Arborescent Polypeptide Micelles For Drug Release

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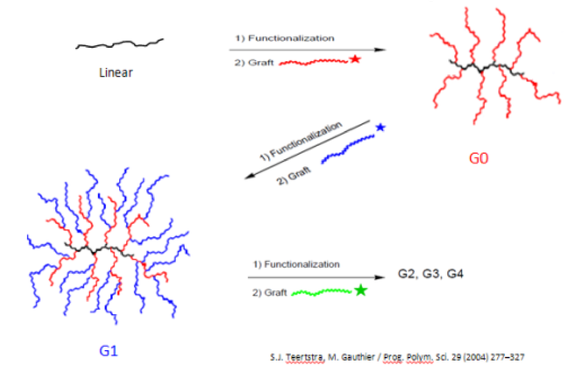
Abstract

Polymeric micelles have attracted much attention as promising drug delivery agents because their size and structure are similar to natural carriers in biological systems. One advantage of polymer micelles for drug delivery is their long blood circulation time. The size of polymer micelles generally ranges from 20 to 100 nm and recognition by the reticuloendothelial system, the main reason for the removal of particles from the blood compartment, is considerably lowered for particles in that size range. Another advantage arises from the specific core–shell structure of these micelles. The hydrophobic core surrounded by a hydrophilic shell forms a microcontainer that is isolated from the surrounding environment. Therefore, drug molecules entrapped in this microcontainer are protected from the environment and drug inactivation by inactivating species in the aqueous (blood) phase can be avoided. The micellar structure may also be tailored to achieve targeting or other desirable properties.

The synthesis of biocompatible and biodegradable arborescent polymeric micelles with narrow molecular weight distributions (MWD) is now reported. The optimization of the peptide-coupling reactions was carried out, and the success of the grafting reactions quantified in terms of their grafting yield and coupling efficiency.

The Synthesis of Successive Generations of Arborescent Polymers



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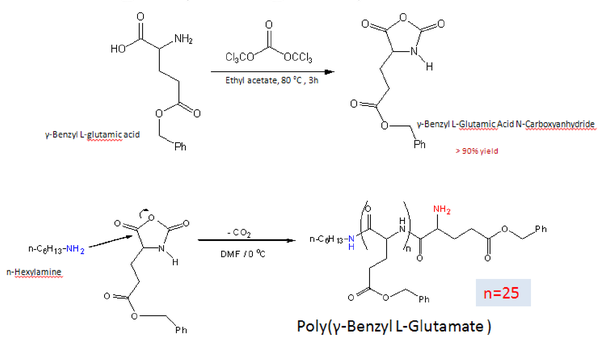
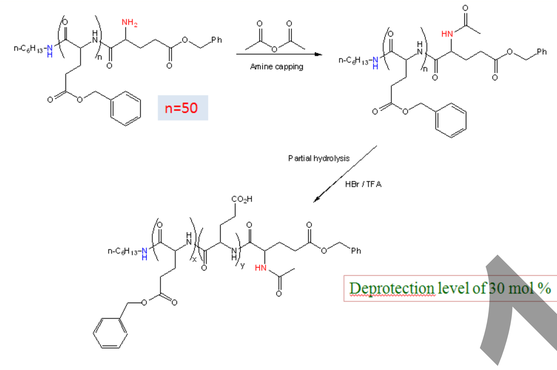
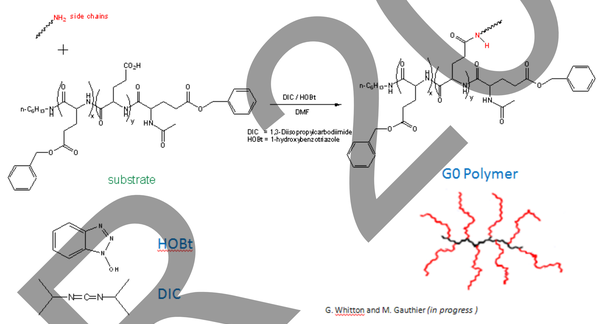
Synthesis of Side Chains (Ring Opening Polymerization)



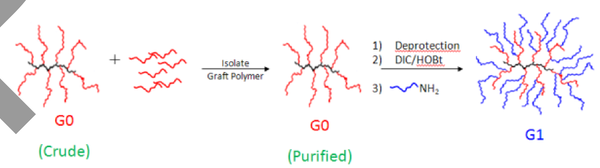
Synthesis of Substrate (Backbone)



Grafting Reaction

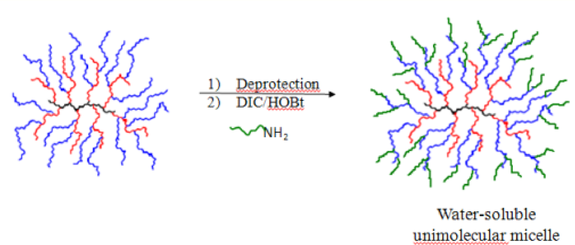


Generations 1, 2,…



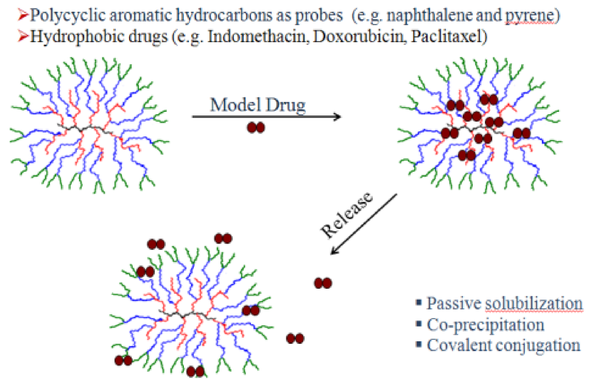
➢ Isolate graft polymer using preparative GPC column

Micelles: Shell Addition



➢ Last grafting cycle: Hydrophilic side chains (Polyglycidol).

Encapsulation and Release



Ring Opening Polymerization

Sample Name	Temperature (°C)	Target DP_n	^{1}H NMR DP_n	$M_n^{H\ NMR}$	M_n^{app} (SEC)	PDI
Poly(Bz-Glu)-2[a]	0	20	23.9	5,500	7,700	1.11
Poly(Bz-Glu)-3[a]	25	50	67.0	14,000	13,300	1.16
Poly(Bz-Glu)-9[b]	0	20	13.9	3,300	4,900	1.15
Poly(Bz-Glu)-10[c]	0	20	25	5,800	5,500	1.15
Poly(Bz-Glu)-18[a]	0	20	25	5,800	5,600	1.09

[a] *n*-hexylamine initiator, [b] 3-amino-1-propanol initiator, [c] 5-amino-pentanol initiator

➔ Chain functionality ($-NH_2$) level will determine which method is best

The Grafting yield and Coupling Efficiency

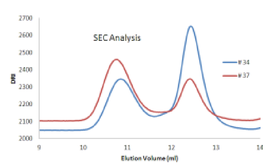
Sample Name	Solvent	Time (h)	MALLS M_n	MALLS M_w/M_n	Grafting Yield (%)	Coupling efficiency (%)
30	DCM/DMF	64	59,500	1.02	50	55
26	DMF	64	65,800	1.02	55	64
27	DMSO	64	78,400	1.03	59	79

Influence of solvent

Influence of reactant molar ratios

Molar ratio → NH_2 : CO_2H : DIC : HOBt : TEA
1 : 1 : 1.5 : 1.5 : 1.5

T= 25 °C in all reactions, Coupling reagents= DIC/HOBt



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

T= 25 °C in all reactions, solvent= DMF, Time= 64 h, Coupling reagents= DIC/HOBt

Conclusions & Future Work

- Systematic variations in side chain size and coupling site density necessary to optimize the grafting yield
- Synthesize G1, G2… etc. polymers with narrow MWD
- Modification to generate water-soluble micelles: Addition of hydrophilic segments
  Addition of polyglycidol or Glu(OtBu) segments of different lengths
- Encapsulation of hydrophobic PAH and model drugs
  Passive solubilization, co-precipitation, and covalent conjugation
- Study the solubilization and release kinetics
  Fluorescence and UV-Vis spectroscopy measurements

Acknowledgements

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