Review

Bioengineered Scaffolds for Thermo-responsive Drug Delivery in Wound Healing

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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
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 leucocytes. Moreover,
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 prorregenerative 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), polyethylene glycol (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 (\(\Delta G\)) to negative values represent the condition under which polymers are soluble [51]. This happens when the change in entropy (\(\Delta S\)) 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 \(\Delta G\), 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].
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 $\Delta G$ at a certain temperature, the polymer will not be miscible under those conditions, and two different phases will co-exist [60,61].

![Phase Diagram](image)

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 $\Delta G$ is negative [62]. The previous is due to the negative change in enthalpy ($\Delta H$) 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 $\Delta S$ [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 $\Delta S$ overcomes the negative $\Delta H$, it gives $\Delta G$ 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].
On the other hand, solubility and physical changes of some polymers are due to UCST. Above that parameter, $\Delta S$ and $\Delta H$ 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.
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 acquire 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
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].
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
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         | 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
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].
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 tuning 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 biodegradable drug delivery system according to the wound needs.

Author Contributions: Conceptualization, L.C.H. and J.R.V.; methodology, L.C.H. and J.C.A.; investigation, L.C.H. and J.C.A.; resources, J.R.V. and M.L.C; writing—original draft preparation, L.C.H. and J.C.A.; writing—review and editing, L.C.H and J.V.B.; visualization, J.C.A. and M.L.C.; supervision, J.R.V. and M.L.C.; project administration, J.R.V. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. O’Brien, F.J. Biomaterials & scaffolds for tissue engineering. Materials Today 2011, 14, 88–95, doi:10.1016/S1369-7021(11)70058-X.

2. Singh, B.N.; Panda, N.N.; Mund, R.; Pramanik, K. Carboxymethyl cellulose enables silk fibroin nanofibrous scaffold with enhanced biomimetic potential for bone tissue engineering application. Carbohydrate Polymers 2016, 151, 335–347, doi:10.1016/j.carbpol.2016.05.088.
3. Zhu, J.; Marchant, R.E. Design properties of hydrogel tissue-engineering scaffolds. Expert Review of Medical Devices 2011, 8, 607–626, doi:10.1586/erd.11.27.

4. Okamoto, M.; John, B. Synthetic biopolymer nanocomposites for tissue engineering scaffolds. Progress in Polymer Science 2013, 38, 1487–1503, doi:10.1016/j.progpolymsci.2013.06.001.

5. Tissue engineering for the management of chronic wounds: current concepts and future perspectives - Wong - 2012 - Experimental Dermatology - Wiley Online Library Available online: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1600-0625.2012.01542.x.

6. Sunthonmord, R.; An, J.; Chua, C.K. Bioprinting of Thermoresponsive Hydrogels for Next Generation Tissue Engineering: A Review. Macromolecular Materials and Engineering 2017, 302, 1600266, doi:https://doi.org/10.1002/mame.201600266.

7. Dubský, M.; Kubinová, Š.; Širc, J.; Voska, L.; Zajiček, R.; Zajicová, A.; Lesný, P.; Jirkovská, A.; Michálek, J.; Munzarová, M.; et al. Nanofibers prepared by needleless electrospinning technology as scaffolds for wound healing. J Mater Sci: Mater Med 2012, 23, 931–941, doi:10.1007/s10856-012-4577-7.

8. Emerging applications of stimuli-responsive polymer materials | Nature Materials Available online: https://www.nature.com/articles/nmat2614/briefing/signup/.

9. Wei, M.; Gao, Y.; Li, X.; J. Serpe, M. Stimuli-responsive polymers and their applications. Polymer Chemistry 2017, 8, 127–143, doi:10.1039/C6PY01585A.

10. Mura, S.; Nicolas, J.; Couvreur, P. Stimuli-responsive nanocarriers for drug delivery. Nature Materials 2013, 12, 991–1003, doi:10.1038/nmat3776.

11. Karimi, M.; Sahandi Zangabad, P.; Ghasemi, A.; Amiri, M.; Bahrami, M.; Malekzad, H.; Ghaframanzadeh Asl, H.; Mahdieh, Z.; Bozorgomid, M.; Ghasemi, A.; et al. Temperature-Responsive Smart Nanocarriers for Delivery Of Therapeutic Agents: Applications and Recent Advances. ACS Appl. Mater. Interfaces 2016, 8, 21107–21133, doi:10.1021/acsami.6b00371.

12. Bedoya, D.A.; Figueroa, F.N.; Macchione, M.A.; Strumia, M.C. Stimuli-Responsive Polymeric Systems for Smart Drug Delivery. In Advanced Biopolymeric Systems for Drug Delivery; Nayak, A.K., Hasnain, M.S., Eds.; Advances in Material Research and Technology; Springer International Publishing: Cham, 2020; pp. 115–134 ISBN 978-3-030-46923-8.

13. Heskins, M.; Guillet, J.E. Solution Properties of Poly(N-isopropylacrylamide). Journal of Macromolecular Science: Part A - Chemistry 1968, 2, 1441–1455, doi:10.1080/10601326808051910.

14. Teotia, A.K.; Sami, H.; Kumar, A. 1 - Thermo-responsive polymers: structure and design of smart materials. In Switchable and Responsive Surfaces and Materials for Biomedical Applications; Zhang, Z., Ed.; Woodhead Publishing: Oxford, 2015; pp. 3–43 ISBN 978-0-85709-713-2.

15. Gandhi, A.; Paul, A.; Sen, S.O.; Sen, K.K. Studies on thermoresponse polymers: Phase behaviour, drug delivery and biomedical applications. Asian Journal of Pharmaceutical Sciences 2015, 10, 99–107, doi:10.1016/j.ajps.2014.08.010.

16. Fitzpatrick, S.D.; Fitzpatrick, L.E.; Thakur, A.; Mazumder, M.A.J.; Sheardown, H. Temperature-sensitive polymers for drug delivery. Expert Review of Medical Devices 2012, 9, 339–351, doi:10.1586/erd.12.24.

17. Dunne, M.; Hynynen, K.; Allen, C. Thermosensitive nanomedicines could revolutionize thermal therapy in oncology. Nano Today 2017, 16, 9–13, doi:10.1016/j.nantod.2017.08.001.

18. Kopeček, J.; Yang, J. Polymer nanomedicines. Advanced Drug Delivery Reviews 2020, doi:10.1016/j.addr.2020.07.020.

19. Eming, S.A.; Hammerschmidt, M.; Krieg, T.; Roers, A. Interrelation of immunity and tissue repair or regeneration. Seminars in Cell & Developmental Biology 2009, 20, 517–527, doi:10.1016/j.semcdb.2009.04.009.

20. Strbo, N.; Yin, N.; Stojadinovic, O. Innate and Adaptive Immune Responses in Wound Epithelialization. Adv Wound Care (New Rochelle) 2014, 3, 492–501, doi:10.1089/wound.2012.0435.
21. Mauri, C.; Bosma, A. Immune Regulatory Function of B Cells. Annual Review of Immunology 2012, 30, 221–241, doi:10.1146/annurev-immunol-020711-074934.

22. Takeuchi, O.; Akira, S. Pattern Recognition Receptors and Inflammation. Cell 2010, 140, 805–820, doi:10.1016/j.cell.2010.01.022.

23. Nosbaum, A.; Prevel, N.; Truong, H.-A.; Mehta, P.; Ettinger, M.; Scharschmidt, T.C.; Ali, N.H.; Pauli, M.L.; Abbas, A.K.; Rosenblum, M.D. Cutting Edge: Regulatory T Cells Facilitate Cutaneous Wound Healing. The Journal of Immunology 2016, 196, 2010–2014, doi:10.4049/jimmunol.1502139.

24. Shukla, S.K.; Sharma, A.K.; Gupta, V.; Yashavardhan, M.H. Pharmacological control of inflammation in wound healing. Journal of Tissue Viability 2019, 28, 218–222, doi:10.1016/j.jtv.2019.09.002.

25. Bielefeld, K.A.; Amini-Nik, S.; Alman, B.A. Cutaneous wound healing: recruiting developmental pathways for regeneration. Cell. Mol. Life Sci. 2013, 70, 2059–2081, doi:10.1007/s00018-012-1152-9.

26. Wu, Y.-S.; Chen, S.-N. Apoptotic cell: linkage of inflammation and wound healing. Front. Pharmacol. 2014, 5, doi:10.3389/fphar.2014.00001.

27. Tatler, A.L.; Jenkins, G. TGF-β Activation and Lung Fibrosis. Proc Am Thorac Soc 2012, 9, 130–136, doi:10.1513/pats.201201-003AW.

28. Association of Interferon- and Transforming Growth Factor β-Regulated Genes and Macrophage Activation With Systemic Sclerosis–Related Progressive Lung Fibrosis - Christmann - 2014 - Arthritis && Rheumatology - Wiley Online Library Available online: https://onlinelibrary.wiley.com/doi/full/10.1002/art.38288.

29. Ciaccia, L. Fundamentals of Inflammation. Yale J Biol Med 2011, 84, 64–65.

30. Oberszyn, T.M. Frontiers in;

31. Koh, T.J.; DiPietro, L.A. Inflammation and wound healing: the role of the macrophage. Expert Reviews in Molecular Medicine 2011, 13, doi:10.1017/S1462399411001943.

32. Babensee, J.E. 2.2.2 - Inflammation, Wound Healing, the Foreign-Body Response, and Alternative Tissue Responses. In Biomaterials Science (Fourth Edition); Wagner, W.R., Sakiyama-Elbert, S.E., Zhang, G., Yaszmenski, M.J., Eds.; Academic Press, 2020; pp. 737–746 ISBN 978-0-12-816137-1.

33. Chen, L.; Deng, H.; Cui, H.; Fang, J.; Zuo, Z.; Deng, J.; Li, Y.; Wang, X.; Zhao, L. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget 2017, 9, 7204–7218, doi:10.18632/oncotarget.23208.

34. Vanparijs, N.; Nuhn, L.; Geest, B.G.D. Transiently thermoresponsive polymers and their applications in biomedicine. Chem. Soc. Rev. 2017, 46, 1193–1239, doi:10.1039/C6CS00748A.

35. Li, M.; He, X.; Ling, Y.; Tang, H. Dual thermo-responsive homopolypeptide with LCST-type linkages and UCST-type pendants: Synthesis, characterization, and thermo-responsive properties. Polymer 2017, 132, 264–272, doi:10.1016/j.polymer.2017.11.016.

36. Song, L.; Zhang, B.; Jin, E.; Xiao, C.; Li, G.; Chen, X. A reduction-sensitive thermo-responsive polymer: Synthesis, characterization, and application in controlled drug release. European Polymer Journal 2018, 101, 183–189, doi:10.1016/j.eurpolymj.2018.02.022.

37. Zhang, Q.; Weber, C.; Schubert, U.S.; Hoogenboom, R. Thermoresponsive polymers with lower critical solution temperature: from fundamental aspects and measuring techniques to recommended turbidimetry conditions. Mater. Horiz. 2017, 4, 109–116, doi:10.1039/C7MH00016B.

38. Aseyev, V.; Tenhu, H.; Winnik, F.M. Non-ionic Thermoresponsive Polymers in Water. In Self Organized Nanostructures of Amphiphilic Block Copolymers II; Müller, A.H.E., Borisov, O., Eds.; Advances in Polymer Science; Springer: Berlin, Heidelberg, 2011; pp. 29–89 ISBN 978-3-642-22297-9.

39. Ng, W.S.; Connal, L.A.; Forbes, E.; Mohanarangam, K.; Franks, G.V. In situ investigation of aggregate sizes formed using thermo-responsive polymers: Effect of temperature and shear. Journal of Colloid and Interface Science 2017, 494, 139–152, doi:10.1016/j.jcis.2017.01.067.
57. Sun, Y.; Nan, D.; Jin, H.; Qu, X. Recent advances of injectable hydrogels for drug delivery and tissue engineering applications. *Polymer Testing* 2020, 81, 106283, doi:10.1016/j.polymertesting.2019.106283.

58. Gasperini, L.; Mano, J.F.; Reis, R.L. Natural polymers for the microencapsulation of cells. *Journal of The Royal Society Interface* 2014, 11, 20140817, doi:10.1098/rsif.2014.0817.

59. Jayakumar, R.; Menon, D.; Manzoor, K.; Nair, S.V.; Tamura, H. Biomedical applications of chitin and chitosan based nanomaterials—A short review. *Carbohydrate Polymers* 2010, 82, 227–232, doi:10.1016/j.carbpol.2010.04.074.

60. Pezeshki-Modaress, M.; Rajabi-Zeleti, S.; Zandi, M.; Mirzadeh, H.; Sodeti, N.; Nekookar, A.; Aghdami, N. Cell-loaded gelatin/chitosan scaffolds fabricated by salt-leaching/lyophilization for skin tissue engineering: In vitro and in vivo study. *Journal of Biomedical Materials Research Part A* 2014, 102, 3908–3917, doi:https://doi.org/10.1002/jbm.a.35054.

61. Azuma, K.; Izumi, R.; Osaki, T.; Ifuku, S.; Morimoto, M.; Saimoto, H.; Minami, S.; Okamoto, Y. Chitin, Chitosan, and Its Derivatives for Wound Healing: Old and New Materials. *Journal of Functional Biomaterials* 2015, 6, 104–142, doi:10.3390/jfb60100104.

62. Song, F.; Wang, X.-L.; Wang, Y.-Z. Poly (N-isopropylacrylamide)/poly (ethylene oxide) blend nanofibrous scaffolds: Thermo-responsive carrier for controlled drug release. *Colloids and Surfaces B: Biointerfaces* 2011, 88, 749–754, doi:10.1016/j.colsurfb.2011.08.015.

63. Alf, M.E.; Hatton, T.A.; Gleason, K.K. Novel N-isopropylacrylamide based polymer architecture for faster LCST transition kinetics. *Polymer* 2011, 52, 4429–4434, doi:10.1016/j.polymer.2011.07.051.

64. Sarwan, T.; Kumar, P.; Choonara, Y.E.; Pillay, V. Hybrid Thermo-Responsive Polymer Systems and Their Biomedical Applications. *Front. Mater.* 2020, 7, doi:10.3389/fmats.2020.00073.

65. Kim, B.-R.; Nguyen, T.B.L.; Min, Y.-K.; Lee, B.-T. In Vitro and In Vivo Studies of BMP-2-Loaded PCL–Gelatin–BCP Electrospun Scaffolds. *Tissue Engineering Part A* 2014, 20, 3279–3289, doi:10.1089/en.tea.2014.0081.

66. Zhang, Z.; Cui, H. Biodegradability and Biocompatibility Study of Poly(Chitosan-g-lactic Acid) Scaffolds. *Molecules* 2012, 17, 3243–3258, doi:10.3390/molecules17033243.

67. Boustta, M.; Colombo, P.-E.; Lenglet, S.; Poujol, S.; Vert, M. Versatile UCST-based thermo-responsive hydrogels for loco-regional sustained drug delivery. *Journal of Controlled Release* 2014, 174, 1–6, doi:10.1016/j.jconrel.2013.10.040.

68. Prudic, A.; Ji, Y.; Sadowski, G. Thermodynamic Phase Behavior of API/Polymer Solid Dispersions. *Mol. Pharmaceutics* 2014, 11, 2294–2304, doi:10.1021/mp400729x.

69. Seuring, J.; Agarwal, S. Polymers with Upper Critical Solution Temperature in Aqueous Solution. *Macromolecular Rapid Communications* 2012, 33, 1898–1920, doi:https://doi.org/10.1002/marc.201200433.

70. Zarrintaj, P.; Jouyandeh, M.; Ganjali, M.R.; Hadavand, B.S.; Mozafari, M.; Sheiko, S.S.; Vatanagh-Varnooosfaderani, M.; Gutiérrez, T.J.; Saeb, M.R. Thermo-sensitive polymers in medicine: A review. *European Polymer Journal* 2019, 117, 402–423, doi:10.1016/j.europolyj.2019.05.024.

71. Lu, H.; Du, S. A phenomenological thermodynamic model for the chemo-responsive shape memory effect in polymers based on Flory–Huggins solution theory. *Polym. Chem.* 2014, 5, 1155–1162, doi:10.1039/C3PY01256E.

72. Donnelly, C.; Tian, Y.; Potter, C.; Jones, D.S.; Andrews, G.P. Probing the Effects of Experimental Conditions on the Character of Drug-Polymer Phase Diagrams Constructed Using Flory-Huggins Theory. *Pharm Res* 2015, 32, 167–179, doi:10.1007/s11095-014-1453-9.

73. Jeong, B.; Kim, S.W.; Bae, Y.H. Thermosensitive sol–gel reversible hydrogels. *Advanced Drug Delivery Reviews* 2012, 64, 154–162, doi:10.1016/j.addr.2012.09.012.

74. Sol-gel transition behavior near critical concentration and connectivity | Polymer Journal Available online: https://www.nature.com/articles/pj2015124 (accessed on Nov 29, 2020).
58. Sun, W.; An, Z.; Wu, P. UCST or LCST? Composition-Dependent Thermoresponsive Behavior of Poly(N-acryloylglycinamide-co-diacetone acrylamide). Macromolecules 2017, 50, 2175–2182, doi:10.1021/acs.macromol.7b00020.

59. Käfer, F.; Liu, F.; Stahlschmidt, U.; Jérôme, V.; Freitag, R.; Karg, M.; Agarwal, S. LCST and UCST in One: Double Thermoresponsive Behavior of Block Copolymers of Poly(ethylene glycol) and Poly(acrylamide-co-acrylonitrile). Langmuir 2015, 31, 8940–8946, doi:10.1021/acs.langmuir.5b02006.

60. Clark, E.A.; Lipson, J.E.G. LCST and UCST behavior in polymer solutions and blends. Polymer 2012, 53, 536–545, doi:10.1016/j.polymer.2011.11.045.

61. Sugeno, K.; Kokubun, S.; Saito, H. UCST Type Phase Boundary and Accelerated Crystallization in PTT/PET Blends. Polymers 2020, 12, 2730, doi:10.3390/polym12112730.

62. Roy, D.; Brooks, W.L.A.; Sumerlin, B.S. New directions in thermoresponsive polymers. Chem. Soc. Rev. 2013, 42, 7214–7243, doi:10.1039/C3CS35499G.

63. Ding, Y.; Yan, Y.; Peng, Q.; Wang, B.; Xing, Y.; Hua, Z.; Wang, Z. Multiple Stimuli-Responsive Cellulose Hydrogels with Tunable LCST and UCST as Smart Windows. ACS Appl. Polym. Mater. 2020, 2, 3259–3266, doi:10.1021/acsapm.0c00414.

64. Halperin, A.; Kröger, M.; Winnik, F.M. Poly(N-isopropylacrylamide) Phase Diagrams: Fifty Years of Research. Angewandte Chemie International Edition 2015, 54, 15342–15367, doi:https://doi.org/10.1002/anie.201506663.

65. Pasparakis, G.; Tsitsilianis, C. LCST polymers: Thermoresponsive nanostructured assemblies towards bioapplications. Polymer 2020, 211, 123146, doi:10.1016/j.polymer.2020.123146.

66. Heyda, J.; Dzubiella, J. Thermodynamic description of Hofmeister effects on the LCST of thermosensitive polymers. J. Phys. Chem. B 2014, 118, 10979–10988, doi:10.1021/jp5041635.

67. Heyda, J.; Soll, S.; Yuan, J.; Dzubiella, J. Thermodynamic Description of the LCST of Charged Thermoresponsive Copolymers. Macromolecules 2014, 47, 2096–2102, doi:10.1021/ma402577h.

68. Lee, C.H.; Bae, Y.C. Thermodynamic framework for switching the lower critical solution temperature of thermo-sensitive particle gels in aqueous solvent. Polymer 2020, 195, 122428, doi:10.1016/j.polymer.2020.122428.

69. Zhao, Y.; Ma, J.; Yu, X.; Li, M.-H.; Hu, J. Tunable UCST thermoresponsive copolymers based on natural glycyrrhetinic acid. Chinese Chemical Letters 2020, doi:10.1016/j.cclet.2020.03.057.

70. Niskanen, J.; Tenhu, H. How to manipulate the upper critical solution temperature (UCST)? Polym. Chem. 2016, 8, 220–232, doi:10.1039/C6PY01612J.

71. Zhao, Y.; Ma, J.; Yu, X.; Li, M.-H.; Hu, J. Tunable UCST thermoresponsive copolymers based on natural glycyrrhetinic acid. Chinese Chemical Letters 2020, doi:10.1016/j.cclet.2020.03.057.

72. Asadujjaman, A.; Oliveira, T.E. de; Mukherji, D.; Bertin, A. Polyacrylamide “revisited”: UCST-type reversible thermoresponsive properties in aqueous alcoholic solutions. Soft Matter 2018, 14, 1336–1343, doi:10.1039/C7SM02424J.

73. Mäkinen, L.; Varadharajan, D.; Tenhu, H.; Hietala, S. Triple Hydrophilic UCST–LCST Block Copolymers. Macromolecules 2016, 49, 986–993, doi:10.1021/acs.macromol.5b02543.

74. Schizophrenic Core–Shell Microgels: Thermoregulated Core and Shell Swelling/Collapse by Combining UCST and LCST Phase Transitions | Langmuir Available online: https://pubs.acs.org/doi/abs/10.1021/la500133y?cadena_token=HkLtImYiqAAAAA9xn-TgDfGgS7StC658KBPdIkK85pM-JHLXw-UL-vqKh2npK5pFscs5IB0E_rkBd5h6RPsdFpm8VD.

75. Ieong, N.S.; Hasan, M.; Phillips, D.J.; Saaka, Y.; O’Reilly, R.K.; Gibson, M.J. Polymers with molecular weight dependent LCSTs are essential for cooperative behaviour. Polym. Chem. 2012, 3, 794–799, doi:10.1039/C2PY00604A.
76. Rajan, R.; Matsumura, K. Tunable Dual-Thermoresponsive Core–Shell Nanogels Exhibiting UCST and LCST Behavior. *Macromolecular Rapid Communications* 2017, 38, 1700478, doi:https://doi.org/10.1002/marc.201700478.

77. Kotsuchibashi, Y.; Ebara, M.; Aoyagi, T.; Narain, R. Recent Advances in Dual Temperature Responsive Block Copolymers and Their Potential as Biomedical Applications. *Polymers* 2016, 8, 380, doi:10.3390/polym8110380.

78. Doberenz, F.; Zeng, K.; Willems, C.; Zhang, K.; Groth, T. Thermoresponsive polymers and their biomedical application in tissue engineering – a review. *J. Mater. Chem. B* 2020, 8, 607–628, doi:10.1039/C9TB02052G.

79. Natural and Synthetic Biodegradable Polymers: Different Scaffolds for Cell Expansion and Tissue Formation - Annalia Asti, Luciana Gioglio, 2014 Available online: https://journals.sagepub.com/doi/full/10.5301/ijao.5000307?casa_token=XM5sON4E9UsAAAAA:vSdehZaxSgT7OPD8DaMAj_qXm41NMQBO9aycvJzk928q7CEDZ21UAxigG0HT7zu-VdntzHFEQgr2vT_.

80. Ward, M.A.; Georgiou, T.K. Thermoresponsive Polymers for Biomedical Applications. *Polymers* 2011, 3, 1215–1242, doi:10.3390/polym3031215.

81. Zhao, C.; Tian, S.; Liu, Q.; Xiu, K.; Lei, I.; Wang, Z.; Ma, P.X. Biodegradable Nanofibrous Temperature-Responsive Gelling Microspheres for Heart Regeneration. *Advanced Functional Materials* 2020, 30, 2000776, doi:https://doi.org/10.1002/adfm.202000776.

82. Zhu, Y.; Wood, N.A.; Fok, K.; Yoshizumi, T.; Park, D.W.; Jiang, H.; Schwartzman, D.S.; Zenati, M.A.; Uchibori, T.; Wagner, W.R.; et al. Design of a Coupled Thermoresponsive Hydrogel and Robotic System for Postinfarct Biomaterial Injection Therapy. *The Annals of Thoracic Surgery* 2016, 102, 780–786, doi:10.1016/j.athoracsur.2016.02.082.

83. Covalent Cross-Linked Polymer Gels with Reversible Sol–Gel Transition and Self-Healing Properties | Macromolecules Available online: https://pubs.acs.org/doi/abs/10.1021/ma9022197?casa_token=X3SH0n4E9UsAAAAA:vSdehZaxSgT7OPD8DaMAj_qXm41NMQBO9aycvJzk928q7CEDZ21UAxigG0HT7zu-VdntzHFEQgr2vT_.

84. Guo, Z.; Yin, H.; Feng, Y.; He, S. Functionalization of single-walled carbon nanotubes with thermo-responsive poly(N-isopropylacrylamide): effect of the polymer architecture. *RSC Advances* 2016, 6, 37953–37964, doi:10.1039/C6RA0998K.

85. Porsch, C.; Hansson, S.; Nordgren, N.; Malmström, E. Thermo-responsive cellulose-based architectures: tailoring LCST using poly(ethylene glycol) methacrylates. *Polymer Chemistry* 2011, 2, 1114–1123, doi:10.1039/C0PY00417K.

86. Dickinson, L.E.; Gerecht, S. Engineered Biopolymeric Scaffolds for Chronic Wound Healing. *Front. Physiol.* 2016, 7, doi:10.3389/fphys.2016.00341.

87. Shah, T.V.; Vasava, D.V. A glimpse of biodegradable polymers and their biomedical applications. *e-Polymers* 2019, 19, 385–410, doi:10.1515/epoly-2019-0041.

88. Mughdamm, S.Z.; Thomann, E. Surface forces and friction tuned by thermo-responsive polymer films. *Current Opinion in Colloid & Interface Science* 2020, 47, 27–45, doi:10.1016/j.cocis.2019.12.002.

89. Amado, S.; Morouço, P.; Pascoal-Faria, P.; Alves, N. Tailoring Bioengineered Scaffolds for Regenerative Medicine. *Biomaterials in Regenerative Medicine* 2017, doi:10.5772/intechopen.69857.

90. Zhao, C.; Ma, Z.; Zhu, X.X. Rational design of thermoresponsive polymers in aqueous solutions: A thermodynamics map. *Progress in Polymer Science* 2019, 90, 269–291, doi:10.1016/j.progpolymsci.2019.01.001.

91. Rahmani Del Bakhshayesh, A.; Annabi, N.; Khalilov, R.; Akbarzadeh, A.; Samiei, M.; Alizadeh, E.; Alizadeh-Ghodsi, M.; Davaran, S.; Montaseri, A. Recent advances on biomedical applications of scaffolds in wound healing and dermal tissue engineering. *Artif Cells Nanomed Biotechnol* 2018, 46, 691–705, doi:10.1080/21691401.2017.1349778.

92. Hollister, S.J.; Flanagan, C.L.; Zopf, D.A.; Morrison, R.J.; Nasser, H.; Wheeler, M.B.; Green, G.E. Chapter 3 - Design and Quality Control for Translating 3D-Printed Scaffolds. In *Essentials of 3D Biofabrication and Translation*; Atala, A., Yoo, J.J., Eds.; Academic Press: Boston, 2015; pp. 43–59 ISBN 978-0-12-800972-7.
93. Spontak, R.J.; Ryan, J.J. Chapter 3 - Polymer blend compatibilization by the addition of block copolymers. In *Compatibilization of Polymer Blends*; A.x., A., Thomas, S., Eds.; Elsevier, 2020; pp. 57–102 ISBN 978-0-12-816006-0.

94. Mondschein, R.J.; Kanitkar, A.; Williams, C.B.; Verbridge, S.S.; Long, T.E. Polymer structure-property requirements for stereolithographic 3D printing of soft tissue engineering scaffolds. *Biomaterials* 2017, 140, 170–188, doi:10.1016/j.biomaterials.2017.06.005.

95. Wu, Y.; Heikal, L.; Ferns, G.; Ghezzi, P.; Nokhodchi, A.; Maniruzzaman, M. Bioprinting and its applications in tissue engineering and regenerative medicine. *International Journal of Biological Macromolecules* 2018, 107, 261–275, doi:10.1016/j.ijbiomac.2017.08.171.

96. Mondschein, R.J.; Kanitkar, A.; Williams, C.B.; Verbridge, S.S.; Long, T.E. Polymer structure-property requirements for stereolithographic 3D printing of soft tissue engineering scaffolds. *Biomaterials* 2017, 140, 170–188, doi:10.1016/j.biomaterials.2017.06.005.

97. Seyednejad, H.; Gawlitta, D.; Kuiper, R.V.; de Bruin, A.; van Nostrum, C.F.; Vermonden, T.; Dhert, W.J.A.; Hennink, W.E. In vivo biocompatibility and biodegradation of 3D-printed porous scaffolds based on a hydroxyl-functionalized poly(e-caprolactone). *Biomaterials* 2012, 33, 4309–4318, doi:10.1016/j.biomaterials.2012.03.002.

98. Miguel, S.P.; Figueira, D.R.; Simões, D.; Ribeiro, M.P.; Coutinho, P.; Ferreira, P.; Correia, I.J. Electrospun polymeric nanofibers as wound dressings: A review. *Colloids and Surfaces B: Biointerfaces* 2018, 169, 60–71, doi:10.1016/j.colsurfb.2018.05.011.

99. Angammana, C.J.; Jayaram, S.H. Fundamentals of electrospinning and processing technologies. *Particulate Science and Technology* 2016, 34, 72–82, doi:10.1080/02726351.2015.1043678.

100. Mahalingam, S.; Raimi-Abraham, B.T.; Craig, D.Q.M.; Edirisinghe, M. Solubility–spinnability map and model for the preparation of fibres of polyethylene (terephthalate) using gyration and pressure. *Chemical Engineering Journal* 2015, 280, 344–353, doi:10.1016/j.cej.2015.05.114.

101. Ding, J.; Zhang, J.; Li, J.; Li, D.; Xiao, C.; Xiao, H.; Yang, H.; Zhuang, X.; Chen, X. Electrospun polymer biomaterials. *Progress in Polymer Science* 2019, 90, 1–34, doi:10.1016/j.progpolymsci.2019.01.002.

102. Castillo-Henríquez, L.; Vargas-Zúñiga, R.; Pacheco-Molina, J.; Vega-Baudrit, J. Electrospun nanofibers: A nanotechnological approach for drug delivery and dissolution optimization in poorly water-soluble drugs. *ADMET and DMPK* 2020, 8, 325–353, doi:10.5599/admet.844.

103. Har-el, Y.; Gerstenhaber, J.A.; Brodsky, R.; Huneke, R.B.; Lelkes, P.I. Electrospun soy protein scaffolds as wound dressings: Enhanced reepithelialization in a porcine model of wound healing. *Wound Medicine* 2014, 5, 9–15, doi:10.1016/j.wndm.2014.04.007.

104. Mulholland, E.J. Electrospun Biomaterials in the Treatment and Prevention of Scars in Skin Wound Healing. *Front Bioeng Biotechnol* 2020, 8, doi:10.3389/fbioe.2020.00481.

105. Joseph, B.; Augustine, R.; Kalarikkal, N.; Thomas, S.; Seantier, B.; Grohens, Y. Recent advances in electrosprun polyethylene terephthalate based scaffolds for wound healing and skin bioengineering applications. *Materials Today Communications* 2019, 19, 319–335, doi:10.1016/j.mtcomm.2019.02.009.

106. Meng, Z.X.; Zheng, W.; Li, L.; Zheng, Y.F. Fabrication, characterization and in vitro drug release behavior of electrospun PLGA/chitosan nanofibrous scaffold. *Materials Chemistry and Physics* 2011, 125, 606–611, doi:10.1016/j.matchemphys.2010.10.010.
109. Ji, W.; Yang, F.; van den Beucken, J.J.P.; Bian, Z.; Fan, M.; Chen, Z.; Jansen, J.A. Fibrous scaffolds loaded with protein prepared by blend or coaxial electrospinning. Acta Biomaterialia 2010, 6, 4199–4207, doi:10.1016/j.actbio.2010.05.025.

110. Lutz, J.-F.; Lehn, J.-M.; Meijer, E.W.; Matyjaszewski, K. From precision polymers to complex materials and systems. Nature Reviews Materials 2016, 1, 1–14, doi:10.1038/natrevmats.2016.24.

111. Srivastava, A.; Yadav, T.; Sharma, S.; Nayak, A.; Kumari, A.A.; Mishra, N. Polymers in Drug Delivery. Journal of Biosciences and Medicines 2015, 4, 69–84, doi:10.4236/jbm.2016.41009.

112. Bordat, A.; Boissenot, T.; Nicolas, J.; Tsapis, N. Thermoresponsive polymer nanocarriers for biomedical applications. Advanced Drug Delivery Reviews 2019, 138, 167–192, doi:10.1016/j.addr.2018.10.005.

113. Thermosensitive Polymer Biocompatibility Based on Interfacial Structure at Biointerface | ACS Biomaterials Science & Engineering Available online: https://pubs.acs.org/doi/abs/10.1021/acsbiomaterials.8b00081?casa_token=jC_g0WVYHeAAAAA:WxSsc6fIGNxq7s1oRMMe2d9FB3G2Gf11gyrzarlWckKWykc8ZWSY-APLWjvXZwGPeCk9Q8hI3cG.

114. Bernard, M.; Jubeli, E.; Pungente, M.D.; Yagoubi, N. Biocompatibility of polymer-based biomaterials and medical devices – regulations, in vitro screening and risk-management. Biomater. Sci. 2018, 6, 2025–2053, doi:10.1039/C8BM00518D.

115. Four-Dimensional Printing Hierarchy Scaffolds with Highly Biocompatible Smart Polymers for Tissue Engineering Applications | Tissue Engineering Part C: Methods Available online: https://www.liebertpub.com/doi/abs/10.1089/ten.tec.2015.0542.

116. Cui, Z.; Lee, B.H.; Pauken, C.; Vernon, B.L. Degradation, cytotoxicity, and biocompatibility of NIPAAm-based thermosensitive, injectable, and bioresorbable polymer hydrogels. Journal of Biomedical Materials Research Part A 2011, 98A, 159–166, doi:https://doi.org/10.1002/jbm.a.33093.

117. Anderson, J.M.; Shive, M.S. Biodegradation and biocompatibility of PLA and PLGA microspheres. Advanced Drug Delivery Reviews 2012, 64, 72–82, doi:10.1016/j.addr.2012.09.004.

118. P., B. Wound healing and the role of fibroblasts. J Wound Care 2013, 22, 407–412, doi:10.12968/jowc.2013.22.8.407.

119. Janoušková, O. Synthetic Polymer Scaffolds for Soft Tissue Engineering. Physiol Res 2018, S335–S348, doi:10.33549/physiolres.933983.

120. Polymeric Scaffolds in Tissue Engineering Application: A Review Available online: https://www.hindawi.com/journals/jpps/2011/290602/.

121. Hogan, K.J.; Mikos, A.G. Biodegradable thermoresponsive polymers: Applications in drug delivery and tissue engineering. Polymer 2020, 211, 123063, doi:10.1016/j.polymer.2020.123063.

122. Song, R.; Murphy, M.; Li, C.; Ting, K.; Soo, C.; Zheng, Z. Current development of biodegradable polymeric materials for biomedical applications Available online: https://www.dovepress.com/current-development-of-biodegradable-polymeric-materials-for-biomedica-peer-reviewed-article-DDDT.

123. Ikada, Y. Biodegradable Polymers as Scaffolds for Tissue Engineering. In Handbook of Biodegradable Polymers; John Wiley & Sons, Ltd: pp. 341–362 ISBN 978-3-527-63581-8.

124. Cho, S.J.; Jung, S.M.; Kang, M.; Shin, H.S.; Youk, J.H. Preparation of hydrophilic PCL nanofiber scaffolds via electrospinning of PCL/PVP-b-PCL block copolymers for enhanced cell biocompatibility. Polymer 2015, 69, 95–102, doi:10.1016/j.polymer.2015.05.037.

125. Ji, W.; Yang, F.; Seyedneiderad, H.; Chen, Z.; Hennink, W.E.; Anderson, J.M.; van den Beucken, J.J.P.; Jansen, J.A. Biocompatibility and degradation characteristics of PLGA-based electrospun nanofibrous scaffolds with nanoapatite incorporation. Biomaterials 2012, 33, 6604–6614, doi:10.1016/j.biomaterials.2012.06.018.
126. Xu, C.; Molino, B.Z.; Wang, X.; Cheng, F.; Xu, W.; Molino, P.; Bacher, M.; Su, D.; Rosenau, T.; Willför, S.; et al. 3D printing of nanocellulose hydrogel scaffolds with tunable mechanical strength towards wound healing application. J. Mater. Chem. B 2018, 6, 7066–7075, doi:10.1039/C8TB01757C.

127. Intini, C.; Elviri, L.; Cabral, J.; Mros, S.; Bergonzi, C.; Bianchera, A.; Flammini, L.; Govoni, P.; Barocelli, E.; Bettini, R.; et al. 3D-printed chitosan-based scaffolds: An in vitro study of human skin cell growth and an in-vivo wound healing evaluation in experimental diabetes in rats. Carbohydrate Polymers 2018, 199, 593–602, doi:10.1016/j.carbpol.2018.07.057.

128. Calori, I.R.; Braga, G.; de Jesus, P. da C.C.; Bi, H.; Tedesco, A.C. Polymer scaffolds as drug delivery systems. European Polymer Journal 2020, 129, 109621, doi:10.1016/j.eurpolymj.2020.109621.

129. Garg, T.; Singh, O.; Arora, S.; Murthy, R. Scaffold: a novel carrier for cell and drug delivery. Crit Rev Ther Drug Carrier Syst 2012, 29, 1–63, doi:10.1615/critrevtherdrugcarriersyst.v29.i1.10.

130. Ghosh Dastidar, D.; Chakrabarti, G. Chapter 6 - Thermoresponsive Drug Delivery Systems, Characterization and Application. In Applications of Targeted Nano Drugs and Delivery Systems; Mohapatra, S.S., Ranjan, S., Dasgupta, N., Mishra, R.K., Thomas, S., Eds.; Micro and Nano Technologies; Elsevier, 2019; pp. 133–155 ISBN 978-0-12-814029-1.

131. Nicolas, J.; Mura, S.; Brambilla, D.; Mackiewicz, N.; Covreur, P. Design, functionalization strategies and biomedical applications of targeted biodegradable/biocompatible polymer-based nanocarriers for drug delivery. Chem. Soc. Rev. 2013, 42, 1147–1235, doi:10.1039/C2CS35265F.

132. Platelet-rich plasma-loaded chitosan scaffolds: Preparation and growth factor release kinetics - Kutlu - 2013 - Journal of Biomedical Materials Research Part B: Applied Biomaterials - Wiley Online Library Available online: https://onlinelibrary.wiley.com/doi/full/10.1002/jbm.b.32806?casa_token=g2YO5qOxyBsNGAsUN5WOqloFoOTp_K9hNFwDfzYzfzXs8gQyFLw0nGtDHbZ5pkO2wv9Q.

133. Sponchioni, M.; Capasso Palmiero, U.; Moscatelli, D. Thermo-responsive polymers: Applications of smart materials in drug delivery and tissue engineering. Materials Science and Engineering: C 2019, 102, 589–605, doi:10.1016/j.msec.2019.04.069.

134. Jin, S.G.; Yousaf, A.M.; Kim, K.S.; Kim, D.W.; Kim, D.S.; Kim, J.K.; Yong, C.S.; Youn, Y.S.; Kim, J.O.; Choi, H.-G. Influence of hydrophilic polymers on functional properties and wound healing efficacy of hydrocolloid based wound dressings. International Journal of Pharmaceutics 2016, 501, 160–166, doi:10.1016/j.ijpharm.2016.01.044.

135. Sharma, M.; Waterhouse, G.I.N.; Loader, S.W.C.; Garg, S.; Svirskis, D. High surface area polypyrrole scaffolds for tunable drug delivery. International Journal of Pharmaceutics 2013, 443, 163–168, doi:10.1016/j.ijpharm.2013.01.006.

136. Wu, Y.; Zhou, F.; Yang, L.; Liu, J. A shrinking strategy for creating dynamic SERS hot spots on the surface of thermosensitive polymer nanospheres. Chem. Commun. 2013, 49, 5025–5027, doi:10.1039/C3CC40875B.

137. L. K. Thermoresponsive hydrogels in biomedical applications: A seven-year update. Eur J Pharm Biopharm 2015, 97, 338–349, doi:10.1016/j.ejpb.2015.05.017.

138. Bög, C.; H. C.; Ss, L.; Q. D.; Yi, W.; Xi, L.; Z. L. Poly(carbonate urethane)-Based Thermogels with Enhanced Drug Release Efficacy for Chemotherapeutic Applications. Polymers (Basel) 2018, 10, doi:10.3390/polym10010089.

139. Ghaeini-Hesaroeiye, S.; Razmi Bagtash, H.R.; Boddohi, S.; Vasheghani-Farahani, E.; Jabbari, E. Thermoresponsive Nanogels Based on Different Polymeric Moieties for Biomedical Applications. Gels 2020, 6, 20, doi:10.3390/gels6030020.

140. Sood, N.; Bhardwaj, A.; Mehta, S.; Mehta, A. Stimuli-responsive hydrogels in drug delivery and tissue engineering. Drug Delivery 2016, 23, 748–770, doi:10.3109/10717544.2014.940091.

141. Bakaic, E.; Smeets, N.M.B.; Badv, M.; Dodd, M.; Barrigar, O.; Siebers, E.; Lawlor, M.; Sheardown, H.; Hoare, T. Injectable and Degradable Poly(Oligoethylene glycol methacrylate) Hydrogels with Tunable Charge Densities as
Adhesive Peptide-Free Cell Scaffolds. ACS Biomater. Sci. Eng. 2018, 4, 3713–3725, doi:10.1021/acsbiomaterials.7b00397.

Baldassari, S.; Solari, A.; Zuccari, G.; Drava, G.; Pastorino, S.; Fucile, C.; Marini, V.; Daga, A.; Pattarozzi, A.; Ratto, A.; et al. Development of an Injectable Slow-Release Metformin Formulation and Evaluation of Its Potential Antitumor Effects. Sci Rep 2018, 8, doi:10.1038/s41598-018-22054-w.

Nguyen, Q.V.; Huynh, D.P.; Park, J.H.; Lee, D.S. Injectable polymeric hydrogels for the delivery of therapeutic agents: A review. European Polymer Journal 2015, 72, 602–619, doi:10.1016/j.eurpolymj.2015.03.016.

Andrie, A.T.; Darge, H.F.; Mekonnen, T.W.; Birhan, Y.S.; Hanurry, E.Y.; Chou, H.-Y.; Wang, C.-F.; Tsai, H.-C.; Yang, J.M.; Chang, Y.-H. Ibuprofen-Loaded Heparin Modified Thermosensitive Hydrogel for Inhibiting Excessive Inflammation and Promoting Wound Healing. Polymers 2020, 12, 2619, doi:10.3390/polym12112619.

Biazar, E.; Keshel, S.H. The Healing Effect of Stem Cells Loaded in Nanofibrous Scaffolds on Full Thickness Skin Defects. Journal of Biomedical Nanotechnology 2013, 9, 1471–1482, doi:10.1166/jbn.2013.1639.

Gainza, G.; Villullas, S.; Pedraz, J.L.; Hernandez, R.M.; Igartua, M. Advances in drug delivery systems (DDSs) to release growth factors for wound healing and skin regeneration. Nanomedicine: Nanotechnology, Biology and Medicine 2015, 11, 1551–1573, doi:10.1016/j.nano.2015.03.002.

Ji, L.; Qiao, W.; Zhang, Y.; Wu, H.; Miao, S.; Cheng, Z.; Gong, Q.; Liang, J.; Zhu, A. A gelatin composite scaffold strengthened by drug-loaded halloysite nanotubes. Materials Science and Engineering: C 2017, 78, 362–369, doi:10.1016/j.msec.2017.04.070.

Zhao, X.; Zhao, J.; Lin, Z.Y. (William); Pan, G.; Zhu, Y.; Cheng, Y.; Cui, W. Self-sensitized drug delivery from electrospun fibers. Colloids and Surfaces B: BioInterfaces 2015, 130, 1–9, doi:10.1016/j.colsurfb.2015.03.058.

Liu, L.; Bai, S.; Yang, H.; Li, S.; Quan, J.; Zhu, L.; Nie, H. Controlled release from thermo-sensitive PNVC1-co-MAA electrospun nanofibers: The effects of hydrophilicity/hydrophobicity of a drug. Materials Science and Engineering: C 2016, 67, 581–589, doi:10.1016/j.msec.2016.05.083.

Li, H.; Liu, K.; Sang, Q.; Williams, G.R.; Wu, J.; Wang, H.; Wu, J.; Zhu, L.-M. A thermosensitive drug delivery system prepared by blend electrospinning. Colloids and Surfaces B: BioInterfaces 2017, 159, 277–283, doi:10.1016/j.colsurfb.2017.07.058.

Kordjamshidi, A.; Saber-Samandari, S.; Ghadiri Nejad, M.; Khandan, A. Preparation of novel porous calcium silicate scaffold loaded by celecoxib drug using freeze drying technique: Fabrication, characterization and simulation. Ceramics International 2019, 45, 14126–14135, doi:10.1016/j.ceramint.2019.04.113.

Poomima, B.; Korrpati, P.S. Fabrication of chitosan-polycaprolactone composite nanofibrous scaffold for simultaneous delivery of ferulic acid and resveratrol. Carbohydrate Polymers 2017, 157, 1741–1749, doi:10.1016/j.carbpol.2016.11.056.

Alavarse, A.C.; de Oliveira Silva, F.W.; Colque, J.T.; da Silva, V.M.; Prieto, T.; Venancio, E.C.; Bonvent, J.J. Tetracycline hydrochloride-loaded electrospun nanofibers mats based on PVA and chitosan for wound dressing. Materials Science and Engineering: C 2017, 77, 271–281, doi:10.1016/j.msec.2017.03.199.

Sinha, M.; Banik, R.M.; Haldar, C.; Maiti, P. Development of ciprofloxacin hydrochloride loaded poly(ethylene glycol)/chitosan scaffold as wound dressing. J Porous Mater 2013, 20, 799–807, doi:10.1007/s10934-012-9655-1.

Ehterami, A.; Salehi, M.; Farzamfar, S.; Samadian, H.; Vaez, A.; Ghorbani, S.; Ai, J.; Sabrapeyma, H. Chitosan/alginate hydrogels containing Alpha-tocopherol for wound healing in rat model. Journal of Drug Delivery Science and Technology 2019, 51, 204–213, doi:10.1016/j.jddst.2019.02.032.

Dwivedi, C.; Pandey, H.; C. Pandey, A.; W. Ramteke, P. Nanofibre Based Smart Pharmaceutical Scaffolds for Wound Repair and Regenerations Available online: https://www.ingentaconnect.com/content/one/ben/cpd/2016/00000022/00000011/art00005.
157. Jiang, B.; Zhang, G.; Brey, E.M. Dual delivery of chlorhexidine and platelet-derived growth factor-BB for enhanced wound healing and infection control. Acta Biomaterialia 2013, 9, 4976–4984, doi:10.1016/j.actbio.2012.10.005.

158. Chogan, F.; Mirmajidi, T.; Rezayan, A.H.; Sharifi, A.M.; Ghahary, A.; Nourmohammadi, J.; Kamali, A.; Rahaie, M. Design, fabrication, and optimization of a dual function three-layer scaffold for controlled release of metformin hydrochloride to alleviate fibrosis and accelerate wound healing. Acta Biomaterialia 2020, 113, 144–163, doi:10.1016/j.actbio.2020.06.031.

159. Sahana, T.G.; Rekha, P.D. Biopolymers: Applications in wound healing and skin tissue engineering. Mol Biol Rep 2018, 45, 2857–2867, doi:10.1007/s11033-018-4296-3.

160. Chu, J.; Shi, P.; Yan, W.; Fu, J.; Yang, Z.; He, C.; Deng, X.; Liu, H. PEGylated graphene oxide-mediated quercetin-modified collagen hybrid scaffold for enhancement of MSCs differentiation potential and diabetic wound healing. Nanoscale 2018, 10, 9547–9560, doi:10.1039/C8NR02538J.

161. Lee, C.-H.; Hung, K.-C.; Hsieh, M.-J.; Chang, S.-H.; Juang, J.-H.; Hsieh, I.-C.; Wen, M.-S.; Liu, S.-J. Core-shell insulin-loaded nanofibrous scaffolds for repairing diabetic wounds. Nanomedicine: Nanotechnology, Biology and Medicine 2020, 24, 102123, doi:10.1016/j.nano.2019.102123.

162. Karri, V.V.S.R.; Kuppusamy, G.; Talluri, S.V.; Mannemala, S.S.; Kollipara, R.; Wadhwani, A.D.; Mulukutla, S.; Raju, K.R.S.; Malayandi, R. Curcumin loaded chitosan nanoparticles impregnated into collagen-alginate scaffolds for diabetic wound healing. International Journal of Biological Macromolecules 2016, 93, 1519–1529, doi:10.1016/j.ijbiomac.2016.05.038.

163. Saiedi Garakani, S.; Davachi, S.M.; Bagher, Z.; Heraji Esfahani, A.; Jenabi, N.; Atoufi, Z.; Khanmohammadi, M.; Abbaspourrad, A.; Rashedi, H.; Jalessi, M. Fabrication of chitosan/polyvinylpyrrolidone hydrogel scaffolds containing PLGA microparticles loaded with dexamethasone for biomedical applications. International Journal of Biological Macromolecules 2020, 164, 356–370, doi:10.1016/j.ijbiomac.2020.07.138.

164. Hao, Y.; Tian, R.; Lv, K.; Liu, Z.; Ni, J.; Yuan, P.; Bai, Y.; Chen, X. Stimuli responsive co-delivery of celecoxib and BMP2 from micro-scaffold for periodontal disease treatment. Journal of Materials Science & Technology 2021, 75, 216–224, doi:10.1016/j.jmst.2020.10.027.

165. Zehra, M.; Mehmood, A.; Yar, M.; Shahzadi, L.; Riazuddin, S. Development of NSAID-loaded nano-composite scaffolds for skin tissue engineering applications. Journal of Biomedical Materials Research Part B: Applied Biomaterials 2020, 108, 3064–3075, doi:https://doi.org/10.1002/jbm.b.34634.

166. Fan, Z.; Liu, B.; Wang, J.; Zhang, S.; Lin, Q.; Gong, P.; Ma, L.; Yang, S. A Novel Wound Dressing Based on Ag/Graphene Polymer Hydrogel: Effectively Kill Bacteria and Accelerate Wound Healing. Advanced Functional Materials 2014, 24, 3933–3943, doi:https://doi.org/10.1002/adfm.201304202.

167. Zhou, J.; Yao, D.; Qian, Z.; Hou, S.; Li, L.; Jenkins, A.T.A.; Fan, Y. Bacteria-responsive intelligent wound dressing: Simultaneous In situ detection and inhibition of bacterial infection for accelerated wound healing. Biomaterials 2018, 161, 11–23, doi:10.1016/j.biomaterials.2018.01.024.

168. García-Salinas, S.; Elizondo-Castillo, H.; Arruebo, M.; Mendoza, G.; Irusta, S. Evaluation of the Antimicrobial Activity and Cytotoxicity of Different Components of Natural Origin Present in Essential Oils. Molecules 2018, 23, 1399, doi:10.3390/molecules23061399.

169. Ghasemlou, M.; Daver, F.; Ivanova, E.P.; Rhim, J.-W.; Adhikari, B. Switchable Dual-Function and Bioresponsive Materials to Control Bacterial Infections. ACS Appl. Mater. Interfaces 2019, 11, 22897–22914, doi:10.1021/acsami.9b05901.

170. García-Salinas, S.; Evangelopoulos, M.; Gámez-Herrera, E.; Arruebo, M.; Irusta, S.; Taraballi, F.; Mendoza, G.; Tasciotti, E. Electrospun anti-inflammatory patch loaded with essential oils for wound healing. International Journal of Pharmaceutics 2020, 577, 119067, doi:10.1016/j.ijpharm.2020.119067.
171. Mahmoud, A.A.; Salama, A.H. Norfloxacin-loaded collagen/chitosan scaffolds for skin reconstruction: Preparation, evaluation and in-vivo wound healing assessment. *European Journal of Pharmaceutical Sciences* 2016, 83, 155–165, doi:10.1016/j.ejps.2015.12.026.

172. Wang, Y.; Beekman, J.; Hew, J.; Jackson, S.; Issler-Fisher, A.C.; Parungao, R.; Lajevardi, S.S.; Li, Z.; Maitz, P.K.M. Burn injury: Challenges and advances in burn wound healing, infection, pain and scarring. *Advanced Drug Delivery Reviews* 2018, 123, 3–17, doi:10.1016/j.addr.2017.09.018.

173. Lan, Y.; Li, W.; Jiao, Y.; Guo, R.; Zhang, Y.; Xue, W.; Zhang, Y. Therapeutic efficacy of antibiotic-loaded gelatin microsphere/silk fibroin scaffolds in infected full-thickness burns. *Acta Biomaterialia* 2014, 10, 3167–3176, doi:10.1016/j.actbio.2014.03.029.