ARBORESCENT POLYPEPTIDES FOR CONTROLLED DRUG DELIVERY APPLICATIONS

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Introduction

Objective: To construct amphiphilic arborescent copolymers from L-glutamic acid derivatives 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 drug delivery applications.

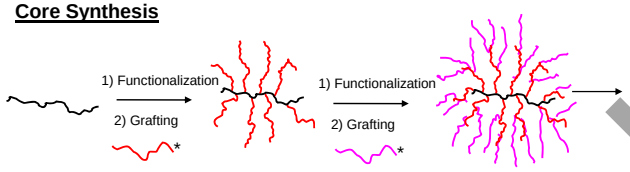
Biocompatibility is a prerequisite for drug delivery. Some of the systems used for that purpose such as block copolymer micelles incorporate biocompatible components in some cases, but are often unstable in highly dilute environments (e.g. blood stream), where their concentration drops below their critical 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 L-glutamic acid derivatives and glycidol.

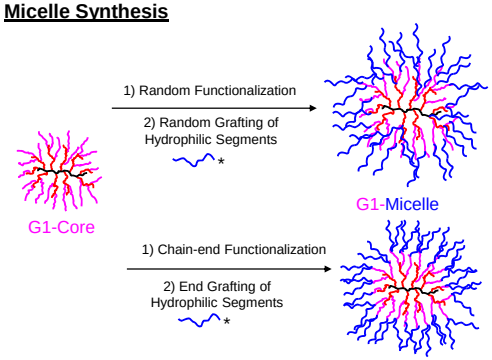
Synthetic Approach

- 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 obtained from ***grafting onto*** scheme
- Process repeated for G1, G2, and so on…

Core Synthesis

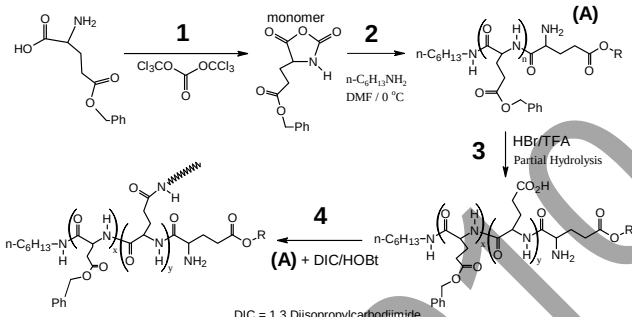


Micelle Synthesis

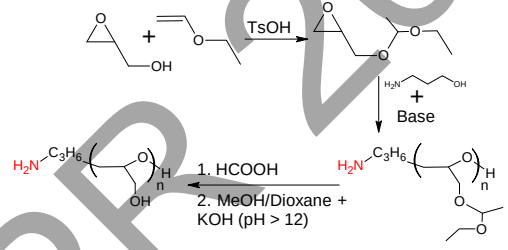


Synthesis

Arborescent PBG (Core)



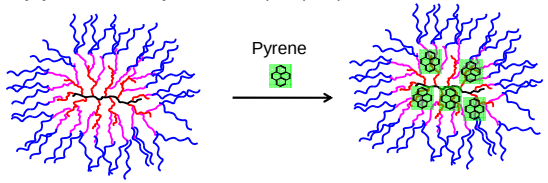
Linear Polyglycidol (Shell)



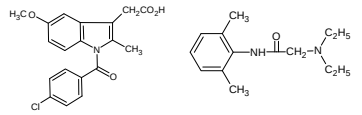
- Same grafting method as for arborescent PBG
- Coupling of poly(glycidol) possible before or after removal of acetal protecting group
- Extra hydroxyl group → Better water solubility than PEO

Solubilization

- Polycyclic aromatic hydrocarbons (PAH) as probes



- Solubilization of Indomethacin and Lidocaine as model drugs



Results

GPC Elution Curves for Arborescent PBG up to G3

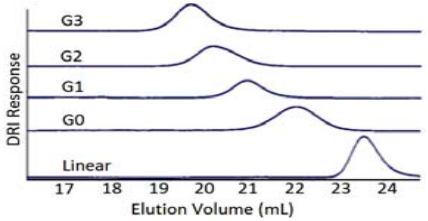


Table 1. Characteristics of Arborescent PBG of Successive Generations

Gen [a]	MALLS M_n	MALLS M_w/M_n	Grafting Yield (%) [b]	Coupling Efficiency (%) [c]	Total Branching Functionality
G0	53,000	1.04	62	58	6.6
G1	133,000	1.06	38	30	28
G2	486,000	1.03	46	50	124
G3	1,057,000	1.03	32	21	289

[a] Using ~5k linear side chains in all grafting reactions
[b] Determined from GPC curves using a DRI detector
[c] Fraction of coupling sites on the substrate consumed in the reaction

Table 2. Hydrodynamic Diameter of Arborescent PBG (nm)

	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 Arborescent PBG-Glycidol Micelles

	MALLS M_n	MALLS M_w/M_n	Grafting Yield (%)[b]	Hydrodynamic Diameter (nm) 1st order	Hydrodynamic Diameter (nm) 2nd order
G0R41-GlyAc10[a]	157,000	1.12	35		
G1R35-GlyAc10[a]	690,000	1.10	17		
G2R34-GlyAc10[b]	2,200,000	1.11	44		
G1E9-GlyAc10[a]	690,000	1.08	44	22.9	18.8
G1E9-GlyAC10-2[b]	614,000	1.02	68		
G3E11-GlyAc10[a]	7,700,000	1.04	46	42.3	39.6

[a] Using 100 % molar excess poly(glycidol acetal) side chains
[B] Using 25% molar excess poly(glycidol acetal) side chains

Acknowledgments

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