Arborescent Polypeptides for Sustained Drug Delivery Applications

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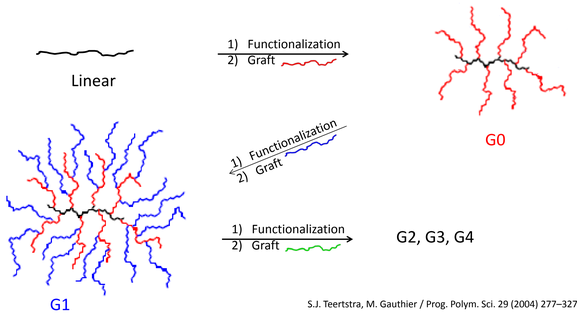
Abstract

Polymeric micelles have attracted much attention as promising drug delivery vehicles, because their size and structure are similar to those of natural carriers in biological systems. One advantage of using polymer micelles for drug delivery is the long blood circulation time of micellar particles. The size of polymer micelles typically ranges from 10 to 100 nm, and their recognition by the reticuloendothelial system, a main reason for their removal from the blood compartment, is considerably lowered for particles below 100 nm. Another advantage arises specifically from the core–shell structure of the micelles, with a hydrophobic inner core surrounded by a hydrophilic shell isolating the nanocontainer from the outer environment. Therefore drug molecules entrapped in the hydrophobic core are protected from the biological environment and inactivation of the drug molecules can be avoided by minimizing contact with inactivating species in the aqueous (blood) phase. The micellar structure may also be tailored to achieve targeting or other desired properties. In this project, the synthesis of biocompatible and biodegradable arborescent polymeric micelles with narrow molecular weight distributions (MWD) was carried out. The peptide coupling reactions used were optimized, and the success of the grafting reaction was quantified in terms of grafting yield and coupling efficiency.

Synthesis of Successive Generations of Arborescent Polymers



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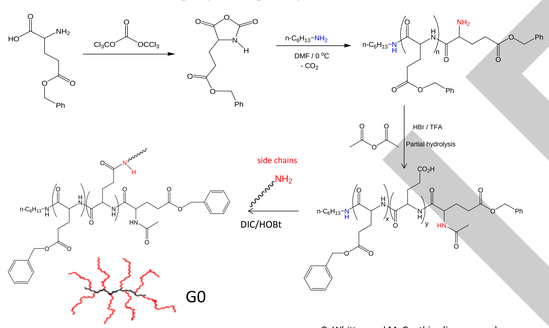
Overall Synthetic Scheme

(Ring-opening Polymerization)



G. Whitton and M. Gauthier *(in progress)*

Acknowledgements

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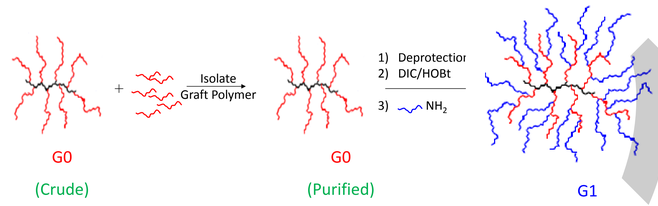
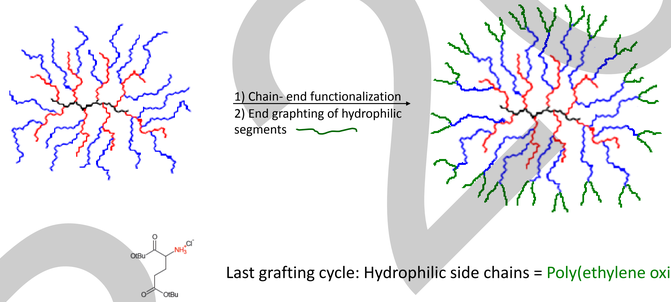
Generations 1,2,…



- Isolate the graft polymer using a preparative GPC system

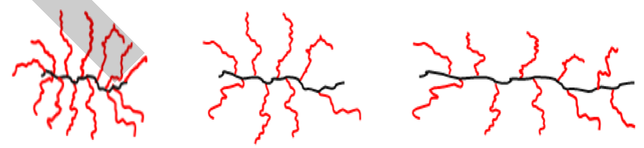
Micelle Synthesis



(Glutamic acid di-*tert*-butyl ester hydrochloride)

Last grafting cycle: Hydrophilic side chains = Poly(ethylene oxide).

Different Core Topologies



DP = 18
Deprotection level = 100%

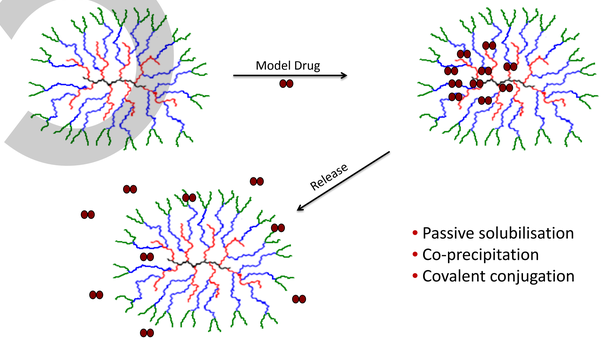
DP = 30
Deprotection level = 31%

DP = 70
Deprotection level = 35%

- PBG substrate
- Characteristics such as the size, shape, and porosity of arborescent copolymers can be tailored to specific requirements by adjusting their composition, branching functionality, generation number, and the size of the side chains in the core and the corona
- The heterogeneous morphology of these molecules is advantageous for applications in solubilization and microencapsulation

Encapsulation and Release

- Hydrophobic drugs(e.g. Doxorubicin, Taxol)



- Passive solubilisation
- Co-precipitation
- Covalent conjugation

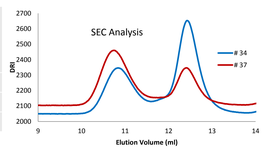
Results

Ring-opening Polymerization of Benzyl Glutamate NCA

Sample Name	Target DP	^{1}H NMR DP$_n$	$M_n^{H\,NMR}$	M_n^{app} (SEC)	PDI
Poly(Bz-Glu)-2	20	24	5,500	7,700	1.11
Poly(Bz-Glu)-3	50	67	14,000	13,300	1.16
Poly(Bz-Glu)-18	20	25	5,800	5,600	1.09

Influence of Reactants Molar Ratio on the Grafting yield and Coupling efficiency

Sample Name	molar ratio Side chains : substrate	MALLS M_n	MALLS M_w/M_n	Grating Yield (%)	Coupling efficiency (%)
27	1 : 1	78,400	1.03	59	79
34	1 : 0.8	67,100	1.05	40	69
37	0.8 : 1	76,000	1.07	62	76



Characteristics of PBG End Grafted Micelles

Copolymer	PBG substrate DP	PBG substrate MALLS M_n	PBG substrate MALLS M_w/M_n	Graft Copolymer MALLS M_n	Graft Copolymer MALLS M_w/M_n
G1PBG-*eg*-PEO	18	197,000	1.07	390,000	1.08
G1PBG-*eg*-PEO	30	186,000	1.05	375,000	1.04
G1PBG-*eg*-PEO	70	160 ,000	1.08	327,000	1.10
G2PBG-*eg*-PEO	18	930,000	1.07	1.9×10^6	1.07
G2PBG-*eg*-PEO	30	870,000	1.06	1.8×10^6	1.08

Conclusions & Future Work

- Modification of the hydrophobic cores achieved to generate water-soluble micelles
  - Addition of hydrophilic segments at chain ends of the core
  - Addition of polyglycidol or polyethylene segments of different lengths
- Encapsulation of hydrophobic PAH and model drugs needs to be achieved
  - Passive solubilization, co-precipitation, and covalent conjugation possible
- The solubilization and release kinetics will be investigated
  - Fluorescence and UV spectroscopy monitoring