

Ultrafast *In Situ* Forming Poly(ethylene glycol)-Poly(amido amine) Hydrogels with Tunable Drug Release Properties via Controllable Degradation Rates

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Introduction

Dendrimers have attracted increasing attention for the preparation of biomedical hydrogels thanks to their uniformity combined with control over their size, architecture, density and surface groups.¹ In most poly(amino amide) (PAMAM) based hydrogels, linear poly(ethylene glycol) (PEG) was employed as crosslinking agent. However, star-shaped PEGs offer various advantages over linear PEGs, such as a higher concentration of end groups, which may result in faster gelation. Furthermore, control over hydrogel degradation is an important item that has yet received little attention regarding PEG-PAMAM hydrogels. This prompted us to prepare *in situ* forming PEG-PAMAM hydrogels by reacting PAMAM with multi-armed PEGs containing either a hydrolysable ester group or a stable amide group near each PEG end.

Experimental Methods

Hydrogels were prepared in NaH₂PO₄/Na₂HPO₄ buffer (pH 8) via the amidation reaction between N-succinimidyl ester (NHS) end groups of multi-armed PEG and amino end groups of PAMAM generation 2.0. To control the properties of the PEG-PAMAM hydrogels, PEGs were used with different arm numbers (4 or 8) as well as different linkers (amide or ester) between the PEG arms and their terminal NHS groups (Figure 1).

Results and Discussion

Rheology measurements showed that the hydrogels form within seconds after mixing the PEG and PAMAM precursor solutions. The storage moduli increased with crosslink density and reached values up to 2.3 kPa for hydrogels based on 4-armed PEG. Gravimetric degradation experiments demonstrated that hydrogels with ester linkages between PEG and PAMAM degrade within 2 days, whereas amide-linked hydrogels were stable for

several months. The release of the model drug fluorescein isothiocyanate-dextran (4·10³ or 2·10⁶ g/mol, FITC-DEX4K and FITC-DEX2000K, respectively) from amide-linked hydrogels was characterized by an initial burst followed by diffusion-controlled release, of which the rate depended on the size of the drug. In contrast, the release of FITC-DEX2000K from ester-containing hydrogels was governed mainly by degradation of the hydrogels and could be modulated via the ratio between ester and amide linkages. Cytotoxicity experiments showed that the PEG-PAMAM hydrogels are non-toxic to mouse fibroblasts.

Conclusions

The possibility to be formed *in situ* and their tunable mechanical, degradation and release properties make these PEG-PAMAM hydrogels appealing as controlled drug delivery systems.

References

1. C. Ghobril, E.K. Rodriguez, A. Nazarian, M.W. Grinstaff, *Biomacromolecules* 2016, **17**, 1235.

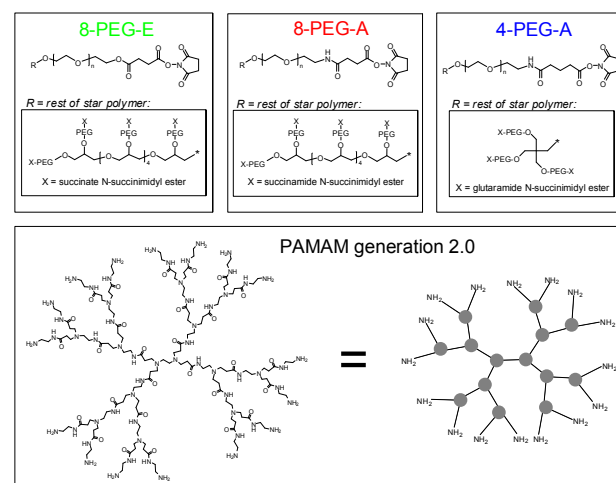


Figure 1. Structure of the PEG and PAMAM hydrogel precursors used in this study.