

anticancer agents that involved HPMA as the polymer (Duncan et al., 2001). They are HPMA copolymer–doxorubicin, HPMA copolymer–paclitaxel, HPMA copolymer–camptothecin, HPMA copolymer–platinite, and an HPMA copolymer–doxorubicin conjugate that also bore galactosamine. Galactosamine was included to target the conjugate to the liver (Duncan et al., 1986) in order to treat primary and secondary liver cancer (Duncan et al., 2001).

Polymer prodrugs of ribavirin have been prepared to test the effect of the polymer promoiety on inhibition of nitric oxide and to seek evidence of a reduction in hemolytic activity. There was concern that the polymer could interfere with inhibition of nitric oxide synthase (the therapeutic basis of ribavirin activity as an anti-inflammatory agent), and anemia proved to be a serious side effect with ribavirin (Guo et al., 2015). HPMA (Wohl et al., 2014; Smith et al., 2015), polyvinylpyrrolidone (PVP; Kryger et al., 2014; Wohl et al., 2014), polymethacrylic acid (PMAA; Wohl et al., 2014), and polyacrylic acid (PAA; Kryger et al., 2013, 2014; Wohl et al., 2014) were included in these studies. Although HPMA demonstrated the lowest toxicity, HPMA and PAA both reduced cytotoxicity. PVP was the only polymer in these studies that blocked inhibition of nitric oxide synthase. PAA exhibited no hemolytic effect (Kryger et al., 2013, 2014) and proved to be the most effective of these polymeric prodrugs.

Among the water-soluble synthetic polymeric materials employed in the covalent modification of drugs, polyethylene glycols (PEGs) are preferred for their biocompatibility and their lack of antigenicity and toxicity (Weiner and Zilkha, 1973; Zalipsky et al., 1983; Dal Pozzo and Acquasaliente, 1992; Li et al., 2014). In addition, these polymers are soluble in water and organic solvents (Weiner and Zilkha, 1973), and they are commercially available in fractions with well-defined molecular weights (Cecchi et al., 1981). PEG prodrugs have two distinct disadvantages. Esters formed with PEG as the source of the alcohol group would possess an electron-withdrawing group in the α -position of the ester that can assist in the rapid chemical hydrolysis of the ester bond (Chung and Cho, 2004). The PEG component in the prodrug is not biodegradable (Zalipsky et al., 1983), which limits the routes of administration available to these prodrugs.

Mattarei et al. (2015) utilized PEG of short chain length with only three, four, or six repeated units in the preparation of *N*-monosubstituted methoxy-oligo(ethylene glycol) carbamate ester prodrugs of resveratrol. The use of oligo(ethylene glycol) instead of poly(ethylene glycol) made it possible to maintain a low molecular weight and to allow a higher drug-loading potential, yet provide the desirable physicochemical properties observed with PEG derivatives. The shorter chain length of the oligo(ethylene glycol), though still not biodegradable, also offered the possible use of conventional routes of administration.

Potential indomethacin (Caprariis et al., 1994) and ibuprofen (Cecchi et al., 1981) prodrugs have been prepared by generating the ester between the terminal hydroxyl of various low molecular weight PEGs and the carboxylic acid of the drug. Indomethacin prodrugs demonstrated rapid reconversion in 80% human plasma in isotonic pH 7.4 phosphate buffer. In the absence of enzymes, in pH 2 or 7.4 buffer, the hydrolysis rate was approximately 200 times slower than observed in the presence of enzymes. Preliminary experiments with porcine esterase indicate that enzymatic hydrolysis was probably catalyzed by esterases, and that the hydrolysis can regenerate the parent drug directly. The tetraethylene glycol–ibuprofen derivative was a viscous oil that was poorly soluble in water. However, a PEG of high molecular weight, consisting of approximately 45 monomeric units and corresponding to a molecular weight of 2000, was esterified at both ends and was still found to be freely soluble.

PEG derivatives of paclitaxel (Greenwald et al., 1996; Nam et al., 2014), camptothecin (Greenwald et al., 1998), and doxorubicin (Rodrigues et al., 1999) have been prepared. It was noted that the molecular weight of the PEG must be “of such magnitude so as to maintain a $t_{1/2}$ (circulation) $>$ $t_{1/2}$ (hydrolysis)” (Greenwald et al., 1996). In the case of camptothecin derivatives, PEG with a molecular weight \geq 20,000 g/mole allowed the bifunctional PEG to be derivatized at both ends and still remain soluble in water (Greenwald et al., 1998). Doxorubicin–polyethylene glycol prodrugs were synthesized in aqueous media by reacting three different maleimide derivatives of doxorubicin