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In situ forming injectable hydrogels for drug delivery and wound repair☆

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ABSTRACT

Hydrogels have been utilized in regenerative applications for many decades because of their biocompatibility and similarity in structure to the native extracellular matrix. Initially, these materials were formed outside of the patient and implanted using invasive surgical techniques. However, advances in synthetic chemistry and materials science have now provided researchers with a library of techniques whereby hydrogel formation can occur *in situ* upon delivery through standard needles. This provides an avenue to minimally invasively deliver therapeutic payloads, fill complex tissue defects, and induce the regeneration of damaged portions of the body. In this review, we highlight these injectable therapeutic hydrogel biomaterials in the context of drug delivery and tissue regeneration for skin wound repair.

Contents

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1. Introduction

1.1. Injectable gels as therapeutic agents

Hydrogels are highly-crosslinked, water swollen networks of hydrophilic polymers, which have been studied extensively over the past six decades, and have demonstrated profound promise as bio-compatible materials in numerous therapeutic applications [1]. These materials can be derived from both natural and synthetic sources [2]. Naturally occurring polymers such as chitosan, alginate, hyaluronic acid (HA), collagen, and gelatin are inherently biodegradable and often come pre-functionalized with integrin binding sites allowing for adhesion and coordinated cellular responses. Unfortunately, the utilization of these materials is limited due to significant batch-to-batch variability and potential immunogenicity within foreign hosts. In contrast, synthetic polymers such as poly(ethylene glycol) (PEG), polyacrylamide (PAM), poly(vinyl alcohol) (PVA), and poly(methyl methacrylate) (PMMA) are appealing due to their strong mechanical properties, tailorable structure and low immunogenicity, but lack innate bio-functionality and must undergo significant post-processing in order to elicit desired responses *in vivo*. More complex, hydrogel systems have also been developed to circumvent the limitations presented through designing scaffolds from a single polymer backbone. These materials come in the form of either co-polymers [3], where multiple backbone groups are crosslinked together, or inter-penetrating networks (IPNs) [4], where a polymer mesh is constructed from the binding of oligomer chains within an already assembled polymeric scaffold. In this manner, hydrogel materials may be precisely modified to highlight the optimal properties of each of their constituent components, resulting in an even greater degree of control towards regenerative outcomes.

Table 1
Examples of materials used for drug delivery and tissue regeneration.

Hydrogel component	Application	Refs.
Local microenvironment		
Temperature driven		
Poly(D,L-lactide-co-glycolide) (PLGA)/PEG triblock copolymers (PLGA-PEG-PLGA)	Drug delivery	51
Polyethylene glycol-poly(L-alanine) (PEG-PLA)	Cell scaffold	56
Poly(*N*-isopropyl acrylamide)	Cell scaffold	58
Soluble ECM/methylcellulose	Cell scaffold	59
pH driven		
PEG-diacrylate (PEGDA), acrylic acid and alginate	Wound dressing	68
Ionic concentration driven		
Alginate/multi walled carbon nanotubes	Cell scaffold	71
Alginate/PEG/hyaluronic acid	Cell scaffold/drug delivery	75
Alginate/PEG	Cell scaffold	79
Self assembly		
Peptide		
RADA16	Cell scaffold/drug delivery	86, 88–90
Fmoc dipeptides	Cell scaffold	91, 92
Nap-GFFYGGGWRESAI/TIP-1 crosslinker	Cell scaffold/drug delivery	93
Leucine-α/β-dehydrophenylalanine	Drug delivery	94
Covalently bonded		
Photo-initiated		
Gelatin-methacrylate	Cell scaffold	108, 109
Gelatin-methacrylate/HA-methacrylate	Cell scaffold	110
Reactive precursors		
8-Arm PEG cysteine/N-hydroxysuccinimide	Drug delivery	122
Carboxymethyl chitosan/dextran	Cell scaffold	124
Konjac glucomannan-tyramine/heparin-tyramine	Cell scaffold/cytokine sequestration	126

Historically, hydrogels were pre-formed and delivery of these materials to target sites in patients necessitated the use of highly invasive surgical procedures. However, influential work in the late 90s demonstrated that hydrogel precursors could be injected through a standard syringe and crosslinked locally through transdermal light-induced photopolymerization [5]. Nowadays, minimally invasive delivery of hydrogels through injection has gained significant traction in the biomedical community. Injectable materials have several inherent advantages over their pre-formed counterparts. In short, associated implantation procedures are lower cost, with patient discomfort significantly reduced after delivery, delicate therapeutic materials dissolved within the materials are shielded from injection associated shear forces [6] and can be released with complex dynamics [7], and lastly tissue regeneration is aided by the ability of these materials to mold into the shape of the injection cavity [8], allowing for universal off the shelf treatment within any non-standard geometry. Continued advances in our understanding of polymer chemistry have fostered the development of numerous biomaterials which can be injected as viscous liquids and subsequently solidified through variations in their local microenvironment (temperature [9,10], pH [10], ion concentration [10]), application of an external stimulus (light [11]), or affinity based self-organization in the case of peptides [12,13] and other physically associating functional moieties [14] (Table 1). This diversity in injectable hydrogel technologies is critical for the recapitulation of complex extracellular environments, organization of cellular behavior, and adequate delivery of therapeutic small molecules. Successfully blending components from these systems will enable the development and optimization of novel therapeutic injectable hydrogels.

In this review, we seek to highlight advances in the design and development of injectable hydrogel materials towards application in skin. We begin by giving a brief, high level overview of skin biology and explain how deviations in responses during the wound healing cascade can lead to the formation of chronic wounds. We next describe and motivate two frequent uses of injectable hydrogels as scaffolds for tissue regrowth and as depots for the release of small molecule or cellular therapeutics. Lastly, we devote the bulk of this review to a description of various injectable hydrogel systems and their wound healing applications. We start with the most basic systems derived from materials whose gelation is induced by simple environmental changes within the site of injection, and build towards newer systems such as guest-host mediated shear-thinning hydrogels, cryogels, and microporous annealed particle gels.

1.2. Rescuing aberrant skin properties with injectable hydrogels

The skin is a highly organized, multi-faceted organ which serves as the primary line of defense for the human body. At the most basic level of classification, skin can be broken down into three main layers, each with unique properties that prove critical to its physiology (Fig. 1a). The outermost layer, the epidermis, is roughly 50 to 100 cell layers thick and is mainly composed of melanocytes and senescent keratinocytes which provide protection against pathogens, UV radiation and mechanical stresses through their production of melanin and keratin respectively [15]. The dermis sits below the epidermis and is comprised of a complex network of structural proteins and proteoglycans which impart mechanical integrity to the overall tissue. Additionally, the dermis plays host to many higher order structures (sebaceous and sweat glands, hair follicles, and arrector pili muscles) and processes (oxygen exchange, nerve signaling) which prove imperative in maintaining cellular nourishment, regulating temperature homeostasis and responding to external stimuli [16,17]. Lastly, the lowermost, subcutaneous layer of skin is mainly utilized as a depot for stored fat but also plays important roles by linking the more superficial layers to underlying muscle and bone [16].

Unsurprisingly, damage to the skin is fairly common. In most scenarios, regeneration is not difficult and takes place through a linear