Available online at www.sciencedirect.com
ScienceDirect
Advanced Drug Delivery Reviews 60 (2008) 1018–1036
Advanced DRUG DELIVERY Reviews
www.elsevier.com/locate/addr

Advances in the synthesis of amphiphilic block copolymers via RAFT polymerization: Stimuli-responsive drug and gene delivery ☆

Adam W. York, Stacey E. Kirkland, Charles L. McCormick *

Department of Polymer Science, The University of Southern Mississippi, Hattiesburg, MS 39406, USA

Received 10 September 2007; accepted 14 February 2008
Available online 26 February 2008

Abstract

Controlled/'living' radical polymerization methods, including the versatile reversible addition–fragmentation chain transfer (RAFT) polymerization process, are rapidly moving to the forefront in construction of drug and gene delivery vehicles. The RAFT technique allows an unprecedented latitude in the synthesis of water soluble or amphiphilic architectures with precise dimensions and appropriate functionality for attachment and targeted delivery of diagnostic and therapeutic agents. This review focuses on the chemistry of the RAFT process and its potential for preparing well-defined block copolymers and conjugates capable of stimuli-responsive assembly and release of bioactive agents in the physiological environment. Recent examples of block copolymers with designed structures and segmental compositions responsive to changes in pH or temperature are reviewed and hurdles facing further development of these novel systems are discussed.

Keywords: Water soluble polymers; Controlled release; Targeted delivery; Bioconjugation; Interpolyelectrolyte complexes; Cross-linked micelles; Stimuli-responsive polymers

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Design and Development Strategies of Polymer Materials for Drug and Gene Delivery Applications". Paper number 133 in a series by McCormick Research Group entitled Water Soluble Polymers.

* Corresponding author. Tel.: +1 601 266 4872; fax: +1 601 266 5504.
E-mail address: Charles.McCormick@usm.edu (C.L. McCormick).

0169-409X/$ - see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.addr.2008.02.006

1. Introduction

Recent advances in controlled/"living" radical polymerization (CLRP) methods are certain to impact future approaches to diagnosis and treatment of infectious and genetic diseases. Specifically, one such technique, reversible addition–fragmentation chain transfer (RAFT) polymerization, allows unprecedented latitude in synthesis of water soluble architectures with precise dimensions and appropriate functionality for conjugation to and targeted delivery of diagnostic and therapeutic agents. Although to date only limited reports have appeared regarding the construction of such novel drug delivery vehicles, it is apparent that the synthetic control afforded by the RAFT process and the resulting facile post-polymerization functionalization, cross-linking, and bioconjugation are advantageous when compared to more conventional processes currently utilized. In the following review, the RAFT process will be discussed, demonstrating its utility for polymerizing a variety of functional monomers, often directly in water and not requiring protecting group chemistry. Selected examples of "smart" polymeric systems prepared by RAFT or other CLRP techniques and designed with precise nanoscale dimensions, narrow molecular weight distributions, reactive pendant or terminal moieties and surface functionality will be presented. In some cases, for example in drug delivery from shell cross-linked micelles or in delivery of polynucleotides from interpolyelectrolyte complexes, significant advancements in protection of the active agent, carrier stabilization, and controlled release have been realized, although formidable challenges remain.

Impetus for research on polymeric delivery vehicles has come from consideration of technical, economic and safety issues. The fact that viral vectors are very effective at targeting and delivering therapeutic agents to the cytoplasm or the nuclear envelope of the cell has been well established. However, shortcomings of viral vectors include the invocation of an immunogenic response by the host, the high cost of manufacturing, and the lack of cell specificity [1]. Thus a number of non-viral delivery systems with low immunogenicity yet specific targeting and controlled activity have been considered. For example, conventional liposomes have been utilized to sequester and transport chemotherapeutics [2], polynucleotides [3], and proteins [4]. Although such systems have been shown to possess many requisite requirements [1,5] for in vivo application including: protection of cargo from degradation, ease of surface modification for targeting, and reasonable manufacturing costs, disadvantages often are reported such as limited solubility and partitioning, less than optimal pharmokinetics, and liposome instability in the physiological environment [6].

More recently research has centered on polymer based carrier systems including polymer–drug conjugates, micelles, polymersomes, and nanoparticles. A major goal of this work is to mimic the highly evolved trafficking and delivery efficiency of viral vectors while avoiding the non-specific toxicity and immunogenicity issues discussed above. Several significant barriers are currently being addressed. The non-viral carrier must be able to degrade or dissociate into low molecular weight species capable of excretion through the kidneys. In the case of non-degradable polymeric carriers, the carrier must be of low molecular weight to be efficiently excreted. Both extracellular and intracellular factors present significant challenges in the successful delivery of active agents via non-viral vectors. Extracellular barriers include, but are not limited to, packaging of the active agents by the carrier, stability and circulation in the bloodstream, and specific cellular binding; intracellular barriers include endosomal release, cytoplasm transport, and release of the active species [1].

Prior to the mid 1980s only limited synthetic tools were available to polymer chemists for construction of delivery vehicles, although Ringsdorf and others, for example, had eloquently proposed model targeting systems [7,8]. Control of polymer architecture, molecular weight and molecular weight distribution, placement of reactive structopendant or structoterminal functionality, and solubility/dispersion in biologically relevant media were obstacles inherent to existing polymer technology. For example, block and star copolymer architectures with appropriate functionality could only be achieved with anionic, cationic, or group transfer chain growth polymerization techniques with limited types of monomers, often requiring protecting group chemistry, under stringent conditions in the absence of water. Fortunately rapid developments in two major areas: dendrimer synthesis and CLRP now allow control over a number of necessary design criteria. Although we focus on the latter area here, excellent reviews on the chemistry and biological applications of dendrimers are found in recent literature [9,10].

The major CLRP techniques include atom transfer radical polymerization (ATRP) [11], stable free radical polymerization (SFRP) [12], reversible addition–fragmentation chain transfer (RAFT) polymerization [13,14], and the specialized area of aqueous RAFT polymerization [15,16]. Although a recent report [17] suggests some opportunities for SFRP, most efforts toward construction of polymeric delivery vehicles with controlled structures and molecular weight have utilized ATRP or RAFT. While each of the techniques has its inherent advantages and limitations, the RAFT process is arguably the most amenable to controlled delivery/controlled activity in the physiological environment due to the variety of functional monomers that can be polymerized directly in water without requiring protecting group chemistry and the facility by which structopendant and structoterminal (both α and ω) functionality can be placed for subsequent conjugation to synthetic or biological molecules. Additionally cross-linking and "click" chemistry are easily conducted on RAFT-synthesized polymers under facile reaction conditions. In fact, it is likely that many controlled delivery polymers previously made by conventional techniques or more tedious CLRP processes will be prepared by RAFT polymerization in the future.

2. RAFT polymerization

RAFT polymerization was first reported by the Australian CSIRO group in 1998 [13,14,18] and later adapted to aqueous