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Review Article

Controlled release of therapeutic antibody formats

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ABSTRACT

The local administration of antibodies can represent in many cases a significant improvement for antibody-based therapies. The benefits of local delivery include high drug concentrations at the target site, the possibility of lower drug dosing and less systemic drug exposure. Currently, the most relevant delivery sites for therapeutic antibodies are the posterior segments of the eye, mucosal surfaces, the articular joints and the central nervous system (CNS). In addition, the oral and pulmonary route may enable non-invasive systemic antibody delivery. However, local antibody delivery to these sites is characterized by short drug residence times and a low compliance of administration. Controlled release (CR) systems can address these limitations and, thereby, enable and improve local delivery applications by achieving long lasting local drug concentrations, improved efficacy-dosing ratios and reduced treatment-associated side effects. The requirements for CR antibody formulations are more complex compared to conventional CR systems for small molecules, and their development poses an enormous technical challenge. Therefore, the review highlights experiences and challenges gathered in the development of the different CR systems for antibodies to date. Additionally, the unmet technological needs encountered in the field are described. This includes a critical evaluation of the limited capability of various CR systems to preserve antibody stability, delivery site specific considerations, as well as the processability of a CR system with a particular focus on drug loading and injectability. We believe that the success of CR and local delivery approaches could create an enormous added value for patients in the future.

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1. Introduction

Today, the vast majority of antibody products are administered systemically via the intravenous (IV) or the subcutaneous (SC) route. Due to systemic distribution and their mechanism of in vivo action high antibody dosing regimens are often necessary to obtain the desired therapeutic effect. Local delivery applications could provide substantial benefits to numerous antibody therapies by achieving (I) higher local bioavailabilities leading to a better treatment efficacy, (II) reduced systemic drug exposure and (III) lower required antibody dosing. Both latter-mentioned factors minimize the side effects of the antibody-based therapy. Furthermore, oral or pulmonary antibody delivery can be a means to enable non-invasive, systemic antibody delivery. However, several factors limit the applicability of local antibody delivery. Due to a high turnover the drug residence time at the delivery sites is often limited resulting in high dosing frequencies and/or a limited efficacy of the treatment. In addition, the administration to these sites is often invasive and associated with injection site reactions and hence local delivery may be less patient convenient than a conventional systemic administration [1,2].

Abbreviations: ADC, Antibody-drug conjugates; ADCC, Antibody-dependent cellular cytotoxicity; AMD, Age-related macular degeneration; bFGF, basic Fibroblast Growth Factor; CDC, Complement dependent cytotoxicity; CDR, Complementarity determining region; CNS, Central Nervous System; CMC, Carboxymethylcellulose; CNV, Choroidal Neovascularization; CR, Controlled release; CTLA-4, Cytotoxic T-Lymphocyte Antigen; dex-HEMA, Hydroxyl Ethyl Methacrylated Dextran; EGF, Epidermal Growth Factor; ELP, Elastin-like Polypeptides; EVAc, Poly (ethylene vinyl acetate); Fab, Fragment antigen binding; Fc, Fragment crystallisable; FcRn, Neonatal Fc receptor; FDA, United States food and drug administration; FTIR, Fourier-transformed infrared spectroscopy; GALT, Gut-associated lymphoid tissue; HIV, Human Immunodeficiency Virus; HSV, Herpes simplex virus; IA, Intraarticular; Ig, Immunoglobulin; IL-1 β, Interleukin 1 β; IL-1Ra, Interleukin-1 receptor antagonist; IOP, Intraocular Pressure; IP, Intraperitoneal; IV, Intravenous; IVT, Intravitreal; Mab, Monoclonal antibody; OA, Osteoarthritis; PDGF, Platelet-derived Growth Factor; PEG, Poly(ethylene glycol); PNIPAAm, Poly(N-isopropylacrylamide); PLA, Poly(D,L-lactide); PLGA, Poly(D,L-lactide-co-glycolide); RES, Reticuloendothelial system; SC, Subcutaneous; scFv, Single chain fragment variable; SDLM, Spray-dried lipid microparticles; S/O/W, Solid in Oil in Water; STD, Sexually Transmitted Diseases; $T_{1/2}$, Terminal elimination half life; TFF, Tangential flow filtration; TGF-α, Transforming growth factor α; TNF α, Tumor Necrosis Factor α; VEGF, Vascular endothelial growth factor; W/O/W, Water in Oil in Water.

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Controlled release (CR) systems can address these limitations and enable more efficient local delivery applications. The first reports regarding local and sustained delivery of antibodies originate from the early 1990s and focused on topical applications [3]. Herein, antibodies were used to treat or to prevent infections on mucosal surfaces. Interestingly, combined with CR devices, antibodies showed promising results for the long-term protection against sexually transmitted diseases (e.g. HIV, herpes simplex virus) [4]. The first parenteral CR antibody systems were developed in the form of microparticles. This approach is technically more challenging compared to the development of implants as these systems are not just required to preserve antibody stability and to provide appropriate controlled release but are also preferably injectable and biodegradable in order to eliminate the need for surgery [5,6]. Commonly used biodegradable CR systems for small molecules and peptides are poly(D,L-lactide-co-glycolide) (PLGA) – based devices. However, PLGA-based systems often failed to preserve antibody stability, and loss of bioactivity during manufacturing and incomplete drug release has been reported. In the years to follow, the interest in CR technology vanished, because of the development of antibodies with long in vivo half-life. Recently, the emergence of several local delivery strategies led again to a reconsideration regarding the relevance of CR systems for therapeutic antibodies. For instance, the prolonged exposure to high antibody concentrations in the joint (e.g. cytokine-inhibiting antibodies) is believed to evoke an improved effect of disease-modifying drugs in osteoarthritis (OA) [7,8]. Similar expectations are prevailing for CNS injuries or anti-cancer applications, where the antibody is directly administered to the tumor site [9,10]. The most prominent example for a potential antibody CR strategy is the anti-VEGF (vascular endothelial growth factor) treatment of age-related macular degeneration (AMD), where CR systems can decrease the dosing frequencies and lead to a significantly improved patient compliance [11,12]. Even for systemic delivery via the SC route CR systems can provide distinct therapeutic benefits. Primarily, antibody fragments without Fc-part or other therapeutic proteins do not have the long serum half-life of Immunoglobulin G (IgG), and protein modification (e.g. PEGylation) is the common strategy to address this limitation [13]. CR systems can represent an alternative means to extend the half-life of antibody fragments and reduce their dosing frequency without modifying the protein structure. Secondly, CR systems may protect the antibody from catabolic processes at the injection site, may avoid the saturation of putative IgG transporters and maximize the efficacy-dose relationship [14]. We hypothesize that these effects could reduce dosing requirements by facilitating improved systemic bioavailabilities and more constant drug-serum levels.

The current review intends to be a comprehensive scientific analysis of the available data in the field of CR and local or systemic delivery of therapeutic antibodies. A brief general overview of antibody structure, relevant formulation and delivery challenges of conventional liquid antibody formulations, antibody pharmacokinetics and the antibody mode of action is given as an introduction. CR systems will be reviewed with particular attention paid to the corresponding delivery application. To this end, we discuss the rational and the potential benefits of CR systems for local or systemic delivery. Finally, we will elucidate in detail existing strategies for the CR of antibodies with an assessment of their pros and cons, and we discuss general requirements and challenges for such systems.

2. Characteristics of therapeutic antibodies

2.1. The structure and design of therapeutic antibodies

IgG and fragments of IgG represent the most abundant protein class in the biopharmaceutical field. IgG consists of two Fab (antigen binding) fragments and a single Fc (crystalizing) fragment. Two pairs of polypeptide chains, two heavy (~50 kDa each) and two light chains (~25 kDa each) form the IgG-molecule. These chains are mutually connected via multiple disulfide bonds and non-covalent interactions. Each heavy and light chain consists of a variable region and of a constant region. A couple of light and heavy chain variable parts form one antigen binding domain of the antibody. The amino acid sequence of the complementary-determining regions (CDR) determines the specificity and the affinity for antigens. Once an antigen is bound to the antibody, the constant region of the antibody mediates immune effector functions, which includes the binding to Fc γ receptors of immune cells for phagocytosis and antibody dependent cellular cytotoxicity (ADCC) and the interaction with serum complement proteins for complement dependent cytotoxicity (CDC) [15,16]. The hinge region, that couples the Fab fragments and the Fc part, allows rapid changes in angle between the Fab-fragments and provides segment flexibility. Glycosylation is a common attribute of IgGs and has to be considered when choosing an adequate expression system for IgG. The polysaccharide moieties are reported to impact antibody functional activity [17,18], pharmacokinetics [19], and the Fc effector functions [20,21]. So far, the IgG1 subclass has been the preferred antibody subclass for therapeutic applications. It combines several beneficial attributes including a relatively flexible and stable hinge region [22], the full set of Fc part effector functions [23,24] and a comparably long terminal half-life [25]. The latter aspect led to low administration frequencies of full IgG molecules and, therefore, caused to some extent that the development of CR systems for those molecules has been considered as less or not at all relevant.

IgG derived fragments, such as Fab or single chain variable fragments (scFv) can replace full IgGs without loss of molecule functionality (Fig. 1). Due to the absence of the Fc-part, the condition precedent for using antibody fragments is that immune effector functions and a long serum half-life are not required for the therapeutic mechanism. Antibody fragments demonstrated certain technical or therapeutic advantages. Their smaller size allows improved tissue penetration [26], which plays a particular role in oncology applications. In addition, they can be manufactured and delivered in higher molar quantities [27]. Because antibody fragments are conventionally not glycosylated, they allow protein expression via prokaryotic expression system. If required, the short serum half-life of antibody fragments can be extended via PEGylation [13] or by utilizing CR systems. In antibody-drug conjugates (ADCs), the antibody portion is covalently coupled to a toxin, which is selectively delivered to the site of action. The high specificity of the drug is reported to result in reduced side effects and a better therapeutic efficacy [28,29]. With several FDA approvals in recent years, antibody fragments [30], ADCs [31] and Fc-part fusion proteins [32] broadened the antibody-based therapeutic platform significantly, and novel antibody formats like, humanized single domains [33,34] or bispecific antibodies [35] are predicted to further increase this diversity.

The generation of various antibody types (Fig. 1) led to molecules with unique functions and strongly differing characteristics (Table 1). Limitations, which are related to these properties like e.g. unfavorable pharmacokinetic behavior or a high systemic toxicity, can be addressed by using CR and/or local delivery strategies to facilitate or support a specific antibody-based application.

2.2. What are the challenges of antibody formulation?

The standards and guidelines of conventional protein formulation should apply in the same manner when developing CR systems for antibodies. Herein, the preservation and analysis of antibody chemical and physical stability, the selection of the

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