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Review Article

Hydrogels and their Metal Nanocomposites: Recent Progresses in Anti-Cancer Drug Delivery and Antimicrobial Wound Healings

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ABSTRACT

Hydrogels are emerging as innovative materials in biomedicine due to their unique physicochemical properties, biocompatibility, and versatility. This review focuses on the development and applications of polymeric hydrogel matrices and silver nanocomposites, emphasizing their role in controlled drug delivery and antimicrobial applications. Polymeric hydrogels derived from natural polymers, such as sesbania gum, hyaluronic acid, and carboxymethyl chitosan, alongside synthetic polymers, such as poly(vinyl alcohol), are highlighted for their ability to achieve sustained and targeted drug delivery. These materials provide a promising platform for delivering bioactive molecules, particularly chemotherapeutic agents, such as doxorubicin, with reduced systemic toxicity and enhanced therapeutic outcomes. The review also delves into the integration of silver nanoparticles within hydrogels, a strategy that imparts robust antimicrobial properties, making these composites highly effective for wound healing applications. Synthesis methodologies, including chemical cross-linking and environmentally friendly green techniques are discussed in detail, providing insights into their influence on the structural and functional properties of the hydrogels. In addition, the article explores the potential of stimuli-responsive hydrogels, capable of responding to environmental triggers, such as pH, temperature, and ionic strength, for precise and controlled drug release. Recent advances in these hydrogel systems are examined, showcasing their applications in cancer therapy, wound healing, and infection management. The review further identifies existing challenges, such as scalability and regulatory hurdles, while proposing future research directions to enhance the efficacy and commercial viability of these systems. Ultimately, this article consolidates the present state of research and underscores the transformative potential of hydrogel-based platforms in advancing personalized medicine and improving patient outcomes.

Key words: Antimicrobial applications, Biocompatible materials, Biomedical applications, Cancer therapy, Controlled drug delivery, Doxorubicin, Green synthesis, Nanoparticle integration, Polymeric hydrogels, Silver nanocomposites, Stimuli-responsive hydrogels, Sustained drug release.

1. INTRODUCTION

The drug is designed for the disease and drug delivery systems are designed for patient compliance. A drug is defined as an active pharmaceutical ingredient (API) that is used for diagnosis, treatment, healing, and curing of illness. Drug delivery is a process of administering the API to a patient in such a way that the amount of API released in a pre-designed manner as per the requirement of a patient with a controlled rate and time [1-3].

2. CANCER

Cancer is a group of diseases characterized by the uncontrolled proliferation and metastasis of certain cells inside the body [Figure 1] [4]. There are several types of cancers, based on the source the most significant types are Breast Cancer, Bladder Cancer, Colorectal Cancer, Gastric Cancer, Glioblastoma Cancer, Follicular Lymphoma Cancer, Lung Cancer, Melanoma Cancer, Multiple Myeloma Cancer, Ovarian Cancer, Pancreatic Cancer, Renal Cell Carcinoma Cancer, etc.

Cancer is one of the top causes of death in affluent countries due to ineffective therapies. It causes approximately 14 million cancer cases and 13 million deaths worldwide, and by 2030, it will cause over 21 million [4,5]. Globalization's effects on the environment and nutrition help spread cancer, impacting one-third of male and female adults and young adults between 15 and 54. Cancer cells can damage healthy cells, tissues, and the host body if left unchecked [6,7]. Different forms of cancer are called after the body part from which they started.

2.1. Treatment of cancer

Cancer is treated potentially by four methods, such as surgery, chemotherapy, radiotherapy, and photodynamic therapy [Figure 2].

2.1.1. Surgery

Surgery is the primary method used to combat cancer as it directly eliminates the affected tissue. This treatment is very efficient

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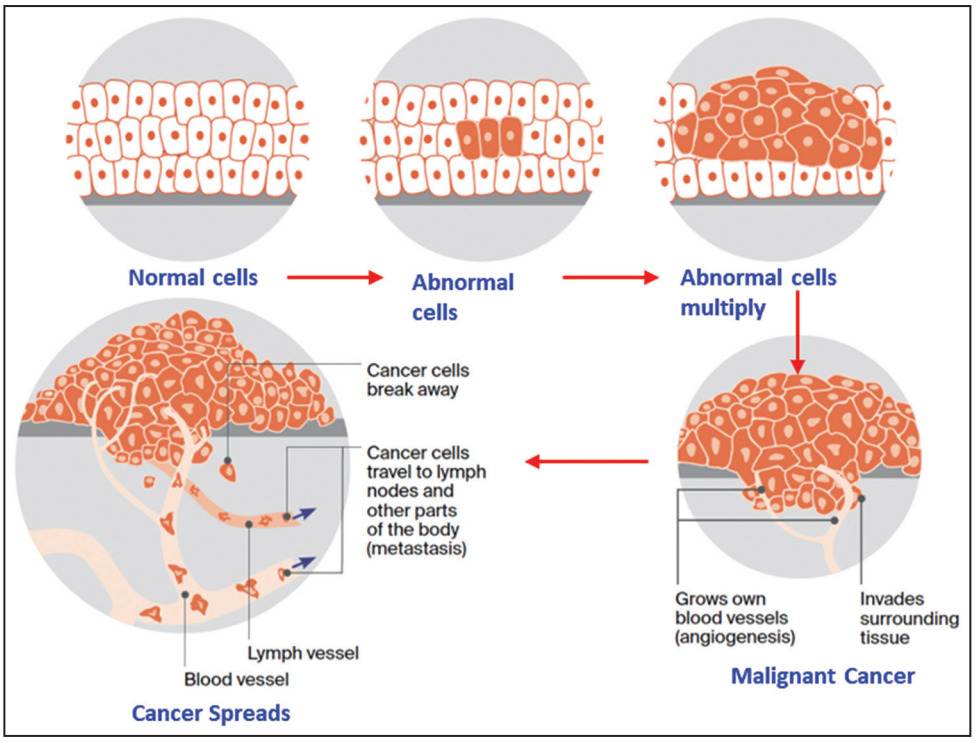

Figure 1: Schematic representation of normal cells, abnormal cells, abnormal cells multiply, malignant cancer and cancer spreads (curtesy with modification from https://www.cancersa.org.au/cancer-a-z/what-is-cancer/).

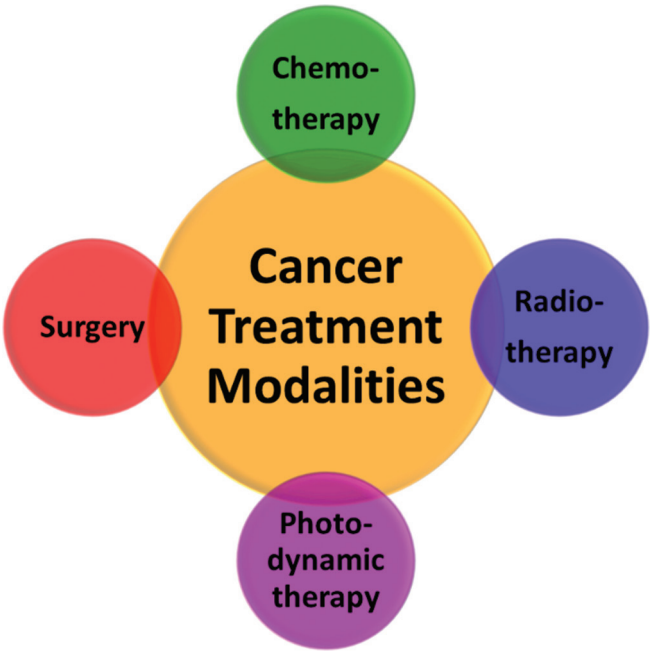

Figure 2: Methods of cancer treatment.

in addressing solid tumors, confined primary tumors, and the corresponding nearby lymph nodes.

2.1.2.Chemotherapy

This approach to cancer treatment involves utilizing a wide verity of chemical compounds to specifically target cancer cells. These chemical compounds are commonly referred to as chemotherapeutic agents. The effectiveness of chemotherapy is greatly influenced by the specific characteristics and stage of the cancer being addressed.

2.1.3. Radiotherapy

Radiotherapy is another procedure that is utilized in the treatment of cancer. Ionizing radiation from X-rays is utilized in radiotherapy, which destroys both benign and malignant tumors.

2.1.4. Photodynamic therapy

Photodynamic therapy is referred to as immunotherapy because photosensitizers possess the capacity to enhance the immune system, therefore assisting in the battle against cancer. Photodynamic therapy is a novel treatment technique that uses photosensitizing drugs, which are activated by light of a certain wavelength, to treat both cancerous and non-cancerous disorders. A photosensitizer is a chemical that, upon exposure to a certain wavelength of light, produces a type of oxygen that is harmful to cancer cells.

Commonly employed techniques include radiation therapy, chemotherapy, and other minimally invasive procedures. Chemotherapeutic drugs and delivery strategies have a greater impact on cancer cells compared to healthy tissue, making them more vulnerable. The main objective of chemotherapy is to eliminate these tumor cells. The therapeutic effectiveness is strongly correlated with the level of targeted ability to eliminate cancer cells and, consequently, improve the patients' quality of life. Chemotherapeutic drugs are frequently employed for targeted treatment because they specifically attack a limited portion of tumor tissue instead of non-threatening by standard cells. Nevertheless, the promise of chemotherapy as a prolonged adjuvant therapy after surgery or radiation has attracted considerable attention. It is imperative to develop novel and enhanced chemotherapeutic drugs. The field of cancer treatment has made significant progress, now encompassing a diverse range of chemotherapeutic medications. Chemotherapeutics are classified into different categories based on their mode of action, chemical properties, and drug interactions. These categories include alkylating agents, antimetabolites, antibiotics, topoisomerase inhibitors, mitotic inhibitors, corticosteroids, and other

chemotherapy drugs [8,9]. Chemotherapeutic drugs often used in traditional chemotherapy include 5-fluorouracil, doxorubicin (DOX), paclitaxel, camptothecin, and other active chemical compounds. Traditional chemotherapeutics exhibit a low therapeutic index due to their systemic dispersion, as opposed to being localized. The outcome may manifest as the unregulated proliferation of cells, leading to the detriment of normal, fully operational cells. Targeted therapy is an innovative treatment strategy that seeks to enhance the therapeutic index while minimizing harm to healthy cells. In this situation, tumor cells might be targeted either actively or passively. Active targeting utilizes antibodies, receptors, or oligonucleotides, whereas passive targeting utilizes macromolecular drug carriers [10,11].

2.2. Chemotherapeutic agents

Chemotherapeutic agents are generally called as antineoplastic agents; these are used to kill cancer cells. They are classified mainly as alkylating substances (nitrosoureas), antimetabolites, inhibitors of topoisomerase, alkaloids found in plants that suppress mitosis, and antibiotics that fight cancer, such as anthracyclines. DOX is one of the potential chemotherapeutic agents, commonly known as anthracycline; it is potentially used in the effective treatment of cancer. It is marketed under several trade names, including Adriamycin. The chemical structure of DOX is shown in Figure 3. It is used to treat cancers, such as bladder cancer, breast cancer, Kaposi's sarcoma, lymphoma, and acute lymphocytic leukemia. DOX is frequently used with other chemotherapeutic drugs. A venous injection is used to administer DOX.

3. DRUG DELIVERY SYSTEMS

A drug delivery system is a product fabricated using a combination of micro and macro molecules to interact with biological systems and produce therapeutic effects. The potential applications of this technology span various fields including drug delivery, wound healing, bone regeneration, bio-sensing, anti-microbial solutions, hygiene products, and cancer treatment [Figure 4] [12]. Various types of drug delivery systems, including polymers, polysaccharides, proteins, lipids, and peptides, are utilized in drug delivery systems to achieve specific physicochemical properties and drug release patterns. These biomaterials come in a range of sizes, from macro to nano [13]. The utilization of composite systems in targeted drug delivery has been implemented to assist in making modifications to pharmacokinetics.

Conventional drug delivery systems (CDDS), such as tablets, capsules, syrups, and eye and ear drops, are quickly eliminated from the body, resulting in dosage levels that fall outside the desired therapeutic range. The medication undergoes rapid metabolism following a single dose, resulting in a subsequent exponential decline in drug levels. The duration of treatment may be insufficient to yield a substantial therapeutic effect, leading to a response that falls short of the desired therapeutic outcome. Figure 5 illustrates the fluctuations in plasma drug levels within a CDDS. Several approaches have been developed to maintain plasma medication levels within the therapeutic range, avoiding both suboptimal effectiveness and potential toxicity. Administering repeated doses at regular intervals may seem more favorable than a single dose. However, this approach can lead to fluctuations in plasma drug levels, often resulting in levels that fall below or exceed the toxic range. Administering multiple dosages in a single day can negatively impact patient compliance. An alternative method involves administering a higher-than-necessary single dose, which may lead to side effects that are unrelated to the drug's desired effects. Controlled drug delivery systems play a crucial role in regulating plasma levels to ensure that they remain within the therapeutic range and prolong the drug's effectiveness within the desired window [14].

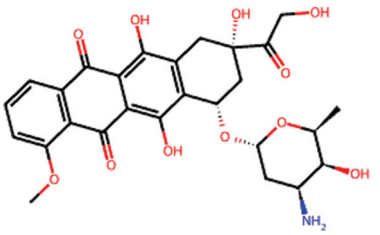

Figure 3: Chemical structure of doxorubicin.

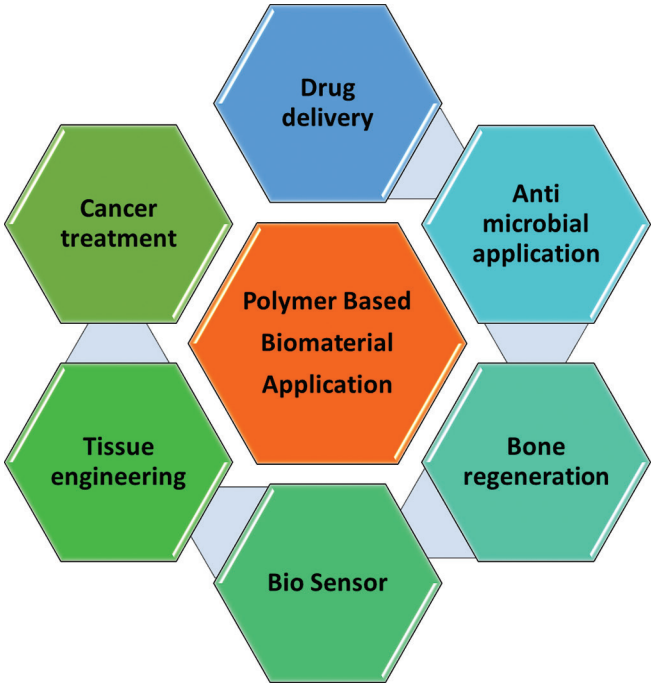

Figure 4: Various biomedical application of polymer-based biomaterials.

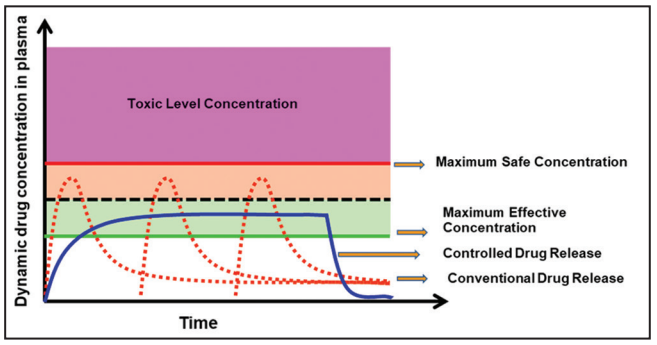

Figure 5: Schematics image of drug in the blood plasma (Conventional dosing [Red Line] and Controlled drug release [blue line]).

3.1. Polymeric drug delivery systems

A diverse range of polymeric materials are accessible for biomedical purposes. However, the number of materials that have been approved for human usage is rather minimal. Hydrogel matrices have recently received a lot of attention for their potential in regulated drug delivery over lengthy periods of time to specific cancer locations. If drug delivery devices are resistant to biodegradation, they may build in the patient's liver after repeated therapy, potentially leading to severe effects. As a result, numerous hydrophilic polymers have been restricted for human usage. Thus, biodegradable polymers are essential in these

applications. Degradable systems have the advantage of eliminating the necessity for surgical removal of the drug-developed device, which can always become a cause of infection. Degradable hydrogel matrices may have additional advantages, such as simplicity of design and predictability of release if the release is exclusively regulated by network swelling and degradation. Biodegradable hydrogels typically have sustained drug release when the initial mesh size of the matrix is smaller than the size of the drug molecule, as the latter cannot leave the gel until the matrix has degraded, so programmable drug delivery carriers are currently of great interest.

3.2. Role of polysaccharides in drug delivery

Polysaccharides have been more significant in the field of drug delivery over the past two decades. Polysaccharides are sub class of natural polymers and its derivatives are finding extensive use in pharmaceutical applications and the biomedical area for drug delivery systems. The primary benefit of drug delivery systems is to achieve an ideal drug concentration, boost the activity of labile APIs, and typically extend the duration of therapeutic effects by protecting against environmental factors. In addition, drug delivery systems help to reduce side effects by maintaining a high initial blood concentration. Polysaccharides have several advantages over synthetic polymers because they are economically affordable, non-toxic, readily accessible, biodegradable, environmentally friendly, and biocompatible.

Chitosan (CS, a natural cationic linear polysaccharide) is made up of N-acetyl-D-glucosamine and D-glucosamine units obtained from chitin deacetylation. Chitin is the second most abundant natural polymer after cellulose, and it has exceptional biological properties, such as non-toxicity, biocompatibility, and biodegradability. In addition, it is a pH-sensitive polymer that dissolves easily at low pH but is insoluble at high pH. Due to these qualities, CS and its derivatives – such as nanoparticles, fibers, films, and hydrogels – have found widespread application in biomedical fields, such as wound dressing, tissue engineering, and therapeutic/diagnostic agent delivery [11,15-22].

Sodium alginate (SA, a natural anionic linear polysaccharide) is obtained from brown seaweed. The composition of the substance is comprised of D-mannuronic acid and L-guluronic acid, which are organized in alternating blocks of β-D-mannuronic acid-β-D-mannuronic acid block (MM) or α-L-guluronic acid- α-L-guluronic acid block and (GG), with additional blocks of β-D-mannuronic acid-α-L-guluronic acid block. (MG) interposed. Its biocompatibility, low toxicity, low cost, and mild gelation induced by the addition of divalent cations, such as calcium ion (Ca^{2+}), barium ion (Ba^{2+}), magnesium ion (Mg^{2+}), and ferrous ion (Fe^{2+}) have made it widely utilized in various biomedical applications. Furthermore, chemical cross-linking helps to get SA-based hydrogels with potential physico-mechanical properties [23-25].

Sesbania gum is derived from the endosperm of seeds of the Sesbania plant; it is a biocompatible and biodegradable natural polymer. Sesbania gum is a galactomannan polymer; it is composed of β-D-mannose molecules linked together by β-(1-4) glycoside bonds, which are generated through the bonding of mannose and galactose. In addition, there are side chains consisting of α-D-galactose that are connected to the C-6 position of the mannose through α-(1-6) glycoside linkages. The sesbania gum polymer is commonly employed as a stabilizer and thickener due to its remarkable attributes, including its high solubility in water and viscosity [26-36].

Hyaluronic acid (HA) is a mucopolysaccharide consisting of glucuronic acid and N-acetyl glucosamine with reactive functional groups (hydroxyl, carboxyl, and N-acetyl). It is a biocompatible and biodegradable polymer; hence it is widely used in drug delivery applications. It is a potential receptor of CD44, and CD44 is over-expressed in many tumor cells [37-40].

3.3. Polymeric hydrogels

Polymeric hydrogels have recently garnered significant interest. Hydrogels are polymer networks that are cross-linked in three dimensions and have the ability to expand or contract in response to changes in environmental stimuli, such as ionic strength, pH, temperature, enzyme presence, and electric field [41-44]. When magnified, they acquire a soft and elastic texture, imitating organic tissue and demonstrating exceptional compatibility with living organisms [13,14,45]. Hydrogels are commonly utilized as drug carriers due to their convenient production and ability to be applied by oneself. Hydrogels can be synthesized by a range of conventional chemical methods [46]. One-step operations include polymerization and parallel cross-linking of multifunctional monomers by the reaction of polymers with suitable cross-linking agents. Similarly, multi-step approaches involve the synthesis of reactive polymer molecules followed by their subsequent cross-linking [Figure 6]. These notable attributes have led to their successful application in several domains such as drug administration, wound healing, bone regeneration, bio-sensing, anti-microbial applications, hygiene products, and cancer treatment [Figure 6].

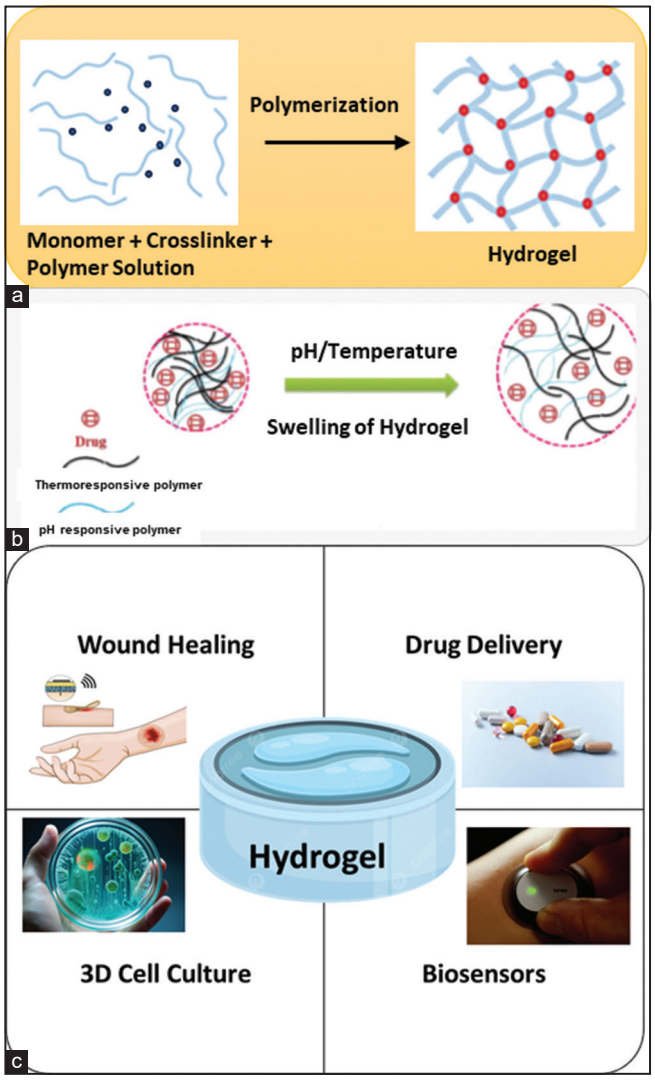

Figure 6: Hydrogel preparation (a), environmental responsiveness (b) and hydrogel applications (c).

Medical technology is utilized to identify novel therapeutic agents that can be delivered to precise locations in the body using specialized carriers. Hydrogels can effectively administer genetically engineered drugs, such as proteins and peptides, to enhance the effectiveness of treatment. The hydrogels can have different structures depending on the preparation methods, such as being composed of a single type of polymer (homopolymeric), a combination of several polymers (copolymeric), partially interpenetrating networks, or fully interpenetrating networks. Recently, researchers have created thermoplastic copolymeric biodegradable hydrogels that possess exceptional mechanical strength, specifically designed for applications in the biomedical industry.

3.4. Polymeric hydrogel nanocomposites

Bio-nanotechnology focuses on making existing products more sustainable, environmentally friendly, and process safe. Metal nanocomposites based on hydrogels are used for both drug delivery and antibacterial applications as wound healing materials [47-56]. The production of size-controlled silver nanoparticles (AgNPs) has proven to be more effective in increasing antibacterial activity. Polymeric hydrogels are superior to other individual polymers and synthetic reducing agents in terms of holding capability and AgNPs delivery. The production of AgNPs from plant material was rapid, environmentally benign, low-cost, and a one-step biosynthetic process. When compared to other individual polymers and reducing agents, the production of size-controlled AgNPs using hydrogels has more advantages for increasing antibacterial activity, because hydrogels have a superior anchoring ability and can produce size-controlled AgNPs. Furthermore, size-controlled nanoparticles are produced in multifunctional hydrogel networks because these structures have a better ability to bind silver ions, which can be reduced to AgNPs in the presence of chemical or natural reducing agents. Thus, functional polymers/monomers in a single hydrogel help in the development of environmentally responsive materials, making it suitable for biomedical use.

4. POLYMERIC HYDROGEL IN ANTIMICROBIAL ACTIVITY/WOUND HEALING

Hydrogels have a crucial impact on wound healing because of their distinctive characteristics, including their ability to control moisture, protect wounds, promote cell growth and migration, administer drugs, remove dead tissue, manage pain, monitor wounds, facilitate tissue regeneration, and manage scars [16,47,48,50,53,57-61]. Hydrogels facilitate wound healing by establishing an ideal environment for tissue restoration, reconstruction, and safeguarding. Hydrogels can be utilized for wound treatment in several formats, such as sheets or membranes, gels or pastes, sprays or foams, and fillers. Various hydrogel properties, benefits, and uses are tabulated in Table 1. The main advantages of hydrogel in wound healing are its biocompatibility, flexibility, facile application, and cost-effectiveness. Hydrogels incorporating antimicrobial qualities can effectively decrease infection rates and facilitate the healing of wounds. These hydrogels contain active biomolecules (growth factors, peptides, proteins, HA, collagen, peptides, anti-microbials, anti-inflammatory agents, enzymes, cellulose-based bioactive molecules, stem cell activators) and metals (silver, copper, zinc, gold, titanium, gallium, cerium, calcium) that play a crucial role in promoting wound healing [25,39,43,47,62-69]. The

Table 1: Various hydrogels properties, benefits and uses [69].

S. No.	Hydrogels	Properties	Benefits	Uses
1.	PVP hydrogels	Moisture-retentive, transparent and flexible.	Promotes autolytic debridement, enhances cell growth, and reduces bacterial growth.	Superficial wounds, scarps
2.	PEO hydrogels	Flexible, permeable, and high-water content.	Supports tissue regeneration, delivering drugs, and manages moisture.	Deeper wounds, ulcers, and diabetic foot ulcers
3.	Collagen hydrogels	Biodegradable, biocompatible, and enhance cell growth.	Promote tissue regeneration, improve wound strength, and support angiogenesis.	Chronic wounds, surgical wounds
4.	HA hydrogels	Bio degradable, bio compatible, and enhance cell growth and high-water content.	Promote moisture retention, cell growth, and tissue repair	Chronic wounds, acute wounds, and skin grafts
5.	Alginate hydrogels	Bio degradable, bio compatible and hemostatic.	Support tissue regeneration, reduces bacterial growth manage moisture	Deeper wounds, ulcers pressure ulcers, and diabetic foot ulcers
6.	CS hydrogels	Bio degradable, bio compatible, and anti-microbial	Reduce bacterial growth promotes tissue regeneration and supports wound healing	Wounds with high bacterial loads, surgical wounds
7.	Silicone hydrogels	Flexible, protective, and breathable	Reduce bacterial growth promotes tissue regeneration and supports wound healing	Burn wounds, hypertrophic scars, and keloids
8.	Gelatin hydrogels	Bio degradable, bio compatible, and promote cell growth	Reduce bacterial growth promotes tissue regeneration supports wound healing and delivers drugs	Wound dressing, tissue engineering, and drug delivery
9.	Pectin hydrogels	Bio degradable, bio compatible, and promote cell growth	Reduce bacterial growth promotes tissue regeneration, delivers drugs, and supports wound healing	Wound dressing, tissue engineering, and drug delivery
10.	Hydrogel blends hydrogels	Combines benefits of individual hydrogels	Offers customized wound healing solutions	Various wound types include chronic and acute

PVP: Poly (vinyl pyrrolidone), PEO: Poly (ethylene oxide), HA: Hyaluronic acid, CS: Chitosan.

Table 2: Combination of hydrogels with active biomolecules and metals, which are responsible for wound healing [66,70-73].

S. No.	Combinations	Properties
1.	PVP hydrogel with PDGF growth factor and Ag	Promotes wound healing by enhancing cell proliferation and migration
2.	PVP hydrogel with GHK-CU peptides and Cu	Stimulates collagen synthesis improves wound strength and exhibits antimicrobial properties
3.	PVP hydrogel with collagenase and Zn	Promotes tissue regeneration and reduces bacterial growth
4.	PEO with PDGF and Ag	Enhances wound healing by promoting cell proliferation
5.	PEO with collagen and Cu	Stimulates collagen synthesis and angiogenesis
6.	PEO with Gelatin and Zn	Supports cell adhesion, migration, tissue repair, and provides essential Zn for wound healing
7.	CS hydrogel with PDGF and Ag	Enhances wound healing by promoting cell proliferation
8.	CS hydrogel with collagen and Cu	Stimulates collagen synthesis and angiogenesis
9.	CS hydrogel with HA and Zn	Attracts and retains moisture supporting a moist environment for wound healing
10.	CS hydrogel with Gelatin and Ag	Supports cell adhesion migration tissue repair and provides essential Zn for wound healing
11.	HA hydrogel with PDGF and Ag	Enhances wound healing by promoting cell proliferation
12.	HA hydrogel with VEGF and Cu	Stimulates collagen synthesis and angiogenesis promoting wound closure
13.	HA hydrogel with EGF and Zn	Enhances epithelialization and tissue repair
14.	HA hydrogel with collagen and Ag	Stimulates collagen synthesis and angiogenesis
15.	Pectin hydrogel with PDGF and Ag	Enhances wound healing by promoting cell proliferation and preventing infection
16.	Pectin hydrogel with VEGF and Cu	Stimulates collagen synthesis and angiogenesis promoting wound closure, tissue regeneration
17.	Pectin hydrogel with EGF and Zn	Enhances epithelialization and tissue repair and wound healing
18.	Pectin hydrogel with collagen and Ca	Stimulates collagen synthesis promoting tissue strength and regeneration
19.	Silicone hydrogel with PDGF and Ag	Enhances wound healing by promoting cell proliferation and preventing infection
20.	Silicone hydrogel with VEGF and Cu	Stimulates collagen synthesis and angiogenesis promoting wound closure, tissue regeneration
21.	Silicone hydrogel with EGF and Zn	Enhances epithelization and tissue repair and promotes wound healing
22.	Silicone hydrogel with collagen and Ca	Stimulates collagen synthesis and angiogenesis promoting wound closure, tissue regeneration

PDGF: Platelet-derived growth factor, VEGF: Vascular endothelial growth factor, EGF: Epidermal growth factor, PVP: Poly (vinyl pyrrolidone), PEO: Poly (ethylene oxide), HA: Hyaluronic acid, CS: Chitosan, Ag: Silver, Cu: Copper, Zn: Zinc, Ca: Calcium.

combination of hydrogels with active biomolecules and metals, which are responsible for wound healing are tabulated in Table 2.

5. LITERATURE SURVEY

Cancer treatment has predominantly depended on tumor dissection followed by chemotherapy with promising anti-cancer agents, such as 5-fluorouracil, DOX, and paclitaxel. While surgical techniques remain promising and largely accepted for specific solid tumors, non-invasive and minimally invasive treatments have garnered significant interest to mitigate and eliminate problems following surgical interventions. Hydrogels have been thoroughly examined as carriers for medication release. Nonetheless, among many drug delivery carriers, hydrogels are cost-effective, facile to manufacture, and optimally engineered for low-invasive drug administration [74]. Therefore, in this section, we have compiled material on hydrogel-based drug delivery methods, specifically for DOX.

Hydrogel nanoparticles based on polyethylene glycol (PEG) and Pluronic® F127 were synthesized using the inverse emulsion photopolymerization technique with 8.7% DOX encapsulation. The release kinetics showed a slow, diffusional release that lasted for more than a week, followed by a small burst of about 10% at 37°C [75]. Micro-hydrogels based on poly(vinyl alcohol) and poly(methacrylate) were synthesized using a chemical cross-linking technique, achieving an efficient DOX loading of around 50% (w/w). Micro-hydrogels exhibit a potent cytotoxic effect on LoVo colon cancer cells [76]. CS-DOX conjugates, acrylated Pluronic, and DOX hydrogels were synthesized using both physical and chemical processes at 37°C. CS-DOX hydrogel achieved sustained release, demonstrated an effective cytotoxic impact on human lung adenocarcinoma cell lines and drastically reduced tumor volume over 1 month [77]. Charged hydrogels synthesized from oligo(poly(ethylene glycol) fumarate) (OPF) and sodium methacrylate (SMA) by a photo-cross-linking technique for the controlled release of DOX. OPF-SMA hydrogel exhibits good biological activity and demonstrates an effective cytotoxic effect on human lung cancer cells and explained in the schematic representation of Figure 7 [77].

DOX-encapsulated pH-responsive microhydrogel cubes and spheres synthesized from poly(methacrylic acid) (PMAA) and poly(vinyl pyrrolidone) (PVP). DOX-loaded PMAA-PVP hydrogel cubes and spheres exhibit 50% and 90% cytotoxicity when cultured with HeLa cancer cells for 24 and 48 h, respectively. Results indicate that the micro-hydrogels exhibit potential pH sensitivity, enzymatic breakdown, and shape-regulated drug delivery [78]. A thermo-responsive injectable hydrogel based on single-wall carbon nanotubes (SWCNTs) was created for DOX-release hyperthermia therapy. SWCNT hydrogel improves the efficacy of chemotherapeutics, overcoming systemic adverse responses, and has the potential for treating gastric cancer [79].

pH-sensitive hydrogels produced from Salecan gum and poly(acrylic acid) (PAA) utilizing N,N′-methylene diacrylamide (SPM). SPM hydrogels successfully encapsulated 69.4% DOX. The release of DOX from SPM hydrogels at pH 7.4 exhibited a minimal drug release of 12.3 wt% within 24 h. However, DOX release at pH 4.0 exhibited a significant drug release of 40 wt% within 6 h. Cytotoxicity assessments

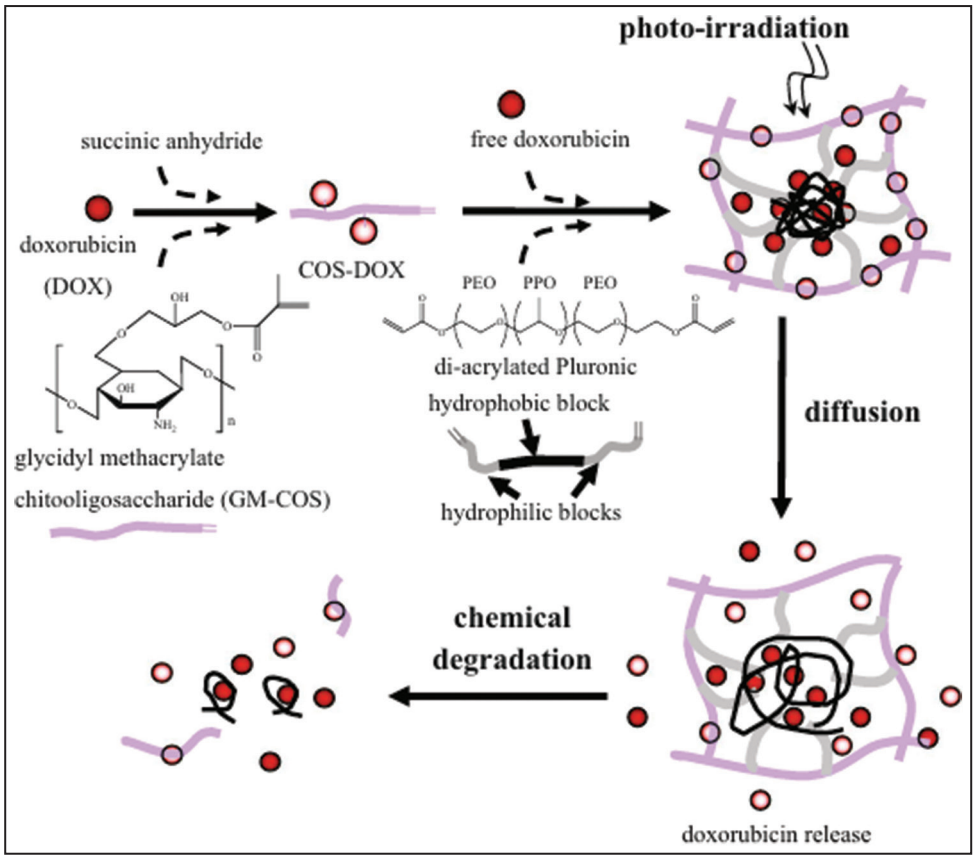

Figure 7: Graphical representation of Glycidyl methacrylate – Chitooligosaccharide (GM-COS)/Pluronic hydrogel for anti-cancer therapy. The figure was reprinted with permission from Elsevier (Cho *et al*. 2009).

on A549 cells demonstrated that pure SPM hydrogels were non-toxic, whereas the DOX-loaded SPM hydrogels retained biological activity and the potential to induce cancer cell apoptosis [80]. A similar way DOX-loaded hydrogels made from Salecan-*co*-poly(N-isopropylacrylamide-*co*-methacrylic acid) (SNIPA-PMA). DOX-loaded hydrogels maintained their biological activity and the ability to promote cell death in cancer cells, according to cytotoxicity studies conducted on HepG2 and A549 cells. In contrast, pure SNIPA-PMA hydrogels were shown to be non-toxic [81].

The injectable hydrogels made from hydrazone-cross-linked sericin/dextran are biodegradable and biocompatible. The results of this hydrogel show that the drug delivery system works and that the optical monitoring strategy based on sericin is effective in living organisms. This could be a way to improve hydrogel design for chemotherapies so that they are more efficient and safer [82]. Thermosensitive magnetic hydrogel synthesized from telechelic difunctional poly(ethylene glycol) cross-linked CS (CS-PEG) for DOX, docetaxel (DTX), and the combination of both drugs. The drug release patterns of DOX and DTX-loaded CS-PEG are analyzed under an alternating magnetic field. A significantly enhanced synergistic effect on the triple-negative breast cancer cell line is achieved by comparing the therapeutic efficacy of the co-delivery of DOX/CS-PEG hydrogel and DTX/PLGA nanoparticles with the administration of DOX or DTX/PLGA nanoparticles alone [83].

Gold nanoparticles loaded Salep-*g*-poly(acrylic acid) (GSP) hydrogel nanocomposites were created by employing N,N-methylenebisacrylamide as a cross-linking agent. DOX encapsulation and release of GSP nanocomposite hydrogel rely only on metal-organic interactions [84]. Thermo-responsive self-assembled micellar-type hydrogels synthesized from alginate-g-poly(N-isopropylacrylamide) (Alg-PNIPA) with varying molecular weights of PNIPA using atomic transfer radical polymerization. Alg-PNIPA hydrogels demonstrate effective DOX encapsulation, prolonged release of DOX, and cytotoxicity against multidrug-resistant AT3B-1 cells [85]. Photo, stimuli-responsive and multicompartment hydrogels synthesized from poly(N-isopropylacrylamide)-*b*-poly(4-acryloylmorpholine)-b-poly(2-((((2-nitrobenzyl)oxy) carbonyl)amino)ethyl methacrylate) (PNIPA-AMP-NCAM). Carrier-based on PNIPA-AMP-NCAM designed for the synergistic delivery of both hydrophilic gemcitabine (GCT) and hydrophobic DOX [86].

pH and redox stimuli-responsive injectable nanohydrogels (NHGs) are synthesized from poly(acrylic acid-*co*-4-vinylphenylboronic acid) (PAA-PVPB) through one-step reflux precipitation polymerization to serve as effective nanocarriers. The hydrogel was engineered for the administration of the hydrophilic medication combretastatin-A4 phosphate (CA4P). The DOX-encapsulated PAA-PVPB NHGs were incorporated into the injectable hydrogels through reversible chemical bonds (boronate ester) to establish a dual drug delivery system. The combination therapy of CA4P and DOX through a PAA-PVPB NHGs delivery method is a promising strategy for enhanced cancer treatment efficacy [87]. NHGs are synthesized from dextran and DOX using a Schiff base conjugation reaction. They are pH-sensitive and possess the capability to localize into endocytic compartments of tumor cells [88].

Polymer-drug nanoparticulate hydrogels (carboxymethyl cellulose [CMC]-DOX) are formed from CMC and DOX through electrostatic interactions. CMC-DOX hydrogels serve as possible transdermal drug delivery systems by effectively targeting melanoma cancer cells while exhibiting reduced cytotoxicity toward normal cells [89]. Initially, micelles composed of Pluronic F127 and α-tocopheryl PEG

1000 succinate were loaded with paclitaxel (PTX), resulting in the preparation of P-TPEGS. In the second phase, P-TPEGS micelles were incorporated into a Pluronic F127/HA (PF127/HA) hydrogel containing a pre-determined quantity of DOX [P-TPEGS-PHA-DOX]. DOX was entirely released from the P-TPEGS-PHA-DOX hydrogel within 12 h, whereas 40–80% of PTX was released from the various formulations over a period of 3 days [90].

Graphene quantum dot doped CMC hydrogel nanocomposite films were fabricated for the controlled release of DOX. These films have shown potential cytotoxicity against K562 blood cancer cells [91]. Glycol CS (GCS) based hydrogels, synthesized using visible light irradiation, are encapsulated with DOX for the treatment of thyroid cancer. The DOX release occurs initially in a rapid burst over 18 h, thereafter transitioning to a steady release phase [92]. A hydrogel based on GCS was developed by mixing complexes of beta-cyclodextrin and PTX along with DOX for the treatment of breast cancer. The drug release occurs in an initial burst over 3 h, followed by a steady release for 7 days [93]. Metal-organic hydrogels synthesized from complexes of guanosine monophosphate (GMP) with Fe^{3+} and Ca^{2+} ions. *In vitro,* drug-release profiles indicate that the release is pH-dependent. Nonetheless, Ca^{2+} cross-linking of the Fe-GMP hydrogel markedly improved the biocompatibility of the drug delivery method [94].

MPP-responsive injectable hydrogel of HA formulated through the integration of micelles containing doxorubicin-loaded poly(D, L-lactide)-poly(ethylene glycol)-poly(D,L-lactide). This hydrogel exhibits potential in regulating the growth of oral squamous cell carcinoma tumors [95]. Injectable hydrogel composed of ester-diol-based polyurethane grafted CS, created by the encapsulation of tetracycline hydrochloride and DOX. The drug-embedded hydrogel demonstrates potential cytotoxicity against the B16–F10 melanoma cell line [96]. pH-responsive injectable hydrogel of CMC (CMC-NH_2 and CMC-CHO) synthesized by integrating micelles containing Nile Red dye and doxorubicin-loaded poly(ethylene oxide)-block-poly(2-(diisopropylamino)ethyl methacrylate) as the core component. The drug release profiles demonstrate that the hydrogel formulations are pH-responsive, sustained, and slow-releasing [97]. Biocompatible pH-responsive PEG is produced using glyoxylic hydrazone links and DOX integration. PEG-DOX hydrogels were absorbed effectively by A549 cells, resulting in cell death [98]. Stimuli-responsive self-assembled hydrogels prepared with ac-(RADA)4 $CONH_2$ peptide for curcumin and DOX administration to treat neck-and-head cancer [99]. NHGs carrier formulated from lysine-modified poly(vinylcaprolactam) cross-linked with PEG diacrylate. These NHGs carriers demonstrated considerable cytotoxicity against the breast cancer (MCF-7) cell line [100].

Magnetic hydrogel (Al-G-M) carriers are synthesized from oxidized alginate and gelatin by a Schiff base reaction, subsequently accompanied by the *in situ* formation of iron(II,III) oxide. Al-G-M carriers demonstrated substantial pH-dependent drug delivery of DOX and cytotoxicity against HeLa cells [101]. pH-responsive (intracellular biological stimuli) hydrogel carriers are made from poly(vinyl alcohol) (PVA)-functionalized ionic liquid (PVA-IL). PVA-IL carriers showed significant pH-dependent DOX drug delivery and cell-killing efficacy against MCF-7 and HeLa cells [102]. CMC, starch, and ZnO are physically crosslinked with ferric chloride to form nanocomposite hydrogel (CMC-S-ZnO) carriers. CMC-S-ZnO carriers displayed significant pH-dependent DOX drug delivery and cytotoxicity against human colon cancer cells (SW480) [103]. Composite hydrogel (CS-C-G) carriers are made from CS, cellulose nano whiskers, and graphene using a Schiff base reaction. CS-C-G carriers exhibited significant pH-dependent drug delivery of curcumin and DOX [104].

Peptide-based hydrogels and nanogels were formulated from Fmoc-FF either independently or in combination with (FY)3 or PEG8-(FY)3 through the solvent-switch approach. Peptide-based gel carriers exhibited significant pH-dependent drug delivery of DOX and cytotoxicity toward MDA-MB-231 breast cancer cells [105]. Peptide-based hydrogels were formulated from FEFKFEFK (F8), FKFEFKFK (FK), FEFEFKFE (FE), FEFKFEFKK (F8K), and KFEFKFEFKK (KF8K) (F: phenylalanine; E: glutamic acid; K: lysine) through the self-assembly technique. Figure 8 demonstrates that peptide-based gel carriers are responsible for drug-peptide interactions, they exhibited significant enzymatic degradation-dependent drug delivery of DOX and cytotoxicity against 3T3 murine fibroblast cells [106].

pH-sensitive hydrogel carriers synthesized from nitrosalicyl-CS imine and aldehyde HA through a Schiff base reaction. These carriers demonstrated potential pH-dependent dual drug delivery of cisplatin and DOX, along with enhanced cytotoxicity effects on A549 lung cancer cells [107]. Eco-friendly and pH-responsive hydrogel synthesized from sodium alginate-g-poly(acrylic acid) (Alg-g-PAA) by simple free radical polymerization using MBA as a cross-linker. Alg-g-PAA hydrogel showed significant pH-dependent DOX drug delivery [108]. pH-responsive hydrogel synthesized from a combination of dextran, CS/gelatin/xanthan, and poly(acrylamide) through straightforward photopolymerization with ultraviolet light irradiation (365 nm). The biopolymer hydrogel demonstrated a potential pH-dependent effect on drug delivery of DOX and cytotoxicity toward keratinocyte tumor cells [109]; these results indicate that the developed formulation may be helpful for the therapy of cutaneous squamous cell carcinoma.

Biocompatible and pH-responsive hydrogel synthesized from combinations of poly(acrylamide-co-acrylic acid/maleic acid)-hydroxyapatite by simple free radical polymerization. Hydroxyapatite composite hydrogel showed significant pH-dependent DOX drug delivery at pH 4.5 and 37°C [110]. A transdermal system of pH-responsive NHGs synthesized from β-cyclodextrin-g-poly(acrylic acid) and HA by controlled radical polymerization. DOX was loaded up to 96.07 ± 2.01% and released a maximum of 90.0 ± 2.6% at pH 5.5 [111]. Gold nanoparticles incorporated into CS-g-PNIPA (GCP) hydrogel nanocomposites were produced by gelatin using genipin as a cross-linking agent. The encapsulation and release of DOX in GCP hydrogels are solely reliant on metal-organic interactions, as well as pH and temperature; additionally, there are increased cytotoxic effects on MCF-7 cancer cells [112].

Kim *et al*., manufactured Ag nanocomposite poly(NIPA-co-APA) hydrogels employing monomers APA and NIPA, as well as cross-linker MBA, by radical redox polymerization [113,114]. The particle size of AgNPs in this study was determined to be within the range of 5-10 nm, as confirmed by both transmission electron microscopy and particle size analysis. The silver nanocomposite hydrogel (SNCH) has demonstrated excellent antibacterial efficacy against both Gram-positive and Gram-negative bacteria. Cha *et al*. from the same research group created SNCHs by combining PVA and poly(Am-co-APA) by redox polymerization [115]. The antimicrobial efficacy of hydrogels loaded with AgNPs was assessed against gram-negative *Escherichia coli* and gram-positive *Staphylococcus aureus* bacteria. The study determined that the particle size of AgNPs fell within the range of 10–20 nm.

Rao *et al*. synthesized semi-interpenetrating network (semi-IPN) hydrogels by combining the natural polymer NaAlg with Am and DMAEMA [116]. They utilized the crosslinker MBA and conducted the polymerization process by radical redox mechanisms. This study involved the *in situ* production of AgNPs by reducing Ag ions to Ag^0 nanoparticles within semi-IPN hydrogel networks. The reduction process was facilitated by utilizing $NaBH_4$ as a reducing agent. The SNCH demonstrated effective antibacterial activity against both

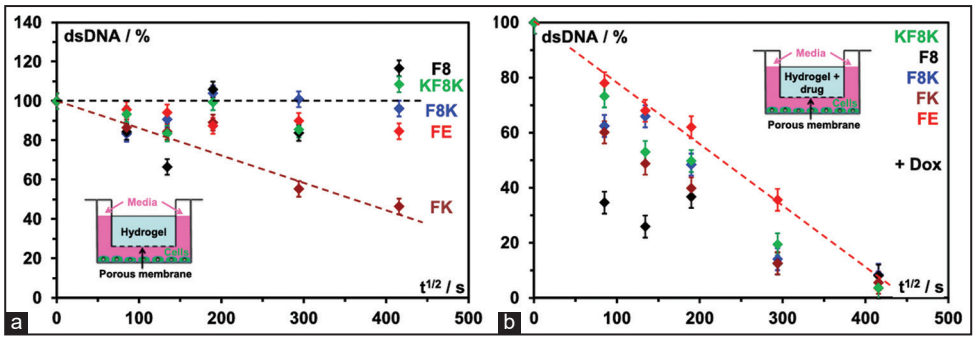

Figure 8: Fraction of double-stranded DNA versus t1/2 obtained for 3T3 murine fibroblast cultured in presence of: (a) hydrogels (14 mM) and (b) Doxorubicin loaded (240 µm) hydrogels. The figure was reprinted with permission from American Chemical Society (Elsawy *et al*. 2022).

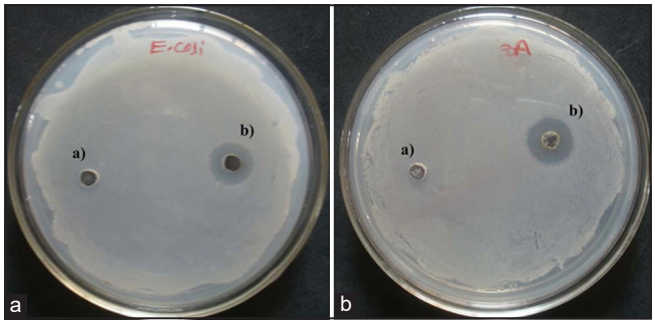

Figure 9: Antibacterial activities: (A) on *Escherichia coli.* for (a) P(NIPAM-GT) and (b) P(NIPAM-GT)4-AgNC hydrogels; and (B) on *Staphylococcus aureus* for (a) P(NIPAM-GT) and (b) P(NIPAM-GT)4-AgNC hydrogels. The figure was reprinted with permission from John Wiley and Sons (Jayaramudu *et al*. 2017).

Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacteria. The semi-IPN hydrogels that were created exhibited cytocompatibility and biodegradability.

Jayaramudu *et al*. [117] created SNCHs that are temperature-sensitive and based on green tea (GT) to inhibit bacterial proliferation. By employing GT as a reducing agent, the temperature-sensitive hydrogels were synthesized through free radical polymerization of NIPA monomer. The hydrogels that were developed were found to inhibit bacterial growth when tested with gram-negative (*E. coli*) and gram-positive (*S. aureus*) [Figure 9]. These hydrogels are effective in inactivating these bacteria as a result of the high stabilization of the antibacterial properties of the AgNPs, using a straightforward redox polymerization technique. Rao *et al*. [117] created SNCHs on the basis of TG biopolymers from monomer Am. The antibacterial activity of the AgNPs that were prepared in this study was evaluated against gram-negative *E. coli* and gram-positive *B. subtilis* bacteria. The TEM analysis of the nanoparticles indicates that AgNPs with an average diameter of approximately 5 nm were generated within the polymer matrix.

6. AIM AND SCOPE OF THE PRESENT WORK

This thesis builds upon the extension research activity in Prof. K.S.V. Krishna Rao's Polymer Biomaterial Design and Synthesis Laboratory [11,16-18,44,50,51,53,54,56,116,118-142]. The focus of this research has been on fabricating polymeric hydrogels for delivering bioactive chemicals in drug delivery. The objective of this thesis is to develop hydrogel matrices and Ag nanocomposites for the controlled release of DOX and their use in antimicrobial applications. The hydrogel matrices are created using a combination of natural polymers (such as propylene glycol alginate, HA, carboxymethyl CS, sesbania gum), synthetic polymer (poly(vinyl alcohol)), and various monomers (including (acryl amide, 3-sulfopropylmethacrylate, acrylamidoglycolic acid, dopamine). Such studies play a crucial role in developing potential formulations for large-scale commercialization. Medical and pharmaceutical firms can explore flexible areas such as once-a-day formulation and controlled release using polymeric hydrogel matrices. Therefore, the thesis aims to address the aforementioned problem in a timely and comprehensive manner.

7. CONCLUSION

Polymeric hydrogels and silver nanocomposites represent a transformative frontier in biomedicine, particularly in the realms of drug delivery, antimicrobial applications, and wound healing. This review has highlighted the versatility and efficacy of hydrogels derived from natural polymers such as sesbania gum, HA, and carboxymethyl CS, as well as synthetic polymers, such as poly(vinyl alcohol). These materials demonstrate exceptional potential for sustained and targeted delivery of bioactive molecules, especially chemotherapeutic agents, such as DOX, thereby reducing systemic toxicity and enhancing therapeutic outcomes in cancer treatment.

The integration of AgNPs into hydrogel matrices further expands their functionality, offering potent antimicrobial properties that make them ideal for wound healing applications. Innovations in synthesis methods, including environmentally friendly green approaches, have enabled the development of hydrogels with superior mechanical strength, environmental responsiveness, and controlled drug release profiles. Stimuli-responsive hydrogels, which react to pH, temperature, and other environmental triggers, offer precise drug release capabilities and pave the way for more effective and personalized therapies.

Despite their promising attributes, challenges remain in the large-scale production, long-term stability, and regulatory approval of these systems. Addressing these issues through interdisciplinary research and collaboration will be key to translating these materials into clinically viable solutions. In conclusion, hydrogel-based systems, particularly those enhanced with nanocomposites, hold immense potential to revolutionize cancer therapy, infection management, and wound care. By advancing the design and application of these materials, researchers can contribute significantly to improving patient outcomes and addressing critical healthcare challenges.

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