DRUG - ELUTING BIORESORBABLE VASCULAR STENTS MANUFACTURED BY MICROINJECTION MOULDING

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Introduction

Since FDA approval for peripheral vascular in 1990 and for coronary vascular procedures in 1994, tens of millions of people in the world have undergone a coronary or peripheral stenting procedure. Today, because of frequently encountered late complications related to implantation even the newest generation of metal vascular stents, optimal treatment of coronary heart and peripheral artery disease entails the need to search for new solutions. Looks that stents manufactured with use of biodegradable polymeric materials represent an attractive alternative, which allow revascularization modality and finally full regeneration of the vessels [1]. The most commonly used polymers for bioresorbable stents are poly(L-lactide) (PLLA) and poly(lactide-co-glycolide) (PLGA) [2]. However, the future of such stents is not obvious, as evidenced by the withdrawal from the sale of previously approved and commonly used Absorb stents (Abbot Vascular). However, this does not mean, that this company and others are giving up for research on this technology [3]. The selection of optimal material, implantation techniques and production technologies are still objects of intensive investigations. Now, there are at least 15 bioresorbable stent programs in progress, with five in the advanced development stages.

Two years ago, in our previous performance [4], we presented the preliminary results of our work on obtaining biodegradable vascular stents based on L-lactide/glycolide/ trimethylene carbonate terpolymer using the new technology of microinjection moulding.

Today, in the study we present more advanced results showing possibility of manufacturing on this way peripheral and coronary stents, their properties and tests of surgical suitability carried out in vivo on a domestic swine model.

Materials and Methods

The L-lactide/glycolide/trimethylene carbonate terpolymer was obtained in bulk by two-step synthesis. In the first step, TMC oligomer was prepared by ROP using zinc acetylacetonate as a catalyst and butandiol as initiator. The obtained oligocarbonate was used in the second stage of the synthesis as a macroinitiator of the copolymerization reaction of L-lactide with glycolide. Obtained product was granulated and used in further processing. In the production of stents, MicroPower 15t micro-injection moulding machine was used with injection moulds made in the Alexander TOOLS (Chwaszczyno) company. The stents mouldings were covered with a polymer layer containing sirolimus, then two tags from platinum were affixed to the end stent segments. The finally stents were conditioned at 60°C to stress relaxation, final crystallization and elimination of post-processing contraction. The stents were crimping on the balloon dilatation catheters Mozec (Meril) with using specialist crimping machine at 45°C. After packaging, the produced implantation systems were sterilized with electrons beam at a dose of 15kGy. A total of 25 stents were implanted into the peripheral arteries (profunda femoris) of 10 animals. All stents were implanted under quantitative coronary angiography (QCA) guidance. Independently during procedures performed on animals was assessed the possibility and behavior of stents during conducted treatment as well as course of implantation using the techniques of intravascular imaging OCT (Optical Coherent Tomography).

Results and Discussion

The investigations were conducted with terpolymers of different composition (70% L-LA 10% GL 20% TMC, 82% L-LA 10% GL 8% TMC, 76% L-LA 9% GL 15% TMC), which were synthesized within the framework of the project. All of them, proved to be more suitable for injection processing compared to the previously used commercial poly (L-lactide). Using synthesised terpolymers, a better filling of the mould nest was obtained, mainly due to the high melt flow rate at the processing temperature (relatively small molecular weight terpolymers of about 40-50 kDa, and possess microblock chain microstructure). The optimization of the processing conditions and of heating and cooling of injection moulds allowed for obtaining stents with properties very close to the assumptions. Manufactured stents were subjected to mechanical tests and attempts of optimization of the crimping process on the catheter and opening at conditions occurring during surgery. A series of manufactured implantation systems with peripheral stents have been used in the preclinical studies on the swine model. The first results of these studies are rather promising, but unfortunately they presented the lack of the required repeatability of the properties of the produced stents, which was manifested by their collapsing few days after implantation. On the other hand, it was shown that a part of the examined stents maintained the vascular walls properly and displayed the self-expanding effect after the implantation.

Conclusions

It has been confirmed that by adapting a suitable polymeric material with a relatively low viscosity in the processing conditions and good mechanical properties, having the appropriate shape of the final stent and the precise injection machine allowing rapid injection under high pressure, it is possible to obtain such thin-walled products as vascular stents. It seems that by further process optimization, and mainly achieving repeatability of all operations, the stents with good functional properties possible to use in clinical treatments can be obtained.

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References

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