Published in final edited form as:

Curr Pharm Biotechnol. 2015 ; 16(7): 621–629.

Drug Delivery Systems for Wound Healing

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Abstract

Protein, gene, and small molecule therapies hold great potential for facilitating comprehensive tissue repair and regeneration. However, their clinical value will rely on effective delivery systems which maximize their therapeutic benefit. Significant advances have been made in recent years towards biomaterial delivery systems to satisfy this clinical need. Here we summarize the most outstanding advances in drug delivery technology for cutaneous wound healing.

Keywords

Biomaterial; coacervate; controlled release; drug delivery; hydrogel; microparticle; scaffold; wound healing

INTRODUCTION

Wound healing is a highly coordinated process which relies on precise spatiotemporal presentation of signals to succeed. Significant progress has been made in identifying these signaling molecules and their mechanisms of action in both healthy and diseased states [1–5]. Consequently, there has also been great interest in applying these signals therapeutically to accelerate healing, or enable healing which will otherwise never occur naturally. The current limitation for therapies involving proteins, genes, and small molecule drugs has been a delivery system which can effectively enable their full therapeutic benefit. Namely, a delivery system in the context of wound healing should do the following for its cargo: 1) Maintain its bioactivity through protection from proteolysis in the wound bed, 2) Localize its bioavailability by preventing rapid dilution in wound fluid and systemic uptake and

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CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

distribution, 3) Facilitate its release or presentation within the wound at a physiologically relevant rate and duration. If these goals are achieved, a successful delivery system will also minimize the dosage and application frequency necessary for efficacy.

Here we aim to highlight recent advances in delivery systems for wound healing applications. As the topic has been thoroughly reviewed several times in the past [6–8], we place particular emphasis on those systems developed in recent years (>75% of references have been reported since 2008). We identify 5 vehicle types which include hydrogels, scaffolds, particles, complexes, and coacervates (Fig. 1) and provide numerous examples to discuss their advantages and potential drawbacks. In effort to provide adequate depth, we limit our scope to biomaterial-based delivery systems for proteins and small molecule drugs with demonstrated efficacy for skin wound healing but not bone, muscle, or other epithelial defects such as those of the cornea. We include several systems for sustained release of genes and plasmids but not trans-membrane vehicles for gene transfer as these have a separate set of criteria and limitations [9, 10]. We also exclude biomaterial scaffolds for delivering cells in the classical tissue engineering paradigm, as well as therapies which have already received FDA approval as these have been reviewed extensively [11–13].

HYDROGELS

Hydrogels are one of the most highly utilized delivery vehicles. They are versatile, able to form from nearly any water-soluble polymer. They also feature a number of tunable parameters such as porosity, swelling ratio, and cross-link density to offer some control over release rate. A final advantage is that to an extent, they may mimic the mechanical properties of the granulation tissue and maintain a moist wound environment [6, 14].

Hydrogels are often formed from naturally occurring materials because of their abundance and good biocompatibility. Chitosan is one such natural hydrogel commonly employed in controlled release vehicles, appealing in part for its inherent benefits in the wound healing process [15]. Chitosan membranes have been used to cover a wound and slowly release antibiotics such as silver sulfadiazine as they swell. These membranes can be single layer [16] or bilayer [17], and their release may be tuned by variable addition of a second component such as alginate [18]. Chitosan sponges have also been described for controlled release of several different antibiotics to prevent microorganism infection [19–22] and have been evaluated *in vivo* [23]. Chitosan hydrogels delivering fibroblast growth factor-2 (FGF-2) have proved successful in extending the protein's bioactivity and improving wound repair in diabetic mice [24, 25]. Another major advantage of hydrogels for wound healing applications is that they may be designed to polymerize on demand and thereby conform to the defect space. For example, chitosan hydro-gels, designed to polymerize by enzyme-catalyzed cross-linking as injected into the defect, and were used to delivery rutin, a flavonol glycoside with healing properties [26]. Similarly, photo-cross-linkable chitosan hydrogels have been developed to polymerize in the wound after 20s of exposure to UV light [27].

Fibrin is another naturally derived material often used in wound healing applications, owed to its involvement in wound hemostasis [28]. In one intriguing study, fibrin was tethered to plasmid hypoxia-inducible factor-1α (HIF-1α) via a peptide linker which resulted in a

robust angiogenic response within the wound bed [29]. In another case, fibrin was employed as a carrier for adenovirus-mediated endothelial nitric oxide synthase (eNOS) gene transfer which up-regulated wound nitric oxide (NO) levels [30]. Interestingly, the release mechanism of adenovirus in this approach is through fibrinolysis, initiated by local cells which are then promptly transfected [31]. This therapy was then advanced to co-deliver plasmid eNOS with the Rab18 gene which regulates inflammatory cytokine and proteolytic enzyme secretion. This unique approach targeting angiogenesis, inflammation, and proteolysis was tested in a hyperglycemic ulcer model using rabbits and led to numerous positive healing measures [32]. Growth factors have also been delivered using fibrin gel. For example, delivered keratinocyte growth factor (KGF) successfully stimulated healing in a skin-grafted humanized mouse model [33]. Likewise, fibroblast growth factor-1 (FGF-1) delivered by a modified fibrin gel resulted in angiogenesis and may potentially be used to treat chronic wounds [34, 35].

A common strategy to facilitate delivery vehicle loading is to conjugate heparin or other glycosaminoglycans with affinity to growth factors, cytokines and morphogens [36]. Heparin-conjugated fibrin was developed to sequester heparin-binding factors from platelet-rich plasma (PRP) including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and FGF-2, and provide their sustained release. When applied to full-thickness mouse wounds, healing measures such as epithelialization and angiogenesis were enhanced compared with PRP alone or unmodified fibrin [37]. These results demonstrate the importance of protein loading and stabilization in development of delivery systems, particularly those for proteins with short half-lives. Drawing too from this concept, synthetic extracellular matrix (ECM) films were formed by cross-linking chondroitin sulfate and heparan sulfate and loaded with FGF-2. When applied to large excisional wounds on genetically diabetic *db/db* mice, the films induced dramatically faster wound closure by mimicking native ECM function in the wound bed [38].

In another utilization of natural materials, gelatinhyaluronate sponges were loaded with epidermal growth factor (EGF) and silver sulfadiazine. In rat excisional wounds, the two molecules acted synergistically to significantly reduce inflammation and increase cell proliferation in the early stages of healing [39]. A hydrogel of pure alginate was developed for the targeted, short term release of SDF-1α protein which improved healing of incisional wounds in pigs [40] and excisional wounds in mice [41]. Finally, combining these materials in a composite matrix of gelatin and oxidized alginate allowed the slow release of a cyclic adenosine monophosphate (cAMP) analog which influenced keratinocyte proliferation and migration, ultimately accelerating re-epithelialization of full-thickness wounds in rats [42, 43].

Synthetic polymers, while lacking the inherent biocompatibility of natural materials, do feature highly controllable and reproducible material properties [44]. Polyethylene glycol (PEG) is one of the most widely utilized hydrophilic polymers for drug delivery and is known for its good bio-compatibility [45]. A disulfide cross-linked PEG hydrogel was developed for the sustained release of doxycycline for wound healing. This vehicle was evaluated in an interesting mouse model of chemical warfare wounds. Skin permeation of doxycycline was enhanced by the hydrogel which correlated to better wound healing

measures [46]. PEG was also combined with another common synthetic polymer, poly(ε-caprolactone) (PCL), in a hydrogel for sustained release of micelles containing curcumin, a natural drug derived from the turmeric plant which has healing properties. Curcumin-delivering hydrogels successfully enhanced healing of both incisional and excisional wounds on rats [47].

Although hydrogels have been used successfully in numerous pre-clinical wound models, they do suffer one significant drawback as delivery vehicles. The nature of their formation and composition leads to a large burst release due to partial non-loading of the drug or its rapid efflux from the gel as it swells [48]. This can be particularly dangerous because systemic drug levels may become elevated and lead to unwanted side effects at distal locations. Regranex®, an FDA-approved carboxymethylcellulose hydrogel containing PDGF and indicated for diabetic ulcers, serves as an unfortunate example. A retrospective study found that it led to increased risk of cancer mortality and resulted in a black box warning issued by the FDA in 2008 [49].

SCAFFOLDS

Scaffold is a general term, so in this section we will specifically discuss porous scaffolds which are implanted rather than injected or polymerized *in situ* as is possible with hydrogels. This is usually not a drawback for wound healing applications as most wounds are superficial and relatively easy to access for manipulation. In fact, a scaffold may be the best choice when good mechanical properties or a long degradation time are desired. Their 3-D structure also encourages cell infiltration and enables strategic patterning of stimuli to precisely direct tissue regeneration [14].

Natural materials are often utilized in scaffolds similar as hydrogels, though they need not necessarily be hydrophilic. Collagen is most common and there are well-established methods for reducing its antigenicity and applying cross-links for long-term mechanical stability [50]. In one example, curcuminincorporated collagen matrices (CICM) were developed to improve full-thickness wound healing in rats [51]. The same collagen scaffold was used to release Glycyl-histidyl-lysine (GHK), a matrikine with numerous healing properties such as angiogenesis and growth factor activation [52, 53]. Interestingly, the group has also investigated the sustained release of both reactive oxygen species (ROS) [54], and antioxidants [55] into the wound bed. FGF-2 impregnated pure gelatin sheets were also demonstrated to improve the granulation region thickness and collagen density in diabetic rat wounds [56]. These sheets also demonstrated efficacy in several patients with chronic non-healing wounds, however a randomized controlled clinical trial is necessary to conclusively assess the benefit of this therapy. An advanced wound dressing was formed from chitosan cross-linked collagen loaded with FGF-1 and demonstrated accelerated healing of diabetic rat wounds [57]. FGF-2 was also delivered by a collagen-gelatin scaffold and tested in normal wounds [58], and furthermore in a diabetic pressure ulcer model using mice [59]. In another study, the release of platelet lysate from the same scaffold was evaluated and a dose-dependent response of lysate concentration on wound healing outcomes was observed [60]. A “gene-activated” bilayer dermal equivalent (BDE) was constructed from a collagen-chitosan sponge and contained plasmid DNA en coding for

VEGF complexed with a non-viral gene delivery vector. The BDE enhanced vessel density and overall tensile strength of newly formed dermal tissue in both full-thickness excisional wounds [61] and burn wounds [62] in pigs.

Drug loading of scaffolds is often by adsorption or entrapment and is therefore poor for some non-ideal drug-scaffold combinations. One method of improving loading efficiency is by modifying the therapeutic protein itself. In one instance, VEGF was modified with a collagen-binding domain which enhanced its affinity to the endogenous ECM and retention in the granulation tissue 7 days after application to rat wounds [63]. The fusion protein was then loaded into a collagen scaffold with enhanced efficiency and greatly improved vascularization in diabetic rats, also reducing VEGF levels in the serum compared to the native protein [64]. A similar approach was used to modify neuronal growth factor (NGF) and demonstrated accelerated re-epithelialization in a rabbit ischemic ulcer model [65].

Another natural material, hyaluronic acid (HA), was used to form sponges for the sustained release of EGF and arginine, which accelerated epithelialization of diabetic rat wounds by inducing moderate inflammation in the early stage of healing [66]. Similar sponges also containing collagen were found to induce better neovascularization in a genetically type 2 diabetic mouse model compared to a commercial artificial skin [67].

Scaffolds developed using synthetic polymers often employ the fabrication technique of electrospinning. Electrospun scaffolds offer advantages of high surface area and tunable fiber diameter which may closely match those of native ECM proteins, promoting cell adhesion [68]. Core-sheath type electrospun poly(ethylene glycol)-poly(D,L-lactide) (PELA) nanofiber mats containing FGF-2 were implanted into diabetic rat wounds where they enhanced angiogenesis after 2 weeks and the scaffolds degraded completely within 4 weeks [69]. The large surface area and porosity of electros-pun scaffolds allows for rapid hydrolytic degradation of polymer fibers. Similar scaffolds were also developed to provide controlled release of plasmid FGF-2. When implanted into skin defects of diabetic rats they led to improvements in numerous healing measures [70]. PEG/PCL block copolymer nanofibers have also been synthesized with chemically-immobilized EGF on their surface [71]. These scaffolds had some moderate effects on the healing of normal mouse wounds, but the results were greatly enhanced by the addition of FGF-2 within the core of co-axial fibers [72]. Likewise, curcumin has also been delivered using electros-pun nanofiber mats of PEG/PCL or PCL alone, which were shown to accelerate wound healing of normal rats and diabetic mice, respectively [73, 74].

Natural polymers are often difficult to electrospin on their own and are therefore blended with synthetic polymers. One group investigated chitosan and poly(ethylene oxide) (PEO) co-electrospun with PRP as a growth factor source. The bioactivity of the proteins was demonstrated to withstand the electrospinning process with *in vitro* assays, however this therapy still requires *in vivo* validation [75]. In at least one report, chitosan scaffolds providing sustained release of EGF showed no significant benefit over unloaded scaffolds towards the healing of excisional porcine wounds [76]. These data highlight the importance of *in vivo* testing, as *in vitro* assays cannot fully recapitulate the complex environment of a wound.

Not all scaffolds are formed by electrospinning. Modified chitosan was also used to synthesize porous foam dressings for release of neurotensin (NT) to modulate the inflammatory stage in diabetic wounds. The chitosan scaffolds delivering NT increased early wound closure dramatically compared to unloaded scaffolds by mitigating the acute inflammatory response and increasing collagen deposition by dermal fibroblasts [77].

PARTICLES

Nano- and microparticles are another highly studied type of drug delivery system which hold certain advantages over hydrogels and scaffolds. With respect to wound healing applications, particles may by injected by fine-gauge needle into the healthy tissue surrounding the wound so as not to complicate healing within the wound bed. They may also be tuned through numerous parameters to have complex release profiles unobtainable with gels and scaffolds [78, 79].

Poly(lactic-co-glycolic acid) (PLGA) is the most common polymer used to synthesize particles for controlled delivery. One rationale is that the lactic acid produced as the PLGA degrades may actively participate in the healing process, stimulating collagen synthesis and angiogenesis [80]. PLGA nanoparticles were developed to protect the activity of curcumin and release it over 8 days. When evaluated in full-thickness splinted excisional wounds in mice the combined effect of lactate and curucmin reduced the inflammatory response and enhanced angiogenesis and granulation tissue formation [81]. Similar nanoparticles were also used to release EGF albeit much more quickly, lasting only a day. Still, when applied to excisional wounds in diabetic rats the therapy induced the greatest number of proliferating cells and slightly accelerated wound closure compared to free EGF solution [82].

Particles have also been developed to deliver genes or plasmids. One example are biodegradable poly(β-amino esters) (PBAE) nanoparticles used to deliver plasmid Sonic hedgehog, a morphogen known to play multiple roles in tissue regeneration. After intradermal injection of the particles at the periphery of mouse wounds, upregulation of multiple growth factors and greater neovascularization in the wounds was observed [83].

In a unique and interesting approach, nanoparticles of a silica, PEG, and chitosan composite were used to provide slow and sustained release of NO to wounds. NO is known to have both immunoregulatory and wound healing properties. The nanoparticles applied topically accelerated healing of both infected and uninfected mouse wounds [84, 85]. Furthermore they were directly compared to the common NO-donor, diethylenetriamine (DETA NONOate) and showed superior results in a mouse wound model of diabetes combined with immunodeficiency, which has significant clinical relevance [86].

Nanoparticles need not necessarily be polymeric; in fact, lipids hold an advantage of rapid self-assembly without requiring organic solvents. One group developed two types, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) for delivery of EGF. The loading efficiency of NLCs was greater than that of SLNs, as is common with encapsulating cargo within a shell versus entrapping it in a matrix. Both types of lipid particles delivering EGF significantly accelerated healing of full-thickness wounds in *db/db* mice, however four

applications were necessary, possibly due to the inability of the vehicle to adequately sustain release [87].

Particles are also easily incorporated within other carrier systems to augment their functionality. They may be used to extend release if the inherent rate is too quick, or to provide biphasic release kinetics. For example, a polyurethane scaffold embedded with gelatin-coated PLGA microparticles, each releasing PDGF, produced a quick burst followed by slow prolonged release [88]. Likewise, distinct release kinetics for multiple factors will be very important for certain applications [89]. Nanofiber composite scaffolds of chitosan and PEO were synthesized for fast release of VEGF and combined with nanoparticles providing slow sustained release of PDGF. Dual release resulted in fast closure of full-thickness wounds in rats, driven by an enhanced angiogenic response [90].

In one notably elaborate delivery vehicle, VEGF and PDGF were placed in gelatin nanoparticles and combined with FGF-2 and EGF embedded in electrospun collagen and HA nanofibers for sustained release of 4 factors at once. Accelerated wound closure, increased collagen deposition and improved angiogenesis were all observed when the scaffolds were implanted in excisional wounds on diabetic rats [91]. Complex scaffolds with their own functionality have also been developed to compliment the delivery of a single factor. For example, an inner gelatin hydrogel layer for maintenance of a moist wound environment and containing FGF-2 micro-spheres was layered below an outer polyurethane membrane to protect the wound. This bi-layer scaffold proved effective at healing porcine full-thickness wounds [92].

Gelatin microparticles delivering FGF-2 suspended in a gelatin hydrogel showed good results in a porcine pressure-induced decubiticus ulcer model [93]. In another approach, gelatin microspheres were conjugated to a catechol-type protease inhibitor, loaded with doxycycline, and incorporated into a collagen dressing [94]. Their ability to reduce MMP levels in the wound bed and prevent infection was evaluated in a bacteria-challenged excisional wound model in rats [95]. Finally, gelatin microparticles delivering FGF-2 were dispersed within a collagen sponge and enhanced angiogenesis and cell proliferation in a mouse model of pressure ulcers [96].

One group loaded chitosan microparticles with EGF and VEGF and suspended them in a dextran hydrogel for application to burn wounds. The therapy did show a beneficial effect in a rat burn wound model, however weekly applications were necessary, indicating that the release duration was too short [97]. Another group suspended PLGA nanoparticles delivering VEGF and FGF-2 in a composite hydrogel and applied it to full-thickness wounds on diabetic mice. This combined therapy led to improved wound closure compared to control scaffolds but not compared to the scaffold with free growth factors [98]. These results highlight some potential drawbacks of particulate delivery systems. Most require organic solvents which can reduce the bioactivity of fragile protein drugs significantly. Additionally, constant release rate is difficult to achieve because they inherently follow first-order kinetics due to changing surface area as the particles degrade [78].

COMPLEXES AND CONJUGATES

A fourth type of delivery system comprises complexes and conjugates. Conjugates are typically formed by chemical bonds while complexes are typically formed by physical interactions. Both approaches seek to sequester soluble drugs in order to stabilize and extend their half-life or to provide targeting and facilitate their interactions with cell receptors. In one of the simplest examples of conjugation, PEG was attached to FGF-1 to improve its thermal and structural stability *in vivo*. In diabetic rat wounds, PEGylated FGF-1 led to complete wound closure 4 days faster than free FGF-1 and 7 days faster than control [99]. Complexes may also be used to improve skin permeation, of interest for wounds which have formed a protective scab or to treat deep tissue injury preceding a pressure ulcer. A low molecular weight version of protamine, a cation-rich nuclear protein, was developed to complex with the N-terminus of EGF. Protamine-EGF complexes showed 11-fold greater transdermal penetration than free EGF and demonstrated efficacy in healing full-thickness wounds on both normal and diabetic mice [100] and in a mouse burn wound model [101].

Another very interesting approach involves engineering ECM mimetics, considering its significance in orchestrating the regenerative process [36, 102, 103]. One such approach is a synthetic peptide fragment of fibronectin containing its growth factor binding domain for protein loading, an in-tegrin-binding domain to localize the complex to cells, and a factor XIIIa sequence for cross-linking to form a matrix to facilitate injection. The multi-functional recombinant fibronectin was applied for co-delivery of VEGF and PDGF to diabetic mouse wounds, where it induced angiogenesis and accelerated wound closure [104]. The same group used a similar approach to deliver the cytokine CXCL11 which, synergistic with fibronectin, promoted diabetic wound healing in *db/db* mice [105]. Along similar lines, vitronectin complexes with insulin-like growth factors (IGFs) can enhance keratinocyte migration and protein synthesis [106], and similar effects were observed with EGF and FGF-2 [107]. In their first pre-clinical evaluation, vitronectin complexes of IGFs and EGF accelerated healing of partial-thickness burn wounds in pigs, although this approach did require multiple administrations per week [108]. To improve the clinical usefulness, HA was then added as a carrier system for vitronectin:GF complexes [109]. In a clinical pilot study, this therapy demonstrated convincing efficacy at re-epithelializing venous leg ulcers, and also showed promise for treating other types of chronic wounds [110]. These results provide strong evidence for consideration of the role of the ECM in growth factor signal transduction when designing controlled delivery vehicles.

Another group designed polymer-growth factor conjugates using a “Polymer Masking-UnMasking-Protein Therapy (PUMPT)”. They demonstrated that succinoylated dex- trin conjugated to EGF can stabilize the protein until the polymer degrades at the target site and “unmasks” its bioactivity [111, 112]. The group went on to evaluate dextrin-EGF in full-thickness diabetic mouse wounds and the therapy had marked success [113]. In another unique approach *S*-nitrosothiols (RNSOs) were grafted onto a polymer backbone and then interpolymer complexes were created to form a cross-linked polymer network. This vehicle provided sustained release of NO for at least 10 days and accelerated healing of excisional wounds in diabetic rats, although the mechanistic benefits were not explored [114].

The specificity of complexes and conjugates may be seen as a disadvantage because many cannot be used as a platform for delivery of different types of molecules. Because they are designed with a specific target in mind, the synthesis and optimization process can become time-consuming. On the other hand, a specialized delivery vehicle will often lead to better outcomes compared to delivery with a generalized release platform.

COACERVATES

Coacervates are an interesting new class of drug delivery vehicles developed only recently for controlled release of proteins and small molecule drugs. Coacervates are nanometer-sized liquid droplets, held together and apart from their environment by hydrophobic forces [115]. As delivery vehicles, they feature rapid preparation by self-assembly not requiring organic solvents, and high loading capacity [116]. Preparation in aqueous solution is convenient and circumvents the risk of protein denaturation or residual organic solvents in conventional particle synthesis. Coacervates are also distinct from polymeric particles in their mechanical properties; they are soft and deformable which is particularly amenable to a wound environment where they may reside without impeding the massive influx of cells. This deformable nature allows for quick adsorption and spreading to coat polymeric scaffolds and provide drug release for tissue engineering applications [117]. Although they are a relatively young technology with just a decade’s worth of experimental validation, the advantages several coacervate systems have shown over conventional delivery methods bears much promise for their utility in the future [118].

One well-described coacervate system is elastin-like peptides (ELPs). These are recombinant proteins which resemble the hydrophobic regions of tropoelastin which undergo spontaneous coacervation above a tunable transition temperature [119]. Fusion proteins containing ELPs and KGF were developed and self-assembled into coacervate particles at body temperature. A chronic wound model was performed using an insulin-resistant diabetic mouse strain, and the fusion peptide led to markedly enhanced granulation and re-epithelialization [120].

A second coacervate system is a polycation:heparin complex which was developed specifically for the controlled delivery of heparin-binding growth factors [121, 122]. The growth factor is pre-bound to heparin, then a synthetic poly-cation is added which instantly forms liquid coacervate droplets by charge-based complexation (Fig. 2A). Within the coacervate the growth factor is protected from the proteolytic wound environment and its bioactivity upon release is enhanced by heparan sulfate preotoglycan-like interactions. This coacervate was utilized to sustain the release of heparin-binding epidermal growth factor (HB-EGF) with near zero-order release kinetics for at least 10 days. A single application of the HB-EGF coacervate to full-thickness excisional mouse wounds accelerated wound closure by enhancing wound granulation, re-epithelialization, keratinocyte proliferation, and angiogenesis (Fig. 2B) [123].

One drawback of coacervates is their relative instability in the body. They are held together by relatively weak interactions which may dissociate by large environmental changes in pH or ionic strength. However, these are typically stable within a particular tissue in the body.

On the other hand, this responsiveness may also be used to build in stimuli-responsive specificity.

CONCLUSION

A wide variety of biomaterial-based delivery systems exist for proteins, genes, and small molecule drugs with wound healing applications. Hydrogels, scaffolds, particles, complexes, and coacervates have each demonstrated success in numerous *in vivo* models and each may be optimal for a particular application or circumstance. However, wound healing is an extremely complex process and it is important to understand the etiology of each wound type and develop similarly complex delivery systems for individualized treatment. Towards this goal, it will be necessary to combine different types of biomaterials to develop composite systems capable of delivering multiple factors with precise release kinetics.

Acknowledgments

The authors would like to thank Dr. Mantosh Sinha for providing the hydrogel image, Dr. Eric Jeffries for providing the electrospun scaffold image, and Mr. Andrew Glowacki for providing the microparticles image. This work was supported by grants from the National Institutes of Health (NIH 2T32HL076124), the National Science Foundation (NSF IIP-1444774), and the American Heart Association (12EIA9020016).

Biography

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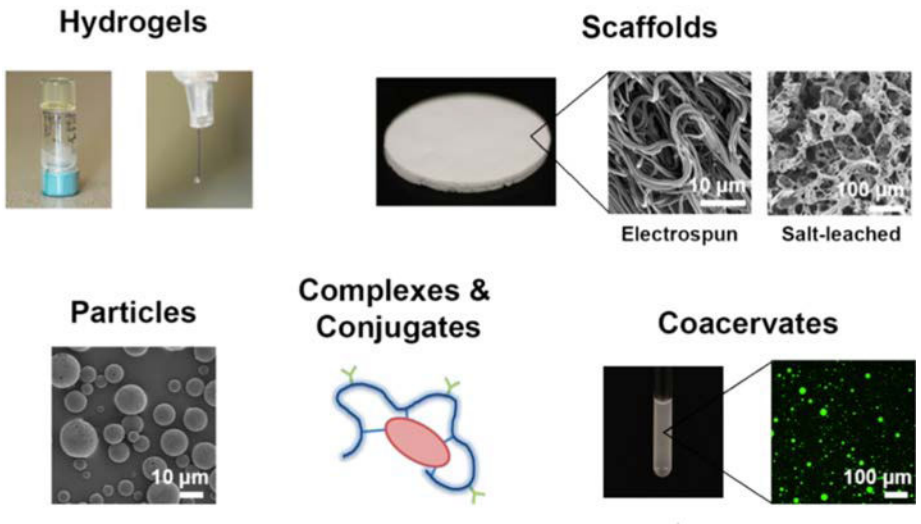

Fig. 1.
Five types of delivery systems.

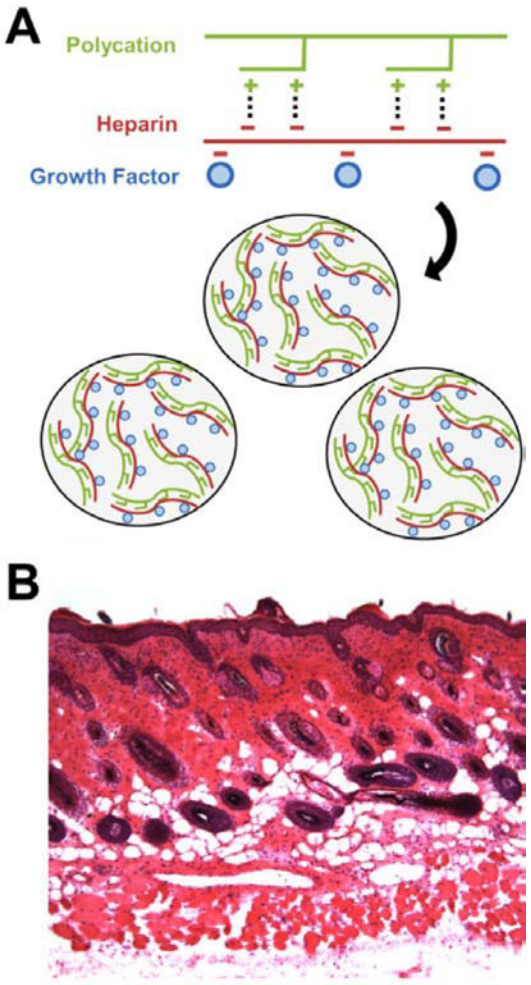

Fig. 2.

(**A**) A polycation:heparin coacervate forms by charge interaction and loads heparin-binding growth factors. (**B**) The HB-EGF coacervate was evaluated in a mouse skin wound healing model.