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Drug Release from Novel Rubbery Coatings

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Summary: Poly(styrene-*b*-isobutylene-*b*-styrene) (SIBS) block copolymer, a thermoplastic elastomer, is used in clinical practice as the drug-eluting polymeric coating on the Taxus® coronary stent. We have been developing new architectures comprising an arborescent *arb*PIB core synthesized by inimer-type living carbocationic polymerization of isobutylene (IB) by the 4-(2-methoxy-isopropyl)styrene and 4-(1,2-oxirane-isopropyl)styrene inimers in conjunction with $TiCl_4$, from which polystyrene is blocked (D_SIBS). These novel self-assembling ''double'' networks have unique properties. ElectroNanospray™, a proprietary technology developed at the University of Minnesota, was used to coat coronary stents with selected D_SIBS polymers loaded with Dexamethasone, a model drug. This paper will demonstrate how drug release profiles can be influenced by both the molecular weight of the DIB midblock and spraying conditions of the polymer-drug mixture.

Keywords: cationic polymerization; coatings; drug delivery systems; elastomers; SIBS

Introduction

Biomacromolecular engineering, defined as the precision design, synthesis and characterization/testing of biomacromolecules, provides unprecedented control over material properties.[1] We combined ElectroNanospray™, a proprietary technology developed at the University of Minnesota,[2] and novel rubbery biomaterials based on polyisobutylene (PIB) to achieve controlled drug release from these rubbery coatings. The thermoplastic rubbers or thermoplastic elastomers (TPE) have PIB soft segments with microphase separated glassy (amorphous) domains such as polystyrene (PS).[1,3–7] In TPEs, discrete glassy microphases, embedded in a continuous elastomer phase, provide ''thermolabile crosslinks'', giving rise to rubbery properties. TPEs do not need to be vulcanized and, therefore, offer many advantages over chemically crosslinked rubbers, while being processible as thermoplastics. Poly(styrene-*b*-isobutylene-*b*-styrene) (SIBS) linear triblock copolymer is used in clinical practice as the drug-eluting polymeric coating on the Taxus® coronary stent. Coronary stents revolutionized interventional cardiology to treat narrowing of the coronary arteries caused by the build-up of atherosclerotic plaque (heart disease), the major cause of death for both women and men in the United States.[8,9]

Although metal stents significantly decreased the chance of vessel restenosis (renarrowing of the artery), approximately 20 to 30 percent of patients still developed significant scar formation and restenosis. A new solution to the problem has been the development of Drug Eluting Stents, made by coating a standard coronary stent with a thin polymer film containing a drug, which is released in controlled amounts directly into the region of the injury, thus preventing the formation of scar tissue at the site of coronary intervention.

We have been developing new polymer architectures comprising an arborescent *arb*PIB core synthesized by inimer-type living carbocationic polymerization of isobutylene

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(IB) by the 4-(2-methoxy-isopropyl)styrene and 4-(1,2-oxirane-isopropyl)styrene inimers in conjunction with $TiCl_4$, from which polystyrene is blocked (D_SIBS). These novel self-assembling "double" networks have unique properties. This paper will discuss how material properties and spraying conditions influence the surface morphology of the resulting rubbery coatings, and the release profile of the model drug dexamethasone incorporated into the coating of drug eluting stents.

Experimental Part

The polymers were synthesized and characterized as previously reported.[1,6,7] They were then mixed with dexamethasone DXM and sprayed onto steel plates and stents and drug release profiles were obtained as reported.[8,9]

Results and Discussion

D_SIBS provides more flexibility in material properties in comparison with its linear counterpart. For example, linear SIBS with $M_n > 150{,}000\ g\ mol^{-1}$ cannot be produced due to limitations in the manufacturing process. Branching in D_SIBS provides additional control over the viscosity and size of the polymer. Table 1 summarizes the molecular weight and composition characteristics of three such copolymers.

Table 1.
Properties of the D-SIBS used.

ID	Block M_n ($kg\ mol^{-1}$)	M_w/M_n	PS (w%)	#PS blocks
TPE4	70	4.5	32.8	4.1
TPE1	110	2.4	23.1	3.2
TPE5	220	1.8	29.4	3.2

Figure 1 shows coated stents and SEM images of representative coatings. Coatings were remarkably uniform on both internal and external surfaces with no visible webbing. Depending on the spraying conditions, smooth or particulate films were produced.

Table 2 summarizes drug release data. The smooth film of TPE4 showed a burst release of 20.3% of the DXM loaded into

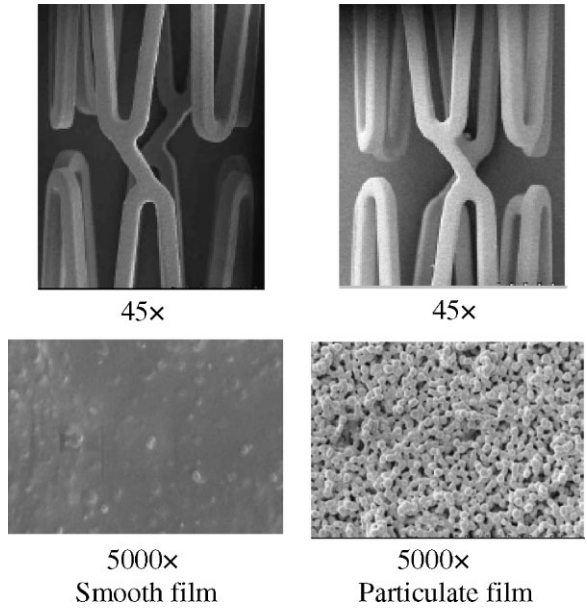

Figure 1.
SEM images of coated stents: TPE4 + DXM.

Table 2.
Drug release from D-SIBS.

ID	PIB M_n	PS	% Release			
	(kg mol^{-1})	(w%)	S*		P**	
			B	C	B	C
TPE4	47	32.8	20.3	26.7	3.3	23.2
TPE1	85	23.1	3.2	20.2	3.1	19.7
TPE5	154	29.4	2.6	14.0	6.3	26.7

*Smooth film; **Particulate film; B = burst release; C = cumulative release.

the film in 6 hours, followed by a very slow release reaching 26.7% by day 28. The particulate film of TPE4 showed 3.3% burst release in 6 hours, followed by continuously decelerating release reaching 23.2% by day 28 (Figure 2). In the case of TPE1, both films showed ~3% burst release in 6 hours, followed by a slower release reaching 20% by day 28. In contrast with TPE4, the smooth film of TPE5 showed less burst release (2.6%) than the particulate film (6.3%). Both films displayed gradual release, but the rate was much slower for the smooth film. The cumulative release was only ~14% for the smooth film.

The burst release in Taxus® was attributed to the drug particles exposed on the surface,[10] similarly to the smooth film of TPE4. It is desirable to reduce the burst release without reducing the cumulative release. The burst and cumulative release data for a hybrid film of TPE4/DXM, with 25% particulate film on top of the smooth coating is shown in Figure 2. The burst release was 10%, half of that of the smooth film, while the cumulative release (22.3%) decreased only slightly.

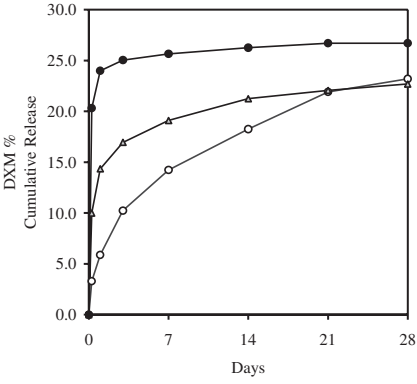

Figure 2.
Drug release profiles of TPE4. (•) smooth film; (o) particulate film; (Δ) hybrid film.

These differences might be explained with the differences in the M_n of the PIB of the polymers. Neither the burst nor the cumulative release from the smooth films (Table 2) correlated with the PS content of the blocks (Table 1). Despite the nearly 10% w higher PS content of TPE4 compared to TPE1, the former had a higher cumulative release than the latter, in contrast to that reported for the Taxus® stent where the drug was shown to preferentially segregate in the PS phases where it remains trapped.[10] However, both the burst and cumulative release from the smooth films were inversely correlated with the M_n of the PIB blocks (Table 2). More detailed investigations about the drug release will be published shortly.[10]

Conclusion

The results presented here demonstrate that drug release profiles can be influenced by both the molecular weight of dendritic polyisobutylene-*b*-polystyrene and spraying conditions of the polymer-drug mixture.

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