SYNTHESIS, CHARACTERIZATION AND DRUG RELEASE PROPERTIES OF POLY(METHYL METHACRYLATE-*b*-ISOBUTYLENE-b-METHYL METHACRYLATE) AND POLY(HYDROXYETHYL METHACRYLATE-*b*-ISOBUTYLENE-b-HYDROXYETHYL METHACRYLATE)

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Introduction

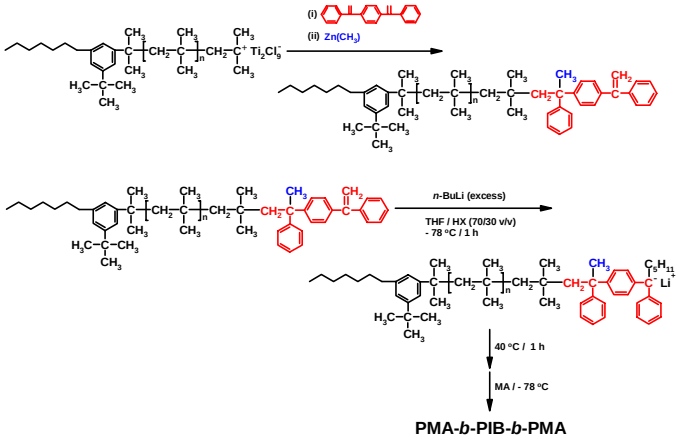
The introduction of drug eluting stents has been the most recent advance in the treatment of cardiovascular disease.[1] Boston Scientific's TAXUS™ stent consists of the Translute™ poly(styrene-*b*-isobutylene-*b*-styrene) (SIBS) triblock copolymer as the polymer matrix with the active drug component paclitaxel (PTx) coated on a stainless steel Express2™ stent platform. SIBS, made by living cationic sequential block copolymerization, exhibits attractive chemical, physical and biological properties for stent coating applications.[2] We hypothesized that the drug release kinetics of PTx may be affected by the nature and hydrophilicity of the end blocks. Block copolymers of IB and polar monomers, such as acrylates and methacrylates, combine the biocompatibility, thermal, oxidative and biostability of elastomeric, non-polar polyisobutylene (PIB) with a variety of properties of polar polymers. Since PIB can only be obtained by carbocationic polymerization, however, there have been many efforts to transform living PIB to a macroinitiator for anionic polymerization. We recently reported on a new methodology to prepare block copolymers comprised of IB and methacrylates via the combination of cationic and anionic polymerization.[3] This method involved the synthesis of DPE end-functionalized PIB by monoaddition of 1,4-*bis*(1-phenylethenyl) benzene (*para*-double diphenylethylene, PDDPE) to living PIB. The resulting macromonomer was metallated with *n*-butyllithium (*n*-BuLi) and the diphenyl carbanion was used to efficiently initiate the polymerization of methacrylates. In this preprint the synthesis, characterization and properties of poly(methyl methacrylate-*b*-IB-*b*-methyl methacrylate) PMMA-*b*-PIB-*b*-PMMA and Poly(hydroxyethyl methacrylate-*b*-isobutylene-*b*-hydroxyethyl methacrylate) PHEMA-*b*-PIB-*b*-PHEMA copolymers and the kinetic drug release of PTx are reported.

Expermental

Chemicals, polymer syntheses and characterizations have been described elsewhere.[3] Paclitaxel release testing, Atomic Force Microscopy, stent expansion and SEM measurements as well as coronary stent coating methods have been previously published.[4,5]

Results and Discussion

Scheme 1 depicts the polymer synthesis. First, living PIB was prepared by the polymerization of IB with the 5-*tert*-butyl-1,3-*bis*(1-chloro-1-methylethyl)benzene (*t*BuDiCumCl)/$TiCl_4$ initiator system in the presence of 2,6-di-tert.-butylpyridine (DTBP) as a proton trap in hexanes (HX)/methylene chloride (MeCl) 60/40 (v/v) at –80 °C. DPE-PIB-DPE was obtained by the reaction of living PIB with 2 equiv. of PDDPE, followed by methylation of the resulting diphenylcarbenium ion with large excess of $Zn(CH_3)_2$ ($Zn(CH_3)_2$]/[$TiCl_4$] = 5/1). Separate model reactions confirmed that *n*-BuLi does not react with the methoxy group formed when the PDDPE capped cation is quenched with methanol. However, methylation was necessary to avoid elimination of methanol and the formation of double bonds during workup that may be metalated by *n*-BuLi. The difunctional macroinitiator was obtained by the reaction of DPE-PIB-DPE with excess *n*-BuLi. The polymerization of MMA was carried out in a THF/HX 70/30 (v/v) solvent mixture because high molecular weight PIB is insoluble in THF at –78 °C. To avoid termination of lithiated PIB formed in the reaction of PIB-DPE with *n*-BuLi, it is essential to ensure the complete absence of protic impurities in the PIB macromonomer. As 1,1-diphenylalkyllithium cannot react with DPE because of steric hindrance, DPHLi could be utilized as a cleansing agent to remove protic impurities present in polymer without the reaction with DPE-PIB-DPE. Therefore, before lithiation of DPE-PIB-DPE with *n*-BuLi, dilute DPHLi solution was added dropwise to the polymer solution until a yellowish color persisted. The macroinitiator was prepared from the reaction of DPE-PIB-DPE with excess of *n*-BuLi in THF at –78 °C for 1 h. After 1 h, the polymer solution was heated up to 40 °C and kept for 1 h to destroy unreacted *n*-BuLi. Then the polymer solution was cooled down to –78 °C and MMA or 2-[(trimethylsilyl)oxy]ethyl methacrylate (TMSiOEMA) (protected HEMA) was distilled into the reactor. After 1 h polymerization time, degassed methanol was added to the reactor to quench the reaction. Table 1 shows the molecular characteristics of the triblock copolymers.



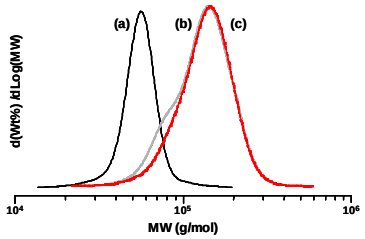
Scheme 1. Synthesis of PMA-*b*-PIB-*b*-PMA triblock copolymer

Table 1. Characteristics of the Precursor DPE-PIB-DPE Macromers and Purified Triblock Copolymers

Polymer	Macromer		[DPHLi]$_o$/ [Macromer]$_o$	M_n	M_w/ M_n	IB[a] (wt%)	Deactivated Macromer (%)[b]
	M_n	M_w/ M_n					
ABA1[b]	55,400	1.11	0	133,000	1.13	45	16
ABA2[b]	55,400	1.11	0.1	100,600	1.12	57	11
ABA3[b]	56,800	1.04	0.2	109,400	1.14	57	6
ABA4[b]	56,800	1.04	0.2	83,400	1.30	67	1
ABA5[c]	53,300	1.08	0.3	86,700[d]	-	62	10

[a] determined by ^{1}H NMR
[b] PMMA-PIB-PMMA
[c] PHEMA-*b*-PIB-*b*-PHEMA
[d] determined by GPC of the benzoylated derivative and ^{1}H NMR

Figure 1 shows the GPC results for the precursor DPE-PIB-DPE, crude and purified ABA1 where DPHLi was not employed. Extraction of the crude polymer by HX for 24 h yielded a polymer, which according to ^{1}H NMR spectroscopy was homoPIB most likely deactivated by protic impurities. In contrast the amount of deactivated PIB could be reduced to as low as 1% when DPHLi was used to cleanse the system. Figure 2 shows the GPC results for ABA2. Although in this case about 6 % polymer (based on the weight of DPE-PIB-DPE) was extracted out by HX, according to ^{1}H NMR spectroscopy this was not pure homoPIB and contained about 8 % PMMA.



F igure 1. Differential molecular weight distributions of (a) DPE-PIB-DPE (M_n 55,400, M_w/M_n 1.11), (b) crude ABA1 copolymer (M_n 121,800, M_w/M_n 1.16), and (c) purified ABA1 copolymer (M_n 133,000, M_w/M_n 1.13).

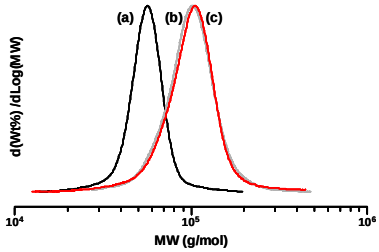


Figure 2. Differential molecular weight distributions of (a) DPE-PIB-DPE (M_n 55,400, M_w/M_n 1.11), (b) crude ABA2 copolymer (M_n 94,700, M_w/M_n 1.12), (c) purified ABA2 copolymer (M_n 100,600, M_w/M_n 1.12).

Figure 3 shows a representative SEM image of an expanded stent coated with the triblock containing 25% paclitaxel. The coating is smooth and conforms with no delamination due to the expansion This indicates that the elongation properties of these TPEs meet the requirements for a drug delivery coating. AFM images of the surface and bulk morphologies of the stent coatings with 0% and 25% paclitaxel by weight are shown in Figures 4 and 5. It can be seen that the block copolymer exhibits typical phase separated morphology, whereas addition of paclitaxel to the coating results in as a separate phase on the surface of the stents.

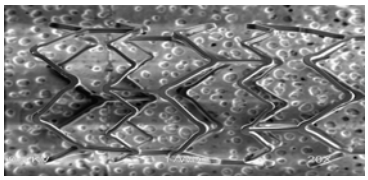


Figure 3. SEM image of a stent coated with 25% paclitaxel / 75% PMMA-PIB-PMMA triblock copolymer after expanding the stent.

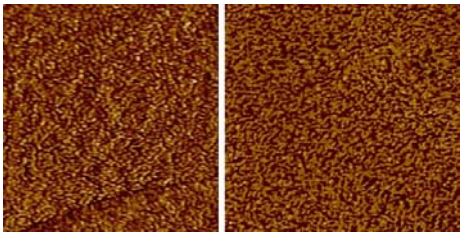


Figure 4. AFM images (phase imaging, 2 micron scans) of polymer-only coated stents showing surface (left) and bulk (right) morphology of PMMA-PIB-PMMA.

The drug release behavior of these stent coatings are shown in Figure 6. While the AFM data shows insoluble precipitated drug on the surface there is no apparent initial PTx burst. It can be seen that the release of paclitaxel appears to be fairly linear with time indicating drug release governed by solubility in the coating matrix.[6]

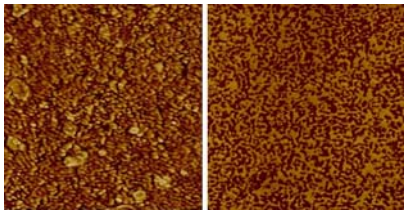


Figure 5. AFM images (phase imaging, 2 micron scans) of 25% PTx containing coated stents showing surface (left) and bulk (right) morphology.

When coatings with and without drug were evaluated by DSC it was found that the T_g of PMMA increased in the presence of the paclitaxel whereas that of the PIB remained constant. Since the Tg of amorphous PTx is reported to be 150°C[7] (compared that of ~100 °C for PMMA), this is an additional indication that the paclitaxel is soluble in the PMMA phase of the triblock. Previous work has also indicated that paclitaxel is not soluble in PIB phase.[8] By comparison, the release of PTx from the PHEMA-PIB-PHEMA triblock (Figure 5) shows a dramatic initial burst in PTx followed by a slow sustained release. It is postulated that the hydrophilic nature of the HEMA block permits rapid swelling of the coating in the aqueous environment.

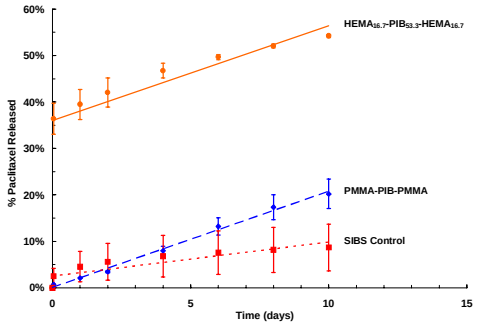


Figure 6. Drug Release Profiles of stents coated with 25% paclitaxel / 75% SIBS, 25% paclitaxel / 75% PMMA-PIB-PMMA (ABA3), and 25% paclitaxel / 75% PHEMA-PIB-PHEMA copolymers.

Conclusions

The PMMA-PIB-PMMA and HEMA-PIB-HEMA triblocks have appropriate mechanical properties for use as drug delivery coatings for coronary stent applications. PTx release from the coatings is linear with time indicating solubility of the drug within the polymer matrix. Both AFM and DSC data corroborate this finding.

References

(1) Stone, G.W. et al., New England Journal of Medicine **2004**, 350 (3), 221.

(2) Richard, R. E.; Barry, J. J.; Kamath, K.; Miller, K. L.; Ranade, S. V.; Schwarz, M. C., 31st Annual Meeting of the Controlled Release Society, Honolulu, Hawaii, USA, **2004**, June 12-16,

(3) Cho, J. C.; Faust, R. Polymer Preprints (American Chemical Society, Division of Polymer Chemistry) **2004**, 45(1), 1099.

(4) M. Schwarz, S. Ranade, and R. Richard, 31st Annual Meeting of the Controlled Release Society, Honolulu, Hawaii, USA, **2004**, June 12-16.

(5) S. Ranade, R. Richard, M.. Schwarz and M. Helmus, 31st Annual Meeting of the Controlled Release Society, Honolulu, Hawaii, USA, **2004**, June 12-16.

(6) Saltzman, W. M. Controlled Drug Delivery Systems. In *Drug Delivery: Engineering Principles for Drug Therapy*, Oxford University Press: New York, **2001**, pp 235-280.

(7) Lee, H.L.; Gi, U.; Kim, J.; Kim, Y.; Kim, S.; Oh, H. and B. Min, Bull.Korean Chem. Soc. **2001**, 22(8), 925.

(8) Ranade, S.; Miller, K.; Richard, R.; Chan, K.; Allen, M. and Helmus,, M., J. Biomedical Materials Research, in press.