Introduction

Poly(2-oxazoline)s (POx) were discovered in 1966\(^1\,2\) but have only recently gained substantial attention as a biomaterial, especially for the development of drug delivery systems (DDS) and polymer therapeutics.\(^3\) One reason for the late recognition of POx in the biomedical field was a lack of commercially available monomers and well-defined, functionalized polymers, while other suitable polymer platforms such as poly(ethylene glycol) (PEG) and Pluronic® block copolymers were readily available from commercial sources. As a consequence, PEG became the most widely used polymer therapeutic and is classified as "Generally Recognized as Safe" (GRAS) by the FDA. However, recent reports on an "accelerated blood clearance" (ABC) effect of PEGylated therapeutics,\(^4\) as well as the rather limited chemical variability of the polymer, has helped make the case for developing suitable alternative polymer platforms. POx has the potential to provide such an alternative in the case of the failure of a PEG-based system. Moreover, POx has the potential to offer more than merely a replacement to PEG because it provides a more versatile chemistry and the potential to tune the "hydrophilic lipophilic balance" (HLB) of amphiphilic POx copolymers.\(^3\,5\)

Chemistry

POx is synthesized by living cationic ring-opening polymerization (LCROP) of 2-oxazolines, typically with alkyl tosylates or triflates as initiators and various nucleophiles (amines, carboxylates, etc.) as terminating agents. The LCROP of 2-oxazolines is relatively slow but proceeds reasonably well at T >40 °C to produce well-defined linear polymers of low dispersity (PDI <1.05–1.3), controllable compositions (random, gradient, and block copolymers) and with end groups that can be quantitatively defined by the initiation and termination reaction. Among other factors, the solvent polarity and nature of the counter ion determine the equilibrium and thus, the "livingness" of the LCROP. A general reaction scheme is given in Figure 1.

**Figure 1.** General reaction scheme of the living ring-opening polymerization of 2-oxazolines.

Biocompatibility of POx

The current interest in POx as an alternative polymer platform to PEG is largely based on recent reports on its exceptional behavior in complex biological environments. Zalipsky et al.\(^6\) first discovered the so-called “stealth behavior” of hydrophilic POx (poly(2-methyl- and 2-ethyl-2-oxazoline) (PMEOx, PEtOx)) that leads to long blood circulation times in animals. Later, Luxenhofer et al.\(^7\) found that upon injection in rodents, hydrophilic POx disperses rapidly throughout the entire organism except the brain and shows very little unspecific organ deposition and rapid renal excretion. Amphiphilic POx of various compositions display no cytotoxicity, low complement activation in vitro\(^8\,9\) and animal testing indicates no adverse properties from neutral hydrophilic or amphiphilic POx. Moreover, depending on the amphiphilic contrast of POx, the cell-uptake can be surprisingly fast even at low polymer concentrations.\(^8\)