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RESEARCH ARTICLE

ADVANCEMENTS IN THERAPEUTICS: THE ROLE OF NANOPARTICLE-INFUSED HYDROGELS IN REVOLUTIONIZING DRUG DELIVERY

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Abstract

Nanoparticles loaded hydrogel has emerged as a promising strategy in the field of drug delivery systems, offering unique advantages in terms of controlled release, enhanced bioavailability, and targeted delivery of therapeutic agents. Nanoparticles, typically ranging from 1 to 100 nanometers in size, serve as carriers for drugs, encapsulating them within their matrix and protecting them from degradation. Hydrogels, on the other hand, are three-dimensional cross-linked networks of hydrophilic polymers capable of absorbing and retaining large amounts of water. It aims to provide a comprehensive understanding of nanoparticles loaded hydrogel in drug delivery systems by elucidating the relationship between nanoparticles and hydrogels and their synergistic effects on drug delivery. Firstly, the properties of nanoparticles, including size, surface charge, and composition, significantly influence their interactions with hydrogels and the encapsulation efficiency of drugs. Secondly, the unique characteristics of hydrogels, such as tunable swelling behavior and biocompatibility, complement the stability and sustained release kinetics of nanoparticles.Furthermore, the incorporation of nanoparticles into hydrogel matrices enhances their mechanical strength and allows for the development of stimuli-responsive systems, enabling on-demand drug release triggered by external stimuli such as pH, temperature, or magnetic fields. The synergistic combination of nanoparticles and hydrogels opens up new avenues for the design of advanced drug delivery systems with improved therapeutic efficacy and reduced side effects. In conclusion, nanoparticles loaded hydrogel represents a promising platform for the development of next-generation drug delivery systems, offering unprecedented control over drug release kinetics and targeting capabilities. This review highlights the importance of understanding the interplay between nanoparticles and

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hydrogels in optimizing the performance of drug delivery systems for various biomedical applications.

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Introduction:-

Innovative developments in the field of drug delivery can be attributed to nanotechnology, which provides appropriate methods for the site-specific and time-controlled distribution of vaccines, nucleic acids, proteins, peptides, oligosaccharides, and small molecular weight medications [1-5]. The sizes of nanoparticles range from 10 to 1000 nm. Depending on the technique of preparation, the medication is dissolved, entrapped, encapsulated, or connected to a nanoparticle matrix, resulting in the formation of nanoparticles, nanospheres, or nanocapsules. Whereas nanospheres are matrix spherical systems in which the drug is uniformly and physically distributed, nanocapsules are vesicular systems in which the drug is contained within a cavity surrounded by a boundary structure, such as polymeric [6]. In the last few decades, nanotechnology has made it possible to find novel approaches to problems in a variety of sectors. The biomedical sciences are particularly interested in the ability to custom-tailor nanomaterials that can interact with biological systems in different ways. This is because nanotechnology platforms have the potential to significantly improve human illness diagnosis, prevention, and treatment [7-9]. A smaller dose is needed to produce a therapeutic effect when using a Drug Delivery System (DDS), which can deliver a targeted and focused therapy. By avoiding systemic toxicity and undesirable side effects, Drug Delivery System capabilities improve the precision, efficacy, and minimal invasiveness of medicines. The design of nanoparticles (NPs), hydrogels, and, more recently, NPs-loaded hydrogel (NLH) systems for drug release applications are drawing interest among the possible DDS techniques currently under study [10-13].

Nanoparticles As Drug Delivery System:

In the field of nanoscience and nanotechnology, research and applications have grown at an unparalleled rate in recent years. There is growing hope that the application of nanotechnology in medicine may result in major advancements in illness diagnosis and treatment. Nutraceuticals, medication delivery, in vitro and in vivo diagnostics, and the creation of better biocompatible materials are among the anticipated uses in medicine [14]. The method of administration determines how effective they are. Traditionally, oral, nasal, inhalation, mucosal, and injectable administration modalities were used in conventional drug delivery systems (or CDDSs) [15]. One of the biggest challenges in the treatment of many diseases is getting the therapeutic chemical to the intended location. Drugs used conventionally are often used with poor biodistribution, low selectivity, and low efficacy [16].

The ability to alter basic qualities including solubility, diffusivity, blood circulation half-life, drug release characteristics, and immunogenicity is unparalleled when working with materials at the nanoscale. Many therapeutic and diagnostic agents based on nanoparticles have been created in the past 20 years to treat a variety of conditions, including diabetes, cancer, pain, asthma, allergies, infections, and more [17-18]. The field of nanomedicine is a recent development that emerged from the nexus of nanotechnology and medicine. Its foundation lies in the ability to manipulate materials at the nanoscale for use in applications related to human health. By altering essential drug characteristics like solubility, diffusivity, bloodstream half-life, and drug release and distribution profiles, the usage of materials in this range has greatly advanced pharmacology [19-22].

Role of nanoparticles in enhancing drug delivery:

Recent scientific discoveries and international initiatives to boost nanotechnology and nanomedicine research demonstrate the expectation that products of nanotechnology will revolutionise modern medicine. These developments directly benefit the field of drug delivery. Nanoparticles are assisting in addressing concerns related to the administration of both modern and traditional medications because of their adaptability in focusing on specific tissues, reaching deep molecular targets, and regulating drug release. Since solids are used in the bulk of drug products, nanoparticles are anticipated to have a significant influence on the development of drug products [23-26].

Types Of Nanoparticles:

1. **Liposomes:** Liposomes are spherical vesicles having an internal compartment that often holds water. They are made up of one or more concentric membranes of lipid bilayers. Liposomes has the capacity to enclose hydrophilic molecules within their internal chamber and lipophilic ones within their membrane. These vesicles range in size from a few nanometers to many microns. Nonetheless, the range of liposomes used in medicine is

50–450 nm [27]. When liposomes are used in pharmacological therapy, drug pharmacokinetics are sometimes improved over the free form of the medication [28].

2. **Polymeric nanoparticles:** This covers both therapeutic drug delivery techniques and the use of vectors to speed up the application and absorption of the drugs into the human body. Indeed, based on specific illnesses and people, various combinations of vectors and active substances may allow for a wide range of personalisation options. When treating an illness, the methods by which active ingredients are administered and delivered to the intended tissue are important considerations [29]. Due to their great stability, biodegradability, non-immunogenicity, potent nutritional value, superior binding ability, and potential to reduce reticuloendothelial system (RES) opsonization, natural biopolymers like gelatin have also been studied [30].
3. **Nanocrystals:** Solid medication particles in the nanoscale range with crystalline properties that are carrier-free are called nanocrystals. Nanocrystals have gained appeal as a medicine delivery system for a variety of illnesses because of their high drug loading—up to 100% [31]. Compared to other nanoparticles, such as polymeric nanoparticles, the high drug loading of nanocrystals ensures effective drug delivery to cells or tissues and maintains potent therapeutic concentration to induce desired pharmacological activities [32]. The augmentation of surface area, dissolving rate, saturation solubility, surface adhesiveness of cell membranes, and oral bioavailability are all brought about by the reduction of particle size to the nanometer range [33].
4. **Metal nanoparticles:** Because of their high surface-to-volume ratio, stability, ability to function through surface modification by chemical means, and relative innocuousness, metallic nanoparticles are also attractive as carriers for the delivery of medications and other active ingredients [34]. Metallic nanoparticles possess certain functional groups that enable their speciality. It is possible to synthesise and modify it such that it can attach to medicines, ligands, and antibodies [35]. Metallic nanoparticles have been produced using a wide variety of prokaryotic and eukaryotic species, as was recently reviewed [36].

Hydrogel:

Three-dimensional polymeric networks known as hydrogels which are able to absorb large volumes of biological fluids or water [37-39]. In order to create a hydrophilic substance with the macromolecular structure of a gel, hydrogels are linked chains of natural or synthetic polymers joined to one another by crosslinkers. They have the capacity to swell multiple times their dry weight and can contain as much as 99% biological fluids or water [40]. Hydrogels can have low levels of toxicity and be biocompatible or biodegradable, depending on the polymers used in their manufacture. They have the capacity to effectively encapsulate molecules, protecting and releasing them over time, raising their local concentration, and lessening their toxicity in the tissues that remain [41]. Due to their high-water content, hydrogels enable the encapsulation of hydrophilic medicines, great biocompatibility, and physical similarities with tissues [42].

Hydrogel As Adaptable Biomaterial:

Conventional techniques for synthesizing biomaterials involve crosslinking via polymer–polymer interaction, crosslinking copolymerization, and crosslinking of reactive polymer precursors. Owing to side reactions, the networks in these hydrogel synthesis methods comprise cycles, unreacted pendant groups, and entanglements, which limit the control over their intricate structure. Additionally, weak mechanical qualities and sluggish or delayed reaction times to external stimuli have been identified as shortcomings of conventional hydrogels [43]. The ability to replicate the dynamic changes of native extracellular matrix (ECM) has been achieved in recent decades by adaptable hydrogels with reversible connections. Cells can receive dynamic mechanics from native ECM, which is dynamic and remodelled with stress relaxation [44-45].

Biomedical Application of Hydrogel:

Hydrogels are an important class of biomaterials that find extensive application in several biomedical segments because of their exceptional biocompatibility, mild manufacturing conditions, and water-retention capacity. Their special qualities—such as their flexibility and regulated swelling behavior—amplify their wide range of applications in wound healing, biosensors, tissue engineering, targeted medication administration, bone and cartilage regeneration, and electrical and soft robotic components [46]. Hydrogels are useful in medical implants, prosthetic muscles or organs, robotic grippers, diagnostic devices, artificial muscle stabilisation, intimal thickening in animals, and thrombosis reduction because they mimic the behavior of human organs in response to changes in environmental conditions such as pH, temperature, enzymes, and electric field [47-50].

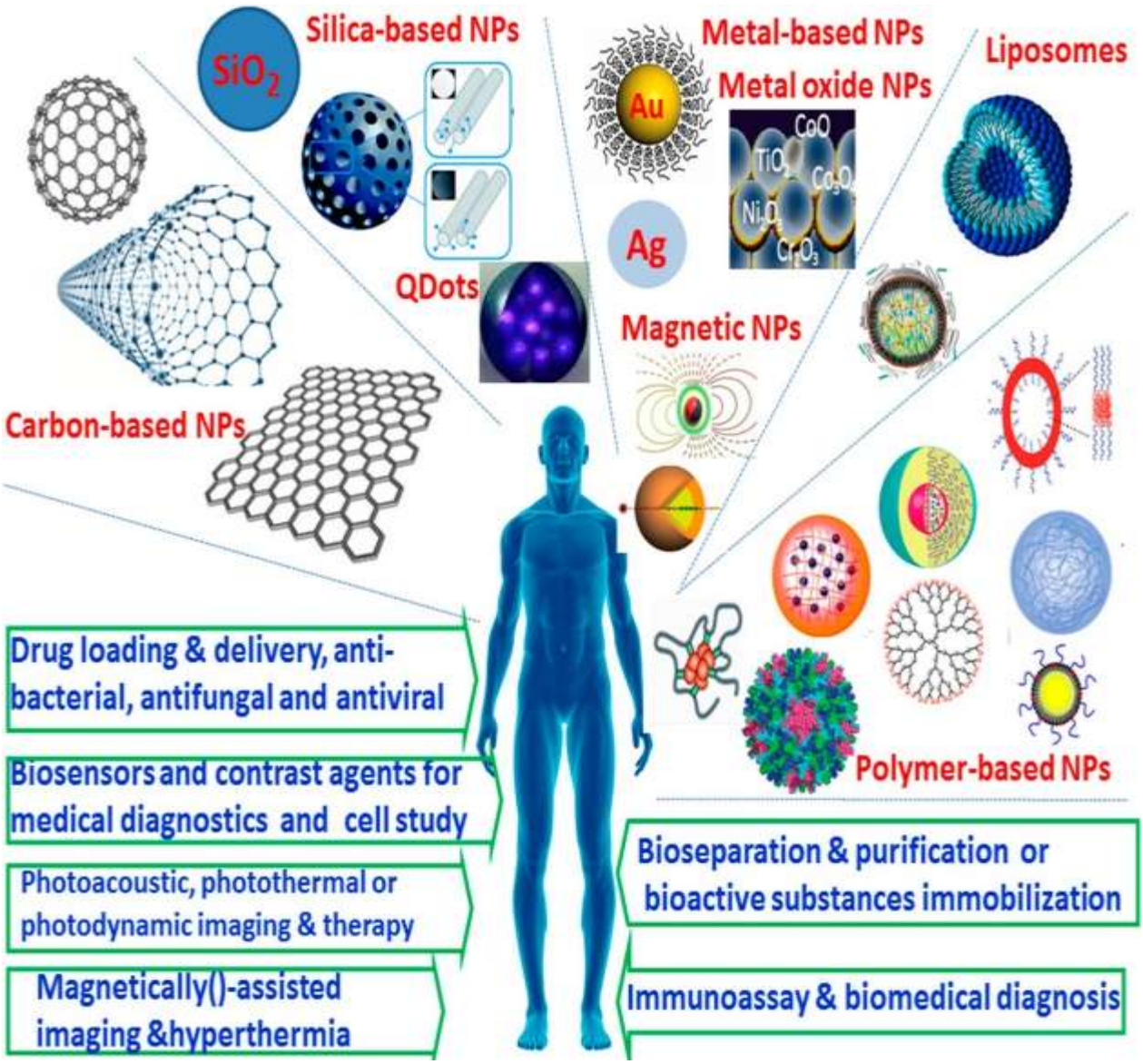

Figure 1:- Examples of typical nanoparticles and their applications in biomedical fields.

Property Of Hydrogels:

The most important properties of hydrogels is their ability to swell. Three processes occur when hydrogels swell: (i) water diffuses into the network of hydrogel molecules (referred to as primary bound water); (ii) polymer chains relax; (more water entering the network is referred to as secondary bound water); and (iii) the hydrogel network expands (more water entering the network is referred to as free water). Flory-Reihner's theory states that swelling results from the polymer chains' elastic properties and their affinity for water molecules [51]. There is a state called gel that is halfway between liquid and solid. There are a lot of fascinating relaxing behaviour brought on by these half liquid, half solid characteristics that aren't present in either pure solid or pure liquid. From the perspective of their mechanical characteristics, the hydrogels are distinguished by a viscous modulus that is significantly smaller than the modulus of elasticity in the plateau region and an elastic modulus that displays a prominent plateau that extends to times no less than a couple of seconds [52]. The swelling ratio is reduced when the crosslinking density of a hydrogel is higher than when it is lower, since a higher crosslinking density impedes the mobility of the polymer chains. Higher degrees of swelling can result from the crosslinking agent including hydrophilic groups as opposed to hydrophobic groups, which collapse in the presence of water and lessen hydrogel swelling. The physical characteristics of the gel, including mechanical strength, degradation, and diffusion of trapped molecules, are influenced by the mesh size of the swelling network [53].

Hydrogels and their application in

1. **Targeted Drug Delivery**: An optimal delivery system would be one that releases drugs in reaction to environmental changes, allowing for highly controlled release and the reduction of non-specific side effects in off-target locations. As a result, sensitive drug delivery devices that can adapt to changes in pH, temperature, ionic strength, or glucose concentration have been developed. These devices are useful for treating diseases like diabetes and cancer, which are marked by physiological changes that are unique to each stage of the disease locally. In order to make the hydrogel responsive to environmental cues, its polymer composition is changed [54]. Hydrogels are a promising new class of smart, stylish, and "smart" drug delivery systems that can precisely target specific medication locations and regulate drug release. To control the hydrogels so that the drug releases at the desired location, enzymatic, hydrolytic, or environmental stimuli are frequently sufficient [55].
2. **Controlled Drug Delivery:** The drawbacks of conventional drug formulations have been addressed by the introduction of controlled drug delivery systems (CDDS), that are designed to administer medications at certain rates for predetermined lengths of time. Hydrogels are an excellent option for medication delivery applications due to their amazing qualities. Two elements can be controlled to achieve high porosity hydrogel structures: the hydrogel's affinity for the aqueous environment where swelling occurs as well as the level of cross-linking in the matrix. Hydrogels' porous architectures allow for the high permeability of many medications, allowing for the loading and, under the right circumstances, release of drugs [56].
3. **Gene Delivery:** The process of introducing foreign DNA particles into host cells is known as gene delivery, and it can be carried out through both viral and non-viral means. Viruses have the ability to insert their DNA into host cells, which is how genes are delivered into those cells. Both the retroviruses and adenoviruses have been employed for this reason. Because these viral vectors may produce high gene expression and effective transduction, they are used. Nevertheless, due to their potential to cause immunogenic responses or mutagenesis in transfected cells, viral vectors are used very seldom. Because these methods are less difficult and do not use viruses, scientists are becoming more interested in them. The use of a gene gun, electroporation, and sonication are examples of non-viral approaches. The use of polymers, such as poly-L-lysine (PLL), polyamidoamine dendrimer (PAMAM), polyethylenimmine (PEI), PGA, PLA, and PLGA, for gene transport has recently been initiated by researchers. In a diabetic mouse model, the application of PEG-PLGA-PEG hydrogelto transport the plasmid-beta 1 gene accelerated the healing of wounds [57].
4. **Wound Healing:** According to studies, wounds that are moist—that is, have a moist microenvironment—heal more quickly, inhibit wounds more successfully, and are less prone to infection overall. During the wound healing process, a moist wound dressing can help to renew and repair the dermis and epidermal tissue by creating and preserving a humid atmosphere around the wound. The following qualities are essential for an optimal wound dressing: excellent biodegradability, no cytotoxicity, antibacterial activity, absorption of water, and retention [58].
5. **pH-sensitive Hydrogels in Drug Delivery**: The pH shift is one of the crucial environmental factors for DDS since it happens at numerous particular or diseased body sites. The human body displays pH fluctuations in specific regions, such as subcellular compartments and certain tissues, including tumoral sites. These variations also occur along the gastrointestinal tract. In pH-sensitive DDS, both basic and acidic polymers are used. The acidic polymers that are most frequently employed for drug delivery are PMAA, PAA, poly (L-glutamic acid), and polymers that contain sulfonamide. Typical instances of fundamental polyelectrolytes comprise poly(2-(diethylamino) ethyl methacrylate) and poly(2-(dimethylamino) ethyl methacrylate), biodegradable poly(β-amino ester), and poly(2-vinylpyridine). Different techniques were also utilised to extract and determine the pH of pH-sensitive hydrogels [59-62].

Hydrogel-Nanoparticle Composites:

The production of nanocomposite hydrogels (NCHs), also known as nanocomposites, for biomedical purposes has therefore been made possible by recent advancements in hydrogel technology; at the moment, there is a considerable and growing amount of scientific interest in their development. NCHs are hydrated polymeric networks that can be immobilised in the matrix either covalently or non-covalently. They have a 3D structure that is physically or covalently crosslinked and are swelled with water in the presence of nanoparticles or nanostructures [63]. In this study, we provide a brief overview of the numerous synthesis routes that have been used to create NP-hydrogel networks and discuss how NPs have improved the nanocomposites' various characteristics in comparison to traditional materials [64]. However, over time, novel hydrogels known as composite hydrogels—which are made of several polymers and monomers—have been created. Since this composite hydrogel is composed of separate

components, it can exhibit a range of properties. Whereas composite hydrogels can perform a variety of tasks by mixing different polymers [65-66].

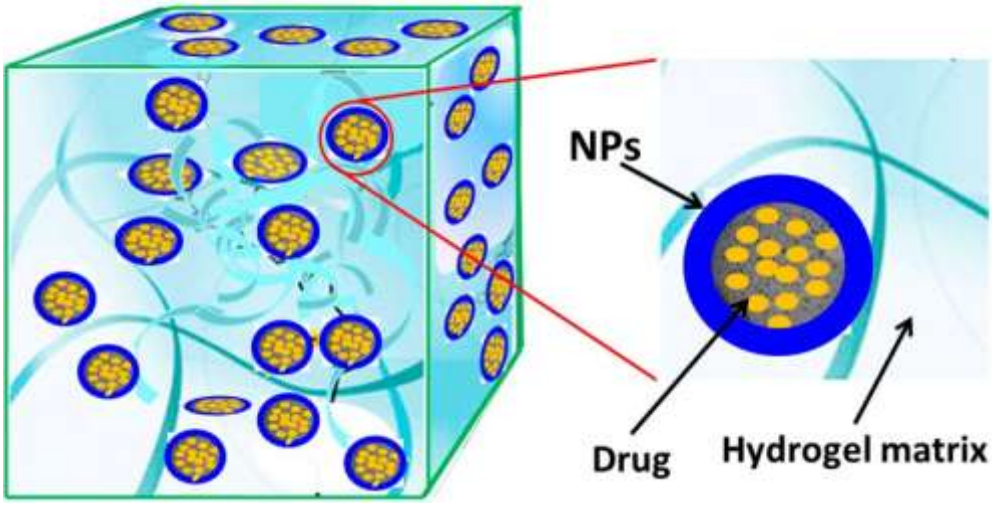

Figure 2:- Schematic illustration of typical nanocomposite hydrogels from hydrogels and drug-loaded nanoparticles (NPs).

Bioprinting With Nanoparticle-Loaded Hydrogels:

A technique called "bioprinting" uses chemicals and cells to mimic the structure and capabilities of human tissue [67]. A significant improvement over traditional tissue engineering techniques, which involve seeding cells after construct fabrication, is the ability of bioprinting to produce three-dimensional structures through the simultaneous deposition of biomaterial scaffolds and cells to the appropriate locations. Appropriate biomaterials also offer optimised microenvironments for embedded cells with high cell viability and functionality [68]. The ability to create scaffolds with various material, bioactive, and biological components through 3D bioprinting opens up new possibilities for wound healing treatments [69-72]. Hydrogels' biocompatible material qualities make them great options for biomedical applications, such as 3D bioprinting [73]. In order to address these drawbacks, a novel approach to 3D printing has surfaced termed 3D bioprinting. This manufacturing technique allows living cells to be combined with biocompatible substances, most commonly hydrogels, to create a single structure known as bioink. Cells and other biological components are ensnared inside the printable mixture during 3D bioprinting, which at least partially replicates the physiological 3D environment that the native tissue displays [74-75]. Thus, creating 3D bioprinted scaffolds with tissue engineering and incorporating nanomaterials may aid in simulating the natural tissue microenvironment. This method may also be applied to the 3D screening of cell-biomaterial interactions and the stimulation of effective tissue regeneration, a technique based on bioprinting that produces nanoliter-sized 3D cell-laden hydrogel arrays with gradients of extracellular matrix (ECM) components by adjusting the volume ratio of two hydrogels, such as poly(ethylene glycol) (PEG) dimethacrylate and gelatin methacrylate (GelMA) [76].

Characterization techniques of nanoparticles:

Table1:- Characterization techniques with description.

Characterization Technique	Description	Reference
SEM (Scanning Electron Microscope), TEM (Transmission Electron Microscopy), STM (Scanning Tunneling Microscopy), ESEM (Environmental Scanning Electron Microscope), TERS (Tip-Enhanced Raman Spectroscopy)	Used for assessing morphology, size, and topography of nanoparticles.	[77]
XRD (X-ray Diffraction), EDX (Energy-Dispersive X-ray Spectroscopy), FTIR (Fourier Transform Infrared Spectroscopy), FCS (Fluorescence Correlation	Used for analyzing fundamental properties and optical characteristics of nanoparticles.	[77]

Spectroscopy)		
Dynamic Light Scattering, Zeta-potential	Light scattering techniques for measuring size and surface charge, targeting infection, cancer, and cardiovascular applications.	[78]
NTA (Nanoparticle Tracking Analysis)	Visualization and recording of nanoparticle movement for quick characterization without sample damage.	[79]
AFM (Atomic Force Microscopy)	Useful in preclinical characterization for observing nanostructures and chemical compositions under physiological conditions.	[80]
SALD (Spray-Assisted Laser Desorption), ICP(Inductively Coupled Plasma), MS (Mass Spectrometry)	Detecting and characterizing gold nanoparticles, presenting an alternative to conventional techniques.	[81]
Automated Analysis	For facilitated detection and morphology identification of nanoparticles.	[82]
Solid-State Nanopores	Shape characterization and discrimination of single nanoparticles for real-time analysis.	[83]

Future Prospective:
Future developments in multimodal drug delivery, including personalised therapy and combination treatments, appear promising when it comes to hydrogel systems loaded with nanoparticles. Smart hydrogel design advancements will allow for precise, triggered release of drugs in response to physiological cues, improving therapeutic efficacy and reducing adverse effects. Theranostic platforms that combine therapeutic and diagnostic features present prospects for better disease management, especially in the fields of regenerative medicine and cancer therapy. For clinical translation, safety and biocompatibility must be guaranteed, necessitating the creation of non-toxic formulations and thorough preclinical validation. In general, further research is needed to fully realise the promise of hydrogel systems loaded with nanoparticles for clinical applications.

Conclusion:-

In conclusion, the application of hydrogel loaded with nanoparticles in drug delivery systems is a novel strategy that has the potential to revolutionise medicine. Hydrogels and nanoparticles work together to provide previously unheard-of control over drug release kinetics, targeted distribution, and therapeutic efficacy. The development of smart hydrogel systems and multifunctional nanoparticles offers customised therapies, reduced side effects, and improved patient outcomes. As studies continue, resolving issues with safety, biocompatibility, and clinical translation will be essential to maximizing the therapeutic potential of these cutting-edge platforms. Future medication delivery could be revolutionized with the use of nanoparticles loaded hydrogel and interdisciplinary collaboration, which could lead to more effective and customized medicines.

The primary characteristic that draws attention to hydrogel nanoparticles is their capacity to react to specific stimuli present in the surrounding media. This is achieved by using a variety of responsive polymeric architectures during the nanoparticle manufacturing process. This characteristic has thus created new opportunities for the creation of "smart drug delivery systems" utilizing nanotechnology. The pH-responsive, thermo-responsive, photo-responsive, magnetically responsive, and ultrasound-responsive stimuli responsive hydrogel nanoparticle systems have been extensively researched and have demonstrated varying degrees of success in accomplishing their intended drug delivery goals.

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