Advanced Drug Delivery Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Biomedical applications of polymers derived by reversible addition – fragmentation chain-transfer (RAFT)☆

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ARTICLE INFO

Available online xxxx

Keywords:
Reversible addition-fragmentation chain transfer
RAFT
Radical polymerization
Drug delivery
Biomedical applications
Toxicity

ABSTRACT

RAFT- mediated polymerization, providing control over polymer length and architecture as well as facilitating post polymerization modification of end groups, has been applied to virtually every facet of biomedical materials research. RAFT polymers have seen particularly extensive use in drug delivery research. Facile generation of functional and telechelic polymers permits straightforward conjugation to many therapeutic compounds while synthesis of amphiphilic block copolymers via RAFT allows for the generation of self-assembled structures capable of carrying therapeutic payloads. With the large and growing body of literature employing RAFT polymers as drug delivery aids and vehicles, concern over the potential toxicity of RAFT derived polymers has been raised. While literature exploring this complication is relatively limited, the emerging consensus may be summed up in three parts: toxicity of polymers generated with dithiobenzoate RAFT agents is observed at high concentrations but not with polymers generated with trithiocarbonate RAFT agents; even for polymers generated with dithiobenzoate RAFT agents, most reported applications call for concentrations well below the toxicity threshold; and RAFT end-groups may be easily removed via any of a variety of techniques that leave the polymer with no intrinsic toxicity attributable to the mechanism of polymerization. The low toxicity of RAFT-derived polymers and the ability to remove end groups via straightforward and scalable processes make RAFT technology a valuable tool for practically any application in which a polymer of defined molecular weight and architecture is desired.

Contents

☆ This review is part of the Advanced Drug Delivery Reviews theme issue on "Editor's Collection 2015".

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http://dx.doi.org/10.1016/j.addr.2015.05.016

1. Introduction

Synthetic polymers are employed in a variety of biomedical applications. In addition to structural biomaterials and device components, polymers may also be used for the controlled delivery of therapeutic agents. While a diverse range of polymers may be generated by numerous polymerization reactions, radical polymerization is among the most robust and widely applicable methods. The biggest drawback to conventional radical polymerization (i.e. large dispersity and poor control over molecular mass) is addressed by the use of living radical polymerization techniques such as Nitroxide Mediated Polymerization (NMP) [1,2], Atom Transfer Reduction Polymerization (ATRP) [3,4], and Reversible Addition Fragmentation chain Transfer (RAFT) polymerization [2,5,6]. Alone among these techniques, RAFT polymerization allows control to be achieved in existing polymerization processes simply by the inclusion of a single additional compound. Moreover, the use of potentially toxic metal salts is not required. RAFT also permits the facile generation of complex structures of polymers including multi-block copolymers, star polymers, bottle brush polymers, hyper branched polymer and surface coatings to name a few [6]. RAFT mediated polymerizations can also generate polymers with a variety of reactive end-groups, allowing for example the coupling of bioactive molecules, depending on the design of the RAFT agent itself. These qualities make RAFT polymerization a very attractive tool for the generation of biomedical polymers. As research into applications involving the interaction of biological systems with RAFT generated polymers grows, one would want to be assured that toxicity, for example arising from the presence of RAFT polymer end groups, was not of concern. Importantly, one needs to be able to distinguish between any toxicity associated with the polymer chemistry or design of the molecules (e.g. polymers with amine side chains designed to interact with negatively charged biological molecules in various delivery applications) and any toxicity associated with the RAFT process *per se* (such as the presence of RAFT end groups). There remains few detailed *in vivo* toxicity studies, however, as RAFT becomes more widely applied in biological systems, we expect that this situation will rapidly change.

2. RAFT technology

The compounds that mediate RAFT polymerizations are referred to as RAFT agents or sometimes, more generally, chain transfer agents and take the generic form shown in Fig. 1, consisting of a thiocarbonylthio group with substituent "Z" and "R" groups [1,5].

Following initial chain transfer reactions, a growing polymer chain replaces the R group. As the full name suggests, RAFT agents aid in the control of polymerization via reversible addition across the thiocarbonylthio group and subsequent fragmentation reactions as seen in Fig. 2 [5,6].

Initiation results in the polymerization of monomer (M) to actively extending polymer chain P_n^* with rate constant k_p. The radically terminated chain propagates across the thiocarbonyl group of the RAFT agent yielding a radical intermediate that may fragment to release the polymer chain or the R group from the RAFT agent. The liberated R group radical then re-initiates polymerization, generating an actively extending polymer chain P_m^*. Polymer chains with terminal thiocarbonylthio groups are dormant, but are in dynamic equilibrium with active, propagating radical polymer chains. Polymer chains (P_n and P_m) with terminal thiocarbonylthio groups are dormant; they do not react directly with available monomer. Only $P_n^{\cdot}$ and $P_m^{\cdot}$ actively participate in polymerization reactions, but these propagating radicals may chain transfer to dormant thiocarbonylthio compounds, becoming dormant themselves while activating previously dormant chains. The equilibrium between active propagating chains and dormant thiocarbonylthio-bound chains provides equal probability for all chains to grow, resulting in polymers with narrow molecular weight dispersities [5,6]. When a typical RAFT polymerization is concluded, a large majority of the polymer chains generated will contain the dormant thiocarbonylthio group, permitting subsequent block extension of polymers grafted from the original polymer.

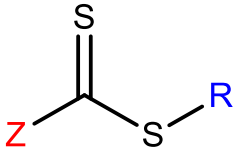

Fig. 1. General molecular structure of RAFT agent, consisting of a thiocarbonylthio group with "Z" and "R" substituents.

RAFT mediated polymerization takes advantage of the initiation and polymerization conditions of the unmediated radical polymerization techniques; only the addition of an appropriate quantity of RAFT agent to a polymerization mixture is necessary to achieve molecular weight and dispersity control. RAFT mediated polymerization is, therefore, amenable to radical thermal, redox [7,8] and photochemically initiated [9,10] polymerizations. Furthermore, scale up protocols such as the use of continuous flow reactors, are readily adapted to accommodate RAFT control [11] and end group removal [12].

The identity of the R and Z groups affect how well this equilibrium is met and maintained, which determines the quality of the control achievable in any given polymerization reaction. Because the kinetic behavior among the different classes of monomers varies, different RAFT agents are generally required to control the respective polymerizations [13,14]. Suitable substituents for various monomers are presented in Figs. 3 and 4. Many versatile RAFT agents, as of the time of writing, are commercially available and many more have been reported in the polymer research literature [6,15–17]. In addition, the RAFT agent selection rules have been well described in the literature [6] a summary of which is presented in Figs. 3 and 4 for the Z and R groups respectively.

A detailed discussion of which substituents permit controlled polymerization of which monomers, and the according theoretical explanations have been presented in previous publications and a number of review articles and will not be repeated here [1,6,13,14,16,17]. It does merit mention, however, that recently, switchable RAFT agents, which change activity depending on the acidity of the polymerization reaction mixture, have been shown to be effective for the control of both activated and less activated monomers [18,19]. This brings the concept of a universal RAFT agent one step closer to reality. As the thiocarbonylthio RAFT groups remain following polymerization, various advantageous polymer structures and architectures can be obtained via consecutive polymerizations with RAFT agents of variable functionalities. Linear polymers can be synthesized with multiple blocks [20] (Fig. 5). One recent report demonstrated the synthesis of a polymer with 12 distinct blocks [21]. By this consecutive polymerization of chains of determined molecular weights, RAFT polymerization has given researchers control over the sequence of blocks within a polymer, if not of individual monomer units.

With multifunctional RAFT agents star and graft copolymers can be obtained (Fig. 6) [22].

Due to the versatility of architectures obtainable with RAFT polymerization, it is possible to design and produce synthetic polymers that resemble, with respect to architecture and chemistry, and which interact with or mimic the behaviour of natural biopolymers in a number of critical, functional aspects.

3. RAFT polymers in drug delivery

3.1. Polymer-drug conjugation and grafting

Utilizing of the advantageous characteristics of RAFT mediated polymerization and/or the chemical composition and structure of resulting polymers that may be achieved; various schemes have been successfully applied to aid in the delivery of therapeutic agents. Drug-polymer conjugates, which may have better pharmacokinetic or solubility

Please cite this article as: B.D. Fairbanks, et al., Biomedical applications of polymers derived by reversible addition – fragmentation chain-transfer (RAFT), Adv. Drug Deliv. Rev. (2015), http://dx.doi.org/10.1016/j.addr.2015.05.016