanogels containing proteins have proven to be effective at stopping bleeding in even the most serious situations. A biodegradable gel is formed when proteins are attached to the nanocarriers [43].

Nanogels in Ophthalmic Drug Delivery: This polyvinyl pyrrolidone-poly (acrylic acid) (PVP/PAAc) nanogel was utilized to encapsulate pilocarpine and preserve a sufficient amount at the action site for extended periods using γ radiation-induced polymerization of acrylic acid (AAc) in an aqueous solution of polyvinyl pyrrolidone (PVP) [47].

Nanogels in Local Anesthesia: One of the most important therapeutic goals in dental care is to minimize patient discomfort. Integration of local anesthetics into medication delivery systems might improve regional delivery [48, 49]. Local anaesthetics can be administered more easily and effectively if they are included in delivery methods such as nanogels. This amino ester local anaesthetics was shown to have increased release at high pH when loaded into MEA-EA nanogels via hydrophobic and hydrogen bonding. As a result of deprotonation of acid on nanogels, which causes osmotic pressure and swelling and increases porosity, procaine hydrochloride is released from the nanogel system. When it comes to injection and blood circulation time, nanogels are probably likely the best option [50].

Nanogels in neurodegenerative Disorders: The distribution of ODN to the brain is made easier using nanogel. In order to treat neurodegenerative illnesses, ODN must be administered throughout the body and delivered to the central nervous system (CNS). If injected into the bloodstream, molecules with a larger molecular weight are quickly removed from circulation because the BBB is unable to penetrate them efficiently. Polyelectrolyte complexes (a stable aqueous dispersion) with particle sizes less than 100 nm can successfully traverse the BBB when nanogels are encapsulated or coupled with extemporaneously negatively charged ODN. When insulin or transferrin are applied to the nanogel surface, the transport efficiency is significantly improved [1].

Nanogels in Vaginal Drug Delivery: Various vaginal infections have been treated with antibacterial medicines encased in vaginal nanogels. Other sexual issues, such as vaginal discomfort, can also be alleviated by using these products. Some of the disadvantages of vaginal nanogels include the fact that they should not be used during menstruation or pregnancy. According to researchers, a few nanogels containing antiretroviral medications can minimize the risk of

HIV infection among women. For HIV prophylaxis, a vaginal gel containing Tenofovir has been explored and a two-step desolvation process using HPMC K15M as a gelling agent and a bioadhesive polymer was utilized to create the nanoparticles. During the research on membrane permeation and bio-adhesion, it was discovered that gel had exceptional bio-adhesion and permeability [1, 51].

***In-vivo* behavior of Nanogels:** To ensure that their cargo has a long circulation half-life in vivo and can be delivered to the correct location, nanogels are macromolecular systems. Nanogels and nanoparticulate systems must overcome a number of hurdles in order to do this, especially when supplied via non-intravenous modes of administration such as oral or nasal. Nanogels are created for specific routes of administration so that they can cross any obstacles and enter the circulation unharmed. When it comes to biomolecules, nanogels are very useful since they delay degradation by blocking both rapid clearance and rapid metabolism, which is especially important for tiny molecules. Prolonged circulation is complicated by opsonization of the nanogels, which is followed by clearance through MPS organs like the liver and spleen, where existing monocytes and macrophages suck them up [52].

By increasing the hydrophilicity of the nanogel surface, PEGylation confers ‘stealth' qualities while also reducing the ability of serum proteins to bind to the nanogel's core. However, this is extremely reliant on the size, shape, molecular weight, and density of the PEG utilized in the process [53, 54]. Opsonization and macrophage clearance still occur despite nano systems' long circulation features and reduced MPS absorption due to PEGylation [55] Nanoparticles coated with polyethylene glycol (PEG) tend to accumulate in the spleen rather than the liver, compared to their non-PEGylated counterparts, according to several studies [56]. Nanogels' softness and deformability make them able to evade the spleen's filtering process to some extent. To put this into context, consider that even though they're microns in diameter, they're still capable of passing through the little pores in our blood vessels since they're so flexible and deformable [54,57]. Old red blood cells (RBCs) are removed from circulation mostly because they lose their ability to contract and expand. The nanogels' biomimicry may be an asset when used *in-vivo*. Under physiological pressures, for example, Lyon and colleagues found that spherical acrylamide-based nanogels deform and penetrate membrane holes many times smaller than their hydrodynamic diameter [58].

Similar nanogels have been demonstrated to have different mechanisms and rates of absorption in macrophages depending on their moduli [59]. Microgel particles' biodistribution qualities were found to be adjusted by reducing the modulus of the particles, allowing them to skip organs like the lung where their more rigid counterparts were stuck, resulting in longer circulation durations [60]. Mitragori and coworkers have presented compelling data for the extended circulation period of soft PEG-based hydrogel nanoparticles compared to hard nanogels of the same size [61]. Variations in particle-matrix cross-link density and cross-linking moiety size both influence nanogel deformability [62]. It's easy to boost the hydrogel particle's swell ratio by adding electrolyte moieties to the polymer network of hydrogel particles [63]. As a result, the presence of charged groups on a particle's surface can speed its removal. By employing an approach devised by DeSimone's team, they have been able to produce extremely swollen gel particles with near-neutral charges while maintaining a charged group inside [64].

The circulating blood then distributes a component of nanogels that has evaded the procedures outlined above. Although nanogels are typically too large to pass through the tight junctions of the normal endothelium, in tumors and other inflamed tissues with unique morphological characters such as defective leaky and sparsely compacted vasculature and impaired lymphatic drainage, the well-known enhanced permeability and retention effect can be achieved (EPR) [65, 66]. As an alternative to using EPR, nanogels can be bioconjugated with targeting ligands so that they can be directed to specific receptors or molecules that are differentially over-expressed on diseased cells/tissues. This improves their retention at the targeted site and facilitates their cellular uptake [67–69]. It is possible to target the delivery of nanogels and other nanomedicines to certain tissues or cells by using a variety of small molecules, peptides, antibodiesoranti-bodies

fragments [70]. Nanogels with ligand-mediated targeting have a different biodistribution profile than those without and their distribution is biased towards tissues with high receptor expression. Nanogels can accumulate in areas that aren't supposed to, which might lead to unwanted side effects. These endocytosis methods are based on the nanogels' size and other surface features and their ability to penetrate the tissue matrix to reach their target cells and receptors. Nanogel internalization is a highly sophisticated process that can take place in several ways [71].

The endocytosis process, in general, restricts the particles into intracellular vesicles, from which they are transported into endosomes and subsequently lysosomes. Nanogels are subjected to fluctuating pH of the endosomal/lysosomal lumen, degradation enzymes, or reducing conditions at each of these steps, which are frequently used as triggers for the release of cargo stored inside the nanogels. Depending on the payload, nanogel carriers can be tailored to target or evade certain intracellular organelles. Several factors must be considered when designing nanogel-encapsulated therapeutic agents, such as endocytosis, to ensure that the encapsulated siRNA or oligonucleotides will be released into the cytosol in their active form [72]. As a result, there has been a rise in the use of nanogels made of bioresponsive polymers to promote escape via osmotic effects, binding to the membranes, or fusion, as well as the use of pH-sensitive or reducible cross-linkers to facilitate nanogel destabilization following internalization and increase delivery efficiency [73–76]. Minimizing toxicities linked with the body's accumulation of carriers is also dependent on nanogel degradability [77]

Lipogel and Future Perspective of Nanogels: Bures *et al.* attached the lipid vesicle system with "Lipogel," a hydrogel invented by Chujo *et al.* [78, 79] Lipogel is a unique dosage form that not only has a high drug loading efficiency but also enhances the mechanical characteristics and provides well-defined dimensions of hydrogel [80]. Nanogels have been synthesized before using lipid bilayers, but the lipid bilayer plays a vital role for prolonged-release and possible surface modification this time around. Poly (N-isopropylacrylamide) (pNIPAM) microgels encased in a single 1- palmitoyl-2-oleoyl - phosphatidylcholine lipid bilayer were developed by Qasim Saleem *et al.* [81, 82]. They were monodisperse, thermoresponsive and hydrophobically modified. Its hydrogel core is a cross-linked pNIPAM core wrapped by a significantly cross-linked acrylic acid (AA)-rich poly (NIPAM) core. Bilayer formation is encouraged by hydrophobic modification sites provided by the AA units on its non-textured surface.

The results validated the lipogel's structure and documented their characterization in great detail, concluding that lipogel might be used as drug delivery vesicles. Lipogels were initially proved by Wang *et al.* [80] to be a potential drug delivery technology for the anticancer medication 17-DMAPG when it was first tested. It was found that the lipogel's PAA hydrogel core was generated by UV-initiated DEAP activation and polymerization of AA and BA inside liposomes. Through electrostatic interactions, the lipogel may be able to actively encapsulate 17-DMAPG and achieve continuous release of the cargo [83].

CONCLUSION: Traditional and modern therapies have several drawbacks, such as nonspecific side effects and a lack of consistency, which nanogels may help solve. All-new research in recent years has focused on developing new polymeric systems and unique systematic procedures with beneficial roles in therapeutics and new advances in the fabrication of nanogel designs. There is a bright future for nanogels in the treatment of cancer, intestinal problems, gene transfection, protein folding, and enzyme enzymology, thanks to recent breakthroughs in nanogel development. The current success of nanogel-based drug delivery systems can be attributed to the widespread usage of commercial nanogel formulations. There are still several shortcomings that need to be addressed immediately in drug delivery using nanogels as therapeutic and diagnostic instruments. To generate nanogels on a large scale, cost-effectiveness and technological issues need to be addressed in the development process. Pharmacokinetic and pharmacodynamic issues still need to be addressed thoroughly. By overcoming these difficulties, nanogels can pave the way for a new generation of medications to enhance patient care. The solubility of medications that are poorly water-soluble can be

improved using nanogel. Much work is still needed to bring new nanogel-based formulations to the market sensibly and expeditiously, notwithstanding recent advances in this area.

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