

The Low Viscosity of PolyPEG[®] Compared with Linear and Branched PEG

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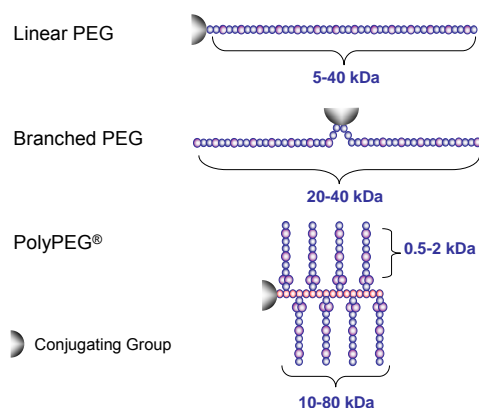
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Introduction

Protein and oligonucleotide therapeutics are frequently modified by conjugation to polyethylene glycol (PEG) in order to overcome the serious limitations that can arise due to their short half-life, immunogenicity and/or toxicity¹ in the body. Several such PEGylated products have been approved. These rely on either multiple conjugations of relatively low molecular mass PEGs (ca. 5000 Da), or conjugation of higher molecular mass PEGs (ca. 20-40 kDa). The viscosity of PEG frequently limits the concentration of formulated biologicals for therapeutic use.

PolyPEG[®] comprises a 'comb-like' arrangement of short PEG chains (typically 0.5-2 kDa molecular mass) attached to a polymethacrylate backbone by ester bonds²⁻⁵ (Fig 1). The comb structure of PolyPEG[®] will substantially reduce the viscosity of such conjugates and polymers^{1,6}. This offers the potential for increased and high concentration formulations for ease of dosing of biological therapeutics.

Figure 1. Schematic representation of the structure of linear PEG and PolyPEG[®]



Methods

The specific viscosity (η_{sp}) of various PEGs and PolyPEG[®]s was measured using a glass BS/U tube viscometer (size A, Rheotek). The intrinsic viscosity was calculated by measuring η_{sp}/c at several different concentrations and extrapolating to zero concentration. GPC viscometry analysis was carried out at 50 °C using a PL-GPC 50 Plus (Varian) equipped with 2 x PLgel 5 μ m MIXED-D (300 x 7.5mm) columns⁷. The mobile phase was DMF (+0.1 % LiBr).

Results

In aqueous solution the intrinsic viscosity of linear and branched PEGs increased with molecular mass and was several fold higher than that of equivalent PolyPEG[®]s (Fig 2).

The viscosity of PolyPEG[®] in aqueous solution increased slightly with molecular mass, but by substantially less than that of linear PEGs and was independent of conjugating group (Fig 2). Intrinsic viscosities obtained using DMF-GPC were similar to those obtained in aqueous solution (Fig's 2 and 3).

Figure 2. Comparison of viscosity of linear PEG, and NHS, MAL and CHO PolyPEG[®]s in aqueous solution determined by U-tube viscometry

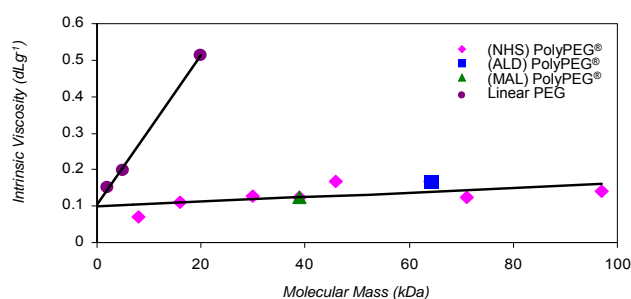
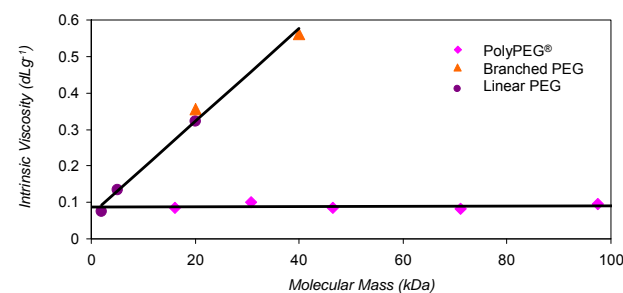


Figure 3. Comparison of viscosity of linear-, branched-PEGs and PolyPEG[®]s by DMF GPC viscometry



Conclusions

The substantial reduction in viscosity of PolyPEG[®]s compared to linear and branched PEGs offers the potential for higher dosing strengths and consequent ease of administration, while maintaining half-life extension.

References

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