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Review Article

COMPARATIVE ANALYSIS OF SILVER AND POLYMERIC NANOHYDROGEL

Priyanka Singh*, Ram Bhajan Sahu, Meena Choudhary

NIMS Institute of Allied Medical Science and Technology, NIMS, University (Rajasthan), India

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ABSTRACT

Silver nanoparticles has great demand in biomedical sectors like antimicrobial agents, wound healing dressings, implants, coatings for contact lens, medical catheters. Their therapeutic efficacy has been improved for wound healing and burning cases by incorporating with hydrogel scaffold. Hydrogels are biocompatible aqueous polymer with capability to retain large quantity biological fluid within its cross linked 3-dimensional structure. Nanotechnology has improved the efficacy of these hydrogel products by nanohydrogel formulation using synthetic chemical agents and natural polymeric materials. Polymeric nanohydrogels exhibit high degree of biocompatibility, biodegradability, mechanical strength, molecular binding abilities in compare to synthetic chemical nanogels. This review article will highlight the synthesis of nanohydrogels, physiochemical characteristics, recent trends and major issues for development of different types of nanohydrogel for biomedical applications. An author has also discussed their significant limitations in terms of clinical potential, toxicity aspects, stability, and societal ethical issue.

INTRODUCTION

Silver nanoparticles (AgNPs) has great demand in industrial sectors due to exhibiting unique physiochemical properties like optical, electrical, and thermal, high electrical conductivity, and antimicrobial activities (Zakia *et al*.2020; Albrecht *et al*. 2006; Rai *et al*. 2009). These have wide application in developing cosmetic products, medical device coatings, optical sensors, anticancer agents, and wound dressings (Zakia *et al*. 2020; Rajawat *et al*. 2018). Hydrogels are currently in higher demand in the area of controlled-release drug delivery for pharmaceutical sectors. These controlled-release drug delivery approaches offer novel system for the specific delivery of therapeutically significant bioactive agents. The conjugation of these nanoparticles with specific polymeric matrices has effectively improved their therapeutic values by affecting their pharmacokinetics, bioavailability, biodistribution, targeted intracellular delivery for specific biomedical usage (Zakia *et al*. 2020; Bhakyaa *et al*. 2016; Thangaraju *et al*. 2012; Nejad *et al*. 2018). They are recently used for advance medical therapy including hormone therapy, laser photodynamic therapy (Sadrolhosseini *et al*. 2019) as shown in Fig1.

The matrices for these nanoparticles may be organic molecule (chitosan, protein, glycan compounds), synthetic polymers, and inorganic molecule (metal and magnetic nanoparticles). In current scenario, biopolymeric matrices are used for formulation of nanohydrogels due to low cost, nontoxic and green approaches. These biopolymeric nanohydrogels improved their yield, biocompatibility, bioavailability and stability.

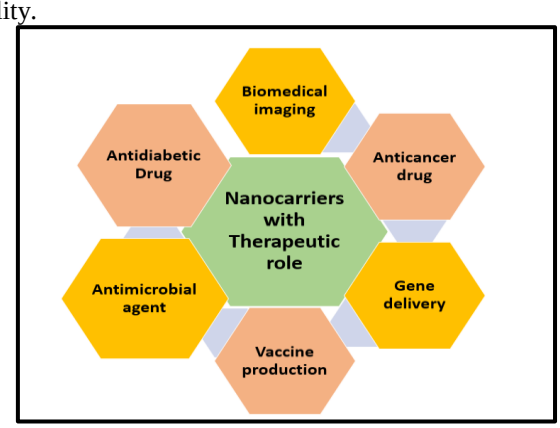

Fig1 Therapeutic Role of Nanoparticles in different field of pharmaceutical sectors

Their biological properties are being affected by the synthetic approach for nanoparticle and types of stabilizers used in synthetic process. The novel synthetic approaches will decide the specific shape, size, stability and properties of nanoparticles (Zakia *et al*. 2020; Capanema Nadia *et al*. 2018). The structure of nanoparticles has been stabilized by considering their electrostatic charges and steric properties. Surfactants, polymers, and dendrimers are commonly used as stabilizer agents for synthesis of nanoparticle (Zakia *et al*. 2020; Kumar *et al*. 2019). Polymeric stabilizers like Poly(vinylpyrrolidone) (PVP), poly(acrylamide) (PAM) have been currently preferred

Corresponding author:* **Priyanka Singh
NIMS Institute of Allied Medical Sciences and Technology, NIMS, University (Rajasthan), India

for formulation of nanohydrogels (Zakia *et al*. 2020; Hosseinzadeh *et al*. 2013; Karimi *et al*. 2014). The current study has been focussed on the novel approaches for synthesis of silver based nanohydrogels. Their physiochemical properties and significant role in pharmaceutical sectors like therapy, wound dressing, drug delivery, and medical equipment coatings will be subsequently discussed. The recent trends with diversified biomedical application, serious issues, toxicity and techno-feasibility approaches have been also studied.

LITERATURE REVIEW

Overview of nanotechnology and types of Nanoparticles

The application of nanoparticles put forward various advantages than other drug delivery systems. Nanoparticles are utilized to augment the solubility of high hydrophobic drugs. Nanoparticles provide sustained and prescribed release of capsulated drugs and enhance the steadiness of therapeutic agents through the using of chemical or physical means. They also assist to distribute the higher concentrations of drugs to the subjected locations because of Enhanced Permeation and Retention (EPR) effect when modified with cell-specific ligands (Goyal *et al*. 2016; Husen *et al* .2014; Siddiqi *et al*. 2017). Nanocarriers for drug delivery has been commercially synthesized using suspension of different types of metallic compounds as shown in Fig2.

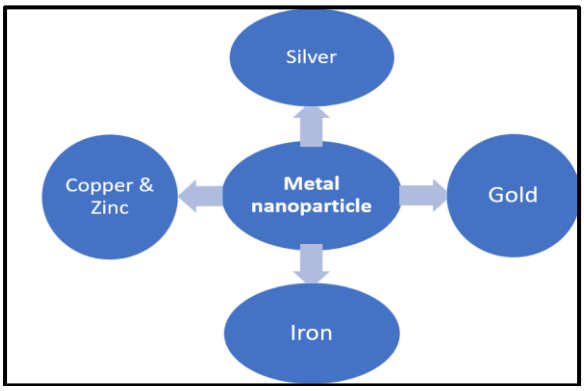

Fig 2 Different types of metallic nanoparticles commercially used in pharmaceutical sectors

These different types metal nanoparticles have broad physiochemical properties in terms of biosynthesis process, surface biochemistry and surface functionalization (Jones *et al*. 2007; Sau *et al*. 2010) as shown in Table 1.

Table 1 Comparison of different synthetic approaches for metal nanoparticles (Ali *et al*. 2016)

Techniques	Product morphology	Advantage	Disadvantage
Physical methodology			
Deposition of gas phase	Spheres	Easy to execute	Problem occurs in controlling the size of particle
Electron beam lithography	Spheres and rods	Well controlled	Requires highly complex machines
Chemical methodology			
Chemical co-precipitation	Spheres	Effective and simple	Inappropriate for the synthesis of stoichiometric phase
Biological methodology			
Microbial extract	Spherical, rod like spheres, irregular spheres	Good reproducibility, high yield	Slow and laborious

Among all these nanoparticles, metal nanoparticles have been widely used for encapsulation of therapeutic drugs, diagnostics and drug delivery (Selvan *et al*. 2009; Baptista *et al*. 2008; Batal *et al*. 2017; Day *et al*. 2009). Metallic nanoparticles of different classes of gold, silver, iron, copper and zinc has been commercially used to improve drug delivery system in pharmaceutical sectors. Synthesis of metallic nanoparticles is rapidly growing in different industrial sectors (Duran *et al*. 2005) as shown in Fig3.

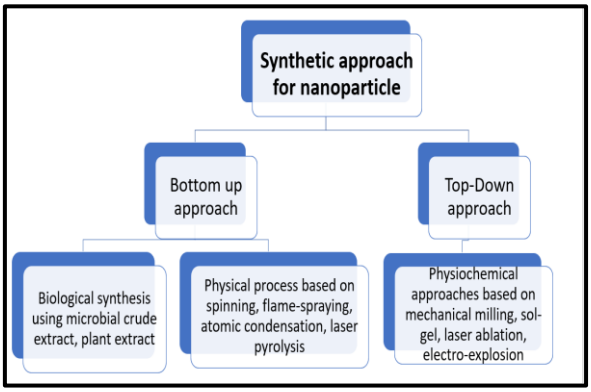

Fig 3 Different Biological and Physiochemical approaches for synthesis of metallic nanoparticles

Gold metal nanoparticles are extensively preferred in medical sectors due to their small size (10−200 nm), diversified functionality, unique optical properties, and non-toxic nature (Lohse *et al*. 2013; Alkilany *et al*. 2010; Bhattacharyya *et al*. 2011). These nanoparticles exhibit higher degree of surface plasmon resonance band depending on their particle size and dielectric strength. Its high intensity of resonance surface plasmon property has been used in image processing and formulation of therapeutic agent. These are mainly synthesized by physical method like microwave, ultraviolet irradiation, photochemical radical and thermolytic process (Guo *et al*. 2010; Wagner *et al*. 2010; Day *et al*. 2009) as shown in Table2.

Table 2 Effect of synthetic approach for development of gold nanoparticles on their morphology and sizes

Method	Morphology	Size (nm)	References
Ion encapsulation	Crystalline	<5	Morita *et al*. 2017
Microwave assisted irradiation	Nanosphere	<50	Luo *et al*. 2018
γ- irradiation	Nanosphere	<6	Le *et al*. 2019
Ultrasound irradiation	Polyhedral	<40	Bhosale *et al*. 2017
Laser ablation	Nanosphere	<15	Vinod *et al*. 2017

In chemical process, gold chloride ($AuCl_3$) has been firstly reduced in a carbon disulfide solvent using phosphorous as reducing agent (Peer *et al*.2007). In biological methods, gold nanoparticles have been developed by treating cell free extract of microbial product with hydrogen tetra-chloroaurate followed by reduction with sodium borohydride, trisodium citrate, or phosphorous (Connor 2005; Kumar *et al*.2013; Lee *et al*.2014) as shown in Table 3.

Table 3 Modification of functional group of gold nanoparticles using different polymers for improving their drug delivery system for varieties of drugs

Polymer	Drug	Morphology	Size (nm)	References

Chitosan	5-fluorouracil	Nanosphere	<20	Chandran and Sandhayarani 2014
Poly ethylene glycol (PEG)	Doxorubicin	Nanosphere	<10	Asadishad *et al*. 2012
Polystyrene sulfonate (PSS)	Doxorubicin	Nanorod	<5	Venkatesan *et al*. 2013
Poly di (carboxylate -phenoxy) phosphazene (PCPP)	Camptothecin	Nanosphere	<30	Sivaraj *et al*. 2018
Glycyrrhizin	Lamivudine	Nanosphere	<15	Broker *et al*. 2016

The chemical modification of gold nanoparticles surface has been attempted using PEG, biotin, paclitaxel and rhodamine B linked beta-cyclodextrin (beta-CD) as theragnostic platform (2012) (Table-2). For therapeutic purposes, nano carriers would be loaded with drugs through non-covalent interactions or by covalent conjugation ((Tran *et al*.2013; Torchilin 2001) using a prodrug processed by the cell (Morgan *et al*.2006). AuNPs provide an excellent platform for Drug delivery system due to functional versatility of their monolayers. Iron oxide nanoparticles with magnetic and plasmonic properties are currently preferred in for the clinical diagnostic study, cellular image processing, and therapeutic anticancer agent (Laurent *et al*.2011; Lowe *et al*. 2002). The combinatorial effect of use of iron oxide nanoparticles supplemented with doxorubicin has increased their therapeutic effectiveness against growth of tumor cell. The antitumor effect might be increased due to the external magnetic field, which finally inducing electron transitions within the structure of nano-complexes (Vinardell *et al*. 2015). These nanoparticles are currently used for designing of biomedical devices to diagnose the magnetic tumor hyperthermia in brain and prostate cancer (Silva *et al*.2011; Johannsen *et al*. 2010; Hauff *et al*. 2011; Danhier *et al*. 2010; Klein *et al*. 2014). Magnetic nanoparticles impregnated with magnetite ($Fe_3 O_4$) with different crystal lattice structure are being developed using different strategies of, co-precipitation, thermal decomposition, hydrothermal synthesis, physiochemical synthesis and microemulsion (Table-1). Copper nanoparticles also showed effective antimicrobial activities and used for designing of biomedical devices (Wang *et al*. 2012; Zhang *et al*. 2008; Khare *et al*. 2014; Narayan *et al*. 2010; Sankar *et al*. 2014; Sivaraj *et al*. 2014). These nanoparticles showed cytotoxic effect against growth of A549 human lung cancer cells and MCF-7 breast cancer cells through ROS generation and oxidative stress (Siddiqui *et al*. 2013). Zinc Oxide nanoparticles (ZnO) have extensive photoluminescence property and used as effective anticancer agent for cancer patients. These nanoparticles are being developed by processing through chemical precipitation, pyrolysis, sol-gel, and thermal decomposition (Batal *et al*. 2018). These nanoparticles are also being preferred as genotoxic drugs due to having tendency to induce micronucleus formation within cell. They cause effective inhibition of growth of cancer cells over the peripheral blood mononuclear cells (Kim *et al*.2013; Kim *et al*.2013; Wiesmann *et al*. 2019; Yun *et al*. 2015; Ryter *et al*. 2007). It has been observed that conjugation of therapeutic agents with zinc oxide nanoparticles showed high therapeutic potential than other nanoparticles in targeted cancer cell (Wahab *et al*. 2014; Wiesmann *et al*. 2019). Platinum associated cisplatin has been commercially used as antitumor agent for treating targeted tumor site. These drugs showed some serious side effects like renal impairment, neurotoxicity and ototoxicity. Platinum impregnated carboplatin has been also used as second-generation anticancer drug with lower extent of side effect (Sakurai *et al*. 2002). These platinum impregnated drugs have been developed by incorporating carrier groups across the targeted tumor cells with high specificity. These platinum nanoparticles have improved the efficacy of hadron-based radiation therapy based on charged particles (protons and isotope of carbon) (Dosanjh *et al*. 2019). This hadron therapy results the denaturation of DNA strand and showed effective therapy against human colon carcinoma cells (Hall *et al*. 2007). Titanium oxide (TiO2) has been commercially used as photo-sensitizing agents for treatment of cancer cells. These nanoparticles have high degree of bioavailability, biocompatibility and stability for a longer time within body fluid. The exposure of tissue with photodynamic therapy results direct illumination of these tissues by ultraviolet or visible light. The photosensitized tissues will be further stimulating the activity of titanium oxide nanoparticles on the target site (Seo *et al*. 2007; Thevenot *et al*. 2008).

Silver nanoparticles (AgNPs) got attention due to its applications such as antimicrobial agents, bimolecular detection and therapeutics agent (Shrivastava *et al*.2009; Sadhasivam *et al*.2010). Over other process, synthesis of nanoparticle from microbial source has significant advantages and eco-friendly because it occurs at relatively ambient pressure and temperature (Gade *et al*. 2008; Narayanan and Sakthivel 2010; Ahmad *et al*. 2003; Ahmad *et al*. 2016). In the field of wound healing, nano-structured materials are creating a center of attention due to their targeting and sustained drug delivery (Patra *et al*. 2008). Among different metallic nanoparticles, silver nanoparticles synthesis has been preferred in the biomedical and pharmaceutical fields due to their "antibacterial", "anti-inflammatory", antiviral and biological labeling properties (Sharma *et al*.2009).

Novel approaches for synthesis of silver nanoparticles

Physical and chemical synthetic approaches

Silver nanoparticles have been extensively used as nanocarrier matrix for therapeutic drugs in pharmaceutical sectors. These sliver nanoparticles provide a large surface-area-to-volume ratio due to their significant small size and spherical. These properties may allow these nanoparticles to attach to surface of microbes with increased permeability and finally results microbial membrane dissolution. AgNPs have versatile applications in medical sectors like diagnostics, imaging, orthopaedics, drug and gene delivery, medical equipment coatings, and wound dressings. They have diversified industrial applications due to exhibiting antibacterial, antimicrobial, anticancer, optoelectronics and semiconductor properties (Thangaraju *et al*. 2012). These could be synthesized through chemical reduction method, electrochemical techniques, irradiation-assisted chemical methods, and pyrolysis as shown in Table4.

Table 4 Physiochemical methodologies for synthesis and stabilization of silver nanoparticles (Iravani *et al*., 2014)

Method	Silver precursor	Reducing agent	Stabilizing agent	Size (nm)
Chemical reduction	$AgNO_3$	$NaHBO_4$	Lipopeptide biosurfactant	2-25
	$AgNO_3$	Trisodium	Trisodium	30-58

		citrate	citrate	
	$AgNO_3$	$NaHB_4$	DDA	5
Electrochemical	$AgNO_3$	Electrolysis cathode: titanium anode: Pt	PVP	10
Physical synthesis	$AgNO_3$	Electrical arc discharge	Sodium citrate	15-30
Photochemical reduction with microwave radiation	$AgNO_3$	Ethylene glycol	PVP	5-10
Photochemical reduction with X-ray	$AgNO_3$	CMCTS, UV	CMCTS	1-8

In general, silver nanomaterials can be synthesized by two approaches of top-down and bottom-up as shown in Fig 3. Top-down method includes the mechanical milling, sol gel process, laser ablation and electro-explosion and suspensions are stabilized by adding colloidal protecting agents (Amulyavichus *et al*.1998; Mallick, *et al*. 2004). Bottom-up approach includes physio-chemical process based on sono-decomposition, thermal decomposition, cryochemicals, electrochemical reduction, laser irradiation, laser ablation, lithography and chemical reduction (Malik *et al*. 2002; Sergeev *et al*.1999; Mafune *et al*. 2000; Hulteen, *et al*.1999; Zhu, *et al*. 2001; Abid, *et al*. 2002; Talebi, *et al*. 2010; Hosseinpour-Mashkani and Ramezani 2014; Zhang *et al*. 2011). The chemical methodology requires metal precursors, reducing agents, and stabilizing/capping agents, organic solvents for synthesis of nanoparticles. The most commonly used reducing agents include borohydride, sodium citrate, ascorbic acid, alcohol, and hydrazine compounds (Tao *et al*. 2006; Wiley *et al*. 2005). Chemical methods result synthesis of high yield of nanoparticle but reducing agents used during this synthetic process like borohydride, thio-glycerol, citrate, and 2-mercaptoethanol are highly toxic and hazardous (Amulyavichus *et al*.1998). The major limitation of this chemical methodology is the sedimentation of surfaces of nanoparticles with chemicals, which results aggregation of silver nanoparticles (Mallick, *et al*.2004). The physical methods for their synthesis are based on physical evaporation-condensation using tube furnace at atmospheric pressure, spark discharging, pyrolysis energy ball milling method, and direct current (DC) magnetron sputtering (Gurav *et al*. 1994; Kruis *et al*. 2000; Magnusson *et al*. 1999; Schmidt-Ott 1988; Tien *et al*. 2008; Pluym *et al*.1993). This physical method has advantage for fast synthesis of nanoparticle using radiation as stimulating factors. The silver nanoparticles will be formed with a narrow size distribution by this physical methodology, but this process is demanding high energy consumption (Elsupikhe *et al*. 2015; Shameli *et al*. 2010; Tsuji *et al*. 2005; Abou El-Nour *et al*. 2010).

Green chemistry approaches

Biological methodologies have been emerged as effective less hazardous approaches in compare to physiochemical approaches for synthesis of silver nanoparticles (Shivaji *et al*. 2011; Zhang *et al*. 2014; Li *et al*., 2019). These green synthetic approaches are considered as simple, cost effective and ecofriendly with production of higher yield of silver nanoparticles using biological products like bacteria, fungi, plant extracts, proteins, vitamins, carbohydrates. This method also includes the use of various enzymatic molecules as precursor for stimulating the synthesis of nanoparticles (Ge *et al*. 2014).

Many scientists have reported the synthesis of biological nanoparticles using crude extract of microbes like *Pseudomonas spp.* (Klaus *et al*.1999), *Lactobacillus spp.* (Nair and Pradeep 2002), *Bacillus spp.* (Kalimuthu, *et al*. 2008); *Escherichia coli* (Gurunathan *et al*. 2009), *Brevibacterium casei* (Kalishwaralal *et al*. 2010), *Fusarium oxysporum* (Shankar *et al*. 2003).

Green synthesis of nanoparticles has been also carried out using plant extracts (Gurunathan *et al*.2015). Fibrinolytic enzyme (Deepak *et al*. 2011), biopolymers (Leung *et al*. 2010,), starch (Kumar *et al*. 2014), and amino acids (Shankar and Rhim 2015) are also being used to these green extracts. These green synthetic approaches for nanoparticles also depend on the nature of organic solvent, reducing agent and non-toxic materials, which result the formation of small size of uniform nanoparticles for their application in biomedical sectors (Gurunathan *et al*. 2014). These microbial crude extract and plant extracts act as reducing agents for controlling shape, size and uniform dispersity of nanoparticles (Gurunathan *et al*. 2009). These green approaches have one more advantage for synthesis of biocompatible and stable nanoparticles. The optimization of environmental factors like temperature, pH, amount of stabilizing factors/ reducing agents/ precursors results the formation of silver nanoparticles with controlled shape, size, and monodisperity (Gurunathan *et al*. 2009; Khodashenas *et al*. 2015). These green silver nanoparticles are extensively used in theragnostic application including anti-cancer therapeutic agent, drug delivery and bioimaging vehicle (Mukherjee *et al*. 2014).

Polymeric nanoparticles

Chitosan Nanoparticles

Chitosan has extensive therapeutic role due to exhibiting active functional group for stimulating immune response, promoting wound healing and activation of antimicrobial properties (Qingye Meng *et al*. 2021; Qi *et al*. 2004). The possible therapeutic effectiveness of these chitosan encapsulated metallic nanoparticles has been shown in Fig4.

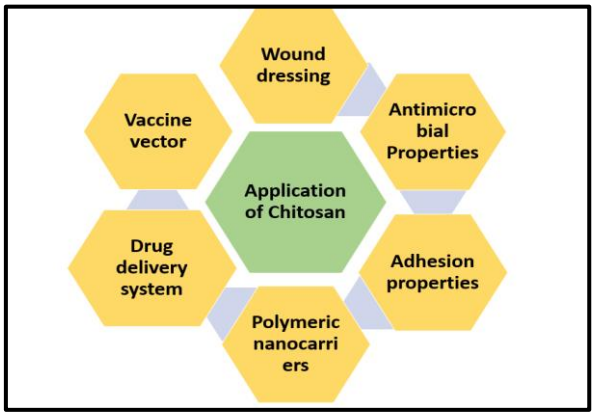

Fig 4 Therapeutic Application of chitosan biopolymer in different pharmaceutical sectors

From last few decades, chitosan has been used as efficient biopolymer to improve stability and biocompatibility of metallic nanoparticles. Chitosan is used as reducing agent during synthesis of gold nanoparticle and improve the drug delivery system of insulin across the mucosal membrane (Ali *et al*. 2016). This insulin impregnated chitosan gold nanoparticles showed higher degree of stability for longer period and significantly lowered the level of blood glucose in diabetic

mice after oral administration. Chitosan-coated silver nanoparticles are also being reported for designing of some biomedical devices, biosensor and cancer therapy. These nanoparticles improved the biodegradability and antimicrobial properties of therapeutic agent. Chitosan loaded copper nanoparticles have also improved the antimicrobial properties against growth of *Staphylococcus aureus*, *Salmonella spp.* and *Escherichia coli.* In recent year, chitosan loaded cobalt oxide nanoparticles have been developed as therapeutic antileukemic agent due to increased level of reactive oxygen species and caspase activation for apoptosis of cancer cell (Ahmed *et al*. 2016).

Mesoporous Silica Nanoparticles: These nanoparticles have high ratio of surface area to volume, uniform size, biocompatibility and surface functionalisation, which are being used for bioimaging and drug delivery system. Silica nanoparticles with size more than 5nm exhibit quantum confinement effect showed significant photosensitizing optical properties. Mesoporous silica nanoparticles (MSNs) and solid core silica nanoparticles are considered as two types of silica nanoparticles. Among these nanoparticles, solid silica NPs could be efficiently used for delivery of imaging probes doped into the core. Mesoporous silica nanoparticles with high surface area and pore volume are commercially used for high drug loading and controlled drug releasing system (Baeza *et al*. 2016; Narayan *et al*. 2018). The drug loading capacity and cellular uptake for specific peptide and antibodies of these mesoporous silica nanoparticles could be effectively modified by adding active functional group of poly-ethylene-imine and poly-L-lysine (Knezevic *et al*. 2015; Castillo *et al*. 2020).

Nanocarbons: Graphene oxide nanoparticles, Carbon nanotubes (CNTs), carbon nanodots (CNDs) are advanced nanoparticles with high surface-volume ratio, high drug loading efficiency and higher stability. Carbon nanotubes are the rolled-up cylinders of graphene sheets with high level of physiochemical and mechanical properties. These carbon nanotubes are classified as single walled carbon nanotubes (SWNTS) and multiwalled nanotubes (MWNTS) on the basis of arrangement of graphene layer in matrix. SWNTS carbon nanotubes are one dimensional nanomaterial with diameter of 1-2 nm and length of 50nm to 1cm. MWNTS carbon nanotubes have multiple layers of graphene with larger diameters (10-100nm). Carbon nanodots consist of carboxylic acid moieties at their surface which improve their water solubility and biocompatibility for subsequent functionalization. The synthetic approach of carbon nanodots include top-down and bottom-up techniques (Figarol *et al*. 2015; Guillet *et al*. 2017) Graphene nanostructures are two dimensional single layered hexagonal packed structures of carbon atoms. Graphene has highly reactive surfaces with low degree of suspension in the solution. This insolubility property could be effectively overcome by oxidizing graphene to graphene oxide. The oxidation activity allows the conjugation of functional groups of loaded drugs onto surface of graphene oxide nanolattice structure (Debnath *et al*. 2021; Faisal *et al*. 2018).

2.2. Development of silver nanoparticles-based hydrogel

Among all nanoparticles, silver nanoparticles extensively used for biomedical applications due to their high level of biocompatibility, bioavailability and antimicrobial properties. The green synthesized silver nanoparticles are currently used for formulation of antimicrobial gel, dressings for burn wound healing, designing of biomedical devices like catheters, implants, and contact lens coatings (Mondal *et al*. 2020; Raza *et al*. 2018). Silver nanoparticles are greatly preferred in pharmaceutical sectors due to exhibiting antimicrobial property. The main limitation of pharmaceutical application of silver nanoparticle is the lower level of nanoparticle surface-binding affinity This limitation could be overcome by using hydrogel scaffolds as an efficient vehicle for drug delivery. These hydrogel scaffold maintain the level of moisture, oxygen and chemical exchange across the dressings and support wound healing process. These hydrogels are three- dimensional cross-linked structure with hydrophilic network of polymers. They are recently in great demand in drug delivery, tissue engineering, and as antimicrobial agents in biomedical sectors (Pangli *et al*. 2021).

When silver nanoparticle impregnated hydrogel dressings are used for wound healing, the nanoparticles will be released from the scaffold matrix and migrated to exposed local cells. Silver nanoparticles loaded collagen hydrogel are commercially used for controlled release of silver nanoparticle to prevent significant cytotoxic activity (Alarcon *et al*. 2015; Pangli *et al*. 2021). Silver ions are being accumulated initially in the vicinity of the hydrogel scaffold and after certain period, they are started to systematically distribute in the vicinity of target organ. These small sized nanoparticles (1-2nm) can passively penetrate cell membranes and dissolve in the cytoplasm to release silver ions. Larger particles will be endocytosed, entrapped and dissolved in an acidic lysosomal environment in many eukaryotic cells. Silver nanoparticles or released silver ions in human cells may disrupt the function of mitochondria by interaction with thiol groups within mitochondrial membrane proteins, reducing mitochondrial membrane potential and disrupting the mitochondrial oxidative phosphorylation process for ATP synthesis. These processes result the generation of reactive oxygen species which further caused the damage of intracellular matrix (Alarcon *et al*. 2015; Akter *et al*. 2018; Xue *et al*. 2016).

Types of Hydrogel Scaffolds

Zwitterionic hydrogel

These polymers have greater affinity for binding water molecules and effectively reduce nonspecific protein adsorption. This provides fouling resistance property to hydrogel scaffold for maintaining catalytic activity within region of protein-rich scaffold. The improved efficacy of zwitterionic hydrogels has been achieved after adding specific biopolymer of polycarboxy-betaine (PCB),4-nitrophenol (4-NP). Hydrogel scaffold result the uniform distribution of silver nanoparticles across PCB hydrogel, improve their catalytic activity and reusability (Zhang *et al*. 2015; Pangli *et al*. 2021). The degree of water content in zwitterionic hydrogels has been examined using UV-VIS absorption measurements and high water content provides effective mass transfer. The larger mesh size of the PCB hydrogel has increased the catalytic activity by providing higher mass transfer. The antibiofouling properties of these PCB impregnated silver nanoparticles with sustain catalytic activity and recyclability will explore its application for wound-healing (Zhang, *et al*. 2015; Zhang *et al*. 2011; Song *et al*. 2019; Pangli *et al*. 2021).

PVA Hydrogels

Poly-vinyl alcohol (PVA) biomaterials are currently being used for biomedical applications due to their biocompatibility, higher stability and bioavailability. PVA as polymeric matrix has been synthesized by polymerization of monomer vinyl acetate as poly (vinyl acetate), and further saponification

reaction to form PVA gel (Cho *et al*. 2018; Arefian *et al*. 2020). These PVA hydrogels have high tensile strength, mechanical strength and biocompatibility with biological tissues for their demand in biomedical applications. These PVA hydrogels are currently used for controlled drug release process of many therapeutic drugs (Noh *et al*. 2015). The crosslinking process for PVA hydrogels can be processed by using many crosslinking agents like glutaraldehyde, epichlorohydrin, acetaldehyde, formaldehyde. Sulfuric acid, acetic acid or methanol are also added to stimulate cross linking process by forming acetal bridging element between the pendant hydroxyl groups of PVA chains. The presence of residue of cross-linking agent during preparation of hydrogels by chemical method will limit its biocompatibility for biological tissue and their application for pharmaceutical purpose (Raphael *et al*. 2016). Glutaraldehyde as bifunctional aldehydes are most common cross liking agent for synthesis of PVA hydrogels. They react with the hydroxyl group of PVA matrix by covalent acetal bonds and improved the mechanical strength of the PVA-hydrogel (Marin and Rojas 2014).

Biodegradable hydrogel

Nanofibrous membranes are commonly preferred for filtration process due to their extensive ability to withstand high fluid flux. These membranes allow the filtration of small sized (micro- and nano) particulates from solution. Chitosan (CS) has high degree of biocompatibility, biodegradability with antimicrobial, wound healing and film forming properties. The development of chitosan-polycaprolactone (PCL) nanofibrous membranes has enable the scientists for using chitosan as natural antibacterial agent for preventing microbial contamination during filtration process (Daels *et al*. 2011; Cooper *et al*. 2013). These types of Nanofibrous membranes have been also synthesized by adding cellulose acetate/silver nanoparticles (Lala *et al*. 2007), poly (vinylidene fluoride)/silver nanoparticles (Yuan *et al*. 2009), chitosan/polyvinyl alcohol/silver nitrate/TiO_2 (Son *et al*. 2009), and inorganic silica/silver nanoparticles (Kyung *et al*. 2007). Chitosan impregnated scaffold has significant antifungal and bacteriostatic characteristics and therefore, preferred as biocompatible dermal scaffold to reduce scars on skins.

Scientist have recently reported gelatin as effective biopolymer for regulating transportation of nutrients ions and cellular growth during regeneration process (Sadeghi *et al*. 2018; Mahboudi *et al*. 2015; Pezeshki-Modaress *et al*. 2013). Chitosan impregnated with glucosamine and *N*-acetylglucosamine biomaterials has been successfully used as biocompatible polymer in *In vivo* study with low degree of inflammatory reaction after implantation in human system (Barikani *et al*. 2014; Baxter *et al*. 2013). The blending of gelatin and chitosan has improved the properties of their scaffold for tissue regeneration (Pezeshki-Modaress *et al*. 2018; Esfandiarpour-Boroujeni *et al*. 2016; Rahman *et al*. 2013).

Lignin-based hydrogels have also showed effective antimicrobial properties using natural lignocellulosic polymeric matrix as antioxidant and antibacterial agent. Lignin impregnated hydrogels are developed by three methodologies of Crosslinking copolymerization, crosslinking of reactive polymer precursors, and crosslinking via polymer-polymer reaction. Other biopolymers like cellulose, hemicellulose, chitosan and alginate are being preferably added to mixture for stimulating the active sites of lignin-based hydrogels. These hydrogels act as suitable absorbent for heavy metal ions, controlled drug delivery system and biosensors due to their properties of biocompatibility, biodegradability, and low toxicity (Yi *et al*. 2019; Sen *et al*. 2015; Naseem *et al*.2016). The hydrogel composite of polyvinyl alcohol has exhibited poor swelling and less mechanical properties, which limited their application for drug delivery system. The development of Lignin-PVA super-absorbent hydrogels by supplementing biomass lignin (raw material) with PVA as matrix template in presence of cross-linking agent of epichlorohydrin has improved their swelling ratio, optimal elasticity and mechanical properties. This lignin impregnated PVA hydrogel has great potential for wound healing due to its antibacterial efficacy, high tensile strength and elasticity (Wu *et al*. 2019). The contribution of PVA will improve the tensile strength, collagen stabilization, and fibril formation in the hydrogel dressing. The collagen matrix consisting of PVA-borate has potential for being used as an injectable matrix for cellular transplantation. A covalent cross-linked hydrogel using the Thiol-Michael addition click reaction has self-healing properties and could be used in regenerative and tissue-engineering medicine. Impregnated chitosan-PEG hydrogels showed high degree of functionality of hydrogel materials for the delivery of silver nanoparticle in diabetic patients with chronic wounds. Hydrogels prepared with PEG provide the slow and sustained release of AgNPs across the membrane matrix. The sustained release of AgNP has been considered as more efficient embedding throughout the hydrogel matrix. The porous structure of the synthesized hydrogel allowed for the take-up of exudates from the vicinity of wound tissue, and penetration of oxygen across them. AgNPs provided the antimicrobial properties, chitosan impregnated PEG will act as a biodegradable carrier and played significant role in stability of hydrogel. This chitosan impregnated PEG hydrogels will enhance in vivo wound-healing capability in diabetic patients (Nosheen *et al*. 2019).

Challenges for using nanohydrogels

In recent years, nanomedicine using metallic nanoparticles are considered as one of the promising strategies in biomedical sectors. Metallic nanoparticles have significant limitations due to unexpected metals ions associated side effects, lack of systematic release of nanodrugs at specific target sites, and development of chemoresistance ((Singh *et al*. 2012; Fanciullino *et al*. 2013). Biopolymeric nanoparticle-mediated therapy has been currently used as most biocompatible and alternative therapeutic strategy. These nanoparticles have been used as drug delivery system through passive or active process after the encapsulation of therapeutic agents (Wicki *et al*. 2015). Scientists are facing major issue with these nano therapies in terms of heterogeneity of target cells and specific formulations to precisely target cells. Biodegradable nanohydrogels has improved their specificity, biocompatibility, safety, efficacy, and reduced their toxicity at target cell site. However, it is significant to address the major challenges of using nanoparticles for biomedical sectors in terms of their biophysiological barriers, improved permeability, limited carrying capacity, and retention effect (EPR), and regulatory issues (Wicki *et al*. 2015). The other serious issue is the damaging of nanohydrogels during transportation and storage. This results the leakage of drug and finally affects their bioavailability at target site.

CONCLUSION

In current scenario, nanotechnology has contributed to the search of new alternatives for improving drug delivery system in medical sectors. Metallic nanoparticles and polymeric nanoparticles have effectively improved the antimicrobial properties of biomolecules. Silver nanoparticles has biotechnological importance in pharmaceutical sectors for diagnostics and imaging, drug and gene delivery, surgical catheters, medical equipment coatings, and wound dressings. Silver-containing dressings are widely used for controlling infection, but conventional dressings reveal inconsistent concentrations of silver and variable tissue injury after prolonged use. The biodegradable hydrogel matrix with silver nanoparticles has improved the antimicrobial and mechanical properties. They have a great demand for biomedical sectors for wound-healing dressing, surgical items, catheters and implant devices. The physiochemical properties of biodegradable polymers impregnated AgNPs have been extensively studied for PVA, chitosan and lignin natural polymer. It is still required some more investigation for exploration of activity of these hydrogel scaffolds in human physiology and their possible toxicity within biological system. These hydrogel scaffolds have been used for improving biocompatibility, biodegradability and stability of nanoparticles for treatment of burns, wound dressings and film formation.

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Availability of data and materials

I agree that all data, materials as well as software application has supported their published claims and complied with field standards.

Role of the Corresponding Author

Dr. Priyanka Singh as corresponding single Author ensures that questions related to the accuracy or integrity of any part of the work are appropriately addressed. I will manage all communication between the Journal and myself before and after publication. I will provide transparency on re-use of material and mention any unpublished material. I also ensure disclosures, declarations and transparency on data statements from author included in the manuscript.

Author contributions

Dr. Priyanka Singh has contributed to the study conception, design, material preparation, data collection and analysis. She has read and approved the final manuscript.

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