Table 45.2 Examples of drug polymer conjugates on the market

Name	Polymer-Drug	Indication
Adagen®	PEG-adenosine deaminase	SCID syndrome
Cimzia®	PEG-anti TNF Fab' fragment	Crohn's disease and rheumatoid arthritis
Oncaspar®	PEG-asparaginase	Acute lymphoblastic leukaemia
PEG-Intron®	PEG-Interferon 2b	Hepatitis C
Pegasys®	PEG-Interferon 2a	Hepatitis B and Hepatitis C
Neulastra®	PEG-Granulocyte colony-stimulating factor	Prevention of neutropenia associated with cancer chemotherapy
Macugen®	PEG-anti-VEGF aptamer	Age-related macular degeneration
Somavert®	PEG-growth hormone receptor antagonist	Acromegaly
Zinostatin Stimalamer®	Syren-maleic anhydride copolymer-Neocarzinostatin	Hepatocellular carcinoma

excretion rates via the kidneys. The renal clearance of compounds from the circulation is dictated by their molecular weight, with clearance rates decreasing with increasing molecular weight up to a threshold of around 45 kDa. Above 45 kDa, renal excretion cannot occur and larger polymers are more susceptible to clearance by the mononuclear phagocytic system (MPS). So, for example, the conjugation of molecules such as paclitaxel (~ 850 Da), and proteins such as interferon (~ 20 kDa) to water-soluble polymers increases their overall molecular weight enhancing drug circulation times and reducing kidney clearance rates.

Protecting against degradation after administration

The polymeric chains in the polymer-drug conjugate can also prevent the approach of antibodies and proteolytic enzymes to the drug. Water-soluble polymers become strongly hydrated and these hydrated polymer strands can promote steric hindrance, and block enzymes and antibodies reaching the drug. This protects the drug from degradation and enhances their plasma half-life and bioavailability. This is of particular advantage to protein-based therapeutic agents that are rapidly degraded by enzymes. However, it has been reported that antibodies against PEG can be generated in vivo and these can remove and neutralize PEG-conjugate products.

Reducing aggregation, immunogenicity and antigenicity

The hydrophilic coating offered by the polymers to the conjugate compound is the key to this property. The hydrated polymer chains can mask the hydrophobic regions in the protein, improve solubility and provide a steric shield that can help prevent protein-protein association, and reduce aggregation. For example, the native proteins in Neulastra® and PEG-Intron® have a high tendency to aggregate, however, PEG conjugation (referred to as *PEGylation or pegylation*) of these proteins can reduce aggregation and subsequently reduce associated immunogenic and antigenic problems. As already noted, the presence of the hydrated polymer in the conjugate can reduce antibody interactions, also reducing immunogenicity. PEGylation of proteins can also help stabilize proteins during lyophilization so helping to produce products with acceptable storage conditions.

Promoting targeting to specific organs, tissue or cells

By conjugation of drugs or proteins to water-soluble polymers, not only can their half-lives be improved, but the specific accumulation of the drug or protein can also be promoted in certain tissues. This can be achieved through the use of targeting groups or the