Drug releasing from biocompatible phospholipid polymer reserver on titanium alloy for cardiovascular stent

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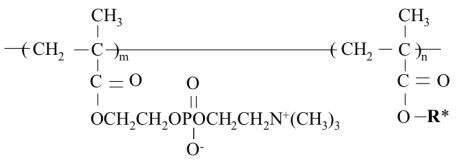
Statement of Purpose

Recently, metal stent placement operation has been done as a new treatment for ischemic heart diseases. Stent placement operation shows much lower invasiveness than usual bypass operation. But stent in itself has low blood compatibility, so it causes xenobiotic reaction, which leads to overgrowth of cells in stent-vessel contact area, then resteonosis in stent occurs and requires replacement operation. To solve resteonosis, studies of stent combined with drug have been conducted. It is called Drug Eluting Stent(DES). This DES needs polymers, which can coat metal surface to provide a biocompatibility and dissolve drugs to function as a drug reserver. The requirements for coating polymers are enough adhesive strength with metal surface, flexibility with stent's expansion, compatibility with tissue such as blood vessel inner wall and blood, insolubility in blood, and controlled release of drugs. In this study we chose three monomers to make polymers meets such requirements. One is 2-methacryloyloxyethyl phosphorylcholine(MPC), which was already known to show good blood compatibility. Other two hydrophobic comonomers are dodecyl methacrylate(DMA) and stearyl methacrylate(SMA). PMD shows lower glass transition temperature(Tg) PMS showed lower melting temperature (Tm) than body temperature(37°C), so they would release drugs easily and have enough flexibility in blood vessel at around 37°C. So we synthesized poly(MPC-*co*-DMA) (PMD) and poly(MPC-*co*-SMA)(PMS). Using these polymers, we made polymer coated pure titanium (Ti) loading water-insoluble fluorescent probe *N*-phenyl-1-naphtylamine(PNA), and evaluated drug release rate.

Methods

PMDs and PMS (Fig.1) were synthesized by radical polymerization using azobisisobutyronitrile initiator then characterized by Gel Permeation Chromatography and



*PMD; R = $(CH_2)_{11}CH_3$, PMS; R = $(CH_2)_{17}CH_3$

Fig.1 Chemical structure of MPC polymers
polymer composition MPC/SMA=30/70;PMS30
MPC/DMA=30/70:PMD30.and 20/80:PMD20

Differential Scanning Calorimetry. Ti plate was dipped into EtOH solution of 2mg/mL MPC polymers and dried under the room condition for 24h, then in vacuum for 24h. This sample was analyzed by X-ray photoelectron spectroscope, peel adhesion test and measured swelling ratio. PNA loading polymer coated Ti was made in the same way. Ti samples were soaked in 10mL water then incubated at 37°C. PNA release was mesured by fluorescent photometer. The medium was exchanged every 24h to assess the effect of PNA concentration.

Results/Discussion

Tg of PMDs and Tm of PMS30 were lower than 37°C, so they should show well flexibility with stent's expansion and contraction in vessel. They were insoluble in water,

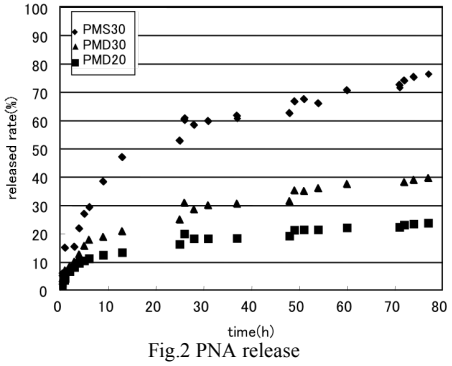


Fig.2 PNA release

so they shouldn't elute into blood and safely usable in vessel. While they were soluble in ethanol and chloroform, so they should dissolve drugs(e.g.Paclitaxel) usually used in DES treatment because their solubility parameter are close to those of such drugs. In fact we confirmed PMDs and PMS dissolved Paclitaxel. The XPS measurements were confined that Ti surface was fully covered by PMDs and PMS. Peel adheision test showed they have certain adheisive strength. Swelling ratio of PMS30 was 200%, those of PMDs were 230%. PNA release from MPC polymers are shown in Fig.2. Afetr 3 days, PMS30 released 80% PNA, while PMD30 released 40%, PMD20 released 25%. PMS had high crystalline so it released PNA more easily than PMDs. The effect of PNA concentration gradient was observed. Every time after exchanging water, PNA release ratio was sharply increased. After PNA release test, coating polymer layer was remained on Ti surface by XPS. So these polymers did not detached from Ti or eluted into water in static condition, and could be safely used *in vivo* environmental treatment such as DES in vessel.

Conclusions

Ti surface was modified by MPC polymers and acquired drug loadability. PMS30 had rapider PNA release than PMDs, so they could be adupted to apporopriate situation. (e.g. PMS30 for a quick act medicines and PMDs for slow ones) These polymers could be applied not only DES but also other metal devices used *in vivo* treatment and required drug releasability.