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An Overview of Nano-gel in the Treatment of Various Diseases as One Part of a Novel Drug Delivery System

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Abstract-

Nanogel represents an innovative platform for tunable drug delivery and targeted therapy in several biomedical applications, from cancer to neurological disorders. The design of the nanocarriers has been a topic of focus among researchers for many years, with the aim of the optimization process and delivering advanced nanomaterials. Chemical reactions, physical interactions, and technical device development are three key areas explored to overcome the shortcomings of traditional nanofabrication approaches. This review proposes to consider the current situation techniques used in nanogel design, highlighting the development of physicochemical methods, microfluidics. Nanogel represents an innovative platform for tunable drug delivery and targeted therapy in several biomedical applications. Chemical reactions, physical interactions, and the production of designed devices are the three key areas being investigated to overcome the limitations of standard nanofabrication technologies. This paper recommends a focus on current nanogel design approaches, emphasizing advancements in physicochemical methodology and microfluidics. Nanogels are a novel platform for customizable drug release and targeted therapy in a wide range of biomedical applications, from cancer to neurological illnesses. The design of these nanocarriers has been a key topic of study for researchers throughout the years, to optimize the techniques and provide improved nanomaterials. This review aims to examine the current state of nanogel design approaches, focusing on the advancement of physicochemical methods and microfluidics.

Keywords- Nano Gel (NG), Cross-linked, Stimuli-Responsiveness, TEM, FTIR.

Introduction-

Nanogel is a three-dimensional hydrogel material with high water storage capacity formed by a crosslinked swellable polymer network that is insoluble in aqueous media. Nanogels can be made from a variety of natural materials [1]. A naturally occurring polymer, a synthetic polymer, or a blend of the two. Their properties include size, charge, porosity, amphipath city, softness, degradability, etc., all adjustable variables [2]. Changes in the chemical composition of nanogels Most of them are spherical particles, but recent advances in synthetic technology have made it possible to create nanogels of any size in many forms [3].

They can also be core-shell construction, with at least one layer of insulation to ensure structural integrity. Nanogels are highly biocompatible and have a high load-carrying capacity for guest molecules due to their hydrophilic nature, and their unique physical characteristics give them distinct advantages over other forms of nanomaterials for biomedical applications [4]. Nanogels not only preserve cargoes from degradation and rejection, but they also help induce a tailored and activated response at the target site due to their unique qualities such as responsive behavior to stimuli. like, soft and swollen [5]. Polymer nanogels can be utilized as a substrate for image probes, boosting their stability and utility. This resulted in the creation of a new class of agents known as "nanohybrids," which are nanogels made up of inorganic components. Diagnostic and imaging agents for many medical diseases can be included in such nanohybrids. The nanogels prevent biomolecules like enzymes and genetic material from degrading, but their macromolecular features extend the cyclic half-life of small molecules, making them an ideal platform for the administration of many therapeutic compounds [6].

Polymer nanogels can be employed to support such image probes, boosting their stability and utility. This resulted in the development of a new class of agents known as "nanohybrids," which are nanogels composed of inorganic components. These nanohybrids can contain a range of diagnostic and imaging agents for various medical diseases. The nanogels prevent the degradation of biomolecules such as enzymes and genetic material, while their macromolecular features extend the cyclic half-life of small molecules and serve as a very convenient platform for the combined delivery of therapeutic compounds [7]. Because of its high load capacity, stability, and sensitivity to environmental conditions such as temperature, nanogel has considerable potential as a drug delivery vehicle. unrivaled in terms of strength, pH, and temperature Since the first review, common medicinal nanocarriers have been developed [8]. In 2002, a paper on the synthesis and application of nanogel was published. This new class of nanomaterials has piqued the interest of researchers. Drug delivery, biomolecules, and imaging agents have received considerable interest [9].

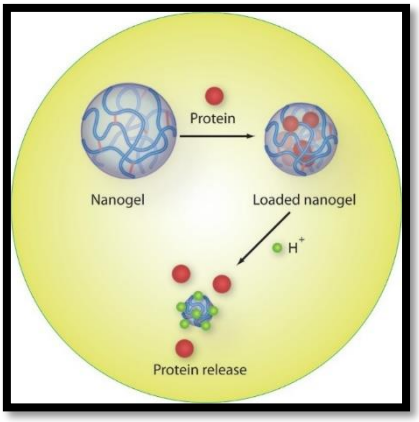

Fig no 1- Diagrammatic representation of Nano Gel [8,9]

Nanogels as a therapeutic drug carrier-

The nanogels are very expandable and can hold up to 30% by weight. or more biological molecules and drugs through electrostatic, van der Waals and/or hydrophobic interactions or covalent bonds with polymer chains. These loading capacities are very high and surpass liposomes and macromolecular micelles. The nanogels collapse under the effect of drug delivery, creating stable nanoparticles in which the biological agent is encapsulated. Dispersion of hydrophilic polymers (eg, PEG) in the nanogel structure can prevent aggregation [10]. During the degradation of the drug nanogel complex, the hydrophilic polymer chains on the surface are exposed and create a protective layer around the nanogel. The controllability and flexibility of polymer chemistry allow for the creation of a wide variety of drug formulations as well as the incorporation of multiple therapeutic goods into the same nanogel carrier. Stimulus-responsive drug release via temperature or pH-induced volume depletion is also attractive for drug delivery applications. Surface functionalization of nanogels could enable them to selectively accumulate in target tissues or cells [11]. The development of nanogels capable of delivering, protecting, targeting, and releasing therapeutic chemicals in a geographically and temporally regulated manner is currently underway, and their logical design has implications. can be the basis for many different applications [12].

Nanogels for small therapeutic molecule delivery-

Significant progress has been achieved in the use of nanogels as a delivery vehicle for physiologically active small compounds in recent years. Nanogels can be a versatile platform for combining various tiny medicinal compounds via electrostatic and hydrophobic interactions, as well as hydrogen bond formation. Because the nanogels swell in the aqueous medium, the items can easily enter [13]. The streamlined design of nanogels can be a powerful tool for modulating drug release rates, influencing carrier-cell interactions, and achieving the medication's targeted therapeutic impact. The capacity of weakly crosslinked polyelectrolyte nanogels to mix molecules with opposite charges is one of its most important properties. For example, cationic crosslinked PEG-polyethyleneimine (PEGPEI) nanogels were investigated for the immobilization of negatively charged particles [14].

These formulations generate colloidal dispersions that are stable at physiological pH and ionic strength and can be lyophilized and redistributed. The complexation technique and similar nanogels have been successfully utilized to mix various nucleosides 5 triphosphate analogs. These drug-containing nanoparticles have been shown to increase the delivery of active base compounds by therapeutic nucleoside analogues in cells and to suppress tumor development in animal models of breast carcinoma [15]. The same group recently showed considerable benefits of active 5'triphosphates of nucleoside reverse transcriptase inhibitors encapsulated in cationic nanogels on medications used in antiretroviral therapy for HIV-1 infection in the central nervous system [16].

Small molecules usually contain only a limited number of ionic groups, capable of interacting with nanogels of opposite charge and additional hydrophobicity, hydrogen or the coordination bond between drug molecules and nanogel could be even more stable electrostatic coupling. Recently, our laboratory demonstrated that the microenvironment formed by hydrophobic domains in the ionic core of the nanogel affects the dissolution release capacity and properties of nanogels. The d- block copolymer, PEG-b. poly (L-glutamic acid), is denatured by aspiration with the elements L-phenylalanine methyl ester. used to synthesize nanogels of small size (about 70 nm in diameter) and narrow particles size distribution. Stable DOX-loaded hybrid nanogels were prepared at high DOX power (30% by weight) [17]. DOX release rate from significantly fewer carriers than unmodified nanogels: one batch of more released 85% of drug incorporation within 8 h for undenatured nanogels was observed while only ~20% incorporated DOX released from hydrodynamically modified nanogels in the same period. These results suggest that the intermolecular interactions in the combination with a more compact mesh kernel can explain the delay and controlled release of DOX from polyelectrolyte nanogels modified in water. It was also found that these DOX-loaded nanogels show improved anti-tumor efficacy versus free DOX in a mouse ovarian tumor xenograft model [18].

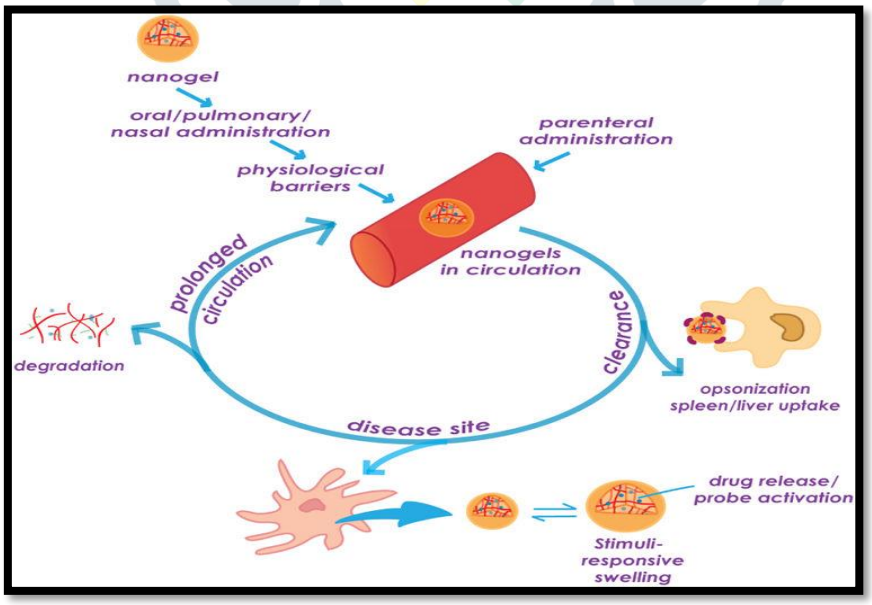

Fig no- 2. In vivo behavior of nanogels.

Fundamental Criteria in NG Synthesis-

In addition to the swelling feature, which may be defined as a "superior" property of Nano-gel, the primary properties that must be considered in the synthesis of these nanomaterials are excellent biocompatibility, biodegradability, colloidal stability, high surface area, and high capacity. Because of particle size and surface qualities, loading offers drug release and active/passive drug release. Other things that can be fine-tuned by carefully tweaking the synthesis routes of Nano-gel are [19]:

1) Causes the release of water and oil-soluble bioactive molecules.

2) Administration route adaptability (i.e., mucosal or parenteral route)

3) Low immunogenicity and decreased NG elimination through mononuclear phagocytosis.

4) Increased absorbency

5) Increase the solubility of medicines with low molecular weight.

6) Lower drug volume in comparison to normal drug delivery [20].

Nano-gels are often composed of natural or synthetic polymers or mixtures of the two. Their ingenious compositions, on the other hand, may involve the incorporation of inorganic components or the grafting of specific biological fragments into the polymer backbone. In the first instance, Nano-gel can function as an imaging probe, combining a variety of diagnostics and contrast ants for various biomedical applications. These systems, known as "nanogel nano-gels," attempt to improve the circadian half-life of compounds, providing a very easy platform for the delivery of therapeutic combinations of molecules [21]. In the second scenario, the conjugation of the targeting ligands, antibodies, or peptides that promote active/passive targeting of Nano-gel to the site of interest and controlled release of the therapeutic substance [21]. Different strategies have been developed to address various applicative scenarios; however, they can all be traced back to fundamental principles of chemistry and physics: interactions among the reactive groups of different molecules and physical parameters- such as viscosity, density, and rheology- represent the basis and key knowledge of Nano-gel design [22].

Classification of nanogels according to their structure-

The architecture of nanogels is used to classify them. Simple (artificial) nanogels, hollow nanogels (including pH or temperature-sensitive nanogels), cross-linked core-shell nanogels (also used to create stimulus-responsive nanogels), hairy crosslinked nanogels, crosslinked multilayer nanogels, and functionalized nanogels are examples of nanogels. Table I shows the classification of nanogels according to their structure.

Table I. Classification of nanogel according to their structure.

Sr. No	Type	Network structure	Example	Reference
1	Simple Nanogel	Cross-linked b) Semi-interpenetrating polymer(semi-IPN) c) Self-assemble	Artificial chaperone, cholesterol-bearing pullulan (CHP) nanogel. Quantum dot nano gel	[23]
2	Hollow nano gel	interpenetrating polymer	Stimuli sensitive/responsive nano gel	[24]
3	Core-shell nanogels	Cross-linked	Stimuli sensitive/responsive nano gel	[25]
4	Hairy nano gel	Cross-linked	Stimuli-responsive nanogel (Shen et al. 2011).	[26]
5	Multilayer nanogels	Cross-linked	Stimuli sensitive/responsive nano gel	[27]
6	Functionalized nanogels	Cross-linked	Polyethylene glycol-b-poly (methacrylic acid) [PEG b-PMA] with PEG terminal aldehyde functionality	[28]

Construction of Nanogels-

Based on the different structures and constituent elements of nanogels, the methods for synthesizing nanogel can be divided into chemical crosslinking and physical self-assembly. Nanogels are chemically formed cross-linking show better stability than physical crosslinking through covalent cross-linking between functional groups on the polymer chain. Meanwhile, the connections are reversible physically cross-linked nanogels often depend on non-covalent interactions, mainly including hydrogen bonding, Van der Waals forces, hydrophobic interactions, host-guest interactions, electrostatic interactions, etc [29]. Although the interaction of non-covalent physical bonds is Relatively weaker than covalent cross-linking, physical self-assembly is More flexible and convenient, as it does not require a complicated response. In this part, Synthetic methods and examples of nanogel preparation are discussed [30].

Physical Crosslinking

Physically cross-linked nanogels are supramolecular particles made up of polymeric molecules formed by non-covalent interactions. The size of nanogel can be affected by polymer different concentrations and environmental conditions, such as ionic strength, temperature, and pH, during nanogel preparation [31]. The semi-permeable method has been described as a physical combination of insoluble substance molecules into a cross-linked polymer network, and the resulting nanogels can then stretch new properties of the fused molecule.

Poly pyrrole (PPY) with photothermal convention, which can be used for photoacoustic (PA) imaging, was introduced in poly (Nisopropylacrylamideco Nisopropylmethacrylamide) cross-linked polyglycerol (RPG) nanogels (p(NIPAmcoNIPMAm)) by semi-penetrating to form PPY/CodPG nanogels. PPY / CodPG nanogels are sensitive and sensitive to near-infrared (NIR) light. Can be used for PA Image-guided photothermal therapy with NIR [32]

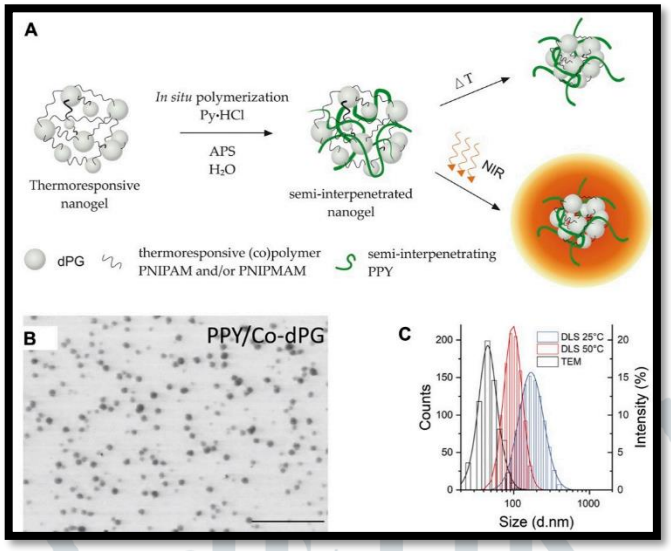

Fig no- 3. Schematic diagram of the synthesis of double-reactive nanogels via the semi-intercalation method. Nisopropylacrylamide (NIPAM) and interwoven poly pyrrole (PPY) based polymer network activated nanogels with near-infrared (NIR) photothermal and thermal induction properties. convention, respectively; (Pyrrole HCl (PY HCI) is a base and ammonium persulfate (APS) is in the form of initiator was introduced for polymerization); TEM image (B) and hydrodynamic size distribution (C) PPY/CodPG nanogels. Adapted [32, 33]

Chemical Crosslinking-

In addition to physical crosslinking, chemical crosslinking is the most developed and versatile strategy for constructing nanogels. Chemical crosslinking methods include polymerization by emulsion, chain transfer by reversible addition-fragmentation (RAFT), crosslinking by click chemistry, and crosslinking produced by the photogram. Amino crosslinking is commonly used to prepare Biodegradable nanogel based on amino acids [33].

Inverse Emulsion Polymerization-

Inverse emulsion polymerization is a polymerization reaction initiated by the emulsification of water-oil emulsifiers in the oil phase [34]. The size of the nanogel can be adjusted by many factors, such as surfactant, monomer and crosslinker feed ratio, and pH. e.g., zwitterionic poly (AABAEGDMA) nanogel is synthesized using ethylene glycol methacrylate (EGDMA), butyl acrylate (BA), and acrylic acid (AA) as monomers. Use N, methylene bis (acrylamide) (BIS), and Nacryloyll glutamic Acid (lAGA), poly (GA), and poly (lAGAcoBIS) hydrogels were prepared by inverse emulsion polymerization, demonstrating that the degree of swelling of the hydrogel increased with the change of pH. More, the presence of carboxylic acids and amide groups in the polymer network plays an important role in the physicochemical properties of the polymer

network, thereby affecting its hydrophilicity and hydration properties [35].

Approaches for the Production of Nanogels –

The ideal drug carrier should have small particles, biocompatibility, biodegradability, high encapsulation efficiency, site-specific treatments delivery, and storage at the site of the operation for an extended period of extended circulation time, and avoid nonspecific interactions with the environment (internal structures). Different synthesis processes can be used to produce specific nanoparticles in the case of macromolecular nanocarriers, such as polymerization in a dispersion medium of suitable monomers under specific reaction conditions, which will generate new reactive polymeric nanoparticles with potential applications in the biomedical field, such as delivery systems for active agents (drugs, molecules, metal, and magnetic nanoparticles, among others) [36]. Among the coincidental events Emulsion polymerization, precipitation polymerization, inverse microemulsion polymerization, anionic copolymerization, and crosslinking between nearby chains are the most commonly utilized methods for NG synthesis. Temperature variation is common in illness conditions and can be easily applied externally, hence temperature variation is one of the most investigated external stimuli for NG [37]. These NGS are important from a biotechnological standpoint because they can undergo a volumetric phase transition, which releases the cargo when the temperature changes. Many people are interested in the controlled design and production of heat-sensitive nanogels because of their unusual ability to expand at low temperatures and collapse at high temperatures in aqueous solution, demonstrating the volumetric phase transition temperature (VPTT). Heat sensitivity and TPPV biocompatible NGs close to physiological temperature can be achieved through full monomer selection and regulated polymerization (in healthy and unhealthy subjects). circumstances) are particularly appealing for biological applications such as medication administration [38].

Table 2- Stimuli-responsive nanogels and their main uses in biomedical applications.

Sr. No.	Nano gel Based on	Synthesis process	Drug	Stimuli-Responsiveness	Therapeutic Field	Reference
1	Poly (ethylene oxide)-poly (propylene oxide)-poly(ethylene oxide)-Polyvinyl alcohol with Fe3O4 nanoparticles (F-127-PVA)	Self-assembly	Ethosuximide	Magnetic field and temperature	Epilepsy	[39]
2	Poly(*N*-isopropyl methacrylamide and *N*-vinylpirrolidone (PNIPAM-VP)	Free radical polymerization	*N*-hexylcarbamoyl-5- Fluorouracil	Temperature	Brain tumours	[40]

3	Polysorbate 80-coated chitosan	Ionic gelation	Methotrexate	Surface modification	Brain tumours	[41]
4	Polyvinylpyrrolidone-poly(acrylic acid) (PVP/PAAc)	g radiation-induced polymerization	Dopamine	pH	Parkinson disease	[42]
5	Poly(ethylene glycol) and polyethyleneimine PEG-PEI	Emulsification-solvent evaporation	Oligonucleotides	Surface functionalization	Brain diseases	[43]
6	Cholesterol-Polylysine	Emulsification-solvent evaporation	Nucleoside reverse transcriptase inhibitors	Surface functionalization	Human Immunodeficiency Virus (HIV)-associated encephalitis and neurodegeneration	[44]
7	Cholesterol-bearing pullulan (CHP)	Self-assembly	CHP nanogel membrane	Natural-based nanogels	Bone regeneration	[45]
8	Cholesterol-bearing pullulan (CHP)	Self-assembly	E1 Prostaglandin	Natural-based nanogels	Wound healing	[46]
9	Cholesterol-bearing pullulan (CHP	Self-assembly	W9-peptide	Natural-based nanogels	Bone regeneration	[47]
10	Cholesteryl group- and acryloyl group-bearing pullulan (CHPOA)	Self-assembly	Human bone morphogenetic protein 2 and recombinant human fibroblast growth factor 18	Natural-based nanogels	Bone regeneration	[48]

The techniques used in the characterization of Nanogels-

Darkfield microscopy-

This technique displays direct images of nanogels in one second after mixing the two polymer solutions. eclipse The Nikon E60 microscope is used to observe images of polymers of cyclodextrin (PBC) and dextran (with hydrophobic lauryl side chains) self-assembled nanogels. Both solutions (dextran and PBC) penetrated the capillary and in the small space came into contact with each other and finally is reflected as a white spot to form a full nano gel [49].

Nuclear magnetic resonance studies-

The magnetic properties of certain atomic nuclei were explained by the nuclear magnetic resonance (NMR) technique. Physical and chemical properties of nanogels as well as the structure, reaction state, and chemical environments of the molecule and electronic structure of molecules can be determined by NMR. Aqueous-based cyclodextrin nanogels are characterized by 1HNMR and 13CNMR spectra, which were Aqueous based with Varian Mercury 300 NMR spectrometer operating at 300 MHz. Cationic nanogel was formed by crosslinking between poly (ethylene oxide) (PEO) and polyethyleneimine where the quantity and ratio were determined by 1HNMR spectra. In another example, a self-assembled nanosuspension of b cyclodextrin (BCD) polymer and dextran with hydrophobic lauryl side chains solution was prepared by the solvent evaporation method [50]. In this nanosuspension formulation, BCD content and substitution in dextran bearing hydrophobic lauryl side chains solution were determined by 1H NMR spectroscopy. 1H NMR. spectrum performed at 25°C on an Inova Varian. spectrophotometer operates at 400 MHz, using a 5mm H Xprobe. Spectra were recorded with an inclination angle of 90°, spectral width of 4000 Hz, and 256 scans of 16 K-points, distribution time was 15 s at 25, 30, 35, and 40 °C. The inverse microemulsion method was used to development of pH-sensitive nanogels of nitrophenol acrylate (NPA) and N-isopropyl acrylamide (NIPA) in the presence of aerosols (surfactants) and ethylene glycol dimethacrylate (crosslinkers). H1NMR spectra showed that the copolymer contained both NPA and NIPA monomers. NMR spectra of nano hydrogels were obtained using CDCl. solvent 3 in one Bruker ACE (250 MHz) device at 20 °C; chemical change measured against chloroform [51].

Raman spectra –

The shift in wavelength of the inelastically scattered radiation aids in providing information on the formulation's chemical and structural characteristics. It is used to determine a sample's chemical bonding, symmetry, and crystallographic orientations. RAMAN spectra are commonly used to determine the structural information of cyclodextrin-based aqueous nanogels. RAMAN spectra were acquired using a Bruker RFS 100/s (spectral disintegration 4 cm–1) [52].

FTIR techniques -

The FTIR technique is used to confirm the structure of the main functional group in the nanogel formulation. The absorption, emission, and photoconductivity of nanogels are determined by the FTIR method. An FTIR. spectrometer collects spectral data over a wide range of spectral data tastes. An FTIR spectrometer (Nicolet 6700) was used to obtain spectral data of the copolymer nanohydrogels. Guerrero Ramirez et al. used FTIR to characterize nitrophenol acrylate (NPA) nano hydrogel copolymer and Nisopropylacrylamide (NIPA) by inverse microemulsion coincidence method. Nano hydrogel FTIR spectra were collected using Smart Orbit accessory with attenuated total reflection. Ketel et al. used FTIR to confirm the polymerization in nanogel of doxorubicin. They also use FTIR for cyclodextrin aqueous nanogels. The cyclodextrin content of the nanogel is measured by quantitative analysis of the band at 1032 cm^{1}. The integral of this range is measured for nanogel samples compared with the standard curve obtained by mixing different amounts of BCD with KBr [53].

Atomic force microscopy -

Atomic force microscopy (AFM), also known as Scanning Force Microscopy (SFM), is a high-resolution form of microscopy. Microscopy with a Scanning Probe (SPM). This approach has 1000 steps. times greater than the optical diffraction limit Generally, AFM is used to determine the size and structure of nanogels. discovered that doxorubicin-loaded Chitin nanogels are made up of spherical shaped nanoparticles that were generated as

part of a biocompatible and thermosensitive core-shell nanogel using AFM. On a Shimadzu, determine the size and structure of a nanogel. The SPM9600 is in tapping mode [54].

Small-angle neutron scattering -

The SANS technique makes it possible to discover different structures of nano compounds (sizes from 1 to 100 nm). SANS was used to evaluate the structural properties of CHP nanogels as well as their interactions with cyclodextrin, or chaperon-like function. SANS further demonstrated that as the CD concentration increased, the scattering intensity of the CHP nanogel also increased [53].

UV-spectroscopy-

The UV Vis spectroscopy approach is used to determine drug entrapment in nanogel. The UV Vis spectroscopy approach refers to absorption or reflectance spectroscopy. the spectral region of Ultraviolet-Visible figured out the entrapment UV spectroscopy efficiency of two hydrophobic compounds (Tamoxifen with benzophenone) also UV spectroscopy was used to determine entrapment efficiency. gelatinized thermosensitive nanogels technique [54].

Conclusion-

The development of systems designed to protect and deliver an active agent in a controlled manner close to the target site is essential for the treatment of existing diseases. In this respect, NGs emerge as useful nanocarriers with multifunctional and responsive properties for tumor imaging and drug delivery. NGS is also widely used in gene therapy to protect the active ingredient and improve the therapeutic effect. Theoretical and practical features of nanogel systems can investigate. They are commonly employed in controlled distribution systems, targeted delivery systems, coatings, and cosmetics. Nanogels are showing potential future advancements, broadening the possibilities for medication delivery. Every new investigation implies the identification of new polymer and mechanistic techniques with a promising function in therapeutics, as well as innovation in nanogel production design. The usage of nanogels allows the biopharmaceutical parameters of an entrapped medicine to be advanced.

Conflicts of interest

There are no conflicts of interest and disclosures regarding the manuscript.

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