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Application of materials as medical devices with localized drug delivery capabilities for enhanced wound repair

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ABSTRACT

The plentiful assortment of natural and synthetic materials can be leveraged to accommodate diverse wound types, as well as different stages of the healing process. An ideal material is envisioned to promote tissue repair with minimal inconvenience for patients. Traditional materials employed in the clinical setting often invoke secondary complications, such as infection, pain, foreign body reaction, and chronic inflammation. This review surveys the repertoire of surgical sutures, wound dressings, surgical glues, orthopedic fixation devices and bone fillers with drug eluting capabilities. It highlights the various techniques developed to effectively incorporate drugs into the selected material or blend of materials for both soft and hard tissue repair. The mechanical and chemical attributes of the resultant materials are also discussed, along with their biological outcomes *in vitro* and/or *in vivo*. Perspectives and challenges regarding future research endeavors are also delineated for next-generation wound repair materials.

Abbreviations: AASF, *Antheraea assama* silk fibroin; BC, benzalkonium chloride; BMP-2, bone morphogenetic protein-2; β-TCP, β-tricalcium phosphate; CDDP, cis-diamminedichloroplatinum; CMC, carboxymethylcellulose; *E. coli*, *Escherichia coli*; EGF, epidermal growth factor; FGF-2, fibroblast growth factor-2; hGH, human growth hormone; HA, hydroxyapatite; IGF-1, insulin-like growth factor-1; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; NSAID, nonsteroidal anti-inflammatory drug; *P. aeruginosa*, *Pseudomonas aeruginosa*; PCL, poly(ε-caprolactone); PDLLA, poly (D,L-lactic acid); PDX, poly(dioxanone); PE, poly(ethylene); PEG, poly(ethylene glycol); PEI, poly(ethyleneimine); PEMA, poly(ethylmethacrylate); PGA, poly (glycolic acid); PGC, poly(glyconate); PGL, poly(glactin); PLA, poly(lactic acid); PLGA, poly(lactic-co-glycolic acid); PLA-DX-PEG, poly(D,L-lactic acid)-poly(p-dioxanone)-poly(ethylene glycol); PLDLLA, poly(L,DL-lactic acid); PLLA, poly(L-lactic acid); PMMA, poly(methylmethacrylate); PNIPAAm, poly(N-isopropylacrylamide); PTMC, poly(trimethylene carbonate); PU, polyurethane; PVA, poly(vinyl alcohol); *S. aureus*, *Staphylococcus aureus*; *S. epidermidis*, *Staphylococcus epidermidis*; TGF-β1, transforming growth factor-β1; TNT, titania nanotube.

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1. Introduction

A wound constitutes any physical injury to the body arising from injuries, diseases, or surgical interventions, characterized by superficial lacerations or penetration to underlying tissues, such as muscles, ligaments or bones [1,2]. Minor wounds often heal through the body's intrinsic repair process that entails four consecutive phases: coagulation and hemostasis, inflammation, proliferation, and remodeling orchestrated by multiple cell populations (neutrophils, macrophages and fibroblasts), as well as through extracellular matrix formation and action of soluble mediators including growth factors and cytokines [3,4]. Restoration is mostly impaired, however, in injuries of greater severity and may lead to wound exposure or tissue abnormalities [5,6].

Consequently, materials frequently employed in the clinic are designed to stabilize the site of injury and aid in the healing process [7–9]. In order to be effective, wound repair devices should ideally possess similar mechanical properties to the tissue undergoing reconstruction [10–12]. Soft tissues (skin, tendon, ligaments, muscles) require more elastic and pliant materials such as polymers, as well as glues, sutures or dressings for wound closure [13–17]. On the other hand, stiff and strong materials, such as ceramics, metals and their alloys, are preferable for repairing hard tissues (bone, cartilage) [18–21].

The need for wound repair devices continues to steadily increase with greater than 114 million patients worldwide enduring wounds from surgical procedures annually [22]. In the United States alone, 36 million patients experienced surgery-related wounds in 2012, and 31 million injured persons visited the emergency room in 2011 [23,24]. The global wound care market totaled $15.6 billion in 2014 and is anticipated to grow to $18.3 billion by 2019 [25].

While many wound repair materials in current clinical use are reported to be effective, devastating wounds – mostly large defects – are highly susceptible to infection, pain, and abnormal inflammation [26,27]. Cumbersome devices often employed for treatment may invoke secondary complications, such as foreign body reactions and chronic inflammation [28–33]. Multiple administrations of oral or injectable drugs may therefore be prescribed to combat these issues [34–36]. Such strategies rely primarily on systemic drug exposure, which may not optimally address local wound complications [37,38].

As a result, developing wound repair devices coupled with localized drug delivery represents an avenue of tremendous interest. This review begins with a general discussion on materials for wound repair and related complications that may arise. Subsequent sections focus on soft and hard tissues – each surveying the landscape for drug-eluting materials and their influence on different aspects of wound healing. Finally, perspectives on future directions in this field are offered.

2. Wound repair devices

To begin, wound repair devices can be categorized according to the mechanical properties of the damaged tissue, namely soft and hard (Figs. 1 and 2). Soft tissues include skin, muscle, tendon, and ligaments, which exhibit relatively high flexibility and elasticity [39], whereby in contrast, hard tissues consisting of bone or cartilage tend to have higher stiffness [40,41].