Asian Journal of Pharmaceutical Sciences 20 (2025) 101007

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Review Article

Electrically conductive "SMART" hydrogels for on-demand drug delivery

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ARTICLE INFO

Article history:
Received 28 December 2023
Revised 17 April 2024
Accepted 20 May 2024
Available online 11 December 2024

Keywords:
Hydrogels
Conductive polymers
Electrically conductive hydrogels
On-demand drug delivery

ABSTRACT

In the current transformative era of biomedicine, hydrogels have established their presence in biomaterials due to their superior biocompatibility, tuneability and resemblance with native tissue. However, hydrogels typically exhibit poor conductivity due to their hydrophilic polymer structure. Electrical conductivity provides an important enhancement to the properties of hydrogel-based systems in various biomedical applications such as drug delivery and tissue engineering. Consequently, researchers are developing combinatorial strategies to develop electrically responsive "SMART" systems to improve the therapeutic efficacy of biomolecules. Electrically conductive hydrogels have been explored for various drug delivery applications, enabling higher loading of therapeutic cargo with on-demand delivery. This review emphasizes the properties, mechanisms, fabrication techniques and recent advancements of electrically responsive "SMART" systems aiding on-site drug delivery applications. Additionally, it covers prospects for the successful translation of these systems into clinical research.

1. Introduction

Recently, polymers have undergone extensive exploration for various biomedical applications, especially in tissue engineering and drug delivery [1,2]. Nanotechnology has significantly advanced the study of numerous drug delivery systems (DDS), such as hydrogels, nanogels, self-assembled nanoparticles, micelles, dendrimers, and polymer brushes [3–8]. Hydrogels have emerged as the most advanced and promising transport system among these systems owing to their high drug-loading capacity, prolonged drug release, ease of fabrication, unique viscoelastic behavior, and biocompatibility [9–11].

Hydrogels possess a unique supramolecular interaction and hydrophilic 3D structural organization, which enables them to exhibit high loading capacity [12,13]. Among the various hydrogels developed, one of the most effective ones that came into clinical use is a copolymer of 2-hydroxyethyl methacrylate and ethylene di-methacrylate, as prepared by

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Peer review under responsibility of Shenyang Pharmaceutical University.

https://doi.org/10.1016/j.ajps.2024.101007

Wichterle et al. [14]. These hydrogels are particularly suitable for drug delivery applications due to their distinct properties, including regulated swelling behavior, flexibility, elasticity, permeability, and the ability to mimic biological tissue's physical, chemical, and electrical activities [15]. A wide range of potential materials for hydrogel synthesis, including dextran, chitosan, alginate (Alg), hyaluronic acid, gelatin, cellulose, collagen, guar gum, nucleic acid from natural sources, and poly (lactic co-glycolic) acid (PLGA), poly lactic acid (PLA), polycaprolactone (PCL), acrylates, and poly (N-vinyl pyrrolidone) from synthetic sources, are accessible. These materials offer biocompatibility, minimal cytotoxicity, high drug-encapsulating capability, and controlled and sustained drug-release behaviors, making them ideal candidates for developing hydrogels of biological relevance [16].

Hydrophilic functional groups, such as -$CONH_2$-, -OH, -SO_3H, -CONH- when judicially attached to a polymeric network, can exhibit both covalent (chemical) and non-covalent (physical) interactions at both intra and intermolecular levels, particularly when exposed to specific stimuli [17,18] Covalent interactions are formed through various mechanisms, including radical polymerization, chemical reactions involving complementary groups, high-energy radiation, and interactions with chemical crosslinking agents like glutaraldehyde, epoxy compounds, isocyanates, metal ions, and enzymatic reactions, among others [19,20]. These covalent interactions contribute to the formation of hydrogels and maintain their enduring stability [21].

The swelling of hydrogels is a diffusion-driven process [22] that primarily occurs in three phases: (1) Water molecules interact with the hydrophilic groups: In the initial phase, water molecules are drawn to and interact with the hydrophilic functional groups present within the polymeric network of the hydrogel. These hydrophilic groups have a high affinity for water, leading to water absorption into the hydrogel. (2) Interaction between water molecules and hydrophobic groups of the polymer network: As the hydrogel continues to absorb water, the hydrophobic groups within the polymer network come into performance. These hydrophobic regions repel water and balance the hydrophilic and hydrophobic forces, contributing to the overall swelling process. (3) Water occupies the void spaces of swollen hydrogels at equilibrium swelling: The swelling process continues until the hydrogel reaches equilibrium swelling, where the water occupies the void spaces within the polymer network, resulting in a swollen and gel-like structure [23].

Factors like crosslinking density and polymer concentration influence the degree of hydrogel swelling. As the crosslinking density increases, the swelling rate decreases [24]. This often occurs because a higher crosslinking density or polymer concentration restricts the movement of water molecules, making it more challenging for water to penetrate and swell the hydrogel. A delicate balance between capillary, hydration, and osmotic forces must be maintained throughout the swelling process. These counterbalancing forces are crucial to preserve the characteristics and structural integrity of the hydrogel. If the forces are not balanced properly, it can lead to undesirable effects, such as the disintegration or deformation of the hydrogel structure [25].

Hydrogels employ three mechanisms for dispensing biomolecules through various delivery systems, such as transdermal, oral, nasal, ocular, parental, and intravenous, namely [26]. (1) Diffusion controlled: This mechanism follows Fick's diffusion theory. It relies on the porosity and tortuosity of the hydrogel. The diffusion rate depends on factors like the size of the drug molecules, the concentration gradient, and the hydrogel's porous structural characteristics; (2) Swelling controlled: This mechanism follows the zero-order kinetic model. It occurs when the rate of swelling of the hydrogel is slower than the rate of diffusion of the active pharmaceutical ingredients. As the hydrogel absorbs water and swells, the drug release rate increases proportionally to the extent of hydrogel swelling. This mechanism can be advantageous for achieving controlled and sustained drug release; (3) Chemically controlled: The enzymatic or hydrolytic cleavage of hydrogel structure triggers the release of actives. This cleavage can occur either through bulk or surface erosion of the hydrogel matrix. As the polymeric bonds break down, the drug molecules are released. This mechanism allows precise control over the delivery rate and on-demand drug delivery [27].

Each of these mechanisms provides specific advantages and can be customized to meet the needs of various drug delivery applications. By understanding and utilizing these mechanisms, hydrogels can efficiently deliver medications through various routes, offering targeted and controlled drug release for improving therapeutic outcomes [28]. Hydrogels can be categorized based on various factors, each of which plays a significant role in determining their properties and potential applications (Fig. 1) [29] such as size (macroscopic, microscopic and nano gels), sources (natural, semi-artificial and synthetic), composition (homopolymer, copolymer, semi-interpenetrating polymer and interpenetrating polymer network), physical structure (crystalline, amorphous and semi-crystalline), crosslinkers (physical and chemical crosslinking) and ionic charges (cationic and anionic).

The selection of materials for the development of hydrogels plays a significant role in various biomedical applications. Certain properties like biocompatibility, biodegradability, enzymatic stability, and swelling behaviour are imperative in contexts of controlled drug delivery. Natural polymers such as Alg, chitosan, gelatin, hyaluronic acid are suitable for these applications. Moreover, collagen and silk fibroin have extensive use in tissue engineering because of their low immunogenicity, porous structure, and good permeability [30]. However, these natural materials have limitations like uncontrolled degradability and inferior mechanical properties. Hence, synthetic polymers like polyethylene glycol (PEG) derivatives, ethylene vinyl acetate (EVA), poly(N-isopropyl acrylamide) (PNIPAM), polyamidoamine (PAMAM), etc., are commonly used for biomedical applications [31]. The combination of natural and synthetic polymers for the development of hydrogel increases its gel strength and durability and stability in the biological environment. Natural hydrophilic polymers are often combined with synthetic hydrophobic polymers in hydrogel preparation. These hybrid hydrogels exhibit long-term and sustained drug release kinetics, excellent mechanical resilience, biocompatibility, and resistance to

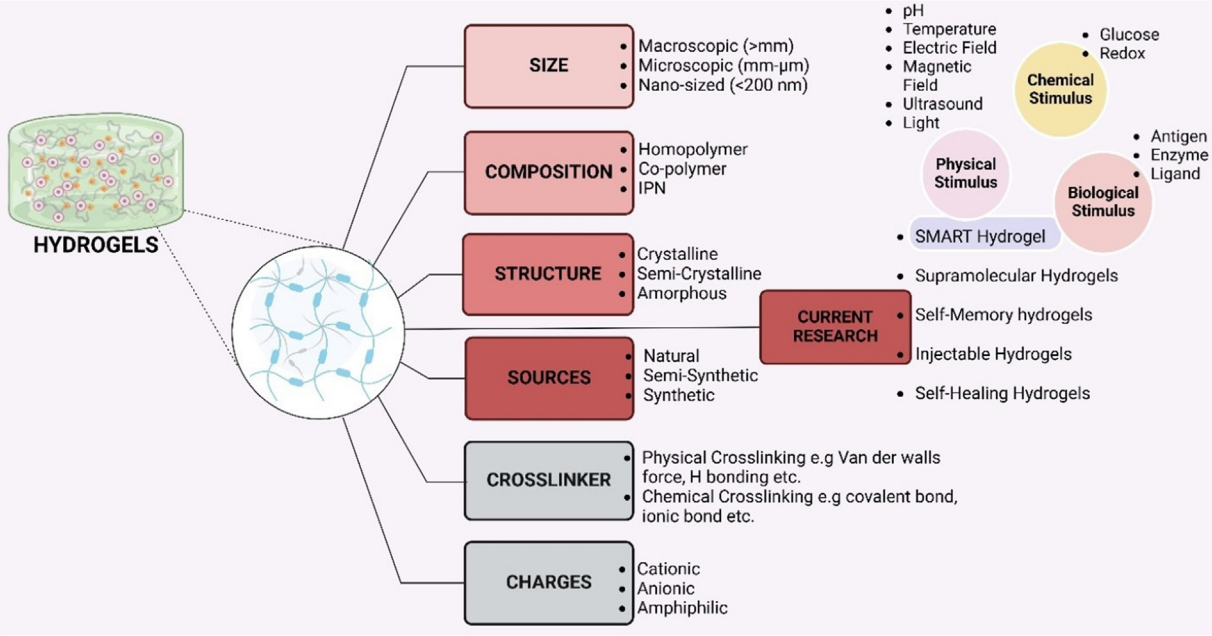

Fig. 1 – Classification of hydrogels.

protein absorption. These attributes render them suitable for a range of applications, including tissue engineering, wound dressing, and bone prostheses [32].

With the advancement in hydrogel research, various specialized hydrogel systems have been extensively studied in biomedical applications, to name a few [33,34] smart hydrogels (respond to specific internal or external stimuli, such as changes in pH, temperature, enzymes, electromagnetic fields, electric and magnetic fields, light, or sound) which includes supramolecular hydrogels; shape memory hydrogels, hydrogel scaffolds; injectable hydrogels; self-healing hydrogels. The ability of intelligent hydrogels to respond to specific triggers and stimuli has gained significant attention, making them promising candidates for various biomedical applications where controlled and targeted drug release or tissue engineering is required [15].

1.1. *Electrically conductive hydrogels (ECH)*

The journey of hydrogel research has taken an intriguing turn toward the realm of intelligent materials, giving rise to the emergence of conductive hydrogel systems. The conductive hydrogels can be classified based on their modes of conduction, such as ionic conductive hydrogels, metal-based conductive hydrogels and ECH (Table 1).

Ionic conductive hydrogels with positive and negative charged groups within the three-dimensional structure consisting of pores that facilitate ion movement and enable conductivity within the hydrogel systems [35]. However, biocompatibility and self-healing properties limit their applications [36,37]. Fundamentally, metals possess exceptional electrical conductivity and mechanical properties. Hence, the metal-based hydrogel systems impart good conductivity and mechanical strength that can be applied in various biomedical applications. However, a significant challenge lies in the crosslinking between the metallic particles and polymer chains, which limits the effectiveness of metal-based conductive hydrogels [38]. Moreover, integrating electroconductive polymeric materials in ECH facilitates diverse properties, including elastic mechanical characteristics, exceptional optical features, robust electrical conductivity, and biocompatibility [39–41]. These remarkable systems have two integral components: a hydrophilic segment endowed with excellent mechanical resilience and swelling capacity and a conducting counterpart that imparts exceptional electrical ability. This marriage of attributes empowers it to undergo reversible physical metamorphoses like size, shape, swelling efficiency, and permeability. Researchers like Guiseppi-Elie et al. first illuminated these systems' unique and enduring properties, tracing back to the late 1990s, notably introducing the concept of ECHs [42].

The cellular electrochemical environment plays a pivotal role in both the development of healthy tissues and the maintenance of vital functions. Essential processes such as generating action potentials, polarization, and depolarization rely on intricate electrical signaling pathways for proper cellular functioning [43]. Furthermore, nowadays, these ECHs, used as substrates for tissue engineering, serve as electrodes for administering external electrical stimulation to cells. Electric fields have diverse effects on tissue and cellular processes, such as influencing differentiation, migration, alignment, organization of cytoskeletal components, promotion of neurite growth in neurons, facilitation of osteoblast calcification, collagen production, and wound healing [44]. The subsequent exploration of ECHs has opened several application dimensions, like e-skins, tissue engineering, bio actuators, wearable sensors, and

Table 1 – Types of conductive hydrogels.

Conductive hydrogels	Conductive part	Examples	Application	Ref.
Metal based	AgNPs, Au@PDA. Cu	OSA/CMCS/AgNPs, PDA/PAM, Ag@Cu	Wound dressings, biosensors, electronic skins, biomedical engineering.	[144,161]
Carbon based	CNT, GO, MXene, rGO	CNT/Gel/CS/PDA, GO/Cellulose, HA-DA, MXene/Cellulose	Biomedical engineering, wound-healing dressings, E-skin.	[162,163]
Polymer based	PPy, PANI, PEDOT: PSS	PPy-PAAm, PAM/SHA/PANI, PEDOT/PSS/GG/HA	Electrically-stimulated drug-release systems, infected chronic wound healing, wearable electronic devices.	[141–143,159,164]
Ion based	Bioionic liquid, NaCl, KCl, LiCl, boric acid, etc. Polyelectrolytes such as Alg, CS, HA, PAA, polymethacrylic acid (PMAA)	PBA-IL-PAM, CS/LiCl NaSS/ DMAEA-Q	Biomedical engineering, wound-healing dressings, E-skin, drug-release systems.	[35–37]

revolutionizing the treatment of various diseases [45]. At this current juncture, the evolution of ECHs has taken an exhilarating trajectory toward pharmaceutical advancement. This new horizon facilitates the fabrication of novel stimuli-responsive (particularly involving electrical stimulus) DDS for precisely delivering therapeutic agents [46].

The fabrication mechanism of ECHs is involved in three ways: (1) adding a conducting polymer in a conventional hydrogel matrix, (2) transporting more ions to the system to increase the ionic conductivity, and (3) adjoining a conducting material like graphene oxide (GO), carbon nanotube (CNT) in hydrogel systems [47]. The addition of conducting polymers such as polypyrrole (PPy), polyaniline (PANI), and poly-(3,4-ethylene dioxythiophene) (PEDOT) is preferred over other methods because they combine the conducting property of metals with the advantageous mechanical attributes of nonconducting polymers without altering the cellular functions [48]. The presence of ions in their structure helps to boost the ionic conductivity in biological media, and the presence of delocalized pi electrons in the conjugated structures provides a conductive channel that induces electronic conductivity [49]. Polyelectrolytes are another significant class of polymers utilized [50]. They may be cationic, anionic, or amphiphilic. Ionic groups on polyelectrolytes can interact electrostatically with other groups of molecules and biopolymers. The most prevalent bio-macromolecules, such as proteins and complex polysaccharides, contain charged species on their backbone and interact with oppositely charged lipid bilayers of cellular and subcellular membranes, making them an outstanding candidate in biomedical applications [51].

Drug loading in ECH relies on the size and charge of the drug molecules. Charged drugs establish electrostatic interactions with the conductive segments of the hydrogel network. Existing literature outlines two distinct methodologies: passive and active approaches. Passive loading in ECHs involves a diffusion-swelling mechanism, while active loading employs doping during post-electropolymerization [52]. Moreover, osmotic pressure governs the release dynamics of the active moiety, driven by the interplay of three factors: elasticity of the polymer chains, affinity between the component polymers, drug molecules, and the surrounding environment, and ionic pressure inside the hydrogels due to the movement of ions within and through them. This interplay induces volume changes in the hydrogel, reaching equilibrium when the osmotic pressure matches that of the surrounding aqueous solution [53]. Upon electrical stimulation, ionic movement or transport occurs within the charged gel, leading to an increased internal osmotic pressure differential and subsequent drug release from the hydrogels [54]. The electrolysis-induced pH gradient alteration in the extracellular environment further contributes to the release of bioactive molecules from polyelectrolyte hydrogels. Upon application of electrical stimulation, the generation and migration of ions towards the respective electrodes cause a pH gradient to form within the hydrogel matrix, ultimately influencing the drug release mechanism from ECHs [55].

The response of an ECH in the presence of an electric field depends upon an electron hopping process in which electrochemical charges move through the polymer during the oxidation or reduction of electroactive polymers (EAPs). Researchers can measure the rate of this process in terms of diffusion coefficient [56]. Using cyclic voltammetry (CV) or chronoamperometry (CA), researchers can employ this coefficient to quantify the effectiveness of charge percolation through the polymer. The electric field-driven diffusion mechanism alters the system's membrane potential and redox state. These factors trigger a pulsatile response mechanism in the presence of a repetitive electric field potential [57]. Overall, the pulsatile responsiveness of ECHs allows for the "on-off" drug release mechanism through (1) charged ion-initiated diffusion of drug molecules, (2) conformational changes that take place during redox switching of EAPs, and (3) electroerosion [42].

Recently, researchers have employed conductive hydrogels in various scalable devices, including actuators, soft electronics, touch panels, energy storage devices, tissue engineering, wearable sensors, biomedicine, and artificial electronic skins. It may be a top choice as a reliable

drug delivery system because of its self-healing capacity, superior mechanical properties, and stimulus-responsive switch on-off mechanism [43]. While ECHs are a viable candidate for drug delivery, they have several drawbacks, including sluggish stimulus-response, burst drug release, a non-specific mechanism for drug release, potential toxicity, limited hydrophobic drug delivery, and low drug encapsulation. Additionally, the electrical conductivity of intrinsically conductive polymer hydrogels is relatively low, the movement of drug molecules in the presence of an electric field depends upon the charges present in their chemical structure, and the electrochemical release profile readily depends upon the ion exchange mechanism between charged drug molecules and surrounding media [44]. These all limit the application of ECHs in drug delivery. Despite these limitations, continuous attempts have been made to create novel hydrogel designs with the excellent qualities of hydrogels in mind to address these problems. The current review aims to draw attention to the critical characteristics of ECH. The current review also concentrates on polymerization techniques and manufacturing processes to create unique conductive hydrogels and know how the various mechanisms of delivery of biomacromolecules, recent research updates on ECH, and its application in different facets of on-demand DDS.

2. Drug delivery mechanism through ECH

ECH consist of a conducting polymeric backbone within the structure which imparts electrochemical properties into the system. The continuous and ordered pi-conjugated structure makes them electrically conductive. When the conductive part gets oxidized, the influx of positive charges reshuffles the π bond distribution along the backbone chains. The electrons get removed in this process, and "holes" are created along the backbone. The conjugated double bond structure provides a path for electrons to move freely through these "holes," which accounts for their conductivity. ECH can switch their redox states reversibly and change their volume, charge, and conductivity. The volume change is due to the reversible changes in the polymeric composition [41]. During oxidation, the strong van der Waals interaction within the polymer network undergoes conformational changes to provide space for the balancing counter anions from the solution that affect the compactness of the polymer structure. By exploiting these properties, researchers can control the drug release rate from conducting polymers (CPs). The release of actives from ECH follows three ways: deswelling, swelling, and erosion, which are described subsequently [45]. Electro-stimulated hydrogels release charged and uncharged guest molecules through diffusion, electrophoresis, forced convection, and drug liberation upon erosion. Different drug release mechanisms are discussed below [46] (Fig. 2).

2.1. *Forced convection of drug in response to gel swelling-deswelling*

ECH swell anisotropically when an electric field exceeds a threshold value, with anionic gels shrinking at the anode and cationic gels shrinking at the cathode. The deswelling equilibrium is slow, resulting in a slower gel response that may be linear but deviated at higher voltages, depending upon the charge transported and applied voltages. The main mechanisms involved in drug delivery through hydrogel deswelling are drug release through stress gradient established within the hydrogel, change in pH around the electrode, and electroosmosis and electrophoresis [48].

Drug release from a gel occurs due to its shrinking and combined response to electrical stimulation. The slope of the curve (drug release *vs* voltage/current) usually decreases at higher voltages/currents and follows a nonlinear behavior. Drug back-flow occurs via convection, causing gel swelling and absorbing some release medium [58,59] Moreover, the molecular size of drug molecules is crucial, as pores in the polymeric gel network prevent the diffusion of larger molecules through ECHs. In an electric field, the charge induced on the drug molecules (drug electrophoresis) also plays an essential role in the release mechanism. Charged pharmaceuticals can be electro-released from hydrogels by moving in opposite directions. Neutral medications are released through forced convection and deformation of the hydrogel matrix at the working electrode. In contrast, charged edrophonium ions are released through ion exchange, swelling/deswelling/bending (deformation), and electroosmosis [59].

2.2. *Drug release by erosion of gel*

Researchers also reported unique electrically induced polyelectrolyte gels that erode in the presence of electric field. The electroerosion of ECHs is due to the movement of ions following the change in pH [20]. Surface erosion follows the stepwise electrical stimulation profile, and disintegration occurs through surface erosion and loss of gel mass. Gel erosion is an applied electric field-dependent phenomenon but does not always show linearity. The rate of gel erosion remains unchanged with time and cycles of electrical stimulation, mainly when 15 and 20 mA fields are applied [60]. Stimulation of an electrode causes gel erosion, leading to the dissolution of a polymer complex and the subsequent release of actives encapsulated within the gel matrix. This gradual release of actives continued until 70 % of the loading was discharged, with significant variations due to uneven disintegration caused by flaws in the gel matrix [61].

Various factors, including the polymer's thickness and density, the composition of the release medium, and the type of electrical stimulation applied, can influence drug release from ECHs. While polymer films with more thickness are expected to hold more drugs, the relationship between polymer thickness and drug release is not necessarily linear [62,63]. Films with more thickness exhibit lower electroactivity that affects the drug release profile. The tissue microenvironment, such as pH, ionic strength, polarity, and hydrophobicity, plays an important role in drug release. For instance, ion transport is influenced by the pH of the biological fluids, with anionic movements prevailing in low pH environments, while cationic movements occur at neutral pH. The drug delivery depends mainly on the physiological conditions of the fluid. For example, a buffer

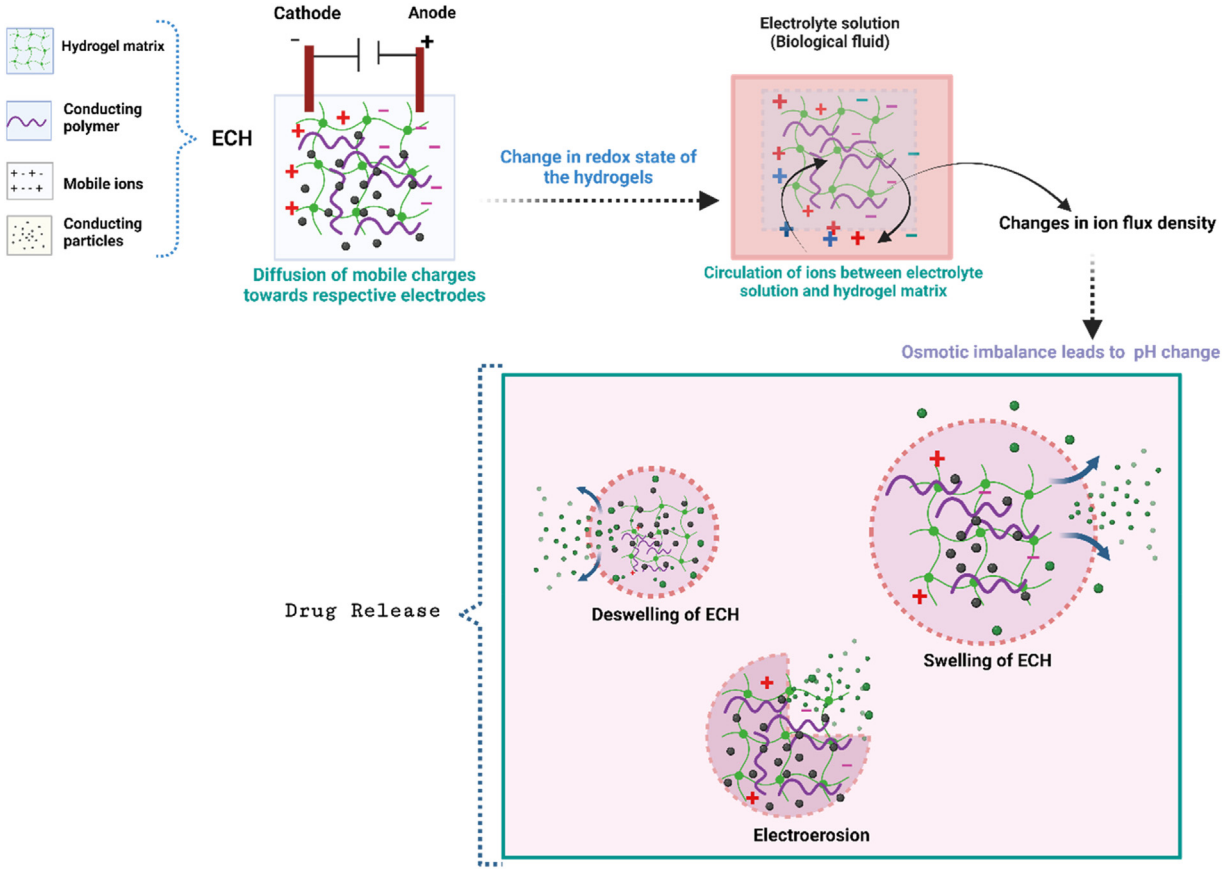

Fig. 2 – Schematic representation of drug release mechanism through ECH.

solution with pH 7.4 would be suitable if the objective is to deliver drugs to extracellular fluid. Additionally, the nature of electrical stimulation affects the drug release profile. The release mechanism involves a combination of electrochemical, chemical, and mechanical actions within CPs, leading to swelling and deswelling that facilitates the drug release profile [63,64].

3. Preparation procedure

The preparation strategy for imbuing conductivity into next-generation ECHs can be classified into four groups based on how it can be achieved: *in situ* polymerization, copolymerization, post-polymerization modification, and composite methods.

3.1. *In situ polymerization*

In this one-step preparation method, the oxidant, such as ammonium persulfate (APS) or sodium persulfate (SPS), and the monomer of the conducting polymers, such as PPy or PANI, are subsequently added to the hydrogel matrix followed by gelation (Fig. 3A). The addition of crosslinked water-soluble polymer matrix, such as chitosan, hyaluronic acid, gelatin, Alg that expands in water, or an electrolyte solution, has been reported by a few authors to contain conducting polymer. The water-soluble ECHs can be synthesized by simply dissolving the monomer in an aqueous polymer solution in the presence of a suitable stabilizer, which is the first step of synthesizing water-soluble ECHs. Next, the monomer is oxidized or polymerized using the appropriate oxidants. This results in an ECH where the conducting unit gets physically entangled with its non-conducting counterpart. The hydrogen bonding and chain entanglements between the constituent units give a dense crosslinked network structure. Incorporating conductive polymers into the hydrogel matrix necessitates modifying their solubility because these polymers are inherently insoluble [65].

For instance, Xu et al. [66] improvised the Schiff base reaction to create a self-healing conductive hydrogel. Chitosan, pyrrole, and these substances were combined and stirred before oxidizing in an ice bath to create the *in situ* polymerized PPy [66]. Using *in situ* polymerization of aniline, Zhao et al. [67] developed an ECH network by grafting aniline oligomers to quaternized chitosan. They crosslinked the system by adding oxidized dextran as a dynamic Schiff base crosslinker. The ECH exhibited a conductivity of 0.43 mS/cm with favourable antimicrobial activity. It was demonstrated that the conductive hydrogel created using this method fosters cell proliferation and maintains cell viability [67].

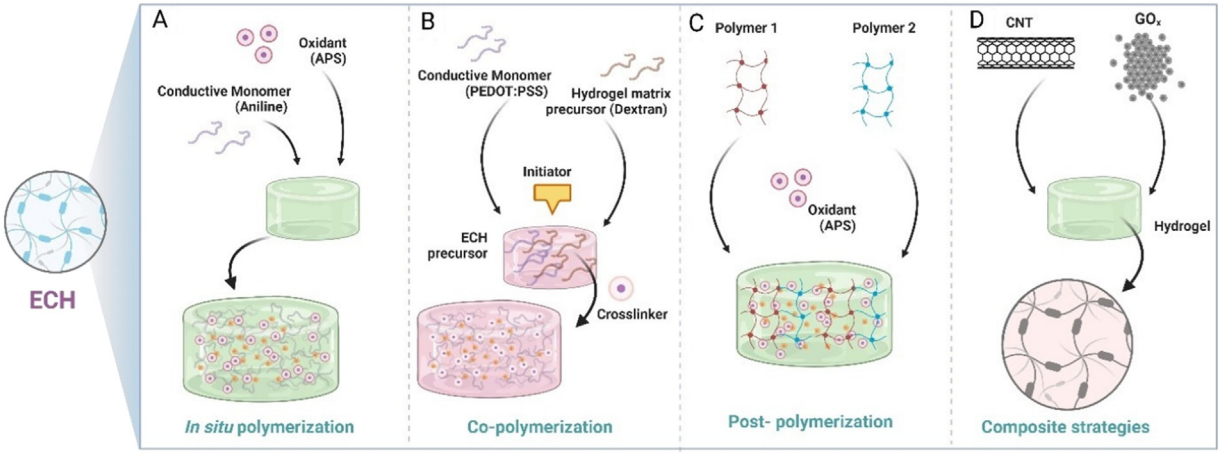

Fig. 3 – Schematic representation of different mechanisms to prepare ECH (A) *In situ* polymerization, (B) co-polymerization, (C) post-polymerization, (D) composite strategy.

3.2. *Copolymerization*

3.2.1. *Direct copolymerization*

Direct copolymerization is essential in producing conductive hydrogels by combining monomers in various proportions and pouring them into hydrogel precursors. The reaction is then triggered by feeding a gelling agent or altering the micro-environment. Controlling monomer concentration in the copolymers to get the desired hydrogel characteristics is a simple but effective way of production for ECHs [68], as shown in (Fig. 3B). To meet the suitable mechanical properties of hydrogels, Jiang et al. created an ECH by utilizing copolymerization of hydrophobic HEMA (hydroxyethyl methacrylate) and hydrophilic AA (acrylic acid) [68]. Such a hydrogel has excellent promise for use in biomedical applications because of its tunable mechanical and conductive capacity. Conductive hydrogels with exceptional mechanical properties can form crosslinks (physical and chemical) between polymeric networks through direct copolymerization. The resulting hydrogel coins the properties of both constituents. Wang et al. synthesized a mechanically robust ECH by adding PANI into a biocompatible P(AAm-co-HEMA) copolymer hydrogel network [69]. Long et al. described the method for preparation of a PDA-PAM crosslinked hydrogel network consisting of PDA, acrylamide (AM), N, N′-methylene bisacrylamide copolymers and tetramethyl ethylenediamine (TMEDA) [70]. Liu et al. prepared PEG/PAMAA conductive hydrogel by simply polymerizing AM and AA monomers on the PEG Gly template to control the growth of the crosslinking network precisely. Due to its high sensitivity and capacity for self-healing, it has become a promising candidate for applications involving medication delivery [71].

3.2.2. *Copolymerization by grafting*

Grafting is another essential method for creating conductive hydrogels due to the porous nature of hydrogel networks, which makes the hydrogels more pliable and softer. Grafting, instead of traditional copolymerization techniques, can increase crosslinking efficiency and entice secondary interactions between constituent polymer networks [72]. Chen et al. developed a novel grafting strategy that grafted acrylonitrile and acrylamide copolymers onto a novel cellulose-based conductive hydrogel. It improves mechanical properties like ultra-stretchability, toughness, and anti-freezing capabilities because of the formation of secondary interactions between the polymer chains. The mechanical and electrical properties of ECH can be improved considerably by grafting conductive oligomers like aniline tetramer (AT) and PPy onto polymer chains and the formation of nanocomposites by adding conducting fillers like GO and CNTs [72]. Zhao et al. created a reasonably conductive injectable hydrogel using a thermal-gelling technique. They graft AT onto a copolymer of PEG and PCL to create an amphipathic AT-PCEC hydrogel with outstanding biocompatibility, anticipated to be a strong contender for biomedical applications [73]. Wang et al. produced a PPy-grafted methyacrylated-gelatin conductive hydrogel network. They improved the system's conductivity using ferric ions with a synergistic improvement in the hydrogel's biocompatibility and capacity for self-healing characteristics. The hydrogel's capacity for self-healing makes it a viable substance for drug delivery [74].

3.3. *Post-polymerization modification*

The polymerization modification can be done by adding a monomer into the hydrogel matrices and subsequently adding an oxidant solution into it. An oxidant-hydrogel mixture can be added to a monomer solution, as shown in Fig. 3C. This procedure offers the chance to induce additional conductivity to the previously created hydrogel. Concurrently, researchers can modify this method as a substitute coating process for various polymers [74]. However, this procedure may need help due to the potential diffusion constraint responsible for the inhomogeneous distribution of the conducting phase over the entire matrix. This method primarily relies on the diffusion of monomer or oxidant solution within the produced hydrogel. Therefore, to achieve a homogeneous conductive hydrogel using this method, optimization of the material used and process

parameters is compulsory [75]. Wu et al. used the post-polymerization method to synthesize gelatin methacrylate (GelMA) based conductive hydrogel [76]. APS, an oxidant, was infused into the manufactured hydrogels to polymerize aniline monomers and develop a conducive PANI-GelMA hydrogel. They used CV to confirm the conductivity of the resultant disk-shaped PANI-GelMA hydrogel, which has a thickness of 1.62 mm. *In vitro* cell tests were used to evaluate biocompatibility.

3.4. *Composite strategy*

This method often entails mixing conductive particles into the hydrogel precursor, such as metals, carbon (CNTs and graphene), and conductive polymers [77]. When these conductive particles are homogeneously dispersed in hydrogel matrices, the resultant hydrogel owns the conductive properties as shown in Fig. 3D. By varying the amount of mixed conductive particles, it is possible to modify the hydrogel's conductivity to a certain extent [78,79]. Dopants are essential because they enhance conductive hydrogels' mechanical stability and conductivity. Contrary to conventional ECHs, hydrogels with conductive dopants have more controlled chemical and morphological characteristics. Among them, polymer dopants have become more significant due to the three-dimensional programmable network that has attracted great interest as one of the most significant methods for modifying conductive hydrogels [80–82].

Researchers have found that the conductivity of chitosan composite hydrogel might rise significantly after adding more chemically modified graphene to the system. Maharjan et al. fabricated GelMA-Au/SiO_2 composite hydrogel to induce conductivity in the GelMA hydrogel by incorporating Au/SiO_2 NPs into the hydrogel matrix. Here, GelMA matrix was combined with gold/silica (Au/SiO_2) hybrid NPs to create a physically robust and electrically conductive GelMA hydrogel for use in biomedical applications. The compressive strength test, conductivity/resistivity measurement, and field emission scanning microscopy (FESEM) were used to characterize the as-prepared GelMA-Au/SiO_2 hydrogels. Thus, the *in vitro* biocompatibility assay was carried out in rat cardio myoblast H9C2 cells to assess the cell compatibility of the as-prepared conductive hydrogel. The outcomes demonstrated that the composite hydrogel maintained GelMA hydrogel's advantageous characteristics, such as its porous shape and biocompatibility, while having improved compressive strength and conducting capabilities [83].

When the hydrogels are directly added to an electrolyte medium like biological fluids, the ions in it (*i.e.*, Na^+, HCO_3^-, Ca^{2+} and Cl^-) are diffused through it, giving the hydrogel an inherent ionic conductive property [84]. Meanwhile, incorporating ions into the hydrogel improves both gelation time and elasticity. For instance, to improve the mechanical properties, Odent et al. developed a collection of ionomer hydrogels by mixing anionic -SO_3H groups modified NPs and cationic NR_4^+ bonded polymer network that interact electrostatically to produce dynamic and reversible coulombic interaction [84]. PPy is utilized as a dopant to prepare a novel conductive hydrogel based on sodium Alg and carboxymethyl chitosan that shows excellent biocompatibility, as demonstrated by Bu et al. Moreover, by changing the dopant concentration, the mechanical and electrical properties of the hydrogel can be altered [85]. Zhao et al. recently created a robust and flexible hydrogel using chitosan networks, polyacrylic acid (PAA), and Fe^{3+} with significant self-healing behaviour. The hydrogel showed enhanced conductivity when doped by PPy particles added into the pre-hydrogel network [86].

Wu et al. synthesized a poly (N-acryloyl glycinamide-co-2-acrylamide-2-methylpropanesulfonic) based conductive hydrogel. It exhibited comparatively high conductivity, excellent self-healing properties, thermal processability, and flexibility when doped with PEDOT: PSS [87]. Additionally, Spencer et al. created a gelatin methacryloyl (GelMA)-based conductive hydrogel doped with PEDOT:PSS. It can have extensive biomedical applications, especially in electrically responsive drug delivery and tissue engineering. Conductivity can be further improved by adding acid dopants as they protonate and thus provide conducting ions. By adjusting the concentrations of acid dopants used, the conductivity of the hydrogel can be tuned [88]. Das et al. developed a folic acid crosslinked, PANI-doped hybrid ECH. The conductivity of the ECH was further enhanced with the addition of AgNPS nanoparticles [89]. Chakraborty et al. developed a novel Fmoc-FF-PANI hydrogel by doping PANI into N-fluorenyl methoxycarbonyl diphenylalanine hydrogel. It shows improved conductivity and biocompatibility and has exciting prospects in biosensing and biomedicine [82].

Wang et al. developed a thermo-sensitive poly (N-isopropyl acrylamide) (PNIPAAm) based injectable hydrogel for drug delivery and crosslinked it by adding phytic acid doped PANI into it [81]. Zhou et al. prepared a biocompatible PPy ECH utilizing tannic acid as a doping and crosslinking agent [90]. Zhang et al. reported an injectable PEDOT:PSS ECH doped with DBSA that enhances its ionic conductivity due to protonation and the formation of ions on the polymer backbone. Due to its self-healing and flexible nature, it has potential applications in soft bioelectronics [91]. Ding et al. made a heparin-doped PANI-based conductive hydrogel network by crosslinking in the presence of methacrylate. Due to its good conductive and biocompatible nature, it has potential use in drug delivery applications [92].

4. Important properties of ECH for controlled and sustained drug delivery

Recently, ECHs have found various applications in drug delivery. It may be an in-situ injectable hydrogel, transdermal patch, or microneedle-based technique. However, most research is based on implantable or TDD delivery systems. Successful implantation of this system *in vivo* experiments requires fulfilling some essential characteristics like morphology, electrical behaviours, biocompatibility, and mechanical behaviour (Fig. 4). As ECHs are composed of two distinct components, assessing individual components and their synergy is essential. The description highlights the important properties that need consideration to render ECHs suitable for drug delivery applications.

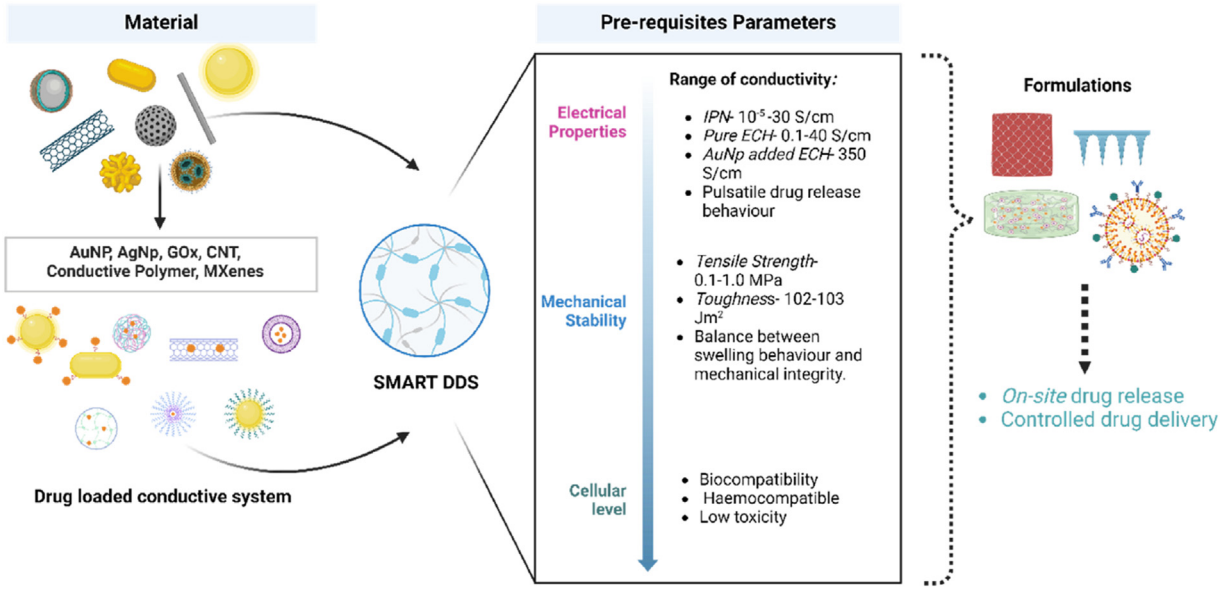

Fig. 4 – Properties of ECH for drug delivery application in brief. Materials used in ECH and different DDS (*e.g.*, microneedles, patches, particles, injectable hydrogels, etc.) with optimal pre-requisite parameters.

4.1. *Electrochemical properties*

The primary rationale behind using ECH in drug delivery is its capacity for the pulsatile release of actives in an electric field [93]. It is due to the delocalization of conjugated π backbone present in their structure that facilitates the formation of a conductive pathway for electron transportation [94]. In addition, the further addition of ionic dopants leads to oxidation and reduction of CP chains that create a microporous pathway that promotes ion diffusion [95]. Conductivity can be induced by either electronic or ionic means [96]. The former is developed by adding CPs, metals, CNTs and GO, and the latter by adding ionic salts and liquids [97,98]. Electronic conductivity happens due to the electronic tunnelling effect, in which the conductive path and resistance change after deformation [99]. Ionic conductivity entirely relies on the presence of ions that move in their respective electrode upon application of an electric field depending on the area and length of the conducting path, which causes the change of resistance and conductivity simultaneously [100]. Recently, double network hydrogels in the form of interpenetrating polymer networks (IPN) have caught the attention of researchers because of their high toughness, elasticity, and customized chemical functionality. They consist of one densely crosslinked, highly elastic, and rigid network and another network is sparsely crosslinked, facilitating covalent or non-covalent bonding between them [101]. High conductivity in the range of 10−5 S/cm to 30 S/cm (in case of IPN) and 0.1 S/cm to 40 S/cm (pure ECHs) are desirable in any drug delivery devices as this causes no harm in surrounding tissue [100]. Researchers prepared a CNTs/SA/PAA ECH through Ca^{2+} gelation, exhibiting significantly high conductivity (22.5 S/cm) [100]. PVA/CNT/graphene ECH has been developed to show superior mechanical properties because of forming an 'island bridge structure', a conductive network structure formed by graphene and CNTs [102]. The network structure shows a reversible formation when stress is applied. Upon the application of stresses, the separated 'island' and 'bridge' units increase the resistance and recover again when they get removed.

One of the valuable strategies to improve the conductivity of ECHs is the addition of metal ions. However, modifying the surface with hydrophilic groups is necessary to achieve the desired dispersion and conductivity, as they tend to aggregate and influence conductive and mechanical properties [103]. Ag-PAM/SA ECHs were prepared to have a conductivity of >350 S/ cm because of the reduction of spacing between Ag flakes due to partial localized dehydration [102]. Recently, researchers widely used CPs to prepare ECHs. Some examples are PDA-doped PPy nanofibers in PAM hydrogels, PA-doped PANI network, and PEDOT:PSS ECHs [104,105]. Researchers also synthesized $FeCl_3$ crosslinked P(AM-co-AA) ECHs, exhibiting an ionic conductivity of 0.31 S/m at room temperature and 0.01 S/m at −20 °C, along with a healing efficiency of 98.7 % [106]. CV and electrochemical impedance spectroscopy (EIS) characterize the ECHs. CV measures the reversible electroactivity of an ECH in terms of oxidation and reduction cycles. The charge storage capacity (CSC) of the ECHs can be determined by measuring the height of redox peaks obtained from the CV cycle. It involves measuring the total availability of charge from the peak of the current *vs.* time curve [106]. The more the CSC of the ECH, the more drug release can occur more efficiently and in a controlled way. Kim et al. compared the CSC value of Alg/PPy hybrid and PPy-polystyrene sulfonate (PPy/PSS) and found the former has a three times higher CSC value [107].

Similarly, Cui et al. developed PEDOT NTs-Alg-based drug delivery devices and observed a significant increase in the CSC compared to PEDOT nanotubes. This is because of the

increase in surface area due to hydrogel coating on electrodes, which thus increases the CSC of CP-coated electrodes [108]. Kleber et al showed that the PDMAAP/PEDOT ECHs exhibit 2.5 times more CSC values than the conventional hydrogels, along with electrical and mechanical stability, even after 1000 CV cycles [109]. EIS measures the charge transfer across various frequencies determined from the Bode or Nyquist plot. For drug delivery from ECHs, the impedance is measured at the electric field frequency that triggers the drug release without affecting its electrical and mechanical stability [110]. The long-term electrical stability of ECH at a particular frequency can be derived from the impedance values. Several reports have been published encompassing the coating of conducting polymers, which increases the electrochemical surface area of the electrode and decreases the impedance values. PPy/PSS grown in an Alg scaffold exhibited a much lower impedance of 7 KΩ compared to 120 KΩ for PPY/PSS film, as the former has a higher surface area than the latter [107].

4.2. *Biochemical properties*

The biological properties of ECH crucial for biomedical applications are antibacterial, hemostatic properties, and stimuli-responsiveness. The strategy for the preparation of antibacterial hydrogels, as per relevant literature, can be broadly classified into two broad areas, *e.g.*, (1) killing bacterial cells by making them interact with the metal ions (*i.e.*, Ag^{+}, $Zn^{2+}$and Cu^{2+}), by applying antibiotics, cationic polymers and metal NPs and (2) adding enzymes to induce antibacterial property within ECHs due to formation of the reactive oxygen species by catalytic reaction, and adding charged polymers as one of the components [111]. Guo et al. developed several polysaccharide-based conductive, antibacterial hydrogels with several properties, including photothermal responsiveness, adhesion, antioxidant, and self-healing abilities that have excellent potential in the biomedical fields, *i.e.*, tissue engineering, drug release, and wound healing [112,113]. Li et al. prepared a molybdenum disulfide-polydopamine (MoS_2-PDA) nanozyme composite hydrogel (MPH) by copolymerizing acrylamide, N-isopropyl acrylamide, acryloyl Ppluronic 127 and MoS2-PDA that has both adhesive and antibacterial properties [114]. They developed four different types of hydrogels, namely hydrogels without functional components (H), hydrogels with MoS_2 added (MH), hydrogels with PDA added (pH), and hydrogels with MoS_2-PDA added (MPH). Quantitative evaluations of the antibacterial efficacy of these hydrogels against *E. coli* and *S. aureus* were made both in the presence and absence of NIR. These findings demonstrated that the synthetic MPH severely negatively impacts *S. aureus* and *E. coli*. Using quaternized chitosan-g-polyaniline (QCSP), Zhao et al. created a quaternized chitosan-based conductive hydrogel for wound dressings with excellent *in situ* antibacterial activity even in non-acid conditions [115].

It has enhanced cutaneous wound healing through endogenous and exogenous antibacterial mechanisms due to the addition of AgNPs [116–118]. The addition of cationic polymers, anion, metal, silicon-based compounds and polyphenols to the structure of conductive hydrogels may improve the haemostasis effect by sealing the wound and absorbing the wound extracts, thus enhancing the coagulation factors [93]. Conductive hydrogels made of gelatin had an effective haemostatic activity. In the work of Han et al. created a GelDA/GO ECH using the horseradish peroxidase catalytic system where dopamine-grafted gelatin (GelDA) was poured with a mixture of 1,4-phenylenebisboronic acid and GO. Applying this to the rat hepatic haemorrhage model demonstrated outstanding tissue adhesion and haemostatic characteristics [118]. The stimulation-responsive hydrogels can release the actives due to changes in size or shape under various external stimuli like electric field, magnetic field, pH, temperature, glucose and light. After adjusting the pH of ECH, it showed the release of amoxicillin from its capsules. The study also revealed how applying an electrical field might release hydrophobic ibuprofen and hydrophilic amoxicillin [54].

For successful *in vivo* implantation, the ECHs should be biocompatible. Different ECHs have been reported for drug delivery applications, demonstrating the biocompatibility of the ECHs hybrids. Kim and coauthors reported the *in vivo* biocompatibility of PEDOT/Alg hybrids. When loaded with brain derived neurotrophic factor, it showed a non-cytotoxicity and anti-inflammatory response that makes it suitable for *in vivo* and *in vitro* experiments in drug delivery applications [94].

4.3. *Mechanical properties*

Highly tough hydrogels with tensile stress ranging from 0.1 to 1.0 MPa and fracture energy 102–103 J/m^2 are crucial in various biomedical applications [119–121]. ECH having superior mechanical properties resembling tissue-like structures minimize the discrepancies between tissue and hydrogel. Therefore, it reduces inflammatory responses. Conventional hydrogels follow no pathways to dissipate energy effectively and thus have inferior mechanical properties, including low stretchability. Thus, developing mechanically robust ECH remains a significant challenge [121]. Researchers have developed a strategy to increase the strength of hydrogels by forming dual network hydrogels with covalent and non-covalent interactions, forming slip ring structures. Adding ions and crosslinking agents further improves mechanical properties by forming dense crosslink structures that help dissipate energy along the networks [123,124]. They are typically composed of two networks; one is brittle, and the other is ductile. After interlocking, they form a network structure that improves the mechanical characteristics of the ECHs and opens avenues for effective energy dissipation [124]. Sun et al. developed a synergetic network hydrogel using PAAm and PEDOT: PSS, providing an ultra-wide sensing range for ECHs [124]. Dynamic bonds, such as hydrogen bonds, act as reversible “sacrificial bonds” for energy dissipation. After stretching, they are likely to break, guaranteeing a quick recovery to their initial forms. Through fine-tuning between PEDOT and other polymers, Xu et al. created a polysaccharide-based ECH that enhances mechanical behaviour [99]. Zhi et al. prepared double IPN hydrogel with superior toughness and efficient energy dissipation capacity, superior tensile modulus, fracture energy, and shape retention

behaviour compared with PAAm and Alg/PAAm hydrogel [122].

The mechanical properties of ECHs were also varied with the swelling ratio of the hydrophilic hydrogel networks [124]. Swelling leads to a change in the pore size that influences the loading of actives, diffusion of drug molecules, and interaction with the surrounding tissues [125]. Resistance to swelling is crucial for conductive hydrogels, as it prevents conductive fillers from diffraction, causing degradation of electrical properties and structural deformation [126]. Researchers construct anti-swelling hydrogels by combining a rigid polymer meshwork, protonating zwitterionic polymers, and making superhydrophobic modifications to the hydrogels [127]. Excellent swelling resistance is achieved using a hydrogel electrode made from acrylate copolymer having amphiphilic characteristics filled with choline-based bio-ionic liquid (BL) [125]. The hydrophobic part repels the aqueous media, prevents the conducting ions diffused out from ECH, and enables stable conducting properties. It also shows excellent adhesion properties due to non-covalent interactions between a hydrophilic portion of the exposed substrate and functional groups of BL and TA. In addition, modified PAA in the presence of dodecyl methacrylate (LMA) and surfactant cetyltrimethylammonium bromide (CTAB) shows superior anti-swelling behaviour due to the electrostatic interactions between CTAB and P(AA-co-LMA) [126]. The hydrophobic contact causes the polymer chains to constrict and agglomerate, giving the hydrogel considerable swelling resistance. The formed gel maintains its integrity even at 25 °C for 15 d However, it starts to swell around 60 % and 150 % when exposed at temperatures of 45 °C and 65 °C, respectively, due to the faster dissociation of interactions between the polymer chains.

During swelling, the network relaxation and volume expansion due to solvation get counter-balanced by the effect of elasticity of the polymer chains between the crosslinked points and helps to maintain a swelling equilibrium. To retain the anti-swelling feature of hydrogels, it is therefore advantageous to restrict the relaxation of molecular chains by forming a high crosslink density [128]. For example, gelatine methacrylate/acryloyl-β-cyclodextrin and reduced graphene oxide composite hydrogels have modest swelling properties because of their high crosslink density, which is greatly influenced by the host-guest interaction of the aromatic moieties. In the meantime, with the increase of rGO levels, the crosslink density also increases, decreasing the hydrogel's pore size, which alters the hydrogel's swelling characteristics [126]. Excellent anti-swelling capabilities can be found in an IPN hydrogel created using a cartilage-inspired method. In comparison to hydrogels not impregnated with $FeCl_3$, the HP(AM/AA)-CS Fe^{3+} hydrogel shows a highly dense crosslinked network formed due to the presence of Fe^{3+} ions that form crosslinks when react physically with functional groups present in CS and AA exhibits outstanding anti-swelling type capabilities [100].

While unrestricted crosslinking may cause ECH to lose electrical sensitivity, more hydrophobicity can make them brittle [128]. Managing swelling behaviour while maintaining mechanical properties and electrical conductivity has been a challenge till now.

5. Drug delivery through ECH

Depending upon the application, drug delivery devices can be fabricated in many ways, like ECH patches for transdermal delivery, electrically stimulated on-site DDS, and coatings on electrodes for neural implants are some of the examples [129]. The release of drugs mainly depends upon the charges present on the CP component. When an electrical stimulus is applied, the charges change their respective position, causing the alteration of pore size and volume of the IPN structure, resulting in the release of the drug. Additionally, the polymer structure, CP concentration, drug content, the interaction between drug and polymer chains, polymer-polymer interaction, and degree of crosslinking have also influenced it [130]. The following subsections discuss various DDS based on ECHs (Table 2).

5.1. *Electrically stimulated on-site drug delivery*

ECHs can release various kinds of actives like anti-inflammatory drugs, antibiotics, and anti-cancerous drugs using active and passive targeting. Due to the leaky vasculature and inadequate lymphatic drainage of the tumour microenvironment, the enhanced permeability and retention (EPR) effect plays an essential role in passive targeting. As an alternative, active targeting uses conjugated ligands (such as peptides or antibodies) to the surface of NPsthat bind and recognize tumour tissue by way of overexpressed cellular surface receptors on the tumour cells (Fig. 5). Numerous ligands have shown improved intracellular accumulation, increased accumulation in the tumour microenvironment, and increased therapeutic potency. These include aptamers, transferrin, folic acid, DNA oligonucleotides with receptor-binding capabilities, and antibody therapies.

Perez-Martinez et al. reported a unique strategy to incorporate the drug into PANI fibres and then reinforce it into PAAM hydrogels to form an IPN. The application of a negative potential in a range of −3 to −5 V, the hydrogels contract and result in the release of the drug. The release of the drug depends upon its loading and redox states of the conducting polymers [131]. Lira et al. reported a semi-IPN PAAM/PANI hydrogel. They showed the release of different types of drugs, *e.g.*, a cationic drug, safranin, an anionic drug, pyrocatechol and a neutral drug- tetracycline. The hydrogel network showed the release of drugs depending upon the potential. When it shifts from a negative to a positive potential (−0.2 V, +0.4 V and +0.6 V), the hydrogel transitions from a reduced to semi-oxidized state to an oxidized state. The release of the drug increased from 0.035 to 0.045 and 0.052 µmol, respectively [132]. Kleber et al. reported pulsatile release of anionic actives like dexamethasone (Dex) and fluorescein from PDMAAP/PEDOT hydrogel networks. The release of drugs depends upon the interaction between the components. When a negative potential of −0.5 V was applied for 60 s, it showed a burst release, but if performed under CV sweeps, it showed a sustained and stepwise release pattern [133].

Niu et al. reported TMH@Gel ECH, which has temperature and NIR-II sensitivity, displayed enhanced antibacterial

Table 2 – Recent advancements in electrically conductive hydrogel for on-demand drug delivery.

ECH	Preparation Techniques	Drug loading method	Inferences	Ref.
Collagen-PANI	*In situ* Polymerization	Passive loading of hydrocortisone by diffusion through pores	Co-polymerization with PCL increases thermal stability and Young's Modulus, uniform pore size distribution volume conductivity of 1.1×10^{-3} mS/cm stepwise drug release pattern varied from 60 % to 90 % in the range of 1.5 V to 3 V.	[35–37]
PAAM-PPV	*In situ* polymerization	Salicylic acid doped PPV added in PAAm hydrogel	The release of drug depends upon crosslink density, pore size, electric field and drug size.	[159]
PAAM- PANI	Co-polymerization	Passive loading of safranin	Drug release from the semi IPN structure is higher in open circuit potential condition and in oxidized (0.4 V and 0.6 V) form of hydrogel compared to its reduced form (−0.1 V and −0.2 V).	[163]
PAAM-PANI-APS	*In situ* polymerization	Amoxicillin loaded PANI added into hydrogel precursor	Diffusion led burst drug release due to erosion of hydrogel in the presence of potential of –3 to –5 V, random distribution of nanofibers,	[164]
PEG-PEDOT	Electrochemical polymerization	Single emulsion method with simultaneous polymerization of ECH.	Increased physiochemical adhesion, decreased impedance with increased CDC, long term biocompatibility.	[131]
GelMA-PEDOT-PSS	*In situ* polymerization	Passively loaded 5-fluorourocil by diffusion that occupies the pores, when mixed with hydrogel.	Conductivity increased from 6.1×10^{-3} to1×10^{-2} S/cm with increase of CP (1 to 1.5 wt%), cell proliferation of L929 cells was good without any toxic effects, drug releases by deswelling of ECH and increased from 18.2 % to 23.3 % upon application of 1.5 V to GelMA-PEDOT/PSS	[165]
PDMAA PEDOT: PSS	Electrochemical polymerization	Actively loaded Dex and fluorescein (F) were added during electro polymerization of CP component.	Passive release of F at 0.6 V potential and shows a burst release with a slow release for 28 d and during active release at −0.5 V for 60 s resulted in 133.0 ± 5.4 mg of F release. The release of Dex was higher in the case of microspheres than from coatings.	[133]
PVA-PEDOT: PSS	*In situ* polymerization	Passively loaded NGF by diffusion that occupies the pores, when mixed with hydrogel	When ECH functionalized with sericin it got uniform nodularity and higher CSC compared to when gelatin modification results in larger nodular size, increased cell proliferation in BaF3cells, nitrite growth is higher in drug loaded cells.	[166]
Fe^{3+}PAAM/chitosan-PPy	Co-polymerization	Dex doped into PPy chains forming electrostatic interactions	Fracture energy 12,000 J/m^2 and compression modulus 136.3 MPa, high conductivity of 0.3 S/m due to formation of a conductive path formed by IPN network.	[167]

effects against Gram-positive and Gram-negative bacteria due to photothermal and chemodynamic therapy synergistically [134]. Ganguly et al. synthesized pH and electrically responsive BIS crosslinked PAA-graphene ECH that showed enhanced rubber-like elastic behaviour with excellent biocompatibility and efficient cell adhesion properties [135]. Mongkolkitikul et al. reported a poly(3-methoxydiphenylamine)/pectin ECH crosslinked by $FeCl_2$ and citric acid. The release of ibuprofen from the ECH follows the following four models: Fickian diffusion, Anomalous transport, Case-II transport and Super case II transport. When the electric field of 5 V was applied, the system showed a two-fold increase in release rate due to electrostatic repulsion between the electrode and ibuprofen and owing to the increase of the mesh size [136]. Moreover, Cheah et al. synthesized GelMA/ PEDOT/para-toluene sulfonate (pTS) ECH for the delivery of bovine serum albumin (BSA). The research demonstrated a notable increase in BSA release when a voltage of −0.6 V was applied for over 200 min. Moreover, a 21-d release profile revealed that alternating the voltage between ±0.6 V at a frequency of 0.1 Hz for one h per d significantly influenced the release rate compared to passive release. The cell viability analysis showed excellent cytocompatibility effects with PEDOT/pTS [137,138]. Furthermore, Puiggali-Jou et al. studied the potential of stimuli-responsive DDS to deliver curcumin (CUR), a hydrophobic drug. Without electrical stimulation, the release of CUR was slow and minimal (3 %) due to the hydrophobic nature of the drug and its bonding with the matrix. However, 25 % of CUR was released within 2 h in the presence of the electric field. Electrochemical stimulation involved applying

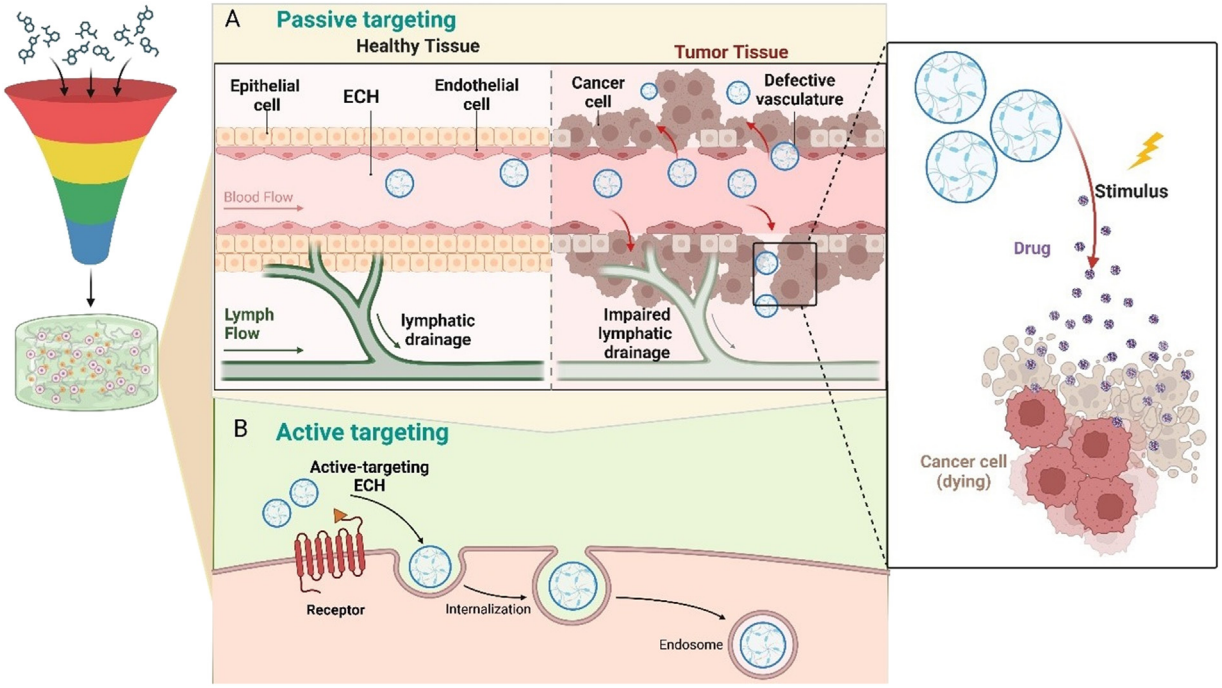

Fig. 5 – Schematic representation of electrically stimulated on-site drug release mechanism in cancer cells through ECH. Targeting of cancer cells by (A) passive and (B) active ways and release of drug in the presence of tumor microenvironment.

voltage of +1.0 or −1.0 V for 2 h to PEDOT/Alg and Alg. After 1 h stimulation, the release of CUR from PEDOT/Alg and Alg was 3.6 % ± 1.0 % and 7.1 % ± 1.0 %, respectively [139]. The limited drug release was attributed to CUR's hydrophobicity. So, the release medium was switched to ethanol, resulting in an increased release of CUR from PEDOT/Alg and Alg to 12.9 % ± 1.7 % and 9.1 % ± 1.4 %, respectively. Negative voltage-controlled drug release exhibited higher levels compared to positive or passive release mechanisms.

The primary limitation of using PPy in ECH fabrication is its limited capacity for carrying drugs. Bansal et al. [140] developed a conducting polymer hydrogel comprising GelMA and PPy to address the issue. Biocompatibility study was done on undifferentiated human neuroblastoma cell line (SH-SY5Y), neurons revealed that exposure to the extract for 24 h had minimal impact on cell viability, with average viabilities of 94.3 % ± 2.94 %, 91.7 % ± 6.27 %, and 90.0 % ± 3.73 % for GelMA/Glu, PPy/Glu and GelMA/PPy/Glu, respectively, compared to the control group's viability of 95.4 % ± 4.90 %. The CSC and electrochemical stability of the system were studied by CV. Glutamate (Glu), an anionic drug, was loaded into GelMA/PPy and PPy through electropolymerization at +0.9 V. PPy, in its oxidized state, due to constant oxidizing potential, formed electrostatic interactions with negatively charged Glu. The porous network of GelMA/PPy/Glu facilitated higher drug loading. Both systems were applied to a gold electrode (1 cm^2) to assess passive and active drug release profiles. Without stimulation, Glu release from GelMA/PPy/Glu, PPy/Glu, and GelMA hydrogel was 25.0 ± 6.82 µg, 7.2 ± 1.59 µg, and 2.1 ± 0.53 µg, respectively. GelMA/PPy/Glu exhibited a 14-fold increase in Glu release compared to conventional PPy/Glu films. Electrical stimulation (−0.6 V) resulted in a fivefold increase in Glu release compared to passive release. Application of constant CV sweeps yielded a total Glu release of 20.7 ± 5.50 µg over 4 h, with no significant difference observed between different types of electrical stimulation (CV ± 0.6 V at 100 mV/s and constant oxidation at +0.6 V). However, constant reduction potential at −0.6 V increased Glu release from GelMA/PPy/Glu compared to PPy/Glu (106.8 ± 7.48 µg *vs.* 7.20 ± 1.59 µg). The study also showed that reduction-driven drug release was six times higher than oxidation and five times higher than unstimulated release, indicating that negatively charged molecules exhibit increased release under negative potential due to electrostatic repulsion forces. Conversely, positive potential promotes electrostatic attraction between the anionic drug and CP chain, potentially driving drug release through diffusion.

Researchers have explored Hhyaluronic acid-based hydrogels with PANI or rGO to fabricate ECH [142]. Interestingly, combining PANI and rGO showed a synergistic effect, increasing conductivity by one order of magnitude to 10^{-5} S/cm. Moreover, sustained voltage over 140 min enhanced cumulative ibuprofen release, with release percentages of 35 %, 60 % and 86 % for 0, 1 and 3 V, respectively [58]. Sun et al. developed an ECH hybrid film (D@G/P-CD) made of PEDOT and dopamine-graft-chitosan (CD) for controlled drug release and delivering external electrical signals to neuronal cells. GO nanocomposites were initially loaded with the neuroprotective drug 7,8-dihydroxyflavone (7,8-DHF) through π-π stacking. Subsequently, the drug-loaded nanocomposites were deposited within a PEDOT film. The film was coated with CD to enhance biocompatibility. This hybrid system effectively delivered signals, including electrical and

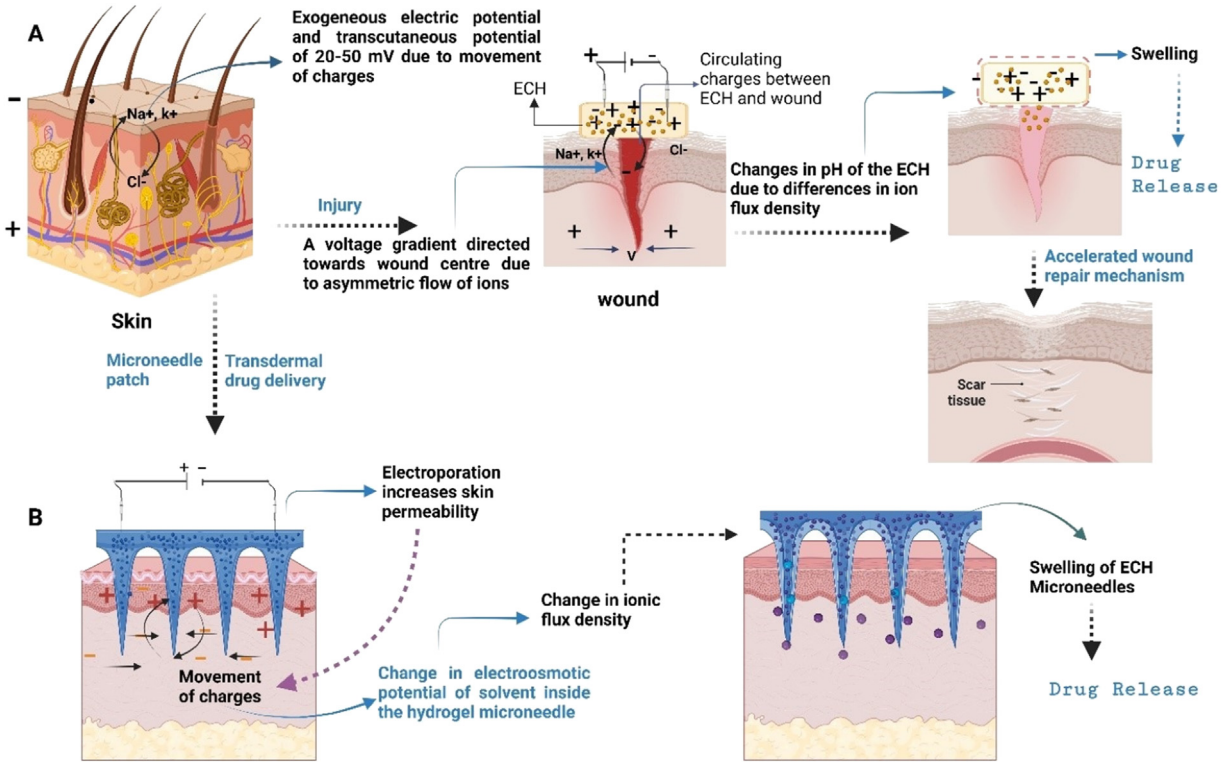

Fig. 6 – Schematic illustration of transdermal drug delivery mechanism through ECH (A) transdermal patch; (B) microneedles.

nano topographical signals via GO and the drug, to neural cells. This resulted in neuronal mitochondrial biogenesis, confirmed through immunofluorescence staining and gene expression analysis. Despite the potentially damaging effects of extreme electrical stimulation on conductive films, such as delamination and cracking, the D@G/P-CD film maintained its structural integrity even after 200 release stimulations [143].

5.2. *Transdermal delivery system*

The first experiment regarding the development of a transdermal drug delivery system started in the 1970s, but it was in the 1980s when, finally, the technology was commercialized. Transdermal delivery of actives means delivery through the skin and directly introducing it into the blood circulation system (Fig. 6). It has several advantages as it does not require passing through the harsh environment of the intestine and hepatic cells and easily bypasses their first-pass effect.

The transdermal delivery system also improves the stabilization and durability of active drugs in blood and improves patients' compliance. However, the lipophilic nature and compact construction of cells in the skin make it challenging to deliver macromolecules like peptides and proteins [145,146]. Therefore, researchers have been trying to enhance its performance by various means. Hasan and co-authors reported the binding of liposomes by iontophoresis, in which the applied electric field induces penetration by promoting endocytosis and disturbing the compactness of the cells. Oktay and co-authors reported on a transdermal drug delivery system composed of GelMA and PEDOT: PSS. They showed the release of 5-fluorouracil, the most common topical agent used to cure superficial basal cell carcinoma.

5.2.1. *Transdermal patches (TP)*

TP delivers the drug by iontophoresis, electro-thermal effect, and electroporation. The characteristics important for delivery through patches are the peeling effect, adhesion, and structure. Iontophoresis facilitates the delivery of ionic and polar molecules through the skin in a non-invasive way [146]. Applying an electrical stimulus of <0.5 mA/cm^2 current density improves the migration of the macromolecules instead of increasing the permeation without causing any physiological harm. The main issue regarding delivery by patches is the composition of the first layer of skin, stratum corneum (SC). It is the most insulating layer, having a degree of hydration of around 15 %, and consists of sweat glands, hair follicles, and sebaceous glands [147]. Every component contributes to drug delivery in the presence of an electric field (Fig. 6A).

A group of researchers reported the transdermal delivery of 8-arginine vasopressin. They compared the penetration of actives through follicles and sweat glands in human skin with animal skin having compact SC. They reported that the mediation of actives in the former is far greater than in the latter, proving that the former has inferior electrical resistance. The macromolecules having a size of <100 nm can mediate the compactness and rigidity of SC. Otherwise, the electrical stimuli activate the trans-appendageal pathway through follicles and glands on the

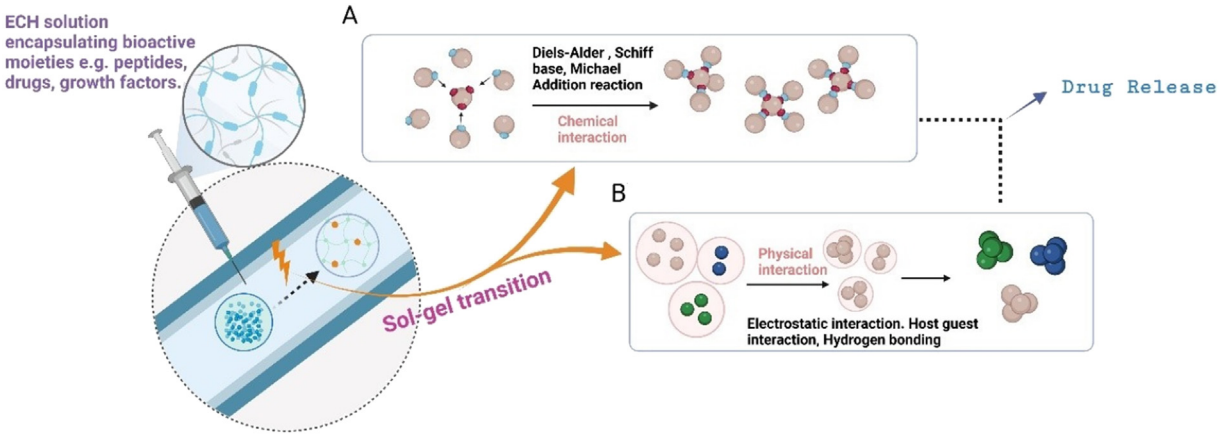

Fig. 7 – Schematic illustration of the formation of *in situ* injectable hydrogels by (A) chemical interactions and (B) physical interactions triggered by electrical stimulus.

skin, providing an alternate route for transdermal delivery. The trans appendageal delivery can deliver the drug into the hypodermal region of the skin as it uses the long-interconnected channel of follicles and glands [148].

Electro-thermal DDS can change the shape and volume of the ECH and release the drug from the system that is thermo-sensitive [149]. Bagherifard et al. reported a transdermal patch in which the PNIPAM microparticles, prepared by microfluidic technique, were incorporated into Ca-Alg hydrogel, and micropatterned gold heating elements were placed on it. The system has a potential application in wound healing as it can deliver various drugs and growth factors in the presence of electric field-driven heating [150].

In electroporation, a high-energy electric field enhances the cell membrane permeability to absorb the actives. This technology has been explored the most because of reversible pore formation and less damage to the surrounding tissues. The lipophilic nature of the skin allows the diffusion of hydrophobic drugs by adjusting the diffusion rate with the applied electric field [151]. Wei et al. reported a TP for the delivery of nucleic acids by electroporation. The patch was prepared by placing gold electrodes closely on the perylene substrate. The nanomachine can deliver the actives deep into the skin layers and help in cancer silencing when applied in a mice mode [152]. Zhao et al. reported that phosphate solutions and PEG-based ionic circuits can be achieved using the iontophoresis principle to deliver micro and nanoparticles. It can safely deliver the nano and microparticles when a high electric field of 87 mA/cm^2 is applied to the eyes without causing any damage [153].

5.2.2. *Microneedles (MNs)*

Microneedle conductive patch (MCP) is one of the transdermal DDS systems that has caught the attention of many researchers recently (Fig. 6B). A microneedle is a set of many microprojections supported by a base with a millimeter length and micrometer diameters [154]. They have some unique advantages that make them different from others, like non-invasive techniques, the delivery of drugs to any layer of skin where patients feel no pain, and easy-to-take activities in proper time. It was first proposed by Gerstel and Plac in 1971. Since then, it has been modified several times. Researchers have reported the combination of microneedles with ECH and its working principles, which include iontophoresis and electroporation [155]. Jeong et al. reported polyvinylpyrrolidone (PVP)-based MCP crosslinked by gamma rays. Then, PVP- polysaccharide (PVPS) blended GO is used to induce the release of the drug through electrical stimulation. This MCP has effective mechanical properties (rigidity, toughness) when it enters the skin. By applying the electrical field of 5 V, the release of the drug increases by twofold in comparison with PVPS alone [156]. Bok et al. reported a dual-responsive MCP of hyaluronic acid (HA) that releases the drug quickly due to the synergistic effect of ultrasound and iontophoresis [157]. Yang et al. developed innovative patches for electrically controlled and on-demand transdermal drug delivery to enhance drug penetration through the skin barrier. This system comprises conductive (MNs) and a two-electrode microneedle patch (t-EMNP). Two types of MNs were fabricated using polylactic acid platinum (PLA-Pt) and polylactic acid platinum PPy (PLA-Pt-PPy) [158]. The model drug, fluorescein, was loaded onto the MNs through polymerization, with drug loading influenced by both the polymerization time and fluorescein concentration. Longer polymerization times (1, 2 and 3 h) increased drug loading due to thicker PPy film formation; however, excessively thick films hindered MN penetration into the skin. Fluorescein concentration also affected drug loading, with higher concentrations leading to more significant drug deposition on the MNs. Drug release studies used an electrochemical workstation with a three-electrode system and phosphate-buffered saline (PBS) as the working solution. Electrical stimulation-controlled fluorescein release, altering release rates by varying applied potentials. The initial rapid release was followed by an equilibrium state, with approximately 80 %–90 % of the drug released under electrical stimulation and 10 %–20 % released by diffusion alone. Adjusting the applied voltage influenced drug release efficiency, with higher release observed at −1.5 V due to increased charge transfer and reduction of

Table 3 – Recent advancements in electrically conductive injectable hydrogel for biomedical application.

Injectable ECH	Preparation Mechanism	Crosslinking method	Inferences	Ref.
Cationic Guar Gum-PEDOT: PSS	*In situ* polymerization	Electrostatic interaction, hydrogen bonding	Injectable and self-healable ECH with conductivity of 0.22 S/m and cell viability of 100 % with excellent wound healing characteristics.	[168]
PEDOT:S-Alg-Ad and Poly β-cyclodextrin	Post polymerization	Host-guest interaction and $\pi-\pi$ stacking	ECH shows conductivity of 0.16 S/cm with self-healable and stiffness of 100–3,000 Pa and cell viability of 90 %	[169]
PEDOT: heparin and Aldehyde HA, GC	*In situ* polymerization	Schiff base reaction, electrostatic interaction	Excellent self-healing, cell adhesion, biocompatible with conductivity of 2.7 S/cm	[170]
DA-PPy andGeIDA	Post polymerization	Catechol-Fe^{3+} coordination	ECH shows good adhesive strength and conductivity of 2.85×10^4 S/cm	[171]
PMNT/PIC	Composite strategy	π-π stacking, hydrogen bonding	Thermal reversibility and biocompatibility, photodynamic antimicrobial activity	[172]
PDA@Ag NPs, PANI, and PVA self-assembly	Composite strategy	Boronic acid esterification	Enhanced and controlled mechanical and conductive properties, easy processability, good self-healing ability as well as good adhesiveness with adhesive strength of 29 kPa	[173]

the PPy backbone. On-off testing demonstrated minimal drug release without electrical stimulation and linear release profiles when stimulation was applied. The system exhibited superior electrochemical and mechanical properties with high drug-loading capacity. Further, researchers incorporated glucocorticoids into these electrically conductive MN patches for atopic dermatitis, and results showed a significant reduction in inflammatory cell infiltration and inflammatory factors [159,160].

5.3. *Injectable hydrogels*

Injectable hydrogels are formed by *in situ* gelation using the physiological environment inside the human body. It is the most efficient and non-invasive way to deliver the drug directly into our blood (Fig. 7). To date, very few studies have reported drug delivery using injectable conductive hydrogels [144]. Qu et al. introduced an OD crosslinked chitosan-PANI ECH that releases a hydrophilic drug-amoxicillin, and a hydrophobic drug-ibuprofen, in the presence of an electric field at a suitable pH. They showed that gelation time varies inversely with the increase in OD concentration. The release of amoxicillin increases from 69 % to 82 % by varying potential from 1 to 3 V within 60 min compared to 34 % release in 140 min in the absence of electric stimuli. However, ibuprofen released around 35 % in 140 min in the presence of an electric field of 3 V compared to 15 % released in the absence of an electric field [102]. The electric field-driven drug release can be related to ions' movement in oxidized or reduced ECH networks. Various ECH-based injectable hydrogels and their applications have been discussed in Table 3.

6. Conclusion and future prospects

The above discussion illustrates that conductive polymer hydrogels can generate various release patterns by adjusting the voltage stimuli, including pulsatile and delayed release. This offers the potential for real-time modulation of drug release after administration, thus allowing for dose adjustment according to the patient's requirements. While this technology is still in its early stages, several different DDS have been investigated, such as TP, injectables and transcranialmethods. These systems exhibit desirable traits, including continuous delivery, biodegradability, compatibility with a wide range of drugs, and versatile preparation methods, which collectively show promise. Stimuli-responsive materials, including ECHs, are garnering increasing attention in research and have been shown to offer improved precision compared to non-responsive counterparts. Examples such as pH- and thermoresponsive polymers utilize the body's physiological conditions to release drugs in response to specific external stimuli. However, fluctuations in the microenvironment due to disease states can lead to unintended off-target release. Additionally, careful control of storage conditions is necessary for thermoresponsive polymers to prevent premature degradation. In contrast, the release mechanism of voltage-responsive polymers is more resilient to changes in the microenvironment.

Nowadays, most of the ECH is prepared by combining the properties of a conventional polymer hydrogel and a conducting material like conducting polymer or conducting fillers so that the electric responsiveness can induce the conventional hydrogel. Despite many biomedical applications like tissue engineering, wound healing, and biosensors, the application of ECH in drug delivery still needs to be improved. Although started a long ago, several problems, such- as a high amount of drug encapsulation, on-site drug release without affecting other organs, especially hepatic tissues, highly controlled drug release, and *in vivo* study, long-term release with good mechanical and self-healing properties, still need to be solved.

Most of the literature has reported short-term delivery of actives. However, several diseases require long-term medication therapy, even for a few months. Therefore, researchers have reported the release of drugs from implantable drug-loaded devices. ECH should be appropriately tuned to deliver the drug on-site and with proper dosage for a very long time. For implanted bioelectronics, prolonged *in vivo* treatments pose a significant challenge for conductive

hydrogels, potentially leading to the leakage of salts or electrolytes, compromising their conductivity, and posing risks to human organs. Moreover, the body's immune response to foreign materials must be noticed. Therefore, there is an urgent need for biocompatible conductive hydrogels focused on developing bioabsorbable or highly effective biodegradable materials. Incorporating biodegradable components into conductive hydrogel systems represents a promising approach, aiming to minimize postoperative complications and facilitate broader clinical use. Most studies have reported the *in vitro* study of the ECH, but it is required to perform an *in vivo* test before its clinical trial. The tests should be conducted in proper psychological conditions, with an electrical voltage of −0.6 V to +0.8 V, as it does not cause any harm or alter the psychological environment. However, the choice of a proper ECH material is application-specific. Mechanical properties like toughness and flexibility are a prior concern for tissue engineering applications.

Likewise, biocompatibility is a significant concern for drug delivery applications as most of the conducting polymers are not biodegradable. After the degradation of the other part, they choose the way of renal clearance. Therefore, the excretion pathways of these conducting parts of ECH should be appropriately investigated. However, the efficacy of electrical stimulation in promoting cellular growth and enhancing on-site drug delivery has been established. However, the outcomes can vary unpredictably, depending on the intensity and frequency of the stimulation. Given the lack of clear standards for electrical stimulation parameters such as intensity, frequency, and duration, it is crucial to address the standardization of electrical stimulation protocols to minimize the effects of electric fields or currents on cells and tissues. Currently, the available ECH formulations are compatible with the loading of positively charged actives, and further investigation is needed to confirm their compatibility with neutrally charged drugs. Such research would significantly broaden their clinical applications. Similarly, more research is needed to expand their drug loading capacity, as achieving high drug loading (>90 %, w/w) remains a challenge. Moreover, the integration of DDS with wearable medical devices is still a challenging task. For example, CPs have been investigated as biosensors for drug monitoring. Researchers are working on integrating the biosensors with the DDS. CPs are extensively studied in other fields like electronic skin grafts, biosensors, tissue engineering, wound healing, etc. However, the application of ECH in DDS is still in the infant stage.

The integration of CPs with other electronics has the potential to facilitate an Internet of Things (IoT) infrastructure in healthcare. IoT enables seamless communication between different products, offering real-time data for enhanced clinical decision-making. CPs can connect healthcare products to electronic devices, aligning with IoT techniques. However, ECHs undoubtedly possess many advantages, like biocompatibility and the capability of delivering hydrophobic and hydrophilic drugs formed in nanosized form that are readily acceptable to pathogens by their passive route. Most of the studies have reported the route of formation of IPN structures, monomer modification, and conducting filler modification for better adhesion that can improve its performance. If the promises can be adequately translated, this can be proved to be an effective stimuli-responsive drug delivery system. Also, clinical studies should be promoted by collaborating with pharmaceutical companies to produce it in bulk by solving its complex chemistry and response behaviour and adopting a facile preparation strategy.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Acknowledgments

SG and NK both contributed equally for the paper, in terms of review, collection of scientific data. We used the Biorender student license (BioRender.com) for the illustrations in this article. We would like to acknowledge the Ministry of Human Resource and Development (MHRD) Government of India for funding.

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