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NANOGEL BASED TOPICAL DRUG DELIVERY: SAGA OF PROGRESSIVE PHARMACOTHERAPEUTIC JOURNEY AND RECENT APPLICATION PERSPECTIVES

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ABSTRACT: Systems made of nanogel have been researched from a theoretical and practical standpoint. They are frequently utilized for coatings, cosmetics goods, targeted delivery systems, controlled delivery systems, and controlled delivery systems. Using the approach of making nanogels from polymer precursors, the gels are produced. The manufactured nanogels are acceptable to consumers since they are stable, delicious, and acceptable. Systems made of nanogel have been researched from both a theoretical and practical standpoint. They are frequently utilized for coatings, cosmetics goods, targeted and controlled delivery systems. This entrapment is made possible by the employment of nanogels. Future advancements in nanogels look promising and will increase medication delivery options. Every new investigation involves the development of cutting-edge polymer and mechanistic techniques with a potential function in treatments and innovation in nanogel manufacture. The advancement of biopharmaceutical characteristics of medicine expands the usage of these materials in several industries or other distribution methods. One of the best drug delivery technologies for ensuring a regulated or sustained medicine release is undoubtedly nanogels. However, a flawless delivery system must be created, providing accurate information on the interactions between the drug and the carrier and the impact of size and drug loading on drug release.

INTRODUCTION: The creation of new medications is no longer adequate for drug therapy in the modern day. Nevertheless, it also entails the creation of an effective drug delivery mechanism to achieve drug concentration at the site of action. The carrier system, which enables a regulated and localized release of the active medication by the particular needs of the therapy, also influences the *in-vivo* fate of the drug in addition to the features of the drug.

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Controlling the drug's distribution rate using various contemporary technologies in light of significant study is now the toughest issue. Any drug delivery system's major goal is to deliver the right amount of medication to the right place in the body to attain and maintain the appropriate drug concentration promptly [1].

Since the skin is simple to approach, has a big surface area with extensive circulatory and lymphatic networks exposure, and the route is non-invasive, drug administration through the skin has long been considered a promising idea. Because the medicine penetrates the deeper layers of the skin or mucous membranes, topical formulations are employed for localized effects at the application site. Bypassing first-pass metabolism is the topical delivery system's key benefit. Another benefit of

topical preparations is the avoidance of the hazards and inconveniences of intravenous therapy as well as the various circumstances of absorption, such as pH fluctuations, the presence of enzymes, and stomach emptying time [2]. For medications that might have negative side effects on the whole body, such as non-steroidal anti-inflammatory medicines, topical administration is crucial (NSAIDs). It is used for the long-term management of osteoarthritis, ankylosing spondylitis, and rheumatoid arthritis. To reduce its gastrointestinal adverse effects and maintain comparatively stable medication levels at the application site for extended durations, there is much interest in developing non-oral dosage forms [3].

The major symptom of rheumatoid arthritis (RA), a chronic, systemic inflammatory illness, is synovitis in the tiny joints, notably in the hands and feet. Synovial hyperplasia produces erosions and joint abnormalities, whereas persistent synovitis causes discomfort, swelling, stiffness, limited mobility, and joint space constriction. Systemic and extra-articular characteristics may exist. Social life is significantly impacted by RA symptoms such as pain, loss of physical function, exhaustion, and others. Long medication administration periods are required for the treatment of RA. Long-term drug use and the simultaneous use of many medications can both promote non-compliance. Because they need to be taken more often, medications with short biological half-lives usually have major problems [4].

Nowadays, nanotechnology is a rapidly expanding discipline. Several different carriers may be used to deliver the medications to the damaged organ under these circumstances. We are getting closer to finding a safe and effective cure for the condition thanks to new medications using nanotechnology and improved knowledge of rheumatoid arthritis and osteoarthritis. Novel topical carriers such as microemulsion, nanogel, niosomes, liposomal hydrogel, deformable liposomes, and solid lipid nanoparticles have been explored for improving skin penetration (SLNs). However, they have drawbacks such as ineffective drug encapsulation, drug ejection during storage, and excessive water content in the formulation [5]. With their extremely adaptable features, nanogels are one of the most efficient drug delivery technologies for delivering medications directly to sick tissues. These systems effectively incorporate different medications and improve their delivery and retention to the intended organ. Because they are more specific, they require less medication in free form and have less adverse effects on other organs from drug buildup. Nanogels are cutting-edge drug delivery systems that can help identify several problems with both traditional and contemporary treatment modalities, including nonspecific side effects and poor stability. Topical treatments using nanogels have received much attention since they essentially eliminate the problems associated with other carriers [6].

The term "nanogel" refers to strongly crosslinked hydrogels with a size between 20 and 200 nm. Nanogels are three-dimensional hydrophilic networks that can absorb huge amounts of physiological fluid or water without undergoing structural changes. These include oral, pulmonary, nasal, parenteral, intraocular, and other modes of administration. Due to their tiny size, they have a higher penetration capability and greater drug-loading capacity.

They release the medication using a combination of mechanisms, including photochemical internalization, photoisomerization, volume transition, and pH responsiveness. They may be categorized according to whether they respond to stimuli or not, as well as the links in the gel structure's network chains. Cancer, diabetes, inflammation, bone regeneration, and other diseases can all be treated with nanogels. The cutting-edge medication delivery technology for both hydrophilic and hydrophobic medicines is nanogels [7].

High drug loading capacity, biocompatibility, and biodegradability of materials based on nanogels are crucial factors in designing an efficient drug delivery system. For optimum therapeutic efficacy and little toxicity or side effects, drug molecules put into the nanogel must be maintained and not transported out or prematurely leaked while circulating. By solving the issues with both traditional and contemporary therapies, such as nonspecific effects and low stability, nanogels can play a crucial role as a promising and new drug delivery technology. It seems that nanogels are great choices for targeted medication delivery [8].

Properties of Nanogel:

1. Degradability and biocompatibility
2. A higher drug loading capacity,
3. Swelling in aqueous media,
4. Solubility
5. Colloidal consistency
6. The non-immunological reaction
7. Size of particles [9]

Advantages of Nanogels:

1. Nanogels are very biocompatible, making them a promising drug delivery technology.
2. High biodegradability is essential to prevent nanogel material from building up in the body's organs and causing toxicity and negative consequences.
3. Nanogels do not cause any immunological reactions since they are inert in the bloodstream and internal aqueous environment [10].

Limitations of Nanogels:

1. Even if the manufacturing method is not extremely expensive, removing the surfactant and the solvent is expensive once the preparation process is complete.
2. If any remnants of polymers or surfactants are still present in the body, negative repercussions might result.
3. A portion of the particles are smaller than three micrometers.
4. Because of average size and weight, scaling up is difficult [11].

Criteria for Selecting Nanocarrier Drug Delivery Systems:

1. The drug's stability is subpar.
2. Drugs that are insoluble.
3. Medications with low absorption
4. Medicines have a poor therapeutic index and low specificity.
5. Medication having a quick biological half-life [12].

Drug Selection Criteria for Controlled Drug Delivery System:
Physical Properties:

1. The molecular weight of the drug must be under 500 Daltons.
2. Topical drug administration is not appropriate for medications with strongly acidic or alkaline solutions.
3. The drug needs to be sufficiently lipophilic.
4. The pH of the drug's saturated aqueous solution should range from 5 to 9 [13].

Biological Properties:

1. The medicine must not irritate the skin directly.
2. Topical distribution is appropriate for medications that break down in the gastrointestinal system or is rendered inactive by the hepatic first-pass effect.
3. Under topical application's near zero order release profile, drug tolerance must not form.
4. The medication shouldn't cause the skin to develop an immunological response.
5. Drugs that must be delivered continuously or have negative side effects on tissue other than the intended target can also be prepared for topical administration [14].

Targeted Drug Delivery: A unique drug delivery system is known as targeted drug delivery, in which the pharmacologically active ingredient or medication is exclusively given to the site of action or absorption and not to non-target organs, tissues, or cells. Most traditional dosage forms introduce drugs into the body through dispersion and passive diffusion, where they finally reach the site of action. The medication also spreads to tissues away from the target spot. A substantially greater dosage must be administered to the patient to obtain therapeutic concentration in the intended tissue due to nonselective distribution. However, medication activity at places other than the target site may cause toxicity or another unfavorable outcome.

Anti-inflammatory medications can be administered *via* the skin using topical drug delivery to treat acute and long-term pain and inflammation. Site-specific drug delivery systems' primary objectives include lowering medication toxicity and improving drug selectivity and therapies index. Nanocarriers have demonstrated exceptional benefits over traditional dosage forms in the oral administration of hydrophobic medicines in recent years and have attracted a great deal of attention. To increase therapeutic effectiveness and sustained drug release features while addressing issues like poor solubility and limited oral bioavailability of pharmaceuticals, innovative drug delivery methods are now being investigated more and more. The following are the objectives of the site-specific drug delivery system:

1. Exclusive medication delivery to the body's particular sick cells or areas.
2. Adverse effects and medicine dosage reduction.
3. To regulate how often and at what rate drugs are delivered to pharmacological receptors.
4. Keep the medicine and the body apart until the substance reaches the intended action location [15].

Formulation Techniques: These are reported methods of nanogel preparation:

1. Coacervation / Precipitation / Precipitation polymerization.
2. Desolvation method.
3. Emulsion crosslinking.
4. Emulsion droplet coalescence method.
5. Emulsion polymerization.
6. Emulsion solvent diffusion method.
7. Ionic gelation method.
8. Micro-emulsion template method.
9. Solvent Displacement method/ Nano-precipitation method.
10. Solvent emulsification / Evaporation method / Emulsion solvent evaporation technique [16].

Evaluation Techniques: Evaluation parameters of nanogel include:

1. **Visual Observation:** The prepared nanogel formulation is inspected visually for their color, appearance, and consistency.
2. **pH Determination:** The pH values of 1% aqueous solutions of the prepared nanogels are measured by a pH meter (Digital pH meter).
3. **Homogeneity:** The developed nanogel is tested for homogeneity by visual inspection after the nanogel has been set in the container. It was tested for appearance and presence of aggregates.
4. **Grittiness:** The formulation is evaluated microscopically for the presence of particles if any.
5. **Viscosity Study:** The viscosity of the formulated batches is determined using a Brookfield viscometer with spindle 64 at 10 rpm.
6. **Extrudability Study:** After gels were set in the container, the formulations were filled in the collapsible tube. The extrudability of the formulation is determined in terms of weight in grams required to extrude a 0.5 cm ribbon gel in 10 seconds.
7. **Spreadability Coefficient:** It consists of a wooden block that is attached to a pulley at one end. Spreading coefficient is measured on the basis of “slip and drag” characteristics of nanogel.
8. **Particle size:** The particle size of nanogel is determined by photon correlation spectroscopy (PCS) that analyzes the fluctuations in light scattering due to Brownian motion of the droplets using a Zetasizer.
9. **Zeta Potential:** The selected formulation's zeta potential is measured using a Zetasizer.
10. **Raman Spectroscopy:** The shift in wavelength of the inelastically scattered radiation helps to give information about the chemical and structural data of the formulation. It is used to determine chemical bonds, symmetry of molecules, and crystallographic orientations of a sample.

11. **Total Drug Content:** The diluted supernatant solution is analyzed using a UV spectrophotometer, against blank/control.

12. **Skin irritation study: Determining** the effect of nanogel on the skin of rabbits. Rashes, signs, symptoms, redness, whirls, *etc*. are determined.

13. **Entrapment Efficiency:** The diluted supernatant solution is analyzed using UV spectrophotometer, against blank/control.

14. ***In-vitro* Drug Diffusion:** I*n-vitro* drug release studies are carried out using Franz diffusion cell.

15. **Drug Release Kinetics:** The obtained drug release data is modeled mathematically to obtain; hence drug release profile can be correlated with drug release kinetic models.

16. **Fourier Transformed Infrared (FTIR) Spectroscopy:** To study any possible interaction between drugs and excipients.

17. **Differential Scanning Calorimetry (DSC):** To study any possible interaction between drugs and excipients.

18. **Scanning Electron Microscopy (SEM):** The shape and surface morphology of the nanogels prepared with optimized parameters is observed by scanning electron microscopy.

19. **Stability study:** A stability study is conducted on the optimized formulation as per ICH guidelines for 90 days duration[17].

Nanogel Properties:

Biocompatibility and Degradability: Biocompatibility is one of the most desirable properties of nanogels and is a requirement sine qua non for any nanotechnology employed for therapeutic purposes. This implies that when utilized, they do not cause any negative biological reactions at the molecular, cellular, or organ levels. Typical foreign body reactions to tiny particles include immunological, thrombogenic or mutagenic activation, resulting in unwanted physiological or anatomical alterations like allergies, blood clot formation, or disease states like cancer. Although it is believed that nanogels made of well-known biocompatible polymers or biomacromolecules are less likely to cause these unfavorable biological responses, the fact that they are included in nanoparticles does not guarantee their safety as non-toxic substances.

Although various nanogel formulations have proved to have no harmful effects in cell toxicity and cell viability experiments used to evaluate biocompatibility, this is not consistently well investigated utilizing *in-vivo* preparations. The ability of nanogels to biodegrade into suitably tiny, non-toxic breakdown products with a chemical makeup that does not elicit any of these reactions is therefore crucial for removing nanogels from the body.

One strategy has been to make tetralysine and oligoethylenimine polymer nanogels that break down when exposed to glutathione at concentrations that are similar to those found inside cells, anticipating eventual breakdown of the nanogel into the nontoxic polymers from which the nanogels were initially created [18].

Swelling Behavior: Several variables affect how much a nanogel swells in aquatic settings, including: i) the crosslinking density. The swelling of cationic nanogels was strongly influenced by the cross-linker concentration at high ionic strengths, but at low ionic strengths, it was also influenced by the charge concentration, and ii) environmental variables such temperature, pH, and ionic strength. It has been demonstrated that crosslinked PEG-b-PMA core-shell nanogels inflate with rising pH as a result of the ionization of the carboxylic groups in the PMA. In contrast, PEG-cl-PEI nanogels contracted when pH rose from 8.5 to 10, a consequence of amino group deprotonation in the PEI [19].

Drug Loading Capacity and Drug Release: Many different methods may be used to load drugs into nanogels. These consist of i) covalent conjugation of biological agents, which is possible during or after the manufacture of nanogels. To create nanosized hydrogels, modified enzymes were copolymerized with acrylamide in both inverse microemulsion and diluted water solutions; ii) Chemicals are physically trapped inside nanogels. This method added proteins to pullulan nanogels modified with cholesterol and siRNA

added to hyaluronic acid, or HA, nanogels. PEG and pluronic F127-based amphiphilic crosslinked nanogels with doxorubicin put into and released from them; and iii) Drug loading based on passive or diffusion. Dextranlysozyme nanogels have been individually loaded with silver nanoparticles and dexamethasone using just diffusion while incubating the nanogels in excess drug or nanoparticle solution on a shaker.

The drug loading that is produced by these methods is often rather low, at less than 10% by weight. There are several different processes by which drugs are released from nanogels. In a mouse model of lung damage, the diffusional release of dexamethasone from dextran-lysozyme nanogels is sufficient to reduce the development of pulmonary inflammation. In contrast, exposure to silver nanoparticles from the same nanogel construct prevents bacterial growth. Nanogels maintained in vitro diffusional doxorubicin release for up to one week.

The simplest mechanism is diffusional release, which has been applied clinically in nanomedicine methods. When the nanogel structure is broken down physiologically or chemically, nanogels can also release medicines. For example, doxorubicin release from pH-sensitive drug-loaded nanogels was dramatically accelerated at lower pH values, increasing the amount of drug taken up by non-small lung cancer cells in a mildly acidic pH environment. Additionally, chemicals that are responsive to various environmental stimuli can be released *via* nanogels. We have created disulfide crosslinked POEOMA nanogels that biodegrade into water-soluble polymers and release cargo when exposed to glutathione tripeptide, a substance that is ordinarily present in cells [20].

Size and Shape: Dynamic light scattering and electron imaging techniques can show that spherical particles with a diameter of 20 to 200 nm are commonly produced during the manufacture of nanogels. Using micromolding and photo-lithographic methods, which also offer control over nanogel size, form, and chemical composition and allow for loading medicines and macromolecules, it is feasible to create other shapes. Given that spherical nanoparticles are subject to more phagocytosis and mechanical retention in the microvasculature than discoid and ellipsoid nanoparticles, one major benefit of employing non-spherical nanogels is their ability to circulate intravascularly for a longer period. In contrast to the micro and nanofabrication technologies, spheroidal hydrogel nanoparticles are easier to make during chemical synthesis and more suitable to scaling up.

Although surface characteristics such as charge, PEG coating, and proteins conjugated or/and absorbed on the particle all impact the rate of hepatic and splenic absorption, spheroid nanocarriers in size range 20-200 nm seem suitable to vascular transport (main clearing organs of the reticuloendothelial system, RES). As with any carrier, nanogels in this size range circulate long enough to reach their target vascular sites before finally being absorbed by the reticuloendothelial system [21].

Viscoelasticity: Nanogels behave both like a liquid and a solid because they are extremely solvated. These viscoelastic particles may change shape in the presence of flow, making it easier to move through the congested cellular environment and past the extracellular matrix. While conventional rheology techniques, such as cone and plate rheology, may easily describe bulk gels, no nano rheological techniques are currently available to determine the complex modulus. After addressing the impact of substrate and lateral resolution issues, nano-indentation techniques now used on cells and bulk polymeric gels may be expanded to nanogels in the future. Cross-referencing through physical (such as entanglements) or chemical (such as covalent) interchain interactions, nanogel components can be crosslinked. Physical crosslinks inside the nanogels are based on weak interactions between polymer chains, such as van der Waals, electrostatic contacts, or hydrogen bonding and they depend on the flexibility of the chains as well as the concentration of polymer per unit volume. Physically crosslinked nanogels may become greatly diluted and disintegrate after being injected into bodily fluids, which might compromise therapeutic agent delivery and result in unfavorable side effects.

In contrast, a potential technique to make stable nanogels without using surfactants or solvents is

physical self-assembly of premade polymers (or using monomers) followed by chemical crosslinking. This physical self-assembly/chemical crosslinking method is suitable for creating biodegradable stimulus-responsive nanogels constructed of biopolymers. Functional crosslinkers, such as cationic small molecules, can also load drugs while maintaining structural stability in addition to synthetic crosslinkers [22].

Stimulus Responsive Nanogels:

Synthesis of Stimulus Responsive Nanogels:

Disulfide Based crosslinking: Nanogels can be created using a polymer crosslinking technique called amphiphilic random copolymers' self-cross-linking processes. In particular, polymers with pyridyl disulfide (PDS) as the hydrophobic and cross-linkable unit and polyethylene glycol (PEG) as the hydrophilic unit spontaneously builds at the nanoscale in aqueous solutions. By adjusting the polymer concentration and crosslinker concentration and using the lower critical solution temperature (LCST) polymer behavior, it is simple to create nanogels of different sizes. In a very similar manner, dextran containing lipoic acid has been used to create nanogels by thiol exchange. Using this method, doxorubicin-loaded nanogels were created, with the addition of dithiol reitol catalyzing the crosslinking process [23].

Photochemistry-based Crosslinking: Photochemistry is a different crosslinking method that has been used effectively to stabilize polymer assemblies functionalized with either dimerize or polymerizable units. Micelles have been created using hydrophilic block copolymers containing coumarin, which dimerizes when exposed to UV light and is subsequently photochemically crosslinked. Dendrimer nanocarriers have also been created using light-sensitive chemistry; upon exposure to light, they release the medicine they are carrying. These methods can be applied to nanogel formulations and are particularly beneficial because the crosslinking activity can be incorporated in a way that allows for the control of drug release by either inhibiting enzymatic degradation of the substrate with light stimulation at one wavelength or enhancing enzymatic degradation of substrate as a result of increased decrosslinking with light exposure at a different wavelength [24].

Physical Crosslinking: Non-covalent crosslinking techniques have been used to create a number of chemically different nanogels. Cholesterol-modified polysaccharides have been used to create nanogels that use the hydrophobic interactions between the cholesterol groups to create physical crosslinking. Other forces, such as host-guest and electrostatic contacts, have been used in addition to straightforward hydrophobic interactions to create physically crosslinked nanogels, as discussed in [25].

Amine-Based Crosslinking: Since amine groups are extremely reactive with a wide range of chemical moieties, amine-based crosslinking is a desirable method for nanogel production. The creation of shell-crosslinked knedel-like structures employing amine crosslinkers has a well-established approach. Poly (acrylic acid) has been used as the hydrophilic, cross-linkable block in a variety of amphiphilic block copolymers. In addition, a number of activated esters, such as pentafluorophenyl acrylate, p-nitrophenyl acrylate, and *N*-acryloxysuccinimide, have been included as cross-linkable units into copolymers, making these substances suitable for the creation of nanogels. Another method of crosslinking to produce nanogels comes from reactions using isocyanate. For instance, excess 1, 8-diaminooctane has been added to micellar aggregates of 3-isopropenyl-, 2-dimethylbenzyl isocyanate carrying copolymers to produce pH-responsive crosslinked micelles [26].

Click Chemistry-Based Crosslinking: It has been suggested that nanogel synthesis can be accomplished by click chemistry. The corona of micelles created by amidating the acrylic acid groups of poly (acrylic acid)-bpoly (styrene)-based amphiphilic diblock copolymers was first immobilized with amino-containing alkynyl groups. The micelles were then covalently crosslinked by Click reactions between azido dendrimers and Click-prepared micelles to create nanogel networks. Another use of click chemistry is the creation of corecross-linked polyion complex micelles[27].

Classes of Stimulus Responsive Nanogels:

pH-responsive Nanogels for Drug Delivery: The pH in biological tissues and body spaces is not uniform; normal (near neutral) pH of 7.4 is found in blood, acidic pH of 2 or lower is found in the

stomach, and a range of acidic pH values are found in different tissues and pathological sites, including ischemic tissues, wounds, inflammation sites, and tumors. Additionally, the pH of some intracellular spaces, such the endosomal-lysosomal vesicular continuum, eventually shifts from a basic pH of 7 to an acidic pH of 4-6. These local pH values may induce the drug carrier's deconstruction or rearrangement, fusing with or penetration through membranes, shedding components, or release of the drug. Since the pH in such different compartments as the tumor interstitium, an obstructed blood artery, and the lysosomes in every cell in the body is comparable, the spatiotemporal specificity of these pH-mediated alterations is obviously constrained.

An appealing method of improving the delivery of encapsulated cargo to particular tissue sites in the body is to engineer nanogels to be pH-responsive. These nanogels can change their behavior when exposed to a critical pH value (pHc), which can change their behavior regarding swelling or crosslinking and engineer drug delivery. According to this method, nanogels are created to undergo certain chemical or structural changes at pHc, which corresponds to the pH microenvironment of the specific tissue spot where the deliverable medication is intended to be released. Based on the pKa (or pKb) of weakly acidic (or basic) groups contained in the nanogel chemical polyelectrolyte structure, the pHc is chosen. pH-responsive nanogels can be made to be cationic, which causes swelling when the pH falls below pKb, or anionic, which causes swelling when the pH rises over pKa. The pHc will change as more hydrophobic alkyl residues are added to the nanogel polyelectrolyte backbone. Ionic strength has an impact on pKa and pKb as well, which affect pHc in pH-responsive nanogels. Since biological fluids and sick tissues may have high ionic strengths, which are a key factor in the swelling ratios of pH-responsive nanogels, this has an influence on medication delivery.

Crosslinked polyelectrolytes with weakly acidic and/or weakly basic groups acting as proton donors, receptors, or a mix of the two often make up pH-responsive nanogels. The degree of ionization within the polyelectrolyte chain can fluctuate in response to slight variations in the local pH. Nanogel swelling or deswelling can be caused by variations in the degree of ionization's effect on the osmotic pressure inside the nanogel. It has been demonstrated that the swelling of core-shell nanogels made from crosslinked PEG-b-PMA is caused by the carboxylic groups of PMA being ionized in response to rising pH. On the other hand, the deprotonation of the PEI amino groups caused the swelling of nanogels formed of crosslinked poly(ethylene oxide) (PEO) and polyethyleneimine (PEI) (PEG-clPEI) to decrease with rising pH. These swelling behaviors are caused by manipulation of the crosslinking *via* pH adjustment, with the swelling ratio often declining as the number of crosslinks inside the nanogel rises.

The pH in normal tissue (7.4) is higher than the extracellular pH (pHe) in many cancers (5.8 pHe 7.2), which is a primary driving force in the creation of pH-responsive nanogels to facilitate drug delivery 70. Furthermore, the pH of the cytosol inside of cells, which is typically somewhat acidic, is higher than the pH of lysosomes and endosomes, which ranges from 5.0 to 5.5.The pH exposure that nanogels containing cancer chemotherapeutic chemicals experience while being delivered into these habitats has been designed to react, with pH fluctuations causing the release of the hazardous cargo. The drug release can be manipulated to happen in extracellular tissue or intracellularly into endosomes or lysosomes after cellular absorption depending on the characteristics of the nanogel. Including positive and negative charges throughout the polymer chain of nanogels made of amphoteric polyelectrolytes is another design factor for pH-responsiveness.

Due to the existence of an isoelectric point, this property makes such nanogels intriguing for both drug loading release and swelling (IEP). The ability of macromolecular medicines to be loaded into and released from nanogels is significantly impacted by the IEP and the equilibrium swelling ratio in a pH-dependent manner. Large, oppositely charged biomacromolecules can be put into the interior of the nanogel because polyelectrolyte formulations can accommodate their electrostatic interactions. Immobilized polynucleotides loaded into pH-responsive nanogels particularly for the purpose of gene delivery may be a part of the extremely

effective loading. The distinctive swelling that occurs as salt concentration rises at the IEP is another beneficial property of polyampholyte nanogels, which makes them appropriate for medication delivery given that biological fluids contain high ionic strengths [28].

Temperature Responsive Nanogels for Drug Delivery: When the polymer(s) that makeup nanogels experience a volume phase transition, which takes place at the volume phase transition temperature, the nanogels' response to temperature changes rapidly (increase or decrease) in particle size (VPTT). Negatively temperature-responsive nanogels rapidly contract in size with temperature increases over their VPTT, whereas positively temperature-responsive nanogels exhibit a clear and rapid size increase when the temperature rises above the VPTT. Although poly (N-isopropylacrylamide) (PNIPAM) has been used to create negatively temperature-responsive nanogels, positively temperature-responsive nanogels are preferred for drug delivery applications due to their capacity to release compounds that would otherwise be trapped inside collapsed nanogels. Entrapped pharmaceuticals are kept within the collapsed nanogel prior to this being triggered by a localized change in temperature, preventing unwanted early or premature release. Following temperature-induced nanogel size expansion, drug transport out of the swollen nanogel largely happens through diffusion. This drug release mechanism is thought to be more effective than drug ejection from a collapsed negatively temperature-sensitive nanogel.

For exposure to a minor temperature increase to stimulate drug release, the VPTT must be somewhat higher than the average tissue temperature when constructing temperature sensitive drug delivery nanogels. This is significant since a variety of external heating approaches may locally generate hyperthermia, and temperature is typically high in inflamed tissues where medicines are being administered. For these reasons, interest in nanogels with VPTTs above body temperature has recently increased; however historically, many temperature-sensitive nanogels for drug administration have been created to release their cargo when subjected to a rise in temperature. Examples of formulations for temperature-sensitive nanogels include those made of oligo (ethylene glycol) acrylate, poly (Nisopropylacrylamide) and 2-(5,5-dimethyl-1,3-dioxan-2-yloxy) ethyl acrylate. Temperature control is still a fascinating and cutting-edge method for modifying tissue properties, nanogel swelling, and medication loading and unloading for disease therapy [29].

Photoactive/Light Responsive Nanogels: Making biomaterials from photoactive polymers that change bonding or conformation in response to light exposure is another way to make changes in them. Numerous functional groups sensitive to light, such as triphenylmethane, spirobenzopyran, cinnamonyl and azobenzene, alter in size or shape or create ionic or zwitter ionic moieties when exposed to light. When these kinds of reactive polymers are used to create nanogels, a phase transition occurs when the functional groups undergo structural or polarity changes in response to the proper light wavelength. Since, stimulation with light in the visible and UV regions does not penetrate beyond the skin into deep tissues and the UV and visible wavelengths can also damage human tissue even at low power, drug delivery based on this approach is limited to systems that are activated with near-infrared (NIR) light. The stimulation of hybrid nanogels made of temperature-responsive polymers and noble metals, such as Au and Ag nanoparticles, has been carried out using NIR light, which is well transmitted through skin and many other tissues at the millimeter- to centimeter-scale (NP).

Phase change within the polymer constituent, which can then result in drug release, is promoted by the presence of the metal ingredient due to localized heating and light absorption. Because it has extremely low known toxicity, does not self-quench, and offers a significant optical cross-section for imaging, Au-NP is preferred for usage in these systems. Gold has considerable potential for functiona-lization by surface modification with polymers, organic compounds and biomacromolecules using thiol chemistry since it is exceedingly stable at the nanoscale. For application as photothermal therapies, light-responsive, Au-NP-containing nanogels have been created. These photoactive nanogels may be selectively triggered for drug release in a particular disease location by externally administered photo irradiation.

Additionally, for the treatment of cancer, PEGylated nanogels with Au-NP in a crosslinked network core of poly [2-(N,N-diethylamino)ethyl-methacrylate] have been developed. These nanogels were demonstrated to only become cytotoxic when exposed to light, as a result of the heat produced by intracellular nanogels. This shows that light-responsive nanogels containing metal NPs may be effective for localized heating during thermal treatment as well as for the administration and release of cargo drugs. It has been demonstrated that this dual-mode treatment strategy based on hybrid nanogels improves therapeutic effectiveness. Gold nanorods have been integrated into polymeric hydrogels to generate stimuli-responsive materials for biomedical applications. For instance, when exposed to a 770 nm laser at 0.3 W, a crosslinked tert-butyl acrylate network containing gold nanorods was heated and experienced a form shift within a few minutes. Additionally, when exposed to an 808 nm laser, peptide hydrogels containing gold nanorods demonstrated the release of encapsulated dextran [30].

Biomolecule Recognition-responsive Nanogels: A natural mechanism for causing precise changes in biological tissues, cells, and biomolecules as a result of a response to, or alteration of, a specific molecule or ion that is linked with evoking some biological function is known as molecular recognition. By embedding the stimulus-inducing biomolecule into biomaterials, such as nanogels, it is possible to mimic these natural biological processes to promote the release of encapsulated drugs, among other uses. For instance, nucleic acids, peptides, proteins and glucose can all trigger reactions in biomolecule recognition-responsive hydrogels. The latter are of particular importance for the study of diabetes and the creation of insulin delivery systems based on nanotechnology that provide fresh possibilities for the therapeutic management of this common illness. Several kinds of nanogels that react to glucose have been created. We have created polysulfide nanogels with pluronic glucose oxidase (GOx) conjugates. The oxidation of glucose to hydrogen peroxide and D-glucono-lactone, which lowers the local pH, is catalyzed by the GOx enzyme, an oxidoreductase (see above for more detail regarding pH-responsive nanogels).

When there is glucose available, GOx also causes the oxidation of sulfides, which results in the expansion of the nanogel. Inducible swelling and pH changes can aid drug release from GOx-containing nanogels. Based on unique complicated interactions combining glucose and functional groups like phenylboronic acid (PBA) inside the nanogel network, nanogels have also been created for biomolecule-responsive activity. PBA groups can be found in charged and uncharged forms in aqueous solutions. The uncharged form is easily hydrolyzed, but only the charged form produces a stable combination with glucose. Stable glucose-associated complex formation changes the equilibrium, adding more charged groups and making the polymer chain more hydrophilic. This encourages the swelling of nanogels and the subsequent drug release. Numerous research describing the creation of nanogels based on interactions between PBA and glucose have been released.

Additionally, PBA-based amphoteric nanogels that additionally electrostatically bind insulin and shapes like PBA-based glucose-sensitive nanocapsules have been created. Since they release more insulin in the context of greater glucose levels, these amphoteric nanogels provide a further potential therapeutic advantage. Antimicrobials that are secreted in the presence of bacteria that secrete lipases may now be delivered differentially using nanogels. This method, which may be used to treat both intracellular and extracellular infections, works by including a hydrophobic poly (β-caprolactone) fence structure in the nanogel, which delays the release of antibiotics until the fence is broken down by lipase. It has been shown that the resulting encapsulated drug release is bactericidal as intended [31].

Magnetic Field Responsive Nanogels: Another type of hybrid nanogel responds to magnetic fields because it contains magnetic NPs made of either Fe_2O_3 or Fe_3O_4. Magnetic NP-containing nanogels may heat up when exposed to an alternating magnetic field, just like Au or Ag NP-containing nanogels. Due to the application of a strong magnetic field gradient, magnetic nanoparticles may also experience tissue site localisation. Superparamagnetic formulations lack any magnetism for drug delivery when not subjected to

a magnetic field, making the site's orientation dependent on the presence or absence of a magnetic field. However, these formulations may have inherent toxicity depending on characteristics like size, shape and chemical composition. Either emulsion polymerization or *in-situ* synthesis techniques can entrap magnetic NPs in nanogels, but neither technique ensures that the magnetic NPs will be distributed evenly inside the nanogels. The resulting nonuniform magnetic NP content may have an impact on the responsiveness of the nanogel magnetic field for site localization and/or heat generation. A core-shell structure for magnetic nanogels has been created, as seen by transmission electron microscopy. These formulations, along with others, offer a lot of promise for application in drug administration in a way comparable to how photoresponsive /light-sensitive nanogels are used. For instance, nanogels can be directly applied with a persistent magnetic field to the target therapeutic location, where they can then collect and release their therapeutic cargo.

After being loaded with Bleomycin A5 Hydrochloride (BLM), magnetic poly (vinyl pyrrolidone) nanogels were injected into rabbits with squamous cell cancer. After injecting nanogel, the tumor surface was exposed to a permanent magnet for one day. The tumor's size considerably decreased over the following two weeks due to medication release and magnetic field-directed nanogel accumulation inside the tumor. Because magnetic NPs can produce heat when exposed to an alternating magnetic field, they can also be used in nanogels for thermal treatment. This has been expanded to create thermoresponsive magnetic composite nano-materials for multimodal cancer treatment. An alternating magnetic field was applied to magnetic PNIPAM nanogels to generate enough heat to raise the local temperature above the nanogel polymer VPTT using a combination of multiple response-initiated characteristics.

The heat impacts caused considerable nanogel deswelling, which aided in the doxorubicin's release after being encapsulated. This is a particularly creative method of treating disease since it takes use of several unique modalities, such as magnetically guided site delivery of the nanogels, thermotherapy, and drug release for chemotherapy [32].

Specific Reported Studies: Elkomy *et al*., 2016 Adjuvant-induced arthritis (AA) rats were used to study the anti-inflammatory effects of new topical formulations comprising the pain reliever ketoprofen (KET) solid nanoparticles (KET nanogel ointment) [33]. Aiswarya *et al*., 2015 create flurbiprofen-containing topical gel-loaded nanoemulsions utilizing volatile oil. The medicine was delivered to the intended spot *via* the gel at a regulated rate. Flurbiprofen is often used topically to treat osteoarthritis and rheumatoid arthritis. Using pseudo-ternary phase research, individual screening was used to choose the oil phase, surfactant, and cosurfactant. Using 3^2 factorial designs and response surface methods, the Q8 recommendations from the International Conference on Harmonisation were used. The formulations were created using a procedure called spontaneous emulsification. The outcome pointed to the improved formulation as having greater potential for transdermal medication administration than the commercial formulations [34].

Chopade *et al*., 2018 Tenoxicam's transdermal delivery was boosted, and it was also suggested that it may take the role of oral NSAID treatment for rheumatoid arthritis. The current study aimed to create a tenoxicam nanogel with smaller particle size to increase the anti-inflammatory drug's bioavailability and assess the potential of the gel in carrageenan-induced rat paw edema. The current work aims to create a nanosized dispersion of tenoxicam using the modified emulsification-diffusion method and a gelling ingredient called Noveon Polycarbophil AA-1. Standard procedures including rheology, particle size, drug content, and an *in-vitro* diffusion investigation of nanogel are used to describe the formulation Tenoxicam nanogel's anti-inflammatory effect was found to be equivalent to that of regular Diclofenac Sodium gel and has demonstrated edema inhibition of 85% after 4 hours of therapy, according to a rheological analysis of the formulations. Conclusion: Tenoxicam nanogel, which was created, utilizing Noveon polycarbophil AA, has been proven to be safe for use in the treatment of edema and rheumatoid arthritis [35]. Inamdar *et al*., 2018 Transdermal medication delivery relies on the drug formulation staying in the skin for a long time.

One of the most difficult tasks continues to be medication delivery using nanogels. The investigation aimed to create a nanogel with smaller particle sizes to increase the hydrophobic drug's bioavailability. A sufficient concentration of medications must be provided and kept there by the regulated and continuous distribution for it to be effective. High drug loading capacity, biocompatibility and biodegradability of materials based on nanogels are crucial factors in designing an efficient drug delivery system. For optimum therapeutic efficacy and little toxicity or side effects, drug molecules put into the nanogel must be maintained and not transported out or prematurely leak while circulating. The current work aims to create beta sitosterol nanosize dispersion by nanoprecipitation technique and combine it with the gelling agent to create nanogel by dispersion method. 1% of carbopol 934 exhibits superior *in-vitro* drug release compared to other carbopol 934 concentrations [36].

Patil *et al*., 2018 Create a *Pterocarpus marsupium* loaded nanogel for anti-inflammatory purposes and conduct *in-vitro* tests to assess the nanogels. As multifunctional polymer-based drug delivery methods, nanogels swollen nanosized networks made of hydrophilic or amphiphilic polymer chains have garnered a lot of attention. Pterocarpus marsupium extract, carbapol 940, EDTA, ethanol, propylene glycol, methyl paraben, propyl paraben, triethalonamine, and the necessary amount of water were used to make the gels. The gels were created using the nanogels from polymer precursors method. In this method, extract was dissolved in propylene glycol and ethanol and in a separate phase, carbopol was mixed with water to create a jelly-like mixture. Both mixtures were then combined and homogenized in a high-speed homogenizer, where they were homogenized until the consistency of a gel was formed. The generated nanogel proved stable throughout evaluation tests utilizing a variety of parameters, and its particle size was determined to be in the nano range. Consumers can use the prepared nanogels since they are st able, tasty, and acceptable [37]. Talele *et al*., 2017 the bioavailability of anti-inflammatory medicine can be increased by producing nanogel with smaller particle size, which requires a prolonged residence time of the drug formulation in the skin. The study created a diclofenac sodium nanosize dispersion using an emulsion-solvent diffusion technique and a gelling agent to create nanogel. The formulations are distinguished by their particle sizes ranging from 100 nm to 400 nm. Glycerol: Diclofenac sodium nanogels are made utilizing various polymers and a water (20:80 v/v) co-solvent system since it has a higher permeability coefficient than alcohol: co-solvent in water [38].

CONCLUSION: Systems made of nanogel have been researched from a theoretical and practical standpoint. They are frequently utilized for coatings, cosmetics goods, targeted delivery systems, controlled delivery systems, and controlled delivery systems. Thisentrappment is made possible by the employment of nanogels. Future advancements in nanogels look promising and will increase medication delivery options. Every new investigation involves the development of cutting-edge polymer and mechanistic techniques with a potential function in treatments and innovation in nanogel manufacture. The advancement of biopharmaceutical characteristics of medicine expands the usage of these materials in several industries or other distribution methods. One of the best drug delivery technologies for ensuring a regulated or sustained medicine release is undoubtedly nanogels. However, a flawless delivery system must be created, providing accurate information on the interactions between the drug and the carrier as well as the impact of size and drug loading on drug release.

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