ARBORESCENT POLMERS BASED ON AMINO ACIDS

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Introduction

Objective: To construct amphiphilic arborescent copolymers from L-glutamic acid derivatives and a variety of hydrophilic components to make biocompatible, stable polymeric micelles for controlled drug delivery applications. Maintaining a narrow molecular weight distribution (MWD) throughout the synthesis is desirable to allow structure-property correlations and for biomedical applications.

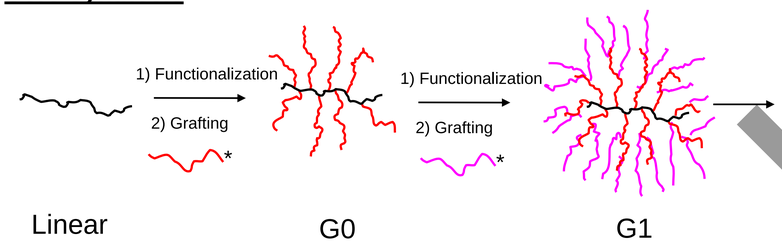
Biocompatibility is a prerequisite for biomedical applications. Systems used for that purpose such as block copolymer micelles incorporate biocompatible components in some cases, but are often unstable in highly dilute environments (e.g. blood stream), where their concentration drops below their critical micelle concentration (cmc).

Amphiphilic arborescent copolymers have the advantage of acting like unimolecular micelles, the stability of the structure being independent of concentration. Furthermore, the size range of arborescent unimolecular micelles is comparable to block copolymer micelles. The amphiphilic arborescent copolymers currently available incorporate a polystyrene core surrounded by a shell of poly(ethylene oxide), poly(2-vinylpyridine), or poly(methacrylic acid). These systems are useful to demonstrate the concept of encapsulation, but not sufficiently biocompatible for biomedical applications. To solve this problem, amphiphilic arborescent copolymers are now generated from γ-benzyl L-glutamate and different hydrophilic segments such as poly(L-glutamic acid) (PGA), polyglycidol, poly(ethylene oxide) (PEO), or poly(2-hydroxyethyl acrylate) (PHEA).

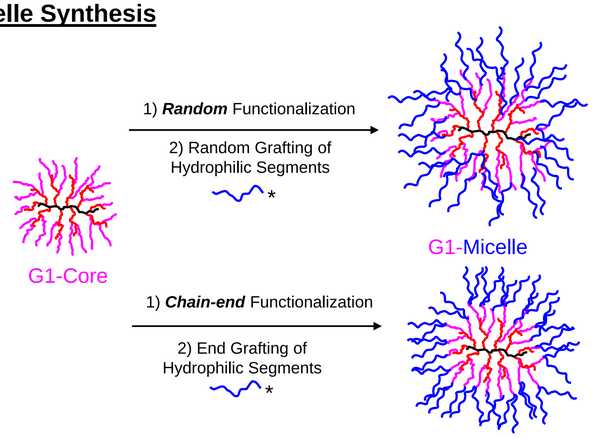
Synthetic Approach

- Linear polymer produced by ring opening polymerization of γ-benzyl L-glutamic acid N-carboxyanhydride
- Grafting substrate obtained by partial deprotection and activation with carbodiimide/HOBt (standard peptide coupling chemistry)
- Branched structure [Poly(γ-benzyl L-glutamate), **PBG**] obtained from ***grafting onto*** scheme
- Process repeated for G1, G2, and so on…

Core Synthesis

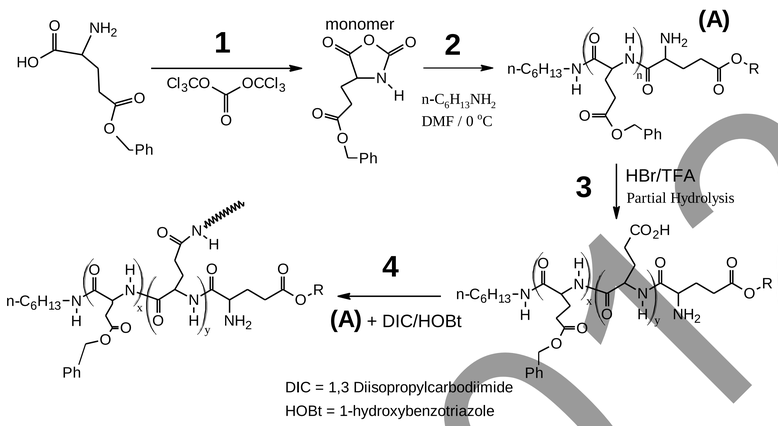


Micelle Synthesis

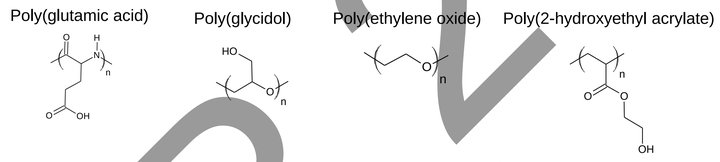


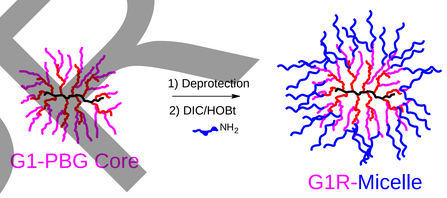
Synthesis

Arborescent PBG (Micelle Core)

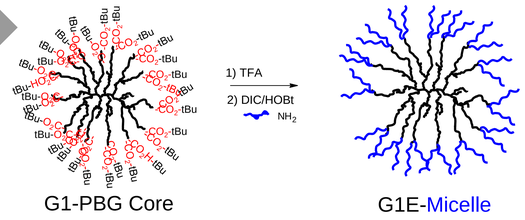


Hydrophilic Segment (Micelle Shell)

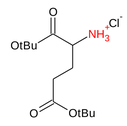




- Same grafting method as for arborescent PBG
- Shell characteristics varied based on hydrophilic components



- Last PBG grafting cycle: Side chains from H-Glu(OtBu)-OtBu initiator



- Functionalization of chain-ends only provides a sharp core-shell interface

Results

Table 1. Characteristics of Arborescent PBG of Successive Generations

Sample #	M_n Side chains	MALLS M_n	MALLS M_w/M_n	Grafting Yield (%)	Branching Functionality
G0	5,700	66,000	1.04	43	10
G1	4,300	235,000	1.05	63	43
G2	4,300	1,100,000	1.06	30	201
G3	4,300	3,300,000	1.07	35	512

Table 2. Hydrodynamic Diameter of Arborescent PBG

	DMF[a] 1st order	DMF[a] 2nd order	DMSO[a] 1st order	DMSO[a] 2nd order
G1	10.7	8.4	15.7	14.1
G2	13.1	12.1	21.3	20.1
G3	24.5	23.5	34.5	32.5

[a] 0.05% LiCl added to suppress aggregation

Table 3. Characteristics of PBG Randomly Grafted Micelles

	MALLS M_n	MALLS M_w/M_n	Grafting Yield (%)	Wt % PBG	Hydrodynamic Diameter 1st order	Hydrodynamic Diameter 2nd order
					THF (nm)	
G1R35-GlyAc8	606,000	**1.10**	17*	39	29.2	25.6
G2R34-GlyAc8	1,780,000	**1.11**	44	62	26.8	25.0
G1R35-GlyAc25	1,800,000	**1.08**	48	13	47.1	45.3
G2R26-GlyAc25	3,740,000	**1.07**	29	29	70.0	66.6
					DMF (nm)	
G1R35-PEO5	1,000,000	**1.07**	33	18	22.5	13.3
G2R26-PEO5	3,470,000	**1.05**	43	28	46.3	36.8
G3R34-PEO5	3,810,000	**1.04**	24	75	--	--
					PBS Buffer (nm)	
G1R38-PGA1.2	--	**1.17**	22	38	217	208
G2R26-PGA1.2	--	**1.22**	32	46	120	98
G3R34-PGA1.2	--	**1.17**	18	39	--	--

[a] 100% excess of side chains used

Table 4. Characteristics of PBG End Grafted Micelles

	MALLS M_n	MALLS M_w/M_n	Grafting Yield (%)	Wt % PBG	Hydrodynamic Diameter (nm) 1st order	Hydrodynamic Diameter (nm) 2nd order
					THF	
G1E9-GlyAc8	609,000	**1.08**	44	39	22.9	18.8
G3E11-GlyAc8	6,800,000	**1.04**	46	49	42.3	39.6
					PBS	
G2E10-PGA2	--	**--**	40	59	47	43

Acknowledgments

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