Controlled Release Characteristics of Arborescent Polystyrene-graft-poly(2-Vinyl pyridine)

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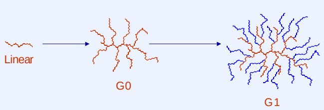
Abstract

Release properties of indomethacin and lidocaine from a dendritic copolymer consisting of a polystyrene (PS) core and poly(2-vinyl pyridine) (P2VP) shell to a 0.05 M HCl solution have been investigated and kinetically analyzed. *In vitro* release tests showed that sustained release characteristics were achieved. Release of lidocaine was greater because of its higher solubility at low pH. The release of indomethacin increased with a decrease in the generation number of the micelles and with initial concentration of probe in the micelles. This is an indication that release might be diffusion controlled. The diffusion coefficients and release rates of indomethacin were calculated by fitting experimental data to the solution of Fick's second law of diffusion. While the initial release rates decreased with generation number, the diffusion coefficients increased, indicating a more diffused structure of higher generation dendritic micelles, probably due to higher electrostatic repulsions between charged P2VP chains. The release decreased sharply at a pH of 4 as the hydrodynamic volume is reduced due to reduction in electrostatic repulsions.

Introduction

The use of polymeric micelles, especially block copolymer micelles has attracted considerable attention in the development of controlled release devices in recent years. In certain applications, the use of block copolymer micelles becomes inadequate. Their shape and stability depend on their immediate surroundings, as these assemblies are held together by weak van der Waals forces. These limitations can be overcome by using dendritic micelles which have a covalently bonded structure. We present here an investigation of the controlled release characteristics of arborescent PS-*g*-P2VP copolymers. The effect of generation number on release is discussed. Experimental data is analyzed by the power law model and the solution to Fick's law.

Synthesis of Arborescent PS-*g*-P2VP

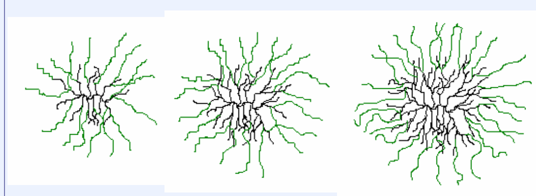


PS | PS Core | G1 PS-*g*-P2VP

- ❑ Linear polystyrene functionalized with coupling sites
- ❑ Living polystyryl anions reacted with substrate
- ❑ Comb-branch (G0) polystyrene core obtained
- ❑ Random functionalization of PS substrate
- ❑ Grafting of living P2VP chains on functionalized PS substrate yields PS-*g*-P2VP
- ❑ Polymeric chains used as building blocks and highly branched, high molecular weight dendritic polymers obtained only after few reactions cycles
- ❑ Anionic polymerization technique coupled with reaction cycles enable the synthesis of well-defined structures with low molecular weight distributions.

Materials

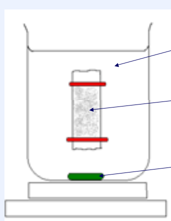
- ❑ **Indomethacin**
- ❑ **Hydrophobic at pH < 4**
- ❑ **Lidocaine**
- ❑ **Hydrophilic at pH < 4**



G1 PS-*g*-P2VP | **G2 PS-*g*-P2VP** | **G3 PS-*g*-P2VP**

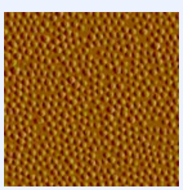
- ❑ Branching functionality increases with generation
- ❑ Core shell characteristics increase with generation

In vitro Release Studies



- ❑ At predetermined intervals 3 mL of dialysate are extracted for UV analysis
- ❑ Fresh 0.05 M HCl added to maintain constant volume and sink condition

Results



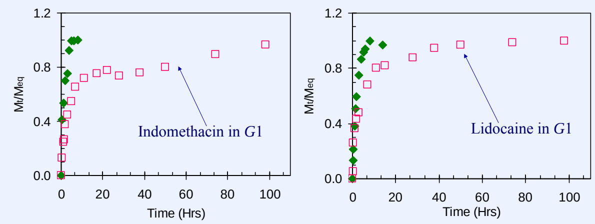
1.2 µm² AFM image of G2 PS-*g*-P2VP

- ❑ Particles are spherical and monodispersed
- ❑ Diameter of particles ≈ 45 nm

Characterization of Copolymers

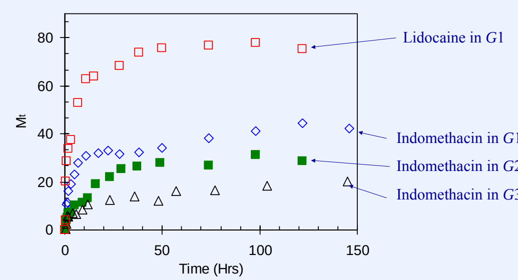
Sample	P2VP Side Chains		Graft Copolymers			
	M_w	M_w/M_n	M_w	M_w/M_n	f_w	Wt % PS
G1	5100	1.06	4.7×10^5	1.08	82	12
G2	5200	1.08	3.7×10^6	1.07	630	13
G3	5300	1.07	2.2×10^7	NA	3400	18

Sustainable Release Characteristics of *G1* PS-*g*-P2VP



- ❑ Rapid release of free probes through dialysis bag (green boxes)
- ❑ Release of probes from dendritic micelle is slow and shows sustained character
- ❑ An initial burst release followed by a slow release to equilibrium is observed for both profiles

Effect of Probe/Micellar Structure on Release



- ❑ 80% of lidocaine released at equilibrium
- ❑ 40% of indomethacin released at equilibrium
  - ❑ Amount of indomethacin released at equilibrium decreases with generation number
  - ❑ A large fraction of indomethacin may be entrapped in the hydrophobic PS core

Data Analyses with the Power Law Model ($M_t/M_{eq} = kt^n$)

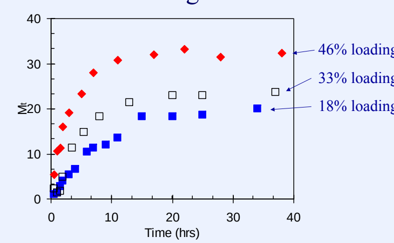
n = transport mechanism

k = interaction between probe and micelle

	Lidocaine	Indomethacin		
	G1	*G1*	*G2*	*G3*
n	0.34	0.60	0.48	0.39
k	0.34	0.21	0.14	0.15

- ❑ Fickian diffusion for lidocaine
- ❑ Combination of transport mechanisms for indomethacin in *G1*
- ❑ Lidocaine interacts more strongly with solvent molecules

Effect of Loading on Release



- ❑ Release increases with loading
- ❑ Release mechanism is diffusion controlled

Calculation of Diffusion Coefficients and Release Rates from Fick's Law

	G1	G2	G3
Diffusion Coefficient (m^2h^{-1})	4.50×10^{-19}	1.68×10^{-18}	1.56×10^{-18}
Radius (m)	12.5×10^{-9}	22.5×10^{-9}	39.5×10^{-9}
Rate (h^{-1}) time = 2 hours	0.074	0.047	0.043

- ❑ Diffusion coefficient increases with generation number
- ❑ Initial rate decreases with generation number
- ❑ Dendritic structure becomes more diffused at higher generation

Acknowledgements

ICCS and NSERC