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Review

Bioengineered Scaffolds for Thermo-responsive Drug Delivery in Wound Healing

Luis Castillo-Henríquez[1,2], Jose Castro-Alpízar[3]; Mary Lopretti-Correa[4]; José Vega-Baudrit[1,5,*]

[1] National Laboratory of Nanotechnology (LANOTEC), National Center for High Technology (CeNAT), 1174-1200, San José, Costa Rica; luis.castillohenriquez@ucr.ac.cr (L.C.H)
[2] Physical Chemistry Laboratory, Faculty of Pharmacy, University of Costa Rica, 11501-2060, San José, Costa Rica
[3] NANOMED Erasmus Programme, Patras University, 26443, Patras, Greece; castro2593@hotmail.com (J.C.A)
[4] Nuclear Research Center, Faculty of Science, Universidad de la República (UdelaR), 11300, Montevideo, Uruguay; mary@cin.edu.uy (M.L.C)
[5] Laboratory of Polymers (POLIUNA), Chemistry School, National University of Costa Rica, 86-3000, Heredia, Costa Rica
* Correspondence: jvegab@gmail.com

Abstract: innate and adaptive immune responses lead to wound healing by regulating a complex series of events promoting cellular cross-talk. An inflammatory response is presented with its characteristic clinical symptoms: heat, pain, redness, and swelling. Some smart thermo-responsive polymers like chitosan can be used to create biocompatible and biodegradable scaffolds with 3D architectures similar to human structures, allowing their efficient and safe use as tissue engineering and drug delivery systems in chronic wounds. Locally heated tumors above polymer lower critical solution temperature can induce its conversion into a hydrophobic form, enhancing drug release until the thermal stimulus is gone, where a lower release is due to the swelling of the material. This paper integrates the relevant reported contributions of bioengineered scaffolds for thermo-responsive drug delivery in wound healing. Therefore, we present a comprehensive review that aims to demonstrate the capacity of these systems to provide spatially and temporally controlled release strategies for one or more drugs used in wound healing. In this sense, the novel manufacturing techniques of 3D-printing and electrospinning are explored for the tuning of their physicochemical properties to adjust therapies according to the patient's convenience, as well as reduce drug toxicity and side effects.

Keywords: drug delivery; immune response; inflammation; critical solution temperature; scaffolds; smart polymers; tissue engineering; thermo-responsive; wound healing.

1. Introduction

Scaffolds are biocompatible and biodegradable support structures that reproduce an extracellular matrix (ECM) environment, where tissue is grown outside the body to mimic a biological process or to replace a damaged body's tissue [1,2]. Regarding that, tissue engineering aims to employ these structures for different biomedical applications that restore, maintain, and improve damaged tissue function. This multidisciplinary field analyses the requirements of the biomaterials needed to produce the scaffolds, such as morphology, and mechanical and surface properties [3,4].

Wound healing is of great interest for tissue engineering. It involves hemostasis, inflammation, proliferation, and remodeling, where each stage comprises different necessary

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biochemical mediators for a successful process [5]. Scaffolds represent outstanding structures for wound healing due to their capacity for tissue regeneration and cell growth. Different novel manufacturing techniques are widely been employed such as 3D bioprinting and electrospinning [6,7]. In addition, they can perform as a drug delivery system when composed of smart polymers that respond to certain stimuli (e.g., pH, temperature, magnetic and electric fields) [8–10].

Thermo-responsive polymers are very useful for scaffold development due to their outstanding performance under a determined change in temperature (e.g., locally heated tumors in inflammation) [11,12]. This change can induce a phase transformation in the polymer, causing the release of a loaded anti-inflammatory, antimicrobial, and/or wound care drug. Heskins et al. were one of the first scientists to work with a thermo-responsive polymer that is poly(N-isopropyl acrylamide) (PNIPAAm) [13]. Currently, polymer therapeutics is a major interest in the nanomedicine field for the development of novel drug delivery systems [14–18].

Here, we present a comprehensive and integrative update of thermo-responsive polymers used for the development of bioengineered scaffolds with drug delivery applications in wound healing. The work is based on the main findings of 158 papers published between 2010 and 2020. The literature search was conducted in Science Direct, Pub Med, and Scopus databases. Therefore, this review aims to demonstrate the capacity of these systems to provide spatially and temporally controlled drug release in wound healing. In addition, the novel manufacturing techniques of 3D-printing and electrospinning are explored for their creation and tuning of their physicochemical properties.

2. Immune response in wounds

The immune system possesses a critical role in discriminating harmful pathogens from the body's healthy tissues. Although it must generate an adequate response to eliminate any strange object it also has to avoid self-tissue damaging to allow a proper wound healing process [19]. In order to accomplish that, immunity is based on two components: the innate and adaptive responses. The first one takes immediate action upon the detection of an invader, while the second one requires the activation of the innate [20,21]. However, there is evidence that one response can be influenced by its counterpart. The previous has been explained by some cells exhibiting functional properties of both, such as dendritic cells, gamma delta (+) T lymphocytes, and Langerhans cells [22,23].

Moreover, the immune response in wound healing is a complex process to return the system to homeostasis; involving cellular and biochemical mediators in response to a tissue injury caused by trauma, microbes, or foreign materials. Consequently, a series of events including coagulation, inflammation, epithelization, proliferation, and remodeling take place leading to wound closure. [24–28]. However, this section aims to provide an overview of the topic, so the attention will be paid to inflammation since it provides the micro-environmental conditions that are necessary for a thermo-responsive drug delivery of wound healing substances through bioengineered scaffolds.

The inflammatory process is an early required phase for wound healing, characterized by five typical symptoms: redness, swelling, heat, pain, and loss of tissue function [29]. Endothelial cells express cell adhesion molecules that promote the binding of circulating leucoytes. Moreover,

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neutrophils are the first inflammatory cells arriving at the injury site, responding to chemokines and being chemo-attracted by C5a and C3a complement activation fragments [30,31]. In addition, platelet aggregation and macrophages degranulation trigger the release of other proinflammatory cytokines such as tumor necrosis factor-α, interleukin-1 (IL-1), IL-6, and growth factors such as the transforming growth factor-beta (TGF-β). As fewer proinflammatory substances are released and more proregenerative mediators are produced, inflammation is reduced and damaged tissues are repaired [32,33].

3. Thermo-responsive smart polymers

In general, water-soluble smart polymers change their physicochemical properties upon the influence of an external stimulus, and some of them are responsive to multiple stimuli. This modification is related to their arrangement, solubility, or the hydrophilic-hydrophobic balance [34–36]. Regarding the thermo-responsive polymers, these have been thoroughly studied and exhibit a volume phase transition at a critical solution temperature (i.e., the temperature where exists a balance in the competition established by hydrophilic and hydrophobic chains), usually referred to as cloud point (T_{cp}), which is responsible for the changes in the solvation-state [37–39]. Usually, topical applications and injectable biodegradable scaffolds made of this type of polymers make use of body temperature to cause a change in the physical properties of the system [40].

According to their origin, this type of polymer can be classified as natural, synthetic, and hybrid. Natural polymers such as chitosan, gelatin, collagen, and cellulose have been widely used for biomedical applications as ECM due to their great biocompatibility and bioactivity. However, their main limitations are related to batch variability and unsuitable physicochemical properties for certain manufacturing processes [41–44].

On the other hand, synthetic polymers such as PNIPAAm, poly(lactic acid) (PLA), poly(ε-caprolactone) (PCL), poly(N-vinyl caprolactam) (PNVCL), polyethyleneglicol (PEG) and polyethylene oxide (PEO) provide greater tunability of their properties and outstanding mechanical behavior that allows using them for different materials processing techniques. Nevertheless, these polymers may not present the same biodegradable performance as the natural, as well as exhibit lower biocompatibility [45,46]. Remarkably, the limitations exhibited by natural and synthetic polymers can be overcome by their blending, obtaining a hybrid polymer [47–49].

Phase transition thermodynamics and critical solution temperature

Polymer solubility is a complex process that depends on their structure and molecular weight, as well as on the viscosity of the system [50]. Based on the Gibbs-Helmholtz equation ($\Delta G = \Delta H - T\Delta S$), changes in Gibbs free energy of the system (ΔG) to negative values represent the condition under which polymers are soluble [51]. This happens when the change in entropy (ΔS) increases due to the diffusion of solvent molecules through the polymer, where polymer-solvent interactions break intermolecular polymeric bonds [52]. An adequate solvent can expand polymer molecules, thus decreasing ΔG, while a poor one causes them to collapse. However, the Flory-Huggins solution theory should be addressed in explaining the temperature's influence on polymer-solvent, polymer-polymer, and solvent-solvent interactions [53–55].

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Thermo-responsive polymers possess a unique property of solid-gel transition above a certain temperature, and some of them suffer this phase transition near the physiological human body temperature (i.e., normothermia). Also, they can be modified to exhibit that change at the desired temperature [53,56,57]. These polymers are classified according to their critical solution temperature in lower critical solution temperature (LCST) or an upper critical solution temperature (UCST) [58,59]. Figure 1 shows a phase diagram where LCST and UCST are represented as solid curves with a single-phase region in between. When the system exhibits a positive ΔG at a certain temperature, the polymer will not be miscible under those conditions, and two different phases will co-exist [60,61].

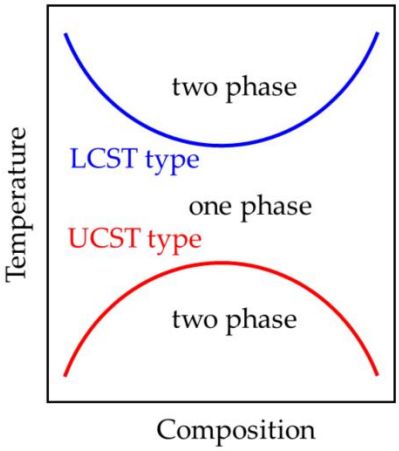

Figure 1. Lower critical solution temperature (LCST) and upper critical solution temperature (UCST) phase transition behaviors of thermo-responsive polymers in solution. Reprinted with permission from Sugeno, K. et al. UCST Type Phase Boundary and Accelerated Crystallization in PTT/PET Blends. *Polymers* 12(11). Copyright (2020) MDPI [61].

In the first place, polymers exhibiting LCST (usually close to normothermia) are completely miscible in aqueous systems below that parameter since ΔG is negative [62]. The previous is due to the negative change in enthalpy (ΔH) for the dissolution process caused by water molecules surrounding the hydrophilic part of the polymer [63]. In addition, the formation of a structured water molecule arrangement around the hydrophobic part of the polymer provides a negative ΔS [62]. However, above the LCST these substances experience a reversible phase transition from a hydrophilic configuration to a dehydrated or hydrophobic state. Heating induces that transition under an entropy-driven process caused by the loss of ordered water molecule arrangement around the hydrophobic polymer chain [64,65].

Phase separation in LCST polymers is influenced by the interruption in polymer-water hydrogen bonding and the increment in hydrophobic interactions in the polymer chain due to further increase in temperature. When the positive overall ΔS overcomes the negative ΔH, it gives ΔG a positive value that results in chain collapse and a decrease of solubility [66–68]. These materials are usually referred to as negative temperature-sensitive polymers or PNIPAAm, and great interest has been paid in their coil-to-globule conformational transition in aqueous systems [64].

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On the other hand, solubility and physical changes of some polymers are due to UCST. Above that parameter, ΔS and ΔH decrease with the increase in temperature, showing the opposite behavior to that shown by LCST polymers, and thus these materials remain miscible in solution [69,70]. Nevertheless, a phase separation governed by the enthalpy of the system occurs at temperatures below the UCST due to the balance between intra- and intermolecular forces, as well as solvation changes [71]. These materials are also called positive temperature-sensitive polymers and are based on a combination of acrylamide (AAm) and acrylic acid (AAc) [72].

Moreover, some systems can exhibit both behaviors as shown in figure 1, where an hourglass-shaped phase diagram shows the overlap of each set of curves. When that happens, phase separation is so well defined that the intermediate region is immiscible. In these cases, the temperature range between LCST and UCST tend to be sensitive to the polymer molecular weight and changes in pressure [73–75]. Although thermo-responsive systems under an aqueous environment are of great interest for biomedical applications it is not usual to see that behavior when using them for that purpose. Furthermore, they are not restricted from using other solvents for additional applications [76,77].

4. Bioengineered thermo-responsive scaffolds

Scaffolds provide templates for tissue regeneration and physical support for cell growth [78]. These can be made of artificial or natural thermo-responsive polymers, which can condition the different biomedical applications due to their effect on the functional attributes [47,79,80]. This type of smart polymers has been widely used as a scaffold in non-invasive methods for different tissues, such as skin and heart [81,82]. The previous is attributed to their injectability and self-healing properties but also their porosity has been highlighted as an outstanding property, which provides enough space for cell migration and tissue vascularization [83].

Moreover, when used for the creation of bioengineered scaffolds for wound healing, these polymers must provide a 3D architecture according to the structural heterogeneity of the host tissue environment [84,85]. The previous allows improving the mechanical and cellular activity (e.g., adhesion and proliferation) required by these structures [86–88]. In addition, scaffold design needs to consider several features such as cell-tissue interaction, vascularization, scaffold degradation, and loading with drugs, growth factors, cells, and antibacterial material. Therefore, preformulation and rational designs of scaffolds for drug delivery systems or biomedical devices are crucial for developing a functional, biocompatible, and non-immunogenic product of quality that accelerates local tissue healing [89,90].

4.1. Novel manufacturing techniques

Scaffolds' relevance lies in their design as bioactive systems than mere cell or drug carriers. Some fabrication techniques provide surface modification, while others take advantage of their physiological thermo-responsive behavior for creating structures with particular and unique geometries. The ability to design a system that can respond to an external stimulus, controlling their degradation, drug release and healing capacity yields special interest in the development of scaffolds [91,92]. A brief overview of some novel techniques is presented below.

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4.1.1. 3D-printing

This technique is probably the most adequate for controlling and modifying the internal microarchitecture of scaffolds. However, not all thermo-responsive polymers are easily employed for 3D-printing. Some natural polymers need to be modified or blended with other polymers in order to adquire the rheological and mechanical specifications [93,94]. Biomaterials need to fulfill the requirements of printability, mechanical strength, and degradation behavior to be subjected to this tissue engineering technique. Regarding that, Printability determines the capacity of a construct to imitate the 3D structure of biological tissues [95,96]. The extrusion method is widely employed for thermo-responsive polymers allowing larger constructs than other alternatives [97].

However, other methods such as inkjet printing have been used by Fischetti et al. where chitosan was blended with gelatin to form a polyelectrolyte complex to improve printability for the fabrication of scaffolds for anisotropic tissues (e.g., skin, skeletal muscle). The printing temperature was set below the LCST of the polymer blend. Tripolyphosphate was used as a crosslinker for the creation of the scaffold, which greatly conditioned its mechanical properties. The scaffold showed cytocompatibility to L929 cells and its stability was related to the content of gelatin [98].

Furthermore, synthetic materials are also employed, offering a better resolution for the bioprinting of scaffolds due to the ease of tunability. Seyednejad et al. developed a 3D scaffold base on hydroxyl-functionalized polyester (poly (hydroxymethylglycolide-co-ε-caprolactone) (PHMGCL). The structure showed enhanced hydrophilicity, higher degradation rate, and improved cell support than a PCL 3D scaffold, representing a great template for tissue engineering [99].

4.1.2. Electrospinning

This polymer processing technology allows obtaining nanofibers with high surface-to-volume ratio, highly porous structures, and diverse morphologies that can be easily controlled through different methods such as melt, emulsion, coaxial, multi-jet, side-by-side, and co-electrospinning [100,101]. However, not all polymers can be employed for this technique since they need to be soluble in a certain solvent [102,103].

Electrospun nanofibers are of great interest to the biomedical and bioengineering industry due to their outstanding properties in terms of biocompatibility, biodegradability, and high drug-loading capacity to perform as drug delivery systems [104]. Regarding that, these nanofibers can be employed for the fabrication of scaffolds for wound healing that provide either an immediate or controlled release of the active pharmaceutical ingredient (API). Therefore, electrospun nanofibers composed of thermo-responsive polymers offer a novel solution to current drug delivery inconveniences for wound healing due to their safety profile [105–107].

Meng et al. fabricated a poly(D,L-lactide-co-glycolide) (PLGA)/chitosan nanofibrous scaffold by electrospinning. The nanofibers exhibited biocompatibility and biodegradability, as well as a higher drug release with increasing concentrations of chitosan [108]. In another approach, Ji et al. fabricated a PCL-based nanofibrous scaffold and loaded the model protein bovine serum albumin (BSA) through coaxial and blend electrospinning. The coaxial electrospun nanofibers showed

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uniform morphology with a core-shell structure, while the blend nanofibers possessed defects on its surface and heterogeneous protein distribution. Regarding their release profile, the coaxial scaffold demonstrated a sustained release and provided more protection to the BSA. Therefore, this work demonstrated how different methods can tune up scaffold's properties according to the manufacturing technique [109].

4.2. Biocompatibility and biodegradability

New generations of thermo-responsive polymers offer the opportunity to synthesize them controlling their architecture and microstructure, thus providing great advances in tissue engineering and drug delivery [110,111]. Their use in the development of bioengineered scaffolds must provide cell support and protection during the healing process, as well as facilitate the deposition method [112]. However, these biomaterials properties (e.g., size, shape, surface area, roughness, chemical composition) influence the host response, causing variations in the intensity and duration of the inflammatory and wound healing processes. The aforementioned defines the biocompatibility of the polymers and scaffolds [113].

Biocompatibility is the ability of an introduced material into a physiological environment to perform as intended without inducing an inappropriate micro-and macroscopically host response [114]. Implanted scaffolds can activate the immune response, which as explained earlier in this review, involves a series of proinflammatory biochemical molecules that trigger the inflammatory process [115]. Precisely, inflammation is a common indicator for determining the host response to a biomaterial, and need to be follow up closely to avoid tissue damage [116,117]. In addition, the presence of massive fibroblast proliferation with associated collagen deposition represents a biocompatibility issue causing extensive scar tissue and fibrous encapsulation [118].

Polymers need to fulfill certain criteria in order to be used for tissue reparation and wound healing. In general, these biomaterials must be water-soluble, non-toxic, non-immunogenic, and safe during the whole process including the excretion (i.e., the size below the renal threshold) [119,120]. When used for drug delivery applications they have to work as drug carriers, reducing the degradation of the API. Furthermore, they should provide a biodegradable character to the scaffolds since these are not intended as permanent within the body [121]. However, their degradation can generate particles that may stimulate an inflammatory response or produce toxic effects. In this sense, the degradation mechanism, kinetics, and its intermediate products have to be taken into consideration, as well as the scaffold´s porosity that is directly linked to the degradation process [121–123].

Cho et al. evaluated cell biocompatibility in a hydrophilic PCL/polyvinylpyrrolidone (PVP)-b-PCL electrospun nanofiber-based scaffold. The authors highlighted the importance of the ECM hydrophilicity as a factor affecting cell adhesion in tissue engineering, and more specifically in PCL. Therefore, they enhanced its surface hydrophilicity through electrospinning with the biocompatible PVP-b-PCL block copolymer. It was reported an increase in the hydrophilic character in the PCL/PVP-b-PCL electrospun nanofibers as the concentration of PVP-b-PCL block copolymer was raised. In addition, the scaffolds exhibited no cytotoxicity, enhanced cell adhesion, and improved viability of primary fibroblasts than showed by the initial PCL scaffolds [124].

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In another electrospinning approach, Ji et al. evaluated the effect of nano-apatitic particles (nAp) on the biocompatibility and biodegradability behavior of 3:1 polymeric electrospun PLGA/PCL-based scaffolds. The research group prepared nanofibers with 0-30 wt% of nAp that were subcutaneously implanted in rats after their creation and following a 3-week pre-degraded status in order to evaluate *in vivo* tissue response. The study reported a delayed polymer degradation dependent on nAp concentration. In terms of biocompatibility, nAp significantly improved the tissue response during 4-week implantation, thus their results are considered as effective for controlling the *in vivo* adverse reaction of PLGA materials [125].

A study conducted by Xu et al. presented a novel method for 3D-printing of nanocellulose hydrogel scaffolds. The printed scaffolds from a 1 wt% nanocellulose hydrogel supported fibroblasts proliferation as well as exhibited suitable biocompatibility and biodegradability behaviors [126]. In another study, Intini et al. developed a 3D-printed chitosan-based scaffold for wound healing in diabetes. They evaluated the biocompatibility and toxicity toward human fibroblasts and keratinocytes, reporting significant in vitro cell growth. In addition, the in vivo evaluation of the 3D-printed scaffolds in diabetic rats showed an improvement in the restored tissue compared to a commercial patch [127].

4.3. Drug delivery applications in wound healing

Scaffolds' behavior and mechanism are highly influenced by the physicochemical properties of the thermo-responsive polymers used for their development but also due to the regulation systems of the biological host. These natural feedbacks (e.g., inflammation, hyperthermia) aims to stabilize any condition that contrasts with the physiological balance [89]. As a result, scaffolds and their constituent biomaterials make use of these biological responses to provide novel tools for drug delivery systems that can be applied to the wound healing process [128]. These systems provide spatially and temporally controlled drug release strategies for one or more API that can accelerate tissue healing, cicatrization process, and regulate the inflammatory response [129,130].

Scaffolds made of synthetic, natural, and modified biopolymers are being loaded with small drugs or biomacromolecules (e.g., proteins, poly(nucleic acids)) [131,132]. For instance, polymers exhibiting the non-linear LCST behavior are the ones employed for wound healing drug delivery [133]. As mentioned before, these systems suffer solubility alterations upon an increase in temperature, usually above the normothermia (37 °C), where a reversible transition from a hydrophilic to a hydrophobic state takes place. Drug release is reduced below their LCST, mainly caused by surface desorption, swelling, and degradation of the polymer matrix. For high-swelling hydrophilic forms, the release depends on the diffusion through the polymer matrix, while for low-swelling polymers the release is subjected to the swelling process itself [134,135].

Moreover, a locally heated tumor presented during inflammation, either caused by tissue damage or as a response upon the introduction of a biomaterial allows enhancing drug release due to polymer chains shrinking [136]. In addition, thermo-responsive polymers can be used as injectable biomaterials in the form of a hydrogel, which allow the *in situ* formation of scaffolds, minimizing the employment of invasive methods, and representing a novel and advanced drug delivery system especially for subcutaneous application [137–140]. In this technique, the

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thermo-responsive polymer is mixed with the API at room temperature for subsequent injection into the body. After that, the body's temperature increase above polymer LCST induces a phase transition that forms a physical gel, favoring the release of the drug from the scaffold [141–143].

Andrgie et al. developed an injectable heparin-conjugated PNIPAAm *in situ* gel-forming polymer with encapsulated ibuprofen to address pain and excessive inflammation during wound healing. *In vitro* analysis showed a reduction of pro-inflammatory mediators due to the released drug. In addition, the hydrogel was applied to wound on the back of mice, revealing that the formulation improved healing compared to a placebo group, thus presenting this *in situ* forming-scaffold as a promising therapy approach [144].

As presented in table 1, there are several drug delivery applications of thermo-responsive scaffolds for wound healing such as pain, inflammation, microbial infections, and prevention of large scar tissue [145,146].

Table 1. Thermo-responsive scaffolds for drug delivery in wound healing.

Polymer system	Delivered Drug	Application	Release time	Ref
Gelatin	Ibuprofen	Inflammation and bone regeneration	100 h	[147]
PLGA	Ibuprofen	Inflammation	30 h	[148]
Poly(*N*-vinylcaprolactam-*co*-methacrylic acid)	Ketoprofen	Inflammation	50 h	[149]
Poly(di(ethylene glycol) methyl ether methacrylate), Ethyl cellulose	Ketoprofen	Inflammation	100 h (80%)	[150]
Sodium alginate	Celecoxib	Hyperthermia	-	[151]
Chitosan, PCL	Ferulic acid, resveratrol	Inflammation, pro-angiogenic	120 h (55% of ferulic acid and 48% of resveratrol)	[152]
PVA, chitosan	Tetracycline HCl	Bacterial infection	4 h (80%)	[153]
Chitosan, PEG	Ciprofloxacin HCl	Bacterial infection	20 h (30%)	[154]
Chitosan, alginate	Alpha-tocoferol	Skin injuries, oxidative process	14 days (77%)	[155]
Eudragit	Gentamicin sulphate	Bacterial infection in diabetic ulcer	12 h (90% at acid pH)	[156]
PLGA	Clorhexidine	Infection treatment	50 days	[157]
PCLA, PVA, chitosan	Metformin HCl	Epidural adhesion, fibrosis	15 days	[158]

Chronic wounds and ulcers caused by different diseases such as diabetes demand advanced therapies for treating them since chronic inflammation and poor tissue regeneration are complications that can lead to amputation [159,160]. Lee et al. developed core-shell nanofibrous

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bioactive insulin-loaded PLGA scaffolds through coaxial electrospinning for sustained release of the synthetic hormone in diabetic rats. The scaffolds exhibited a release of the molecule during four weeks, which promoted diabetic wound healing [161].

Karri et al. explored the application of curcumin in the management of diabetic wound healing. In this study, they developed a novel nanohybrid scaffold that consisted firstly in the incorporation of curcumin in chitosan nanoparticles to a subsequent impregnation into a collagen scaffold, which provides better tissue generation. The study suggests that the synergistic combination of curcumin as an anti-inflammatory drug, and chitosan and collagen as a drug carrier and wound healing scaffold have an outstanding wound healing capacity [162].

Garakani et al. synthesized PLGA microparticles loaded with dexamethasone, which was dispersed in different hydrogels of chitosan/PVP. The obtained scaffolds possessed an amorphous structure that facilitated the dissolution of the microparticles, as well as a high swelling ratio and controlled biodegradability rate. The study reported a slower release upon the addition of PVP. However, the designed scaffolds released 75-85% of the drug after 30 days, while the loaded microparticles fully release the complete dose after 22 days. Therefore, this formulation can be considered as a sustained release thermo-responsive drug delivery alternative for wound healing in a 30 day-course [163].

Also, as reported by Hao et al. thermo-responsive scaffolds have been employed for tissue regeneration and controlling the inflammation caused by periodontal diseases. In this study, a bio-sensitive PLGA/mesoporous silica nanocarriers core-shell porous microsphere encapsulated PLA spongy nanofibrous micro scaffold was developed for local injection delivering of celecoxib into periodontal tissue. The drug release provided significant control of the inflammation, while the scaffold contributed to the formation of new tissue, resulting in an effective approach for treating periodontal disease [164].

The study reported by Zehra et al. presents a concern for scar-free healing and pain management in wound healing. To address this, the research group developed a 3D porous biomimetic scaffold with a novel combination of polymers; chitosan and sodium alginate. Additionally, the scaffold was loaded with ibuprofen. The development resulted suitable for tissue engineering applications due to its nano- and microporous structures. Also, the scaffold showed a sustained drug release in vitro, which is considered ideal for the sake of minimal inflammation and pain management [165].

Furthermore, wounds are vulnerable to suffering from bacterial infection, which can extend the inflammatory process and increase its intensity [166,167]. Several research groups have worked on different strategies that combine natural antimicrobial and anti-inflammatory approaches for wound healing [168,169]. Regarding this, García et al. developed an electrospun PCL-based anti-inflammatory scaffold loaded with thymol (THY) and tyrosol (TYR) essential oils. The study aimed to reduce inflammation and minimize the risk of infected wounds, as well as reducing antimicrobial resistance due to the indiscriminate use of antibiotics. Furthermore, the authors reported that PCL-THY exhibited a more efficient down-regulation of pro-inflammatory genes compared to the PCL-TYR and PCL-THY-TYR systems [170].

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In another approach, Mahmoud and Salama employed the freeze-drying technique for the preparation of norfloxacin-loaded scaffolds for wound treating. The scaffolds were composed of collagen with chitosan HCl or with chitosan low molecular weight. Although the selected chitosan conditioned the mechanical strength, both provided an extended biodegradability and showed almost a 100% release of the antibiotic drug after 24 h. In addition, the in vivo study in Albino rats revealed after 28 days of wound dressing that tissue regeneration time was faster compared to non-treated wounds [171].

Moreover, burn infections are also a major concern in wound healing therapies since they are the most traumatic and physically disabling injuries, leading to high morbidity and mortality rates [172]. In this sense, Lan et al. designed an antibacterial silk fibroin scaffold with gelatin microspheres impregnated with gentamycin sulfate, which were further embedded in the silk fibroin matrix. After 21 days the scaffold not only served as a tissue regeneration template when evaluated in a rat full-thickness burn infection model but provided a sustained release of the API and exhibited stronger antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa.* Therefore, this can be considered as a promising approach for wound healing and burn infection treatment in severely burned patients [173].

5. Conclusions

Thermo-responsive polymers are currently one of the most important materials in nanotechnological, tissue engineering and biomedical fields for the development of scaffolds. Their amphiphilic nature and the ease for tunning of their physicochemical properties through novel techniques, enable the delivery of different drugs and biomolecules for wound healing. Moreover, their self-healing properties make them suitable for the fabrication of scaffolds that provide faster tissue regeneration in the affected area. Special emphasis should be paid to the process parameters under which an optimum design allows obtaining a high-quality, biocompatible and biodegrable drug delivery system according to the wound needs.

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