

Review article

Nanomaterial-based scaffolds endowed with halochromic properties for skin healing purposes

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ABSTRACT

Recently, biomedical engineering has seen significant advancements in nanomaterial-based scaffolds for tissue engineering and wound healing. Incorporating halochromic properties within these scaffolds has garnered substantial interest due to their real-time monitoring abilities for accessing tissue growth and regeneration. This review presents a comprehensive analysis of recent advancements in nanomaterial-based scaffolds with halochromic functionalities for skin biomedical applications. This discussion revolves around the various classes of nanomaterials used in scaffold fabrication, including but not limited to electrospun nanomaterials, polymeric nanomaterials (both of natural and synthetic origins), and nanomaterials based on bio-composites, each offering distinct advantages and limitations in terms of mechanical properties, biocompatibility, and tunability of halochromic response. Emphasis is placed on integrating halochromic moieties, such as pH-sensitive dyes, into the scaffold matrices, with a focus on maintaining optimal cytocompatibility and biofunctionality. A key focus is given to recent *in vitro* studies showcasing the potential of halochromic nanomaterial-based scaffolds in clinical applications. The novelty of this study lies in providing a structured framework for understanding the interaction between halochromic nanomaterials and biomedical scaffolds, identifying challenges, and proposing future research directions to enhance their diagnostic and therapeutic potential.

1. Introduction

Nanotechnology is an emerging field of research that deals with synthesizing materials at nanometric scale. Nanomaterials, characterized by their unique physicochemical properties and small size, offer distinctive advantages in the design of biomedical scaffolds, including the ability to circulate along the body without disrupting blood flow and to resist excretion by the renal canal and other complement systems [1, 2]. These materials, ranging from nanoparticles and nanofibers to nanocomposites, provide tailored structural biocompatibility, tolerability and mechanical characteristics that closely mimic the native extracellular matrix [3–5]. This similarity is essential for promoting cellular adhesion, proliferation, and differentiation, generating a microenvironment ideal for tissue regeneration and effective wound healing. They can be applied to various types of scaffolds, such as mats produced by electrospinning, hydrogels, or a combination of both,

known as composites.

Wound management is a crucial part of healthcare, impacting patients' quality of life and placing a financial strain on the healthcare system. The advancement of smart bandages offers significant promise for wound monitoring and precise treatment [6].

The use of nanomaterials in medicine has enabled innovative strategies to enhance diagnostics, treatments, and therapeutics [7]. Exploiting the unique properties of nanomaterials, such as their high surface area to volume ratio and tunable surface chemistry, has enabled the development of smart dressings, targeted drug delivery systems and biosensors with unprecedented precision [8]. Over the last decade, in Europe, the use of nanomaterials in medicine has been on the rise, driven by significant research and development efforts in academia, industry, and government-funded initiatives [2,9]. Smart dressings are an area of application in which nanotechnology has facilitated the development of highly sensitive solutions (devices, new dressings, etc.)

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that can detect low amounts of biomolecules in bodily fluids such as blood and urine, facilitating early detection and disease/wound management with high sensitivity and specificity [9,10].

Chromic properties allied to smart dressings represent an innovative strategy for medical treatments. The ability to visually monitor changes in the scaffold environment and the evolution of regeneration and healing processes opens a new venue for wound treatment strategies [11]. In biomedical applications, chromic nanomaterials can be designed to respond in real-time to specific biological triggers or changes in physiological conditions such as pH, temperature, the presence of microorganisms, and biochemical signals that are essential for preserving health status [12]. pH-responsive nanomaterials, which undergo color changes in acidic or basic environments are commonly found in biological systems (halochromism). The incorporation of halochromic elements into nanomaterial-based scaffolds not only enhances their functionality but also unlocks the potential for innovative diagnostics and therapeutic tools [13]. Future halochromic dressings differ from commercially available ones by their ability to change color in response to pH changes in a wound. This color change can indicate the wound's condition, such as infection or healing progress, providing real-time, non-invasive monitoring. Traditional bandages lack this dynamic feedback capability and only serve as a protective covering without providing information about the wound's state and requiring constant removal of the bandage, often damaging the newly formed tissue and interrupting the healing process [14,15].

This review aims to explore the synergistic relationship between nanomaterial scaffolds and halochromic agents in the context of biomedicine, focusing on the latest developments and applications of these smart scaffolds in the field of skin healing. Additionally, the challenges and future directions in binding the full potential of nanomaterials with halochromic properties for advancing biomedical technologies will be addressed. This review highlights as well the challenges associated with the stability of halochromic species under physiological conditions, emphasizing the importance of tailored surface modifications and encapsulation strategies to mitigate potential cytotoxicity and degradation events. Finally, the potential pathways for future research of these smart nanomaterial-based scaffolds in clinical settings are discussed, seeking to stimulate creative approaches for advancing the design of such constructs to reach improved diagnostic and therapeutic functionalities.

2. Biomedical scaffolds based on nanomaterials

Nanomaterial-based scaffolds have widespread interest in biomedicine due to their ability to replicate the natural environment of body tissues, mimicking the extracellular matrix, and providing structural support and mechanical protection [16]. These scaffolds play an important role in tissue engineering and wound management for repairing, improving, and maintaining tissue formation [17].

In October 2011, the European Commission defined nanomaterials as natural, incidental, or manufactured materials that contain unbound or agglomerate particles, where 50 % or more of the particles, must be between 1 and 100 nm [18]. These materials have innovative physical (large specific surface area, small size) chemical (resistance to corrosion, high reactivity, catalytic ability), and biological properties (biodegradability, biocompatibility, low immunogenicity, etc.), favoring more effective cellular interactions compared with micro and macroscale materials [16,18,19]. The incorporation of nanomaterials into biomedical scaffolds has demonstrated positive effects on cell adhesion, viability, proliferation, and migration, through biochemical, bioelectrical, or biomechanical signals [16,20,21]. Despite the promising potential of these scaffolds, tissue engineering and wound management faces challenges, such as the lack of suitable biomaterials, difficulties in replicating tissue characteristics *in vitro*, and the absence of precise control over the physiological structure of the scaffolds [22].

In the production of biomedical scaffolds based on nanomaterials,

polymers are used and classified according to their origin as natural or synthetic, and according to chemical composition, as organic or inorganic [16,23,24]. Both natural and synthetic polymers have been explored as biocompatible and biodegradable materials for developing of nano-scaffolds. Natural nanomaterials, which come from microorganisms, human tissues, animals, or plant sources, are generally non-toxic but have high costs due to processing and insulation. Also, their properties' reproducibility is limited [24,25].

In turn, synthetic materials, are more easily obtained with the desirable features and their availability is not as limited. However, like natural materials, they may exhibit batch to batch variation or even production costs [24]. Synthetic materials can be categorized as biodegradable (such as polyesters, poly-anhydrides, and poly-phosphoesters) and non-biodegradable (such as polyethylene and polyethylene terephthalate) [24,26,27].

The use of multiple natural and synthetic polymers, or both, is a strategy adopted to provide a variety of physicochemical and biological characteristics, offering mechanical and biochemical support to cells and controlling regeneration [20,26,28].

Naturally-derived biomaterials used in scaffolds have advantages in wound healing, tissue engineering, drug delivery, infectious disease diagnostics, and regenerative medicine [20,29–31]. Based on the specificity of the structural design, it is possible to distinguish several types of scaffolds, including fibrous, hydrogels, microsphere-based systems, acellular, and composite structures [32]. For optimizing three-dimensional (3D) scaffolds, numerous manufacturing techniques have been used, including conventional electrospinning, solvent casting/particle leaching, thermally induced phase separation (TIPS), freeze drying, gas foaming, powder foaming, sol-gel, etc. Innovative rapid prototyping techniques, such as fused deposition modelling, binder jetting technique, stereolithography, inkjet printing, selective laser sintering, laser-assisted bioprinting, metal-based additive manufacturing and direct cell writing, are, through the deposition of overlapping layers, also able to produce nano-scaffolds in 3D [17,33]. Each approach alters the scaffolds' architecture, influencing pore size, structure, interconnectivity, and mechanical properties [32].

In this section, different types of nano-scaffolds are discussed to understand how their properties contribute to the biomedical purpose. Electrospun nanomaterials are highlighted and finally, bio-composite scaffolds are presented as an approach to combining different types of nanomaterials.

2.1. Polymer-sourced nanomaterials

Polymeric nanomaterials refer to materials with dimensions at the nanometer scale, and they exhibit exceptional optical, mechanical, electrical and catalytic properties. Their characteristics can be adjusted as needed, controlling the size, shape, synthesis conditions and functionalization [34]. Due to their unique properties and functionality, polymeric nanomaterials find several applications, from vaccination to cell and gene therapies, as well as in the design of innovative devices aimed at new wound treatment strategies [18]. In general, they possess high surface-to-volume ratio, adjustable structure, small size and biocompatibility [18,35].

Regarding polymeric nanoparticles, there are two distinct types: (1) nanospheres, characterized by solid and homogeneous structures, in which the active compound and polymer are equally dispersed and (2) nanocapsules, which exhibit a hollow, oily or aqueous structure, with the active elements housed in a reservoir, which is surrounded by a polymeric membrane [35,36]. Polymeric nanoparticles (PNPs) stand out as promising vehicles in the controlled delivery of drugs and regenerative tissue engineering [37,38]. Lu et al. developed silver-decorated mesoporous silica nanoparticles (Ag-MSNs) by means of disulfide bonds (addition of bis (3-triethoxysilyl propyl) disulfide). The study demonstrated that Ag-MSNs possess robust adhesive properties and effective antibacterial activity, offering a promising solution for the

rapid and safe closure of skin wounds. Furthermore, Ag-MSNs proved to be biodegradable and biocompatible, minimizing cellular and systemic toxicity during the healing process. These results indicated that polymeric nanomaterials, especially those derived from Ag-MSNs, represent an innovative and promising approach for the development of advanced tissue adhesives with significant potential for clinical applications in regenerative medicine [39]. On the other hand, polymeric nanocomposites (PNCs), are made of a matrix, the polymer, and a reinforcement or nanofiller. Commonly, these are lightweight and cost-effective and can be molded into different shapes and sizes, making it possible to control surface area, optical properties, catalytic activity and magnetic behaviour [40]. Through the incorporation of small amounts of nanofillers, improvements in the composite properties, thermal, chemical, mechanical or electrical, are recognized [41]. In a study conducted by Yao et al., a matrix of methacrylate hyaluronic acid microneedles encapsulated in metal-organic structures of zinc through the molding method was investigated in order to promote wound healing. The matrix demonstrated excellent antibacterial activity due to the controlled release of zinc ions, as well as citocompatibility. Furthermore, the microneedles matrix was degradable, allowing the continuous release of the active ingredient and, through that, promoting tissue regeneration. The study highlighted the effectiveness of microneedles in accelerating epithelial regeneration and neovascularization, representing a promising treatment strategy for wounds [42].

There are also polymeric nanofibers, which can be modified with polysaccharides, proteins, peptides, natural extracts and even growth factors [43]. Generally, nanofibers with applications in biomedicine are produced through electrospinning, since this technique is remarkable for its versatility in terms of polymers for usage, fiber diameter, and possibility for large-scale production.

2.1.1. Polymeric nanofibers: shaping scaffolds' architecture

Electrospinning is a simple, economical, versatile and promising technique that allows the production of nanofibers with adjustable structures, properties and functions, is valuable for the construction of scaffolds for various applications in industry and research [44]. When produced by this technique, the nanomaterial exhibits exclusive intrinsic properties, highlighting adjustable size distribution, good connectivity, ease of functionalization with bioactive molecules, structural stability, uniformity, compositional diversity, and structural flexibility, augmenting their appeal [24,45]. Therefore, finding potential uses in several areas, covering the field of energy, environment, tissue engineering and biomedical engineering, since they are non-toxic, biodegradable and biocompatible, thus being able to enter into direct and indirect contact with biological systems [46,47]. The technique is based on electrostatic attraction and involves the production of extremely narrow fibers, with diameters ranging from a few nanometers to several micrometers in scale. A polymeric solution is ejected from a needle with a specific diameter by the influence of an electrostatic field, induced by high voltage ranging from 1 to 30 kV [48]. The resulting jet is collected by an oppositely charged collector to assemble the ejected fibers [49,50]. Electrospinning allows consistent production of scaffolds with a large surface area. Electrospun nanofibers can be produced from natural or synthetic polymers, and the mixture of these polymers adjusts the functionality of the resulting nanofibers, offering a remarkable diversity of composition and properties [51–53]. This technique stands out for its ability to mimic the characteristics of the cellular matrix, as they present a highly porous 3D network with excellent interconnectivity [24,54].

The concentration, viscosity, surface tension, polymer structure, molecular weight, solvent type and conductivity of the polymeric solution can influence the efficiency of the process. The intensity of the electric field, the distance from the tip to the collector and the flow rate are process parameters that can also affect efficiency. Finally, there are environmental parameters, such as humidity, pressure, air velocity and temperature, which play a crucial role. All these parameters directly

affect the surface morphology, diameter and texture of the fibers produced [45,51,55,56].

Despite the distinct and advantageous characteristics, electrospun scaffolds still present limitations, such as low cell penetration due to the high packing density of the nanofiber layers, resulting in extremely small pores, which can compromise cell migration, vascularization and adequate tissue interaction, potentially affecting tissue regeneration and cell function [49]. Another limitation is the inadequate load support. For uses as weight-bearing cell tissues, electrospun nanofibrous mats should reach 150 MPa, which due to their high porosity, is extremely hard to accomplish [49,57,58]. The use of toxic solvents (i.e., organic), and low productivity are also among the limitations of the standard electrospinning technique [59]. To overcome several of these limitations combinations of organic with inorganic components, natural with synthetic, natural with inorganic, etc., have been proposed to enhance individual component properties or even generate synergistic effects [61]. Saeed et al. examined a three-layer dressing produced through electrospinning, using polycaprolactone (PCL), polyvinyl alcohol (PVA), and curcumin. This dressing serves to absorb wound exudates, maintain wound moisture, and leverage curcumin's antibacterial properties, addressing gaps found in other conventional dressings, combining wound protection with antibacterial properties. The addition of the PVA layer tripled the absorption capacity, significantly enhancing exudate absorption and reducing foreign body residues in wounds. With 16 % (w/v) curcumin content, the dressing displayed antibacterial activity, effectively eliminating both Gram-positive and Gram-negative bacteria within 48 h [60]. Bayat et al. used electrospinning to produce chitosan nanofibers loaded with bromelain (extract containing proteolytic enzymes extracted from plants of the *Bromeliaceae* family, which includes pineapple) at 2 % and 4 % (w/v) to treat skin burns. The effectiveness of this treatment was evaluated through the reduction of the burned area and histological analysis. Nanofibers loaded with 2 % (w/v) bromelain demonstrated superior properties and improved efficiency in healing skin burns compared to those loaded with 4 % (w/v) bromelain. In this way, chitosan nanofibers with 2 % (w/v) bromelain prove to be a promising natural topical treatment for dermal regeneration in cases of burns [61]. Teixeira et al. developed electrospun mats cross-linked with glutaraldehyde vapor, made from cellulose acetate (CA) combined with PVA, to treat chronic wounds. Mats were functionalized with the antimicrobial peptide Cys-pepiganan and the immunoregulatory peptide Tiger 17. After analysis, they found that Tiger 17 accelerated plasma coagulation, reducing the formation of clots, and making it promising for wound healing. Based on this study, electrospinning mats containing PVA and CA, especially in the optimized ratio of 90/10 % (v/v), showed promise for treating wounds by contributing to the adequate absorption of exudates and effectiveness in combating bacterial infection [62].

2.1.2. Polymeric nano-composite scaffolds

The intelligent combination of different nanomaterials plays a crucial role in the skin healing field. Indeed, the bio-nanocomposites (BNCs), also known as biohybrid materials, green composites or nanobiocomposites, are made of a biopolymer and an inorganic solid [63,64]. These materials are classified under a group of composite materials with diverse components, each possessing distinct properties like antimicrobial or antioxidant activity and are merged under varying conditions including specific temperatures or the presence of a solvent [65]. This involves combining natural element components such as biopolymers, including polysaccharides (cellulose, agar, chitosan), proteins and nucleic acids with inorganic components (nano-reinforcements), such as titanium dioxide, zinc oxide, among others, on a nanometric scale, endowing them with unique properties and making them a promising alternative to synthetic materials [66–69].

Nano-reinforcers exhibit a remarkable surface-to-volume ratio, thus optimizing interactions with the polymeric matrix, resulting in improved material performance, even at reduced amounts of nanofiller. This discrepancy arises from the higher density of binding sites,

facilitating stronger adhesion between the nanofiller and the polymeric matrix. Nano-reinforcements provide more active interaction sites, enabling a more efficient and uniform distribution within the composite material compared to conventional composites, which need larger proportions to achieve similar outcomes [70]. The performance of bio-nanocomposites depends on the dispersion of nanoparticles in the polymer matrix, with such dispersion being affected by the type of solvent, mixing method and size of the nanoparticles. Techniques such as plasma modification, grafting or coating with bio-moieties and chemical modifications, are used to modify the surface of the nanofillers, contributing to increasing the biocompatibility [71].

In bio-nanocomposites, the central challenge is to improve performance by combining the properties of the components. Polymers, being biocompatible and biodegradable, complement the mechanical and thermal properties of the inorganic part, thus bridging the gap between functional and structural materials [69].

Compared to isolated natural materials, bio-composite materials offer several advantages, such as fatigue resistance, ability to resist impacts, rigidity, corrosion resistance, biodegradability, thermal conductivity efficiency, low relative density, environmentally friendly waste stages, light weight and high specific resistance [72]. Additionally, due to their remarkable antimicrobial activity, these materials can function as active agents to effectively inactivate pathogenic microorganisms [73].

Bio-nanocomposites can be classified according to origin, size, and shape of reinforcements and types of matrices used. Based on the shape of the reinforcing particles, BNCs can be categorized into: (1) particle BNCs, which are those that use dimensional particles as reinforcement and reduce permeability, to make composites non-flammable, and to decrease the costs; (2) BNCs with elongated particles, which use elongated particles such as cellulose nanofibers as reinforcement, providing better biomechanical behaviour due to the high aspect ratio of the reinforcement; and (3) BNCs reinforced by layered particles, also called layered polymer nanocomposites, which are divided according to the dispersion rate in the matrix in micro-composites, flocculated/phase-separated nanocomposites, intercalated and exfoliated nanocomposites [74].

BNCs find several applications as drug delivery systems, vaccines, wound dressings and tissue engineering, due to their biocompatibility, and inherent non-toxicity, important for the proper function of the human body without triggering side effects [68,75]. These are still being explored for applications in the electronics, environmental, energy, and cosmetic industries, bioactive implants, among many others [65,76].

As for healing purposes, there is rapid repair when wounds are treated with dressings containing BNCPs. Recently, Bagheri et al. used composite nanomaterials, namely silver nanoparticles (AgNPs) and zinc oxide (ZnO) incorporated into chitosan (CS) and polyethylene oxide (PEO) nanofibers, to develop wound dressings with antioxidant and antimicrobial properties. The results demonstrated that the composite nanomaterials presented synergistic antioxidant and antimicrobial activity [77]. Also, Khorasani et al. developed and characterized heparinized hydrogels composed of PVA, CS and zinc oxide nanoparticles (ZnO-NPs) intended for use as wound dressings. They concluded that the addition of ZnO-NPs improved the mechanical and thermal properties, resulting in a structure with porosity favorable to wound healing. Furthermore, a more sustained release rate of heparin was observed in the presence of ZnO-NPs, while cell viability and antibacterial activity showed promise. Data suggested that PVA/CS/ZnO-NPs/heparin hydrogels may be effective in promoting wound healing, presenting a potentially valuable approach for developing new materials for wound care [78]. Similarly, Yang et al., investigated the incorporation of gold nanoparticles (AuNPs) into electrospun PCL and gelatin nanofibers in order to develop wound care dressings against multi-drug resistant bacteria (MDRB). AuNPs were coated with 6-aminopenicillanic acid, which exhibited excellent biocompatibility. After seven days of culture, a significant rise in the release of gold was observed compared to the

initial day. This suggested that the AuNPs were released over time, which indicated the ability of the nanofibers to trap and release AuNPs, and thus, be able to remediate a wound infection by MDRB, which could be crucial to instigating regeneration [79]. Finally, Masud et al. developed a wound dressing composed of CS, ZnO-NPs and polyethylene glycol (PEG) cross-linked with sodium tripolyphosphate (STPP). The bio-nanocomposite was prepared by a simple solution mixing and casting method. The objective was to control the release of gentamicin (an antibiotic) to improve healing by stopping the proliferation of microorganisms. ZnO-NPs were incorporated to provide antimicrobial properties. *In vitro* and *in vivo* tests confirmed the biocompatibility, enhanced antibacterial activity, and more effective healing with the gentamicin-loaded bio-nanocomposite compared to commercial hydrogel dressings [80].

3. Chromism of nanomaterials

One intriguing phenomenon that has garnered considerable attention in the nanomaterials field is chromism, known as the ability of materials to exhibit reversible and tunable changes in color in response to external stimuli, typically observed in solids and liquids [81]. Chromic nanomaterials, with their dynamic color-changing capabilities, hold immense promise for applications ranging from sensors to smart coatings and biomedical devices [82]. Exhibiting this particular chromic behavior on nanomaterials is advantageous due to their enhanced surface-to-volume ratio, tunable optical properties, and potential for functionalization at the molecular level. The chromic behavior observed in nanomaterials can be attributed to various mechanisms, including changes in the electronic, conformational, crystal, and physical structure of the material or surface chemistry [83]. When external stimuli induce structural changes in the material, there is a corresponding shift in optical absorption characteristics due to modifications in electron density and, consequently, the material undergoes a color change [84]. Various types of chromism, such as photochromism, thermochromism, solvatochromism, electrochromism, mechanochromism and halochromism have been discovered, each triggered by specific stimuli, respectively light, temperature, solvent, electric potential, mechanical forces or pH [85,86]. Among the different types of chromism, halochromism has garnered significant interest due to its sensitivity to pH variations, which are critical indicators of physiological and pathological states. Halochromic nanomaterials change color in response to alterations in the local ionic concentration, making them highly useful for real-time pH monitoring in wound healing and tissue engineering applications.

3.1. Halochromism

Halochromic materials change color based on the acidity or alkalinity of their surroundings in response to the presence of specific ions or changes in ionic concentration. This type of chromism is often used in pH indicators, where the color of the indicator is correlated with the pH of the solution [13,87]. This sensitivity is harnessed through carefully engineered structures or functional groups that undergo reversible alterations, often involving protonation and deprotonation of functional groups in response to changes in pH, leading to shifts in electronic configuration and optical absorption properties. Several compounds found in nature exhibit halochromism under specific conditions [88]. Anthocyanins are natural pigments abundantly found in various plants, particularly in fruits (i.e., berries) and vegetables (i.e., red cabbage and red radish). These compounds demonstrate halochromism by altering their color based on the pH of their surroundings (Fig. 1) [89]. They serve as excellent pH indicators due to their distinct color changes, ranging from red to purple to blue-green. Although these compounds are not exclusively halochromic, their ability to undergo color changes in response to environmental factors makes them invaluable in various applications [90]. Particularly in pH detection and colorimetric assays,

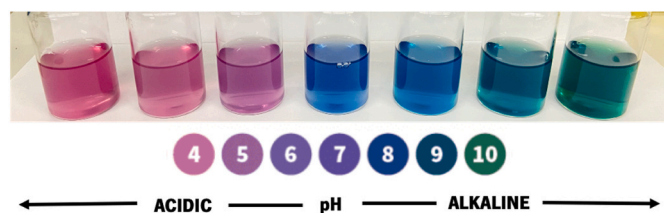


Fig. 1. – Colour shift of different pH solutions in contact with a red cabbage halochromic natural extract. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

natural halochromic compounds offer simplicity, affordability, and eco-friendliness, thus finding widespread usage in laboratories, industries, and educational settings [91]. Halochromism also presents versatile applications in biomedicine, including pH sensing for monitoring cellular environments, disease states and wound healing; drug delivery systems that enable controlled release in response to pH changes, and biomedical imaging for enhanced contrast in pathological tissues [92,93]. Integration of halochromism into biomedical research holds promise for advancing diagnostics, therapeutics, and real-time monitoring of physiological processes, ultimately contributing to improving patient care and outcomes [15]. Moreover, halochromism in nanomaterials within the medical context provides invaluable insights into the importance of this feature in providing visual signals of alterations occurring at the molecular or cellular scale that function as a diagnostic tool, treatment management and evaluation of tissue regeneration and integration [94].

The underlying mechanisms behind halochromism in nanomaterials often involve interactions at the nanoscale level. These materials undergo protonation or deprotonation based on the surrounding pH, leading to variations in electron density and optical properties. For instance, changes in the concentration of ions may induce structural modifications in the nanomaterial, influencing their electronic configurations and subsequently altering their optical properties [95]. Many organic compounds contain functional groups that can gain or lose protons depending on the pH of the solution. The addition or removal of protons can lead to changes in the electronic structure of the molecule, resulting in a shift in its absorption spectrum and, hence, its color. This dynamic behavior can be tuned by selecting specific halochromic dyes, modifying nanomaterial surfaces, or incorporating hybrid structures that enhance stability and response time [96].

This responsiveness provides a basis for designing sensors capable of detecting timely changes (minute) in the surrounding environment. Understanding and harnessing the halochromic properties of nanomaterials opens avenues for the development of innovative technologies with enhanced functionality and sensitivity.

However, the application of halochromism in biomedical contexts still faces significant challenges, despite its widespread use in other industries such as textiles and chemistry. One of the main obstacles lies in the complexity of the biological environment, where factors such as pH, temperature, humidity, and the presence of bodily fluids can interfere with the stability and accuracy of halochromic responses. Besides that, halochromic materials must be biocompatible and safe for direct contact with the body, which is not always easy to ensure. In industrial sectors, conditions are more controlled, allowing for the efficient use of these technologies without the same constraints imposed by biological variability [97].

3.1.1. Nano-scaffolds with halochromic behaviour

The emerging field of nanomaterial-based scaffolds exploits the properties of halochromism, introducing a dynamic dimension to the design and functionality of scaffolds employed in tissue engineering, regenerative medicine and health monitoring [98]. A perfect example of the importance of pH is in wound healing. pH serves as a crucial

biomarker, influencing the progression from inflammation to tissue regeneration. Chronic wounds often exhibit an alkaline environment (pH 7.2–8.9), whereas healing wounds shift towards a neutral-to-acidic pH. This pH transition is essential for cellular activities such as enzyme function, microbial balance, and tissue remodeling. By integrating pH-sensitive halochromic nanomaterials into biomedical scaffolds, wound healing can be continuously monitored, reducing the need for invasive diagnostic methods and enabling timely interventions [99]. Different stages of wound healing are linked with specific pH ranges, with wounds healing better in acidic conditions. Conversely, alkaline environments can lead to the development of chronic wounds [99]. Throughout healing, the wound environment shifts from alkaline to neutral and then acidic. Monitoring wound pH, as an indicator of healing, is suggested for determining effective treatment strategies [100]. This presents a valuable approach for improving diagnostic and therapeutic outcomes in regenerative medicine. By incorporating halochromic dyes and pH-sensitive nanomaterials into scaffolds, these systems enable real-time monitoring of environmental changes, offering a non-invasive means of assessing tissue healing. The mechanistic insights into halochromic behavior allow for further functionalization and optimization to enhance scaffold efficiency [101,102]. Also, in some occasions, it is interesting to incorporate antimicrobial and antifungal properties, providing dual functionality (acting as both pH sensors and active agents against microbial contamination) [103]. Typically constructed from nanostructured polymers or hybrid systems (nanocomposites), halochromic nano-scaffolds achieve antimicrobial and antifungal efficacy through the incorporation of nanoparticles loaded with antibiotics, essential oils, or even isolated antibiotics, which ensure broad-spectrum growth inhibition of bacteria and fungi [104,105].

The incorporation of halochromic elements into biomedical scaffolds allows for real-time, visually observable responses to changes in the local microenvironment. This capability holds potential for monitoring and understanding cellular activities, tissue healing and growth, and the overall performance of the scaffold within the body [95]. The color-changing aspect provides a novel means of assessing the health and integration of the scaffold with host tissues. One of the notable advantages of this approach lies in its potential diagnostic applications and continuous monitoring. The halochromic behavior can serve as a visual indicator of specific physiological conditions, such as variations in pH, ion concentration, or the presence of certain biomolecules and microorganisms. However, halochromic substances do not exhibit a complete spectrum of colors across all pH levels because, beyond certain levels of acidity, the conjugated system remains unchanged. The diverse shades observed stem from variations in the concentrations of halochromic molecules possessing distinct conjugated systems [96,106]. This diagnostic capability could significantly impact the early detection of pathological changes or the success of tissue regeneration, paving the way for more personalized and effective therapeutic interventions [107]. Furthermore, the adaptability of halochromic biomedical scaffolds to different tissue types and environments enhances their versatility. Tailoring the color response to specific signals facilitates the development of smart scaffolds that can dynamically adjust to the needs of diverse tissues or disease states [108]. This adaptability is crucial for creating biomimetic environments that promote optimal cell growth and tissue regeneration. While the field is still in its beginnings, the potential for biomedical scaffolds with halochromic behavior to revolutionize regenerative medicine and textile biomedical engineering (halochromic dressings) is evident (Fig. 2) [109,110]. Continued research and development in this area hold the promise of not only improving our fundamental understanding of tissue engineering and wound healing but also triggering a new era of smart, responsive implants or dressings with enhanced diagnostic and therapeutic capabilities. As research goes deeper into the details of halochromic materials and their interaction with biological systems, the prospects for innovative applications in healthcare continue to expand [110].

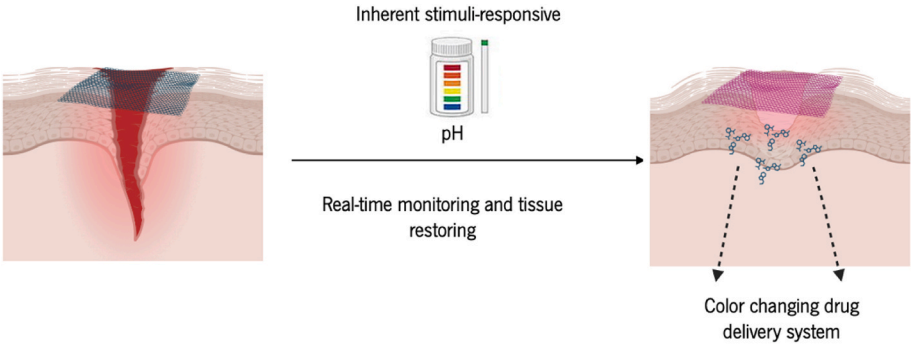


Fig. 2. – Halochromic wound dressing with drug delivery system properties with application on wound healing and tissue regeneration. Adapted from Ref. [110] with CCBY 4.0 permission.

Table 1
Applications of nanomaterials based halochromic biomedical scaffolds in the field of skin regeneration and wound healing.

Nanomaterial	Design Strategy	Halochromic Molecule Features	pH Range	Application	Ref.
Electrospun nanofibers	Electrospinning of poly (methyl methacrylate-co-methacrylic acid) (PMMA-co-MAA) and poly (acrylic acid) (PAA) fibers encapsulated with halochromic bromothymol blue (BTB)	BTB - Synthetic pH indicator; 	5.0–8.0	Chronic wound management and monitoring	[119]
Electrospun nanofibers	Chitosan/PCL nanofibrous matrix blended with halochromic dyes Methyl Red and Rose Bengal	Synthetic pH indicators; Both halochromic dyes possess a functional carboxyl-group that is available for coupling with chitosan, without disrupting the chromophore and leaving halochromism intact; 	0.0–12.0	Wound dressing	[118]
Electrospun nanofibers	Sodium alginate (SA) and PVA nanofibrous mat loaded with anthocyanins extracted from black carrot (BC)	Black carrot natural extract with halochromic properties; Good water solubility, exceptional color resistance at high temperatures, and light stability; 	4.0–10.0	Wound healing monitoring	[94]
Electrospun nanofibers	PCL and PCL/chitosan (80:20) nanofibers loaded with Nitrazine Yellow dye	Nitrazine Yellow dye - Synthetic pH indicator; 	2.0–11.0	pH-sensor with antimicrobial properties for diverse medical applications	[117]
Hydrogel	Methacrylate-chitosan crosslinked with methylenebisacrylamide (MBAA) hydrogel embedded with red cabbage extract	Red cabbage natural extract with halochromic properties; Antioxidant, anti-inflammatory, anticancer, antibacterial, antifungal, and antiviral agent; 	2.0–11.0	pH-sensitive wound dressing	[113]
Hydrogel	SA films containing halochromic <i>Clitoria ternatea</i> Linn. flower extract loaded with gallic acid and resorcinol as model drugs	<i>Clitoria ternatea</i> Linn. flower extract; Antioxidant agent 	5.0–9.0	pH-sensing of the transdermal diffusion of drugs	[122]
Hydrogel	Halochromic hydrogel-based dressing (GelDerm®) that releases the antibiotic gentamicin	Red cabbage natural extract with halochromic properties; Antioxidant, anti-inflammatory, anticancer, antibacterial, antifungal, and antiviral agent; 	4.0–9.2	Colorimetric measurement of pH and release of antibiotic agents at the wound site	[123]
Nanoparticles	Bacterial nanocellulose-based wound dressing impregnated with meso-porous silica nanoparticles (MSNs) loaded with BTB pH-responsive dye	BTB - Synthetic pH indicator; 	5.0–8.0	Real-time pH wound monitoring	[112]
Nanoparticles	Red-cabbage based anthocyanin chromophore extract was encapsulated into alginate NPs via crosslinking and immobilized into cotton gauze medical fabrics	Red cabbage natural extract with halochromic properties; Antioxidant, anti-inflammatory, anticancer, antibacterial, antifungal, and antiviral agent; 	4.5–8.0	Real-time detector for wound healing progress monitoring	[120]

3.1.2. Halochromism for skin regeneration and wound healing

The integration of halochromic features into biomedical scaffolds has noteworthy implications in tissue engineering, particularly in the context of skin regeneration and wound healing (Table 1). This innovative approach brings a dynamic and responsive element to the design of scaffolds, offering unique advantages for monitoring and enhancing the success of skin tissue engineering [108]. However, scaffolds must be developed keeping in mind the basic requirements of biocompatibility, biodegradability, and causing minimal immune reactions and side effects [110]. Despite significant progress being made in the creation of new bandage materials, only a few of them can offer medical staff diagnostic information about the wound's biomolecular composition. Currently, much of the treatment is done by observation, and the accompanying healthcare provider's critical judgment and experience are crucial. Even though some of the current therapies, such as skin grafts, skin substitutions, negative pressure wound therapy, and others, can be helpful, they typically necessitate procedures or surgical intervention. Necrosis, sepsis, and even mortality can result from microbial infection at the site of the wound, which can significantly slow down the healing process [111].

The halochromic behavior allows for the real-time visualization of cellular activities within the scaffold. As skin cells proliferate and differentiate, the color changes in the scaffold can serve as a direct indicator of these processes [112]. This real-time monitoring is vital for assessing the health and strength of the engineered skin tissue. With that in mind, the color-changing properties can be harnessed as diagnostic indicators for the health of the engineered skin [113]. Specific color shifts in response to variations in pH or the presence of certain biomolecules can provide early warnings of potential issues (infection, excessive release of exudates, interruption of the wound healing process), allowing for quick intervention and adjustment of treatment strategies. Color changes may indicate a healthy vascularization process, offering insights into the blood supply critical for the survival and functionality of the regenerated skin. [114]. This feature aids in optimizing the overall success of tissue engineering processes and wound healing.

The adaptability of halochromic behavior enables the customization of scaffold responses to specific environmental factors influencing skin regeneration. The ability to visually track cellular activities, diagnose early issues, optimize integration, and tailor responses to environmental factors contributes to the creation of smart and responsive scaffolds [115]. Variations in color in response to changes in pH or other relevant parameters can be adjusted to mimic the dynamic conditions of the skin microenvironment, fostering improved cellular responses and tissue development [94,115]. Also, halochromic scaffolds can provide a visually intuitive means for healthcare professionals to monitor the progress of skin regeneration. This feature facilitates enhanced patient monitoring, allowing for timely adjustments in treatment plans and strategies based on the real-time feedback provided by the color-changing scaffold [116].

Pakolpakçıl et al. focused their research on developing a novel wound dressing for pH monitoring based on sodium alginate (SA) and polyvinyl alcohol (PVA) nanofibrous mat loaded with the natural anthocyanins extracted from black carrot (BC). The nanofibrous mats were produced by electrospinning and the immobilization of anthocyanins was carried out through direct blending in the polymeric solution. A dressing with halochromic properties that exhibited a visual pH grading between pH 4–10, demonstrating that PVA/SA/BC nanofibrous mat can be used as a pH-sensitive wound dressing for monitoring the healing progress was obtained [94]. Also demonstrating the potential of electrospinnable scaffolds, both Schoolaert, E. et al., and Van der Schueren, L. et al., developed nanofibrous matrices by blending halochromic dyes with polymeric solutions to obtain nanofibrous pH-sensitive wound dressings and opening doors to a broadening of the selection of suitable dye-matrix combinations towards color changes in the pH-range within the neutral to alkaline pH-region [117,118]. The study from Basel

Bazbouz M., and Tronci, G., also highlights the clinical diagnostic potential of incorporating halochromic properties into nanomaterials for wound healing. By developing a two-layer fibrous device via electrospinning, the researchers created a material capable of both exudate management and infection detection through visual color changes. The use of bromothymol blue (BTB) in PMMA-co-MAA fibers enabled pH-sensitive color shifts, signaling infection-induced alkalinity. The findings demonstrate how nanomaterial design can enhance wound monitoring, offering a promising approach for real-time infection detection in chronic wound care [119]. Following another strategy, Alaysuy, O. et al., aimed at developing a novel multifunctional wound dressing with the ability to protect, cure and sense the healing process. Halochromism was provided by red cabbage anthocyanin extract, a compound known not only for its halochromic properties, but also for its ability to function as antioxidant, anti-inflammatory, anticancer, antibacterial, antifungal, and antiviral agent. The anthocyanin chromophoric extract was encapsulated at different concentrations into alginate-based NPs, forming a hydrogel scaffold, and immobilized into cotton gauze to provide a smart therapeutic pH-responsive wound dress to function as an antimicrobial and biochromic matrix providing a comfortable dress sensor to monitor the wound status [120]. Similarly, Eskilson, O. et al., fabricated a pH-sensitive hydrogel-based wound dressing by impregnating meso-porous silica nanoparticles (MSNs) with a pH-responsive dye, as a new effective strategy for rapid colorimetric assessment of wound pH, that can be further for encapsulation and release of bioactive compounds for treatment of hard-to-heal wounds [112]. Mirani, B. et al., patented GelDerm®, a multifunctional wound dressing with significant clinical diagnostic potential for infection detection and treatment. By incorporating a pH-sensitive colorimetric response, GelDerm can visually indicate bacterial infections, while also enabling controlled antibiotic release for targeted treatment. *In vitro* and *ex vivo* tests confirmed its accuracy, comparable to commercial diagnostic systems. Additionally, its integration with smartphone-based wireless monitoring allows patients to track wound conditions remotely, improving telemedicine capabilities. Designed for compatibility with commercial patches, this system offers a non-irritating, patient-friendly solution for managing chronic and acute wounds, holding promise for applications in trauma, surgery, and diabetes care [121].

4. Conclusion and future perspectives

The integration of halochromic properties into nanomaterial-based biomedical scaffolds represents a cutting-edge and promising avenue in the field of biomaterials. The reversible color changes in response to environmental stimuli, add a dynamic dimension to the functionality of biomedical scaffolds applied to wound healing and skin regeneration. This holds significant potential for real-time monitoring of physiological conditions within the body. This feature is particularly advantageous in the development of novel wound dressings, smart implants and tissue scaffolds, where the visual indication of changes at the molecular or cellular level can serve as a diagnostic tool or aid in the assessment of tissue regeneration and integration. Moreover, the halochromic properties contribute to the versatility of these nanomaterial-based scaffolds, allowing for tailored responses to the unique microenvironments of different tissues. This adaptability is crucial for optimizing therapeutic outcomes and minimizing undesired side effects. The field is still in development, and further research is needed to fully explore the scope of applications and refine the design principles of these halochromic nanomaterials. Despite their potential, halochromic nanomaterials in biomedical scaffolds face several challenges that must be addressed to facilitate their practical implementation in clinical settings. One of the primary concerns is the stability of halochromic dyes and nanomaterials under physiological conditions. Many pH-sensitive dyes may degrade or lose their responsiveness due to prolonged exposure to bodily fluids, temperature fluctuations, and enzymatic activity. Encapsulation and

polymer stabilization strategies must be developed to enhance the longevity and reliability of these materials. Another critical challenge is biocompatibility and potential cytotoxicity. Some halochromic compounds, particularly synthetic dyes, may elicit adverse biological responses. Future research should prioritize the development of biodegradable and non-toxic halochromic agents, such as those derived from natural sources like anthocyanins. Integration with existing medical devices and scalability also present significant obstacles. The fabrication of halochromic scaffolds should be compatible with large-scale production techniques while maintaining consistency in material properties. Additionally, regulatory approval for new halochromic biomaterials may require extensive preclinical and clinical validation, necessitating collaborations between researchers, industry, and regulatory agencies. Finally, customization and adaptability for diverse wound types and patient conditions remain an open research area. The ability to adjust the sensitivity and response time of halochromic scaffolds for different applications, such as diabetic ulcers or surgical wounds, would expand their usability and clinical impact. As the understanding of the interaction between nanomaterials, halochromism, and biological systems develops, the potential for innovative diagnostic and therapeutic solutions continues to grow. One of the key future perspectives lies in their use of advanced sensing and detection technologies. Halochromic nanomaterials could revolutionize medical diagnostics by providing real-time, non-invasive monitoring of physiological parameters such as pH levels in biological fluids on chronic wounds.

CRedit authorship contribution statement

Ana R.M. Ribeiro: Writing – review & editing, Writing – original draft, Investigation. **Bruna A.S. Oliveira:** Writing – original draft, Investigation. **Ana Isabel Barbosa:** Writing – review & editing, Investigation. **Catarina L. Seabra:** Writing – review & editing, Supervision, Funding acquisition. **Salette Reis:** Writing – review & editing, Supervision, Funding acquisition. **Helena P. Felgueiras:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

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Data availability

No data was used for the research described in the article.

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