Trends Biomater. Artif. Organs, Vol 22(2), pp 87-92 (2008) *http://www.sbaoi.org*

New Generation Sirolimus Eluting PTCA Angioplasty Balloon Catheter for Restenosis Therapy

Arpit Jariwala, Chhaya Engineer, Haresh Kotadia, Ankur Raval and Devesh Kothwala

Research & Development Division,
Sahajanand Medical Technologies Pvt. Ltd., Surat 395 003, India

Received 05 December 2007; published online 1 August 2008

Drug eluting stents have shown promising antirestenotic effects in clinical practice. Non-stent based local delivery of drug may offer additional flexibility and also reach vessel areas beyond the immediate stent coverage [1]. The purpose of current research was to study the feasibility of Sirolimus coating on intracoronary dilatation balloon catheter and evaluate its release pattern *in-vitro*. The balloon catheter was coated with drug-biodegradable polymers blend in solution form as a single layer to render anti-proliferative and immunosuppressive property. Also it was thought that drug eluting catheter can also prevent catheter related infections, bacteremia and bacterial colonization and thrombus formation after injury in a blood vessel from balloon. Dip coating technique was effectively developed to coat the balloon catheter with Sirolimus drug-polymeric blend for programmed drug release. The drug content and *in-vitro* drug elution kinetics were analyzed using High performance liquid chromatography (HPLC) method. Scanning electron microscopy (SEM) was used to characterize the coating surface uniformity and smoothness. © *Society for Biomaterials and Artificial Organs (India), 20071205-21.*

Introduction

Coronary stent implantation has proven to be an effective technique for the prevention of restenosis in native coronary vessels compared with angioplasty alone. However, the restenosis rates after bare metal stent implantation are still as high as 20% to 40% at 6 months [1]. Drug eluting stents are shown to be safe and feasible in reducing restenosis [2-6]. However, their efficacy and safety have not been confirmed in all clinical settings, especially with regard to treating in-stent restenosis [7].

The percutaneous transluminal coronary angioplasty (PTCA) procedure is most commonly referred to as balloon angioplasty. In this procedure, a catheter having an inflatable balloon at its distal end is introduced into the coronary artery, the uninflated balloon is positioned at the stenotic site, and the balloon is then inflated. Inflation of the balloon disrupts and flattens the plaque against the arterial wall, and stretches the arterial wall, resulting in enlargement of the intraluminal passageway and increased blood flow. After such expansion, the balloon is deflated and removed. During PTCA, it is desirable to deliver a therapeutic agent to an area where the balloon angioplasty is occurring to prevent restenosis, repair vessel dissections or small aneurysms or provide other desired treatment [8].

Catheter based drug delivery was originally developed by Harvey Wolinsky to prevent restenosis after balloon angioplasty [9]. Non-stent based local delivery of drug may offer additional flexibility and efficacy in the entire range of applications. It may also deliver drugs to vessel areas not directly covered by the stent, which could be of special interest for small and tortuous vessels. Furthermore, the drug that is de-

livered by the drug eluting balloon is more evenly distributed on the vessel surface than is the drug bound to the struts of a drug eluting stent [1, 10].

Sirolimus a macrocyclic lactone produced by Streptomyces hygroscopicus which is a potent immunosuppressive agent. In addition to its antibiotic activity, it also possesses effective anti-proliferative and immunosuppressant properties. It inhibits smooth muscle cell proliferation by blocking the G1/S transition [11, 12]. Currently Sirolimus is being successfully used in a stent by Sahajanand Medical Technology Pvt. Ltd (Supralimus Stent) and J & J, Cordis (Cypher Stent).

The aim of the present study was to observe the feasibility of drug coating on percutaneous transluminal coronary angioplasty (PTCA) balloon catheter by dip coating technique and analyze the in-vitro release pattern of Sirolimus on inflation.

Materials and Methods

The PTCA balloon catheters (Arthesys, France) were used in the study (length, 17mm; diameter, 3.0 mm). Sirolimus was obtained from CFM Oskar Tropitzsch, China and used without further purification. Polymer 50/50 Poly DL Lactide-co-Glycolide having inherent viscosity (IV) 0.76 dL/g was procured from Alkermes Inc., USA and Poly vinyl pyrrolidone (PVP K-90/D) of molecular weight 1300000 Da was procured from ISP technologies Inc., Wayne, NJ, USA. Crystal Violet Dye (Merck ltd., Thailand) was used with further purification for checking coating characteristics. The purification was done by dissolving crystal violet dye in methanol and then recrystallize by solvent evaporation. The solvent dichloromethane (DCM) and other chemicals used in the current investigation were of HPLC grade procured from Ranbaxy Fine Chemicals Ltd, India.

Formulations

Conventional PTCA angioplasty balloon catheters (length, 17mm; diameter, 3.0 mm) were used in experiments initially coated with crystal violet dye to check the coating surface homogeneity as well as adhesion. Two Biodegradable polymers-50/50 Poly DL Lactide-co-Glycolide (50/50 PLGA) and Poly vinyl pyrrolidone (PVP)-were dissolved in HPLC grade dichloromethane (DCM) and crystal violet dye was added in this solution. The solution having crystal violet dye and polymers are mentioned in Table 1. The coating was done in a single layer using dip coating technique. The same experiment was conducted again by replacing the dye with Sirolimus blended with biodegradable polymers. The composition of these polymers with Sirolimus (Table 2) was formulated to achieve 40% drug to polymers ratio in 100 ml DCM. The balloon catheters were coated with the drug-polymer blends in order to attain 0.7 µg Sirolimus per square millimeter of balloon surface. The drug and polymers were weighed using analytical balance (Citizen CX-265) having 0.01 mg accuracy.

Drug Release Experiment conducted

The drug coated balloon catheter was being expanded by the means of expansion device (Merit Medical, Ireland) using sterile water up to 8 atm. It is then dipped into the 25 ml standard measuring flask (SMF) having phosphated buffer saline solution pH 7.4. This SMF was immediately transferred in the orbital shaker where the temperature was preset at 37°C and rotations at 55 rpm. At regular time interval of 2, 4, 6, 8, 10 and 12 minutes the aliquots of drug were collected and analyzed for drug release on HPLC. The sink conditions were maintained by adding of fresh PBS after each time interval when the aliquots had been taken.

Coating technique

In the present research study a dip coating technique was used. The balloon catheters were loaded in to the fixture in the compact unit containing dipping and curing modules. Programmable coating and drying period was fixed at 3 min and 2 min respectively to coat the balloon catheter. During dipping the balloon catheters were rotated at 25 rpm and after removal from solution, passed through the air dry curing module for drying. All the coating procedure was performed in class-100 clean room maintaining temperature 24 ± 3°C and relative humidity

55 ± 10%.

High Performance Liquid Chromatography

The HPLC analysis of Sirolimus drug was performed on HPLC-LC-2010 AHT [Shimadzu (Asia Pacific) Pvt. Ltd.] consisted of pumps (2LC-10ADvp), UV detector (SPD-10S (V)vp), Column oven (CTO-10A(C)vp), Autosampler (SIL-10Dvp), Software (LC solution). The analytical column used was X-Terra RP-18 (250*4.6 mm), particle size 5µm from Waters. The drug content was analyzed using mobile phase consisting of acetonitrile: methanol: water (45:40:15 v/v/v) at flow rate of 1.2 ml/min. The retention time for Sirolimus was 3.2 minutes at oven temperature 60°C. Sirolimus was detected by UV absorption at 278 nm. Two balloon catheters were evaluated for Sirolimus content and two balloon catheters for in-vitro Sirolimus release kinetics from biodegradable polymer matrix for 12 minutes in phosphate buffer saline (PBS) solution (pH 7.4) at 37°C with constant agitation at 55 rpm. Both the balloon catheter samples were removed at 2, 4, 6, 8, 10 and 12 minutes from their release vials and analyzed for amount of Sirolimus release in PBS.

Results and Discussion

Coating surface uniformity

The microscopic analysis was carried out using optical stereo microscope (SZX12 Olympus, Japan,) at 60X magnification. Microscopic images of dye and polymer coated balloon catheter (Figure 1) indicates the uniformity of coating on balloon catheter surface.

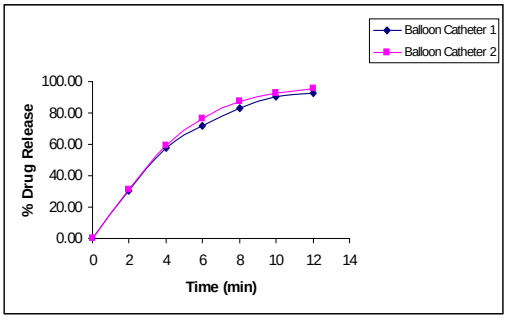

Fig 2: Cumulative drug release profile from baloon catheter in PBS

Drug content and in-vitro release kinetics

Sirolimus drug content on two PTCA balloon catheters was found to be 114.39 µg and 118.97 µg. Similarly, in-vitro release kinetics of drug coated balloon catheter was evaluated using HPLC method. Figure 2 depicts the in-vitro cumulative percentage of Sirolimus release from balloon catheter at regular time intervals. The in-vitro t1/2 (i.e. period of time required for 50% of active substance to be released from the reservoir) was approximately 2 minutes, which can be noted from the percentage cumulative release profile.

Table 1: Formulation containing crystal violet dye and polymers

	Material Name	% in Formulation
1	Crystal Violet Dye	0.83 %
2	50/50 Poly DL Lactide-co-Glycolide	92.56 %
3	Polyvinyl Pyrrolidone	6.61 %

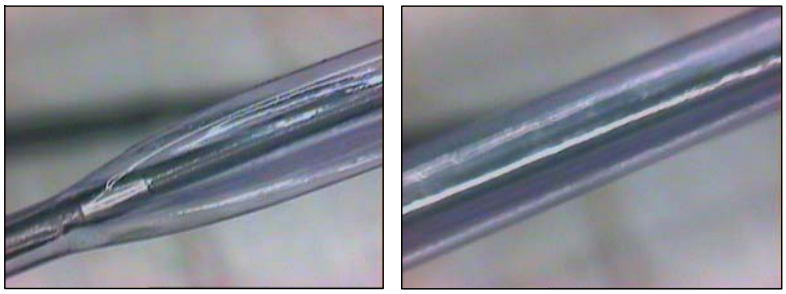

Fig 1: Crystal violet dye and biodegradable polymers coated balloon catheter indicate homogeneity and smooth coating surface

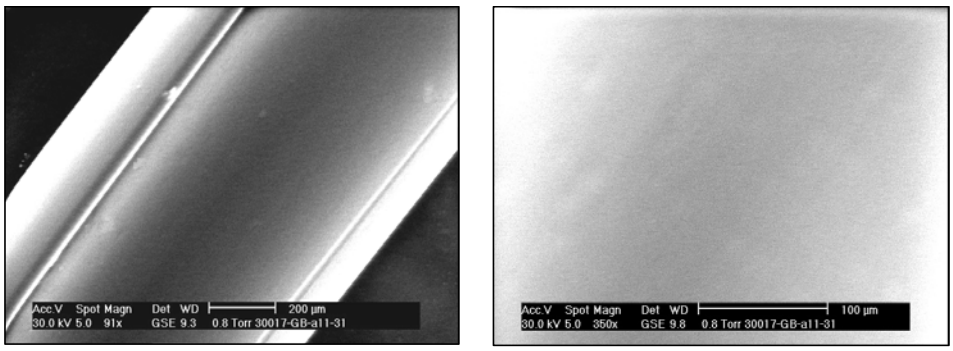

Fig 3: Scanning Electron Microscopy of uncoated balloon catheter

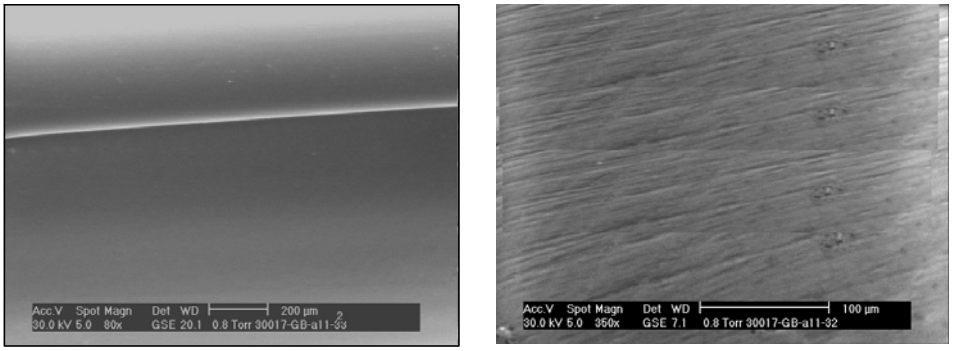

Fig 4: Scanning Electron Microscopy of drug-polymer coated balloon catheter

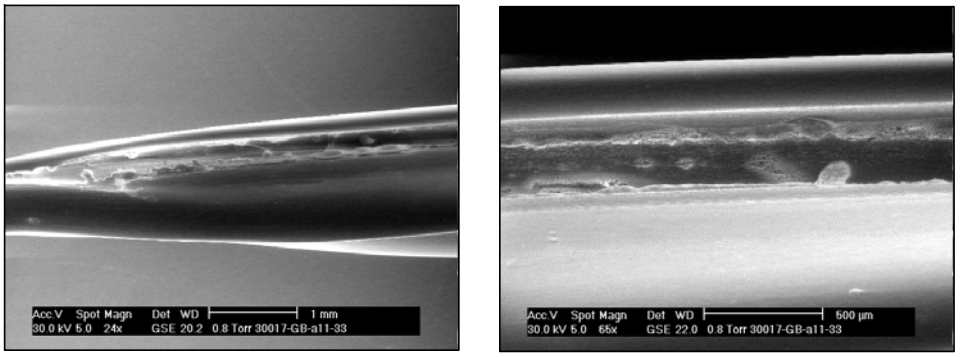

Fig 5: Scanning Electron Microscopy of drug-polymer coated balloon catheter after incubating at 37°C in PBS (pH: 7.4) for 12 minutes

Coating Surface Characterization

The present investigation is directed to develop a method for targeting an agent to a selected site within the vascular system. The device comprises of a balloon catheter including an elongated catheter shaft expandable balloon and thin film of coating around at least a portion of the balloon. The balloon catheter is inserted into the patient, and the balloon moved to the selected site within the vascular system. The balloon is then expanded, forcing the agent to the selected site in the vascular system.

The Scanning Electron Microscopy (SEM) images of uncoated balloon catheter and Sirolimus

coated balloon catheter can be seen in Figure 3 and Figure 4 respectively. The morphology difference is observed due to the drug-polymer matrix on balloon surface. Sirolimus coated balloon catheter represents crack free coating of drug on balloon surface (Figure 4). The drug and polymer is evenly distributed through the surface of balloon catheter and forms adequate adhering film.

The SEM images of Sirolimus coated balloon catheter in Figure 5 was obtained following its 12 minutes incubation in PBS at 37°C. Voids observed on the surface, were regions previously occupied by drug particles that were released from the coating.

Mechanism of drug release

In drug-polymer matrix system, the drug is dispersed or dissolved in the polymer, and the release rate is generally time dependant [13]. The in-vitro release profile (Figure: 2) shows release kinetic mechanism for initial burst phase of approximately 2 minutes (50% of drug). When actual dilatation balloon catheter is inserted into the coronary artery, two major factors govern the drug elution from the surface of balloon catheter. First is the mechanical abrasion experienced by the balloon catheter when it is been expanded; upon which the coated layer is damaged and eventually drug elutes out in the surrounding media. Second is the bulk erosion of the biodegradable polymeric layer, where the ingress of water is faster than the rate of degradation. As from the literature, the erosion kinetics depends mainly on two factors,

1. Diffusion of water into polymer bulk

2. Degradation rate of polymer backbone

If the diffusion of water into the bulk is faster than the degradation of polymer bonds, then the polymer will undergo bulk erosion, because the degradation is not confined to the polymer surface. It can be presumed that when the coated balloon is exposed to the release media, the drug-polymer coated thin film becomes hydrated in presence of aqueous media, leads to generate more porosity throughout the film, which allows more drug to release from coating. Also the thickness of the film plays a vital role on the drug elution. As the thickness of the film is very less the entire surface degradation process proceeds rapidly.

The coating layer consists of Sirolimus drug dissolved within the biodegradable polymeric blend of PLGA and PVP. The combination of amorphous and hydrophobic PLGA with hydrophilic polymer PVP enables the coating to have a programmable drug release with adequate coating integrity.

Whilst present research work is done using in-vitro model, the first mechanism by which the drug can be eluted out will not come in picture. But still we got 80-90 % drug release within initial 10-12 minutes. So we can judge that in the real world, the balloon catheter will release virtually total drug loaded on it within the total expansion time.

Table 2: Formulation containing Sirolimus drug and polymers

	Material Name	% in Formulation
1	Sirolimus	40 %
2	50/50 Poly DL Lactide-co-Glycolide	56 %
3	Poly vinyl pyrrolidone	4 %

Conclusion

In the present study, investigates the drug release mechanism from Sirolimus coated balloon catheter using SEM and HPLC. Drug was deposited on to balloon catheter by dip coating technique provided it good adhesion property with balloon without noticeably affecting its mechanical properties. The coating appears to have allowed the loaded drug to reach the target area. This coating technique of conventional angioplasty balloon catheter allows immediate drug delivery upon expansion. The in-vitro release profile confirms the release rate that is happened due to the surface erosion mechanism.

Acknowledgment

The authors thank to Mr. Manish Doshi, CEO, Sahajanand Medical Technologies and Dr.

Vandana Patravale, UICT Mumbai, for providing excellent technical support. The authors also express their sincere gratitude to Mr. Dhirajlal Kotadia, Chairman, Sahajanand group of Companies, for providing financial assistance to carry out the research work. Contributions from Mr. Jaynish Tailor, Mr. Prakash Sojitra, Ms. Ami Kapadia and Mr. Himanshu Patel are also gratefully acknowledged.

References

1. B. Scheller, U. Speck, C. Abramjuk, U. Bernhardt, M. Bohm, G. Nickenig. Paclitaxel Balloon Coating, a Novel Method for Prevention and Therapy of Restenosis. Circulation, 110, 810-814 (2004).
2. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med., 346, 1773–1780 (2002).
3. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med., 349, 1315–1323 (2003).
4. Colombo A, Drzewiecki J, Banning A, et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation, 108, 788–794 (2003).
5. Grube E, Silber S, Hauptmann KE, et al. TAXUS I: six- and 12-month results from a randomized, double-blind trial on a slow-release paclitaxel eluting stent for de novo coronary lesions. Circulation, 107, 38–42 (2003).
6. Park SJ, Shim WH, Ho DS, et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. N Engl J Med., 348, 1537–1545 (2003).
7. Van der Giessen WJ, Lincoff AM, Schwartz RS, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. Circulation, 94, 1690–1697 (1996).
8. US Patent No: WO 2004/060471 A1; Drug Delivery Balloon Catheter.
9. Goldman B, Blanke H, Wolinsky H. Influence of pressure on permeability of normal and diseased muscular arteries to horseradish peroxidase: a new catheter approach. Atherosclerosis, 65, 215-225 (1987).
10. B. Scheller, C. Hehrlein, W. Bocksch, W. Rutsch, D. Haghi, U. Dietz, M. Bohm and U. Speck. Treatment of Coronary In-Stent Restenosis with a Paclitaxel-Coated Balloon Catheter. N Engl J Med, 355, 2113-2124 (2006).
11. T. Suzuki, G. Kopia, S. Hayashi, L. R. Bailey, G. Llanos, R. Wilensky, B. D. Klugherz, G. Papandreou, P. Narayan, PhD; M. B. Leon, A. C. Yeung, F. Tio, P. S. Tsao, R. Falotico, A. J. Carter. Stent-Based Delivery of Sirolimus Reduces Neointimal Formation in a Porcine Coronary Model. Circilation, 104, 1188-1193 (2001).
12. Szycher M, Armini A, Bajgar C, Lucas A. Drug-Eluting Stents to Prevent Coronary Restenosis (Wakefield, MA: Implant Sciences Corp., 2002);
13. Dickers KJ, Milroy GE, Huatan H and Cameron RE. The Use of Biodegradable Polymers in Drug Delivery Systems to Provide Pre-Programmed Release. Cambridge Centre for Medical Materials, Department of Materials Science and Metallurgy, University of Cambridge; The Drug Delivery Companies Report Autumn/ Winter 2002.