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Dexamethasone eluting biodegradable polymeric matrix coated stent for intravascular drug delivery

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ABSTRACT

Targeted drug delivery systems are used to minimize the adverse effects of the pharmaceutical agents while maintaining the high local drug concentrations. To minimize post-angioplasty complications like tissue hyperplasia and related restenotic events, cardiovascular stents coated with anti-inflammatory, anti-proliferative agents have been proposed. The efficacy and toxicity of local therapeutics depends upon drug release kinetics which will further decide drug deposition, distribution, and retention at the target site. Drug eluting stents (DES) presently possesses clinical importance as an alternative to coronary artery bypass grafting due to ease of procedure and comparable safety and efficacy. This paper focuses on preparation and evaluation of controlled drug release biodegradable systems for stent base drug delivery providing insight of the drug elution mechanism which ultimately governs release kinetics. Multiple layers of dexamethasone-biodegradable polymers were successfully spray coated on Co–Cr alloy L605 metallic stents by modified air brush technique. In vitro drug elution data acquired by high performance liquid chromatography (HPLC) revealed that release of dexamethasone can be modulated up to 3 weeks by optimized use of blends of biodegradable poly-L-lactide-co-caprolactone and polyvinyl pyrrolidone. Surface investigation by scanning electron microscopy (SEM) represented smooth surface finish without any irregularities suggesting the efficacy of utilization of optimal coating parameters for multiple layer coating.

Keywords: Stent; Dexamethasone; Biodegradable polymers; Drug release kinetics

1. Introduction

Drug eluting stents (DES) has revolutionized the field of interventional cardiology by proving its safety and efficacy to prevent restenosis of coronary arteries using local drug delivery in many clinical trials (Colombo et al., 2003; Moussa et al., 2004). The rate of in-stent restenosis (ISR), although less frequent than post-angioplasty restenosis, is becoming increasingly prevalent due to the recent exponential increase in the use of intracoronary stents (Mintz et al., 1998). Restenosis after stent implantation is mainly identified by an inflammatory response to the procedural injury and an intense fibrocellular including smooth muscle cell (SMC) proliferation and organized intraluminal thrombus formation (Radke et al., 2004; Frederick et al., 2002). Unlike angioplasty, the effect of stent injury is more chronic, involving a higher degree of injury and foreign body responses followed by inflammation and other immunological and biochemical reactions that place from hours to months. Prolonged inflammation to vessel wall results in more cellular proliferation and greater lumen loss after stent implantation (Hoffmann and Mintz, 2000). It is broadly established that the primary mechanism at the basis of the entire pathophysiological process of restenosis is inflammation, which is triggered by vascular injury and activates complex biochemical and cellular mechanisms (Gaspardone and Versaci, 2005). Modulation of this inflammatory response may potentially be a target to decrease neointimal hyperplasia and, consequently, in-stent restenosis.

Glucocorticoids (GC) play a vital role in the systemic response to inflammatory mechanisms, with important cardiovascular and metabolic effects. These drugs are widely used for their potent anti-inflammatory and immunosuppressive properties (Valero et al., 2008). Dexamethasone is also

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a glucocorticoid that exert various inhibitory effects on the inflammatory processes (Kawamura et al., 2000; Hickey et al., 2002a) and on smooth muscle cell proliferation (Hickey et al., 2002b; Villa et al., 1994) due to which it has gained widespread interest in the prevention of restenosis (Valero et al., 2008). Dexamethasone coated stents in previous clinical trial (Liu et al., 2002) effectively reduced major adverse cardiac events (MACE) and improve luminal late loss. Consequently this drug has been chosen in this study as a model drug with the blend of biodegradable polymers to coat cardiovascular stent to achieve controlled drug elution and studying their in vitro release kinetics. Drug vehicle plays an important role for the final biological outcome. Till now biocompatible and non-degradable polymers like poly(ethylene-co-vinyl acetate) (Leon et al., 2003), poly(n-butyl methacrylate) (Leon et al., 2003), poly(styrene-b-isobutylene-b-styrene) (Kamath et al., 2006), co-polymers of polyvinylidine fluoride hexafluoropropylene (PVDF-HFP) (Windecker and Juni, 2009) have been used in different drug eluting stent systems for controlled delivery of therapeutic agents in the vascular environment. Despite their clinical successes, stent thrombosis, inadequate endothelial coverage and hypersensitivity to polymer carrier are still major concerns (Virmani et al., 2004). Pathophysiology of late DES thrombosis (stent thrombosis occurring more than 30 days after percutaneous coronary intervention) derived from the histological examination of animal and human arteries containing drug eluting stent indicates that DES can cause substantial impairment in arterial healing characterized by lack of complete reendothelialization and persistence of fibrin when compared with non-coated metallic stents (Finn et al., 2007).

Present research work describes the development of controlled drug eluting stent system that can elute dexamethasone drug via blend of biodegradable polymers. The surface morphology was probed using scanning electron microscopy before and after incubation of stent in phosphate buffer saline (pH 7.4) at 37 °C for 21 days. High performance liquid chromatography was utilized to quantify drug content and to study release kinetics. Drug release data were correlated with the surface morphology changes to establish drug release mechanism for the developed drug eluting system.

2. Materials and methods

The Co–Cr alloy (L-605) 16 mm long Coronnium™ stents (Sahajanand Medical Technologies, India) were used in the study. Dexamethasone acetate (USP) was obtained from Sky Life Science, Gujarat, India and used without further purification. Polymers; 75/25 poly-L-lactide-co-caprolactone (Lakeshore Inc., USA) having inherent viscosity (IV) 1.2 dl/g and polyvinyl pyrrolidone (PVP K-90/D) (ISP Technologies Inc., Wayne, NJ, USA) having molecular weight 1,300,000 Da were used as carriers for drug. The solvent tetrahydrofuran (THF) and other chemicals used in the current investigation were of HPLC grade procured from Ranbaxy Fine Chemicals Ltd., India. Nitrogen gas (98% pure) was used as a carrier gas for drug coating.

2.1. Formulations

Drug coating on stent was carried out in two layers. Base layer contains blend of drug dexamethasone and biodegradable polymers designed to deliver drug at the targeted lesion. Drug-free top layer was coated on stent for prevention on immature drug release from the stent before implantation and protect stent from light and moisture. Drug coating solution was prepared by dissolving the drug dexamethasone and biodegradable polymers in tetrahydrofuran. Formulation of drug coating solution is presented in Table 1. Approximately 56 μg of drug was coated on 16 mm long stent which makes the drug concentration approximately 1.0 μg/mm^2. Dexamethasone stent studied earlier in other clinical trials had a clinical dose range of 0.5 (Liu et al., 2002) to 2.2 μg/mm^2 (Hoffmann et al., 2004). Therefore we selected here an average dose to investigate the drug release kinetics study with dexamethasone.

Table 1 – Drug–polymers formulation for stent coating.

Particular	Concentration (%, w/w)	
	Base layer	Top layer
Dexamethasone	20	0
75/25 poly-L-lactide-co-caprolactone	76	100
Polyvinyl pyrrolidone	4	0

2.2. Coating technique

Conventional air brush technique is effectively used to coat the stent with successive layers drug–polymer solution. Before coating, the stents were weighed using analytical balance (Citizen CX-265) having 0.01 mg accuracy. The machine comprises a spray nozzle having 0.3 mm diameter from which drug–polymer solution was sprayed using nitrogen as carrier gas. Programmable controller box having fixed coating and drying periods, 50 and 20 s, respectively, was used to coat successive layers. Stents were vacuum dried for about 1 h after coating of each layer to eliminate residual solvent on the coated stent. All the coating procedure was performed in class 10,000 clean-room having temperature 25 ± 3 °C and relative humidity 50 ± 10%.

2.3. Surface morphology and characteristics

Scanning electron microscopy (Philips XL30, Japan) was performed to characterize the coating morphology and uniformity on the stent. Surface of drug coated stents after coating and after incubation were taken to observe the effects on surface after drug elution. Moreover to determine the coating homogeneity at outer and inner surface, the coating thickness had been determined around the stent strut by resin embedding method. The coated stent was subjected to be molded in hard resin and cross-sections were taken. The coating thickness was measured by calibrated optical microscope. As the coated stents undergoes variation manufacturing procedures and afterward implantation procedure the coating has to be strong enough to withstand these mechanical stresses. To assess coating mechanical integrity, the stents were crimped on balloon catheter (3.0 mm × 17 mm, Vega) first and then expanded at 8.0 atm to achieve its nominal expansion diameter 3.0 mm using inflation syringe (Merit Medical). The surface has been observed by SEM to look for mechanical damage to coating in both circumstances.