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Review Article

Novel biodegradable polymers for local growth factor delivery

Brian Amsden *

Department of Chemical Engineering, Queen's University, Kingston, ON, Canada

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ABSTRACT

Growth factors represent an important therapeutic protein drug class, and would benefit significantly from formulations that provide sustained, local release to realize their full clinical potential. Biodegradable polymer-based delivery platforms have been examined to achieve this end; however, formulations based on conventional polymers have yet to yield a clinical product. This review examines new polymer biomaterials that have been developed for growth factor delivery. The dosage forms are discussed in terms of their mechanism of release, the stability of the released growth factor, their method of preparation, and their potential for clinical translation.

1. Introduction

Growth factors are soluble extracellular signal proteins that promote the growth, organization, and maintenance of cells and tissues. They bind to receptors on the target cell surface thereby providing signals that modulate the stimulation or inhibition of cellular proliferation, differentiation, migration, adhesion, and gene expression [1]. They have an enormous therapeutic potential, and several are currently in clinical use, including bone morphogenetic protein-2 [2], epidermal growth factor [3], and erythropoietin and granulocyte colony stimulating factor [4]. Other growth factors represent potential treatments for a number of heretofore intractable disease conditions, such as neovascularization of ischemic tissue [5] or the management of non-healing wounds [6].

To appreciate the design considerations inherent in the formulation of an effective growth factor delivery system, it is necessary to understand the physical and biological characteristics of growth factors. *In vivo*, growth factors are secreted by producer cells to coordinate specific cellular actions. They can exert these effects through endocrine, autocrine, juxtacrine, intracrine, or paracrine mechanisms [7,8]. However, their effects are typically restricted to the local environment due to their limited ability to diffuse through the surrounding extracellular matrix, and their short half-lives [8]. They are biologically active at very low concentrations, of from 10^{-9} to 10^{-11} M [9], and their effects can be concentration dependent [8]. Furthermore, for effective therapy their presence in the tissue is often required for extended time frames of from days to weeks [5,10].

Some protein drugs, such as monoclonal antibodies and insulin, can be effectively administered via injection or infusion. However, because of the need for prolonged delivery, the typically short half-lives of growth factors, and the transport and degradative barriers associated with conventional administration by oral, transdermal, or intravenous routes, effective therapy for growth factors using such conventional administration may not be possible [5,10]. A prolonged, local, and sustained delivery of growth factors could therefore provide significant advantages. These advantages include a decrease in the number and amount of required doses, better control of dosing levels and timing of dosing and therefore greater therapeutic effect, more efficient use of growth factor with less likelihood of undesirable side effects, and improved patient comfort and compliance.

The design of an effective polymeric growth factor delivery formulation requires that the mechanism governing growth factor release is slower than all subsequent transport and pharmacokinetic phenomena. A number of polymer-based formulations for local growth factor delivery have been examined. However, achieving effective growth factor release is challenging, as the formulation must meet the following criteria:

1. Maintenance of growth factor structure and bioactivity during fabrication, storage, and prior to and following release from the polymer depot. Patient safety and drug efficacy can be compromised if even a small fraction of the protein molecules is degraded. Of potential concern is the generation of protein aggregates and the production of macro/nanoparticulates from the polymer, which may increase the risk of inducing an immune response in the patient [11,12].

* Tel.: +1 613 533 3093.
E-mail address: amsden@queensu.ca

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2. Generating the appropriate growth factor release, in terms of local concentration and duration, as well as timing, so as to produce the desired therapeutic response. In animal experiments, it has been shown that vascular endothelial growth factor A (VEGF) for example, required a higher initial release for initiation of angiogenesis, followed by steady but lower release rate still within therapeutic window [13], while epidermal growth factor (EGF) required many hours of continuous exposure to be effective [14]. Nevertheless, it should be noted that the same dosing regimens may not be applicable in humans [15].
3. Providing complete growth factor release. Incomplete protein release is not uncommon, and is often a result of protein-polymer adsorption or complexation, protein aggregation, or degradation of the protein [11,12].
4. Biocompatible within the context of the desired injection location. That is, it should not: (i) be mechanically irritating to surrounding tissue, (ii) release degradation products that cause local cytotoxicity, (iii) induce an immunogenic response, or (iv) produce a long-term inflammatory response. A potential outcome of these effects is local irritation to the patient and the formation of a fibrous tissue layer surrounding the formulation. This fibrous tissue layer can act as an additional barrier to growth factor diffusion into the tissue, which may reduce its efficacy [16].
5. Capable of relatively large-scale manufacture without use of potentially toxic impurities/reactants/catalysts, so as to yield a sterile product.

Other desirable features include the capacity for *in situ* formation and/or administration via simple injection through standard gage needles for minimally invasive localization to desired site of action [17], simple and efficient growth incorporation so as to minimize cost of manufacture, and degradability within the tissue so as not to persist at implantation site to cause chronic inflammation or interfere with the desired effect. However, the degradation products of the polymer should not de-activate the protein within the delivery device prior to it being released, or interfere with its action.

Polymeric delivery formulations possessing the necessary design criteria for protein delivery while incorporating most of the listed desirable criteria have been pursued for many years. The formulations examined have most often been based on commonly used polymer biomaterials, such as poly(lactide-co-glycolide), gelatin, collagen, fibrin, poly(ethylene glycol), hyaluronic acid, dextran, alginate, and chitosan [18]. Unfortunately, a formulation based on these polymers has not yet been reported that can satisfy all the necessary design criteria outlined above, necessitating the exploration of new polymer biomaterials for this purpose.

In this review, novel biodegradable polymers that have been designed for the local delivery of growth factors, and those that can be readily adapted for growth factor release, will be presented and evaluated with respect to their potential as effective growth factor delivery approaches by comparison to the design criteria listed above. The focus is on polymer formulations designed for minimally invasive delivery or intraoperative implantation; polymers designed for use in patches for topical application are not discussed. The review has been organized as to the nature of the polymer used to control the release. Hydrogel-based formulations are discussed first followed by an examination of biodegradable hydrophobic polymers.

2. Hydrogels

Hydrogels have been the most studied formulation platform for growth factor delivery. The focus on these materials is based on their high water content, which approximates that of native tissue, and thus hydrogels typically have mechanical properties similar to those of many tissues and hence do not provoke an intense inflammatory response through mechanical irritation. Moreover, the high water content provides a means of allowing release of the large growth factor molecules through diffusion within the aqueous regions between the polymer chains. The structure and mechanical properties of hydrogels are adjustable using a variety of different chemistries. Furthermore, they can be made into injectable formats such as micro- or nanoparticles, thixotropic systems, or *in situ* chemically or physically crosslinking prepolymers and thus are readily implanted into tissue through minimally invasive means.

Growth factor release from the various hydrogel formulations has been designed to occur via diffusion and network degradation, by diffusion coupled with affinity binding of the growth factor to the hydrogel polymer network, or through cleavage of a tether molecule that couples the growth factor to the hydrogel network followed by diffusion of the released growth factor through the hydrogel network. The following section outlines new hydrogel approaches based on each of these release mechanisms.

2.1. In situ forming, diffusion based systems

Many *in situ* forming hydrogels have been designed to provide diffusion controlled release of the growth factor, with the primary design focus being the ability of the hydrogel to form *in situ* with minimal tissue damage or irritation. The rate of release by diffusion of the growth factor through the gel network is primarily governed by the size of the growth factor (*i.e.* its radius of gyration) versus the mesh size of the hydrogel [19]. As the hydrogels are formed from solutions injected into the tissue where they ultimately cross-link, these formulations typically exhibit a relatively large burst effect as dissolved growth factor is liberated at the boundaries of the forming hydrogel. Also, the release of the growth factor is generally on the order of hours or days, as the cross-link densities required to generate long-term delivery are difficult to achieve without increasing material stiffness and thus compromising the generally mild inflammatory response to the implanted hydrogels. These delivery approaches then are often limited to treating conditions requiring relatively short growth factor release durations, or for situations wherein multiple injections spaced days apart are feasible.

There are a number of other challenges in designing effective *in situ* forming hydrogels for growth factor delivery. These challenges include: (1) potential tissue toxicity and growth factor denaturation associated with the gelation chemistry, (2) impractical gelation times, *i.e.* either too rapid or too long, (3) significant swelling following gelation, (4) the possibility of a large burst effect of released growth factor before significant gelation occurs, (5) difficulty in matching the hydrogel degradation rate with the growth factor release rate such that all the drug is released before gel degradation significantly influences the release rate, and (6) the possibility that weak gels are formed, which may be mechanically broken down into smaller particles resulting in increased release rates due to greater overall surface area as well as potential phagocytosis leading to issues with ineffective drug targeting as well as potential inflammation. Despite these challenges, progress toward effective *in situ* forming hydrogels for growth factor delivery has been made.

A number of crosslinking strategies have been studied to form hydrogels *in situ*, which include both covalent and physical crosslinking. Examples of covalent methods include free radical polymerization initiated by UV or visible light in the presence of photoinitiators [20], or through thermal initiators such as ammonium persulfate/N,N,N′,N′-tetramethylethylene diamine (APS/TEMED) [21], Michael addition through vinyl sulfone, acrylate