Controlled Release | Targeted Delivery | Solubility Enhancement

POLYOXAZOLINES: AN ALTERNATIVE TO POLYETHYLENE GLYCOL

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Water-soluble, biocompatible polymers are important building blocks in drug delivery formulations, from micelles to drug-polymer conjugates. Polyethylene glycol (PEG) is often considered the gold standard for biocompatible and inert polymers used in drug delivery formulations. However, the growing demand for suitable polymer candidates with a range of material properties to fit the increasing diversity of drugs has generated a need for new biocompatible multifunctional polymers.

Poly(2-ethyl-2-oxazoline)s and poly(2-methyl-2-oxazoline)s are as extensively studied as poly(ethylene glycol) substitutes in a variety of biomedical applications since they share many of the desirable properties of PEG[1–4] but avoid some of their limitations (**Table 1**). PEG has been widely used in biomedical applications because it imparts "stealth" properties to the drug delivery system. PEGylation, the conjugation of PEG to a biopharmaceutical, has helped generate both clinical and market success for a number of drugs. Although PEG has traditionally been considered bio-inert, recently, serum antibodies against PEG have been detected in patients treated with PEG-uricase[5] and PEG-asparaginase.[6] Moreover, in a pre-treatment screening, over 25% of patients had pre-existing anti-PEG antibodies even though they never received prior treatment with PEGylated drugs.[7,8] This may be due to the abundance of PEG used in everything from beauty products to food. Furthermore, PEGylated conjugates can cause kidney cell vacuoluation in animals following repeated administration of PEGylated therapeutics.[9,10]

Poly(2-oxazolines) may be a suitable alternative to PEG due to their biocompatible properties. For example, radiolabeling of polyoxazoline has shown that the polymer is rapidly excreted by the kidneys and shows no accumulation in the body.[11,12] In addition, *in vitro* studies with poly(2-ethyl-2-oxazoline) and poly(2-ethyl-2-oxazoline) block copolymers were reported to be biocompatibile even at higher concentrations than PEG.[13,14] For these reasons, poly(2-oxazolines) are being investigated in a variety of pharmaceutical and medical applications, e.g., drug-polymer conjugates (POZylation),[15,16] micelles,[17] or grafting onto liposomal bilayers.[18]

Table 1. Property comparison between PEG and Poly(2-oxazoline)s*

Poly(2-oxazoline)	PEG
Polymerization	
Easily synthesized with commercially available materials	Challenging polymerization
No peroxide formation	Forms peroxides
No diol impurities	May have up to 6% diol content as an impurity
Polymer Properties	
Low viscosity	High viscosity at high concentrations
Stable at room temperature	Stable at <–20 °C
Non-hygroscopic	–
Drug Delivery Applications	
Not approved by the FDA yet	FDA approved
High drug loading	Low drug loading
Pendant functional groups allow for active targeting by conjugation techniques	Active targeting is reserved for conjugation to end-functional group only
Readily cleared from the body	May accumulate *in vivo*
–	May be immunogenic for a subset of patients
–	Vacuole formation observed

*adapted from Viegas et al.[15]

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