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Novel Biodegradable Polymeric Matrix Coated Cardiovascular Stent for Controlled Drug Delivery

Ankur Raval[1], Animesh Choubey*, Chhaya Engineer[1], Haresh Kotadia[1] and Devesh Kothwala[1]

**University of Texas Health Science Center at San Antonio,*
TX 78229, USA
[1]Research and Development Division
Sahajanand Medical Technologies, Surat-395 003, India

Drug-eluting stents have been proposed as an alternative approach to decrease neointimal hyperplasia. Polymer coated stents can serve as a reservoir for local drug delivery. In this research work a novel four layer biodegradable/biocompatible polymeric blends (Poly L-lactide, Poly DL-lactide-co-glycolide, Poly L-lactide-co-caprolactone, and Poly vinyl pyrrolidone) was utilized for preparation of paclitaxel drug loaded matrix. Air suspension technique was modified and effectively used for coating the coronary stents with paclitaxel drug and biodegradable polymeric blends. Scanning electron microscopy (SEM) revealed a consistent coating profile devoid of any irregularities like cracking and delamination after crimping and expansion of stent. High performance liquid chromatography (HPLC) established the efficiency of modified air suspension coating technique and controlled release of paclitaxel drug from four layer coated stent.

INTRODUCTION

PTCA and restenosis

The introduction of stent implantation in coronary lesions had a substantial impact on improving early and late outcome compared with balloon angioplasty, providing mechanical scaffolding that reduces the impact of early elastic recoil or dissection and eliminates late lumen loss by circumferential remodeling [1,2]. Implantation of coronary stents is not free of complications. In addition to wall injury at the site of stent deployment, which provides a powerful stimulus to platelet activation and thrombus formation, the surface of the stent itself constitutes a thrombogenic foreign body. Thus, without treatment, a high rate of early stent thrombosis may be expected. Furthermore, together with the impact of the arterial wall injury, a multifactorial process is initiated, leading to neointimal hyperplasia and restenosis. Restenosis is primarily attributed to neointimal hyperplasia. According to both clinical and angiographic definitions, 25-35 % of successfully treated atherosclerotic lesions re-occlude within 3-6 months, generating increased costs for additional revascularization procedures, atherectomy or bypass surgery [3,4]. The pathophysiology of restenosis consists of the complex interaction of cytokines and growth factors with cellular and acellular elements [5]. Blockade of any one factor is often insufficient to inhibit the restenosis cascade. Therefore, attention has to be focused on disrupting essential central cellular processes that would subsequently affect downstream events that ultimately lead to restenosis.

Drug Eluting Stent (DES) and targeted drug delivery

As an alternative to systemic therapy, local drug delivery offers the advantages of allowing high local concentrations of drug at the treatment site while minimizing systemic toxic effects. Numerous pharmacological approaches to reduce restenosis have failed, possibly due to insufficient local drug

concentrations [6]. Delivering medication directly to the site of vascular injury via polymer coated stents is a rational approach to achieve adequate local drug delivery [7,8]. For paclitaxel, local delivery might be achieved by a drug-delivery catheter or by a coated stent [9,10]. Previous *in vitro* studies demonstrated inhibition of migration and proliferation of vascular smooth muscle cells by paclitaxel [9,11]. Also, initial promising *in vivo* studies of systemic and local paclitaxel administration to inhibit intimal growth have been reported [11,12].

Artificial or natural polymers that are biocompatible and biodegradable are often used for the preparation of particulate systems. Such polymers include poly lactic acid (PLA), poly lactic-co-glycolic acid (PLGA), acrylic polymers or copolymers, hyaluronic acid derivatives, and alginates. Among the available biodegradable polymers, the PLA and PLGA are the most widely used [13,14]. Within the body, the lactide/glycolide polymer chains are cleaved by hydrolysis to form natural metabolites (lactic and glycolic acids), which are eliminated from the body through the Krebs cycle primarily as CO_2 and H_2O. Polycaprolactone (PCL) is also used for drug delivery. Drug compounds are mixed in the polymer matrix and gradually become released as the polymer is dissolved in the tissue [15,16].

The drug-polymer coating can be applied by dipping or spraying of solution consisting of drug and polymer, mixed in desired proportion and using evaporative solvent material of relatively high vapor pressure to produce the desired viscosity and quickly establish coating layer thickness. Dip coating is often undesirable for coating complex geometries like stents, since coating solution may get entrapped in the device structure which may typically cause bridging, i.e. forming of a film across the open space between structural members of the device [17]. This can interfere with the mechanical performance of the stent, such as expansion during deployment in a vessel lumen. Bridges tend to delaminate and rupture the coating film during expansion and provide sites that activate platelet deposition by creating flow disturbances in the adjacent hemodynamic environment. In addition, delamination may cause particles to dislodge from the stent surface, potentially leading to other complications. Also multiple layer coating of drug-polymer solution is not possible with dip coating technique, as the freshly coated layer diffuses within the previously coated layers causing there dissolution [18]. Current investigation aims to develop a four layer drug-polymer matrix, programmed to achieve controlled drug release and that can be spray coated by means of air suspension technique on the cardiovascular stent. Unlike the multiple layer coating, single layer coated stents offer constant drug release profile, which is not desirable in the case of local drug delivery where drug demand decreases from the time of stent implantation [19,20]. The coated stents were characterized by scanning electron microscopy and high performance liquid chromatography (HPLC).

MATERIALS AND METHODS

Materials

The SS 316LVM 16 mm MATRIX™ stents (Sahajanand Medical Technologies, India) were used in the study. Polymers; 65/35 Poly DL lactide-co-glycolide**,** 85/15 Poly L lactide-co-caprolactone (Alkermes Inc., USA), poly L-lactide (Purac Inc., USA) having inherent viscosity (IV) 0.60 dL/g, 1.2 dL/g and 1.63 dL/g respectively were used as carriers for drug. Poly vinyl pyrrolidone (PVP K-90/D) was procured from ISP Technologies Inc., Wayne, NJ, USA. The typical molecular weight for PVP K-90/D was 1300000 Da. All as-received polymers used were biodegradable. The solvent dichloromethane (DCM) and other chemicals used in the current investigation were of HPLC grade procured from Ranbaxy Fine Chemicals Ltd, India. Paclitaxel drug was procured from Bioxel Pharma Inc., Canada, conforming standard monographs of USP-26 as specified by the supplier. Nitrogen gas (98% pure) was used as a carrier gas for spray coating.

Drug-polymer formulation

Biodegradable polymers; 65/35 Poly DL lactide-co-glycolide, 85/15 Poly L lactide-co-caprolactone, Poly L-lactide and Poly vinyl pyrrolidone were dissolved in HPLC grade dichloromethane. Solutions having different drug to polymer ratio for four layers (Table 1) were prepared using the paclitaxel drug and biodegradable polymers. Before coating stents were washed with DCM and dried by the means of hot air drier and were kept in amber colored glass vials to avoid any possible particulate contamination. Drug-polymer coating was done in a class-100 (established and validated by Aeolus Technovations, India) clean room having temperature in the range of 25±3°C and relative humidity 50±10 %. Stents were weighed using analytical balance (Citizen CX-265) having 0.01 mg accuracy.

Table 1: Drug-polymer formulation

Layers	Polymers	Drug / Polymer	Drug distribution
Layer A	Poly L-Lactide (67%)	41/59	32.5% (65µg)
	65/35 Poly DL lactide-co-glycolide (33%)		
Layer B	85/15 Poly L Lactide-co-caprolactone (69%)	24/76	45% (90µg)
	65/35 Poly DL lactide-co-glycolide (31%)		
Layer C	65/35 Poly DL lactide-co-glycolide	21/79	22.5% (45µg)
Layer D (Protective layer)	Poly vinyl pyrrolidone	0/100	--

Coating technique

In the present research work a modified air suspension coating technique was effectively used. Conventional technique involves the principle of collision of air and liquid to provide an atomized spray [21,22]. The gas stream flows through the bottom of the chamber through nozzle which carries the solution to be coated. The substrate is kept in the chamber and the velocity of the carrier gas is kept in such a way that the substrate gets fluidized in the stream and coated by the solution [23]. The principle behind the modified air suspension coating remains the same as that for conventional technique but some modifications were done in the motion and position of the spray nozzle and stent. Jets of compressed air introduced into the stream of liquid at the nozzle, break the liquid into tiny droplets that are carried to the surface of the stent. The schematic of modified air suspension coating machine used for coating the stents in current research work is shown in Figure 1. Drug-polymer solution is fed to the feed cup on the top of the spray nozzle which flows through the nozzle under the influence of gravity. The stent (F) was held between two hooks connected to the collets. The stents rotates on its axis. The cone type spray nozzle (E) of diameter 0.2 mm is located about 2 cm from the surface of stent and it oscillates in x-y plane. The adjustable nozzle creates a pressure drop, causing the liquid to atomize into fine droplets. Controller box (C) regulates the motion of nozzle and stent, as well as opening and closing time of spray nozzle. Optimized parameters used for coating are listed in Table 2. Stent rotation (16 rpm), distance between stent surface and nozzle (≅2 cm), spray gun oscillation (44 oscillations/min) were kept constant. Area of coverage was determined by the angle swept by the spray nozzle for 16 mm stent. It could be estimated by trigonometric calculations using distance between the nozzle and the stent surface, stent length and spray pattern.

Table 2: Optimized parameters for drug-polymer coating

Parameters	Value
Nitrogen gas pressure	0.9 to 1.0 kg/cm^2
Flow rate of solution	0.1 ml/min
Spray nozzle open time for one cycle	30 sec
Spray nozzle close time for one cycle	5 sec
Total numbers of cycles for spraying of one milliliter of solution	5
Distance between nozzle and stent	2.0 cm
Angle swept by spray nozzle	50°

Four layers A, B, C and D having different drug-polymer ratio (Table 1) were coated using optimized coating parameters provided in Table 2. Layer D was coated for protection against moisture and it did not contain any drug. It was assumed that this layer would prevent premature drug release in the body while stent implantation. Stents were dried in ambient conditions for about 18-24 hours after coating each layer. Coated stents were weighed and observed under optical stereo microscope (Olympus SZX-12, Japan) for surface smoothness. Scanning electron microscopy (Philips XL30, Japan) was also performed to analyze the coating smoothness and the thickness of the coating on the stent.

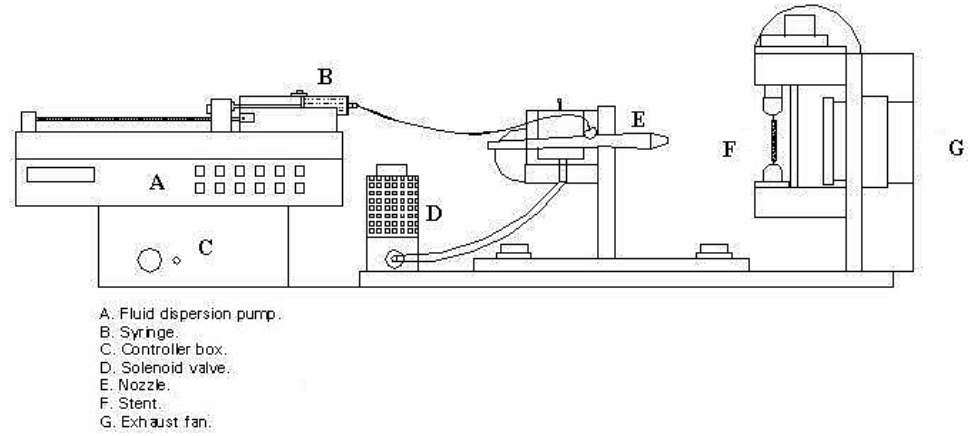

Fig. 1: Gravimetric analysis of four layer drug-polymer coated stents

To ensure the proper coating integrity stents were subjected to balloon expandability test. Drug coated stents were crimped on the balloon (3.0x17mm, Arthesys, France) by means of automatic crimping machine (Machine Solutions, MSI-500, USA). The crimped stents were expanded by expansion device (Medtronic, Skimed-Sedat, USA). Sterile fluid was pumped as an expansion media. Stent was crimped on the balloon and expanded at rated pressure of 6 atm. The balloon was kept dilated on manufacturers recommended pressure for approximately 45-60 seconds and than deflated. Crimped and expanded stent were observed using scanning electron microscope for coating integrity and the effects of crimping and balloon expansion.

High performance liquid chromatography

The HPLC system used for paclitaxel drug analysis was LC-10ATVP pump (Shimadzu, Japan) equipped with UV-VIS detector: SPD-10AVP (Shimadzu, Japan), Rheodyne 1303 integrator (Rheodyne, USA). The column used was ODS PR C-18 (5 µ pore size) 250x4.6 mm (Phenomenex). Gravimetrically assessed stents having weight 200±20 µg

were evaluated using HPLC for precise qualitative and quantitative analysis. Stents were analyzed for drug content using mobile phase consisting of Water: Acetonitrile: Methanol (35:5:60 v/v) at flow rate of 1.0 ml/min. Detector wavelength was set at 227 nm. Three stents were evaluated for paclitaxel content and three stents for *in-vitro* paclitaxel release kinetics from biodegradable polymer matrix over 38 days under simulated biological conditions. Standard solutions were prepared by dissolving 10 mg of paclitaxel drug in 10 ml of mobile phase. This mobile phase was then diluted upto 100 ml. Diluted 20 µl standard was injected in the HPLC column and standard chromatogram for this standardized solution was obtained. The total drug on the stent was dissolved by immersing stents in standard measuring flask containing mobile phase. This mobile phase (20 µl) containing paclitaxel was injected in the HPLC column and chromatogram was obtained. Paclitaxel content on the stent was found by comparing the area under the peak with that of the standard curve. For *in-vitro* paclitaxel kinetics study, stents were incubated in 20 ml of phosphate buffer saline (PBS) solution at 37°C with constant agitation at 60 rpm. Each of the three stents were removed at 1, 7, 14, 28 and 38 days from their release vials and analyzed for amount of paclitaxel release in PBS. Paclitaxel was extracted using DCM which was later evaporated using dry nitrogen gas. Mobile phase was added to this and the resultant supernatant was analyzed for paclitaxel content by HPLC, and the paclitaxel released at regular interval and cumulative amount from each stent was calculated.

RESULTS AND DISCUSSION

Gravimetric analysis of the stents

Table 3 represents the results for the gravimetric study for four layers coated on the stent surface. Six different stents were studied for this purpose and average weight of the uncoated stents was 20.68 mg. After coating of layer A the average weight of stents was 20.86 mg, which indicates an increase of 0.82 % respective to the initial weight. Coating of layer B increased the average weight of stents to 21.23 mg, which indicates that second layer weighs 0.37 mg giving 1.77 % increase in weight. After coating of layer C, the total average weight for six stents obtained was 21.44 mg. Finally, the protective layer was coated and final average weight of four layer coated stent was 21.53 mg. A total of 0.85 mg of drug-polymer was coated on the stent. Weight increase of 4.06 % was recorded after coating of four layers. Figure 2 gives the graphically representation for the variation of stent weight after coating each layer of drug-polymer.

Table 3: Weight and % weight increase of stents after drug-polymer coating

Sample	Average weight (mg)	Weight increase (%)
Uncoated stent	20.68	--
A layer coated stent	20.86	0.82
(A+B) layer coated stent	21.23	1.77
(A+B+C) layer coated stent	21.44	0.99
(A+B+C+D) layer coated stent	21.53	0.42

Modified air suspension coating technique

Uniform spray performance was achieved by maintaining a constant level of solution in the feed cup. For the nitrogen gas pressure less than 0.7 kg/cm^2 adequate atomization were not obtained and uneven spray patterns were observed because of larger droplet size (Figure 3a). Increase in droplet size can cause non-uniform surface, which is not desirable for small implantable medical devices like cardiovascular stents as these surfaces could be highly thrombogenic. In the current study with modified air suspension technique, a decrease in droplet size was observed when the atomizing pressure was increased. At 1.0 kg/cm^2 pressure smooth coating surface was apparent (Figure 3b).

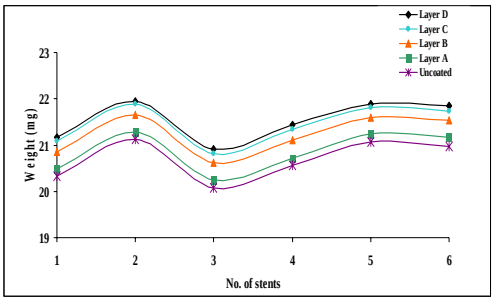

Fig. 2: Schematic of indigenous drug coating machine used in the current study

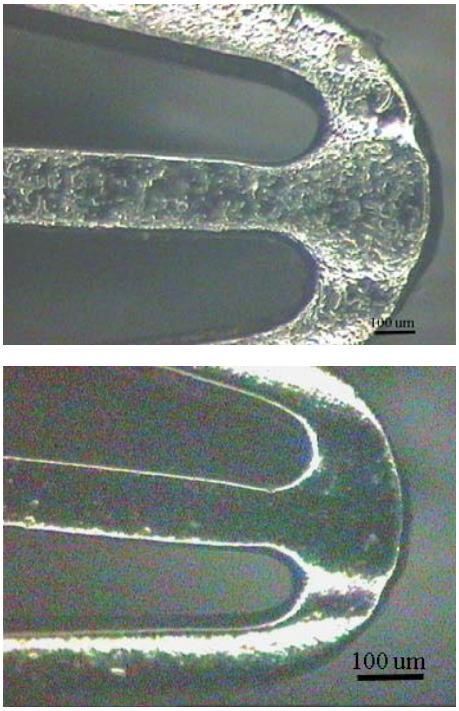

Fig. 3: Optical micrographs showing effect of atomization pressure on surface smoothness of coated stent.

The SEM pictures indicate uniform coating on surface of the stent (Figure 4a and 4b). Figure 5a and 5b revealed the typical coating morphology achieved from air suspension technique. The outer surface, cutting zone and inner surface were found to have homogeneous appearance. Figure 6 depicts SEM micrograph of crimped stent. No impressions of crimping machine jaws were observed on coated surface. Similarly, uniform expansion profile could be noted and the stent surface coating was found to be free from irregularities such as cracking, flacking or delamination (Figure 7). After stent dilation the drug-polymer coating exhibited adherence to the greatest possible extent. This demonstrates that coating film is elastic enough to withstand the expansion mechanism. With no crack formation on the coating film, at the mechanically stressed sites of the stent, SEM analyses revealed complete adhesion of the film.

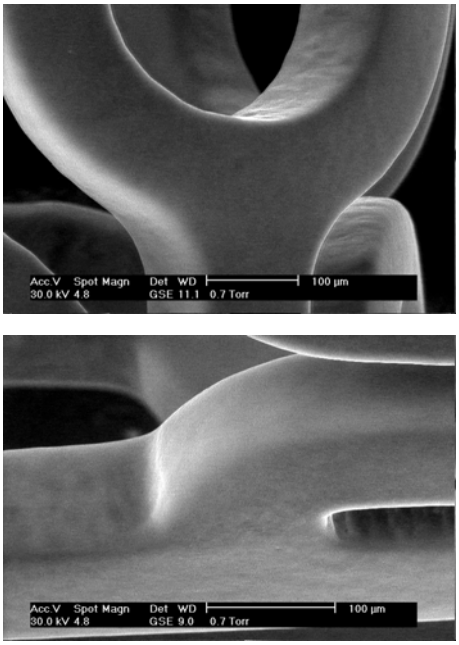

Fig. 4: SEM micrograph showing drug-polymer coated stent

Thickness measurement

A sharp scalpel was used for scratching the coated layer from the stent surface and the thickness was measured using scanning electron microscope. The measurements were taken at different locations and results indicate uniform coating thickness along the entire surface of the stents. SEM micrograph shows the coating thickness of 13-15 µm (Figure 8). The uniform coating thickness can be attributed to the rotating motion of the stent on its axis and oscillating motion of the spray nozzle which creates the wide spray pattern allowing the atomized droplets to access entire surface of the stent.

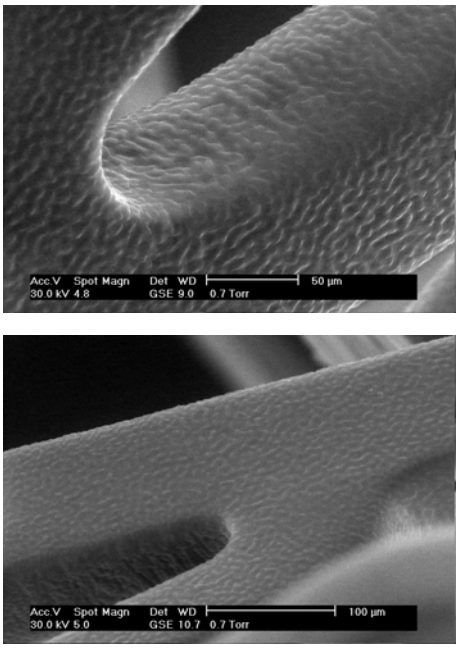

Fig. 5: SEM micrograph illustrating typical morphology of drug-polymer coated stent surface.

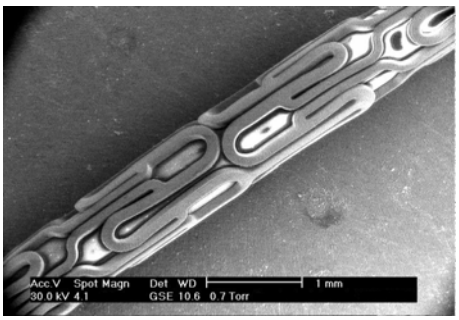

Fig. 6: Scanning electron micrograph showing crimping profile of drug-polymer coated stent

High performance liquid chromatography

Paclitaxel content on 3 stents was found to be 192.17 µg, 199 µg and 194.68 µg. Similarly, release kinetics of 3 stents was evaluated using HPLC. After immersion of stents in PBS, layer D dissolves rapidly as poly vinyl pyrrolidone is highly hydrophilic in nature. After the removal of this protective layer, paclitaxel drug from the stent gets released in buffer solution. Figure 9 represents the *in-vitro* paclitaxel release kinetics for 38 days at regular intervals. It is evident that release of paclitaxel from the polymer matrix shows zero order release kinetics for initial burst phase of 7 days. This event represents dissolution and mediated burst release of paclitaxel particles from the layer C. After the disappearance of the initial burst effect second phase release begins which lasts till the 14^{th} day. Layer C and layer B gets diffused from the stent, and it was found that 68.26 % (130 µg) drug was released after 14 days which approximately equals to the amount of drug loaded in layer C and B as represented by cumulative release graph (Figure 10). For coated stent $t_{1/2}$ (i.e. period of time required for half of the quantity of a substance to be consumed from the reservoir) was initial 7 days time period, which can be noted from the cumulative release profile.

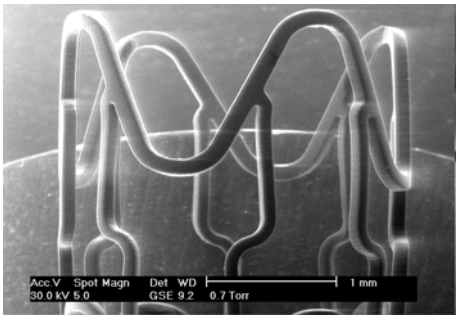

Fig. 7: SEM micrograph showing dilation profile of drug-polymer coated stent

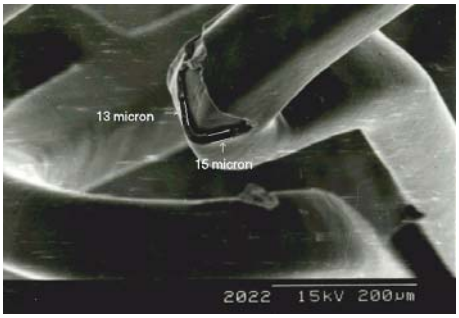

Fig. 8: SEM micrograph showing coating thickness on stent surface at two different locations

Release of paclitaxel from layer A was slow compared to that from layer C and B. This can be attributed to the presence of poly L-lactide in layer A which is hydrophobic and 37 % crystalline in nature and degradation time for this polymer is 18-24 months *in-vivo* [24,25]. Combination of this polymer to 65/35

poly lactide-co-glycolide decreases the complete degradation time of the polymers to a considerable amount for layer A. It was observed that layer A took last 24 days to release showing slower degradation in PBS at 37°C. Drug release from layer A was 31.74 % (60.44 µg) for 24 days. This slow release of paclitaxel from layer A could have a cytostatic effect on the neointimal growth, which is desirable in the later stages of vascular healing.

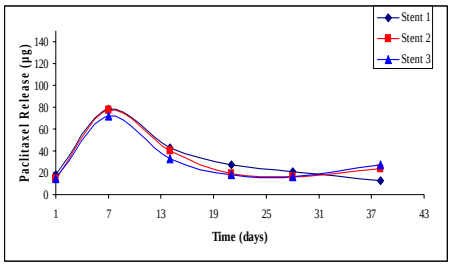

Fig. 9: Paclitaxel release profile at regular intervals for 3 stents in PBS (pH 7.4) at 37°C for 38 days

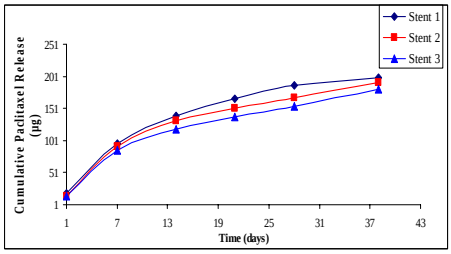

Fig. 10: Cumulative paclitaxel release profile of 3 stents in PBS (pH 7.4) at 37°C for 38 days

Based on the *in vitro* studies conducted the programmed degradation mechanism of drug-polymer coating at the stenotic site can be presumed as shown in Figure 11. Protective layer D being hydrophilic would degrade within a short span of time in vascular environment. Paclitaxel drug from the layer C gets diffused to the surrounding tissues. In the similar manner, *in vivo* release of drug takes place from layer B and layer A. After 38 days, no drug will be present on the surface of the stent. As the drug is dissolved in polymeric matrix, drug release is directly linked to the degradation of the polymer. This degradation occurs throughout the polymer matrix and proceeds until a critical molecular weight is reached where degradation products become small enough to be solubilised. At this juncture, the structure starts to become significantly more porous and hydrated leading to the release of drug dissolved in the polymer [26].

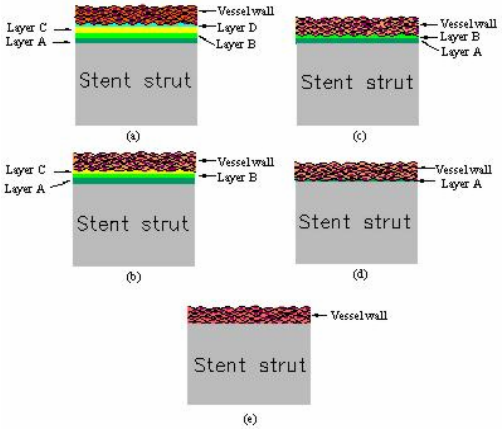

Fig. 11: Schematic showing *in-vivo* degradation of four layer drug-polymer coating

CONCLUSION

This research involved pharmacological coating of stents, based on the notion that sustained local delivery of an anti-proliferative agent provides higher tissue concentrations compared to systemic administration. Modified air suspension technique was successfully employed for four layer coating of cardiovascular stents. Integrity of coated surface was found to be intact after crimping and expansion of stent, as observed in SEM micrographs. Uniform coating thickness ranging between 13-15 µm could be obtained. High performance liquid chromatographic results exhibited consistency in drug content on the stent surface showing reproducibility and accuracy of the modified air suspension coating technique. *In-vitro* release kinetics indicated the release of paclitaxel in 38 days from the biodegradable polymer matrix at different rates (130 µg from layer B and C in 14 days, 60.41 µg from layer A in 24 days), which was intended as per the reported vascular response to the PTCA procedure.

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