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Review

Non-vascular drug eluting stents as localized controlled drug delivery platform: Preclinical and clinical experience

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ABSTRACT

Stents occupy an important place in the medical field for their widespread application. They have been used in vascular as well as in non-vascular organs for various reasons. Among vascular stents, development of coronary drug eluting stents (DESs) has completely revolutionised the percutaneous coronary intervention. Similarly, attempts have been made to make use of this modality in non-vascular organs. This paper focuses on the preclinical and clinical experience with drug-eluting non-vascular stents with emphasis on drug delivery systems and regulatory requirements for their development.

Contents

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1. Introduction

Stents are the hollow tubular medical devices used to unblock the conduits in our body. Primary function of stents is to provide support and prevent occlusion of the stented organ. The term "stent" generally creates an image of coronary stents; however there are stents for other organs as well. Stents can broadly be classified as vascular and non-vascular depending upon the target organ. Vascular stents are used to clear the occlusion in blood vessels and are used for coronary, carotid, renal, iliac, superficial femoral and tibial arterial occlusions [1]. Non-vascular stents on the contrary are used for clearing the occlusion or strictures in the non-vascular conduits, for example in the oesophagus, biliary duct, trachea, bronchi, sinus cavities, ureters, and urethra.

In the early stages, bare stents were developed; however their functionality was short lasting. Most vascular bare stents became occluded due to neointimal growth leading to occlusion, i.e. restenosis. Similarly, non-vascular stents used to clear malignant obstruction were occluded due to malignant ingrowth in the stent. Apart from these limitations the use of stents itself caused side effects such as stent related discomfort, pain, bacterial colonization (i.e. biofilm formation) and benign hyperplastic growth over the stent. In order to prolong the stent's patency and to avoid side effects, DESs were proposed. Several classes of drugs have been combined with stents to improve their performance such as, antiproliferative, anti-inflammatory, antimicrobials and analgesics, and the selection of these agents depends on the specific requirement for each stenting.

DESs are considered as 'combination products' by Food and Drug Administration (FDA), USA. Combination products as per the FDA definition are comprised of two or more regulated components viz., drugs, biological or a device, combined physically or chemically, packaged together or separately with a labelling indicating the combined use of the components [2]. Primary mode of action determines whether a combination product will be considered as a device, biological or a drug product. Stents are considered medical devices because they physically unblock the tubular structures within our body and with the additional inclusion of drug elution function, improve the performance by avoiding restenosis [3].

Coronary DESs were the pioneers in the market. The FDA approved the first bare metallic stent in 1994 and in less than a decade in 2003, Cordis Corporation introduced the first DES, CYPHER™ in US market [3]. Approval of this stent was followed by approval of several other DESs. Increasing interest in the development of device–drug combination products development is partly due to the shorter time (4–8 years) and low costs ($250 million) required for the development in comparison to new chemical entities [(14.2 years and $802 million (2000 dollars) of investment)] [4–6]. Apart from that, increasing clarity of regulatory guidelines has also played a pivotal role in growth of the device–drug combination market. According to the recent estimates the device–drug combination market will reach US$18.54 billion by 2014 with a compound annual growth rate of 11.8%. DESs constitute a major part of this market and are projected to reach US$8.47 billion by 2014 [7].

While there has been tremendous growth in vascular DESs [8,9], the development of DESs for non-vascular applications has remained slow. In this paper, we describe the regulatory perspective of DESs development and then, focus on preclinical and clinical experience with non-vascular stenting, across different organs and disease conditions.

2. Regulatory perspective — drug/delivery system, preclinical and clinical aspects

As with any other product, regulatory requirement forms the basis for ascertaining the quality, safety and efficacy of the product. US-FDA classifies the medical devices in to three classes; class I devices are considered the simplest devices with minimum risk and are subject to general controls (annual product registration, device listing, Good Manufacturing Practice, labelling, etc.), class II devices pose moderate risk and need 510(K) premarket notification prior to marketing and class III devices pose substantial risk, require more stringent evaluation to prove safety and efficacy and have to undergo premarket approval (PMA) before marketing [10]; however few class III devices may undergo 510(K) to get US-FDA clearance [11].

DES development involves regular interaction with the FDA counterparts. Requirements and study designs are discussed during development. In the non-vascular segment of DESs only PROPEL™ sinus DES (Class III) has been approved by US-FDA, while there are many examples of approved vascular DES. The requirements for each device are supposed to change according to class of device, indication, disease, etc. Following requirements are derived from the PMA application summary of the PROPEL™ stent as well as from the guidance available for coronary stents (Class III), which are likely to be stringent on non-vascular stents but give a fair idea about the role of regulatory aspects in the development.

As far as drug and delivery system is concerned, thorough characterization of drug as well as polymer is required. Drug substance and finished product are supposed to have undergone Chemistry, Manufacturing, and Control (CMC) evaluation, which involves material characterization, identity, content uniformity, impurity/degradation product determination, *in-vitro* release studies, particulate counts and endotoxin testing. Extensive biocompatibility assessment of the stent material is required. If the drug is coated on top of the stent as a polymeric layer then characterization related to material and chemistry of polymer, drug loading, coating thickness and adhesion and drug content, needs to be tested. In the case of biodegradable polymers, additional tests to ascertain biodegradation profile (both *in-vitro* and *in-vivo*), and effect of sterilization procedures on degradation and stability of polymer, need to be carried out. Stability also needs to be ascertained over shelf life of the product. It involves assessment of appearance, drug content assay/uniformity, drug identity, residual solvents, impurities/degradants, *in-vitro* release, and sterility and endotoxin tests. An important part of characterization for such devices is the degradation profile near to the end of stent's life; particles generated on degradation and changes in material properties are crucial and required to be tested. Drug release both in *in-vitro* and *in-vivo* conditions forms an important part of the recommendations. It is generally regarded as a quality tool and it is expected that at least 80% of release (as compared to label claim) should be covered in release profile. In this regard release method is supposed to be bio-relevant, if not, it should be able to detect batch to batch differences. Drug release mechanism (erosion, diffusion, etc.) and target release rate from the polymer matrix are required to be proved on sound scientific rationale. Since state of drug (dispersed, continuous phase, reservoir) in polymer matrix affects the release, full physical, chemical and mechanical characterization is required [12,13].

There are two pathways for the marketing approval of the devices, viz., 510(K) and PMA. Under 510(K) application, the manufacturer is expected to demonstrate substantial similarity with an existing predicate device (previously cleared device). Most of the devices on market are approved through 510(K) application. PMA, on the other hand, is a more rigorous process and requires clinical data for proving safety and efficacy of the product [14]. Prerequisite for approval can only be made after classifying the device to an appropriate class. Centre for Devices and Radiological Health (CDRH) determines which process to follow depending on the class of the device. As device related risk increases so do the requirements, making PMA mandatory for the approval [11]. PMA is a fairly complex process and can be divided into four phases. In the first phase preclinical evaluations as well as clinical trial plans are discussed with the FDA. Animal studies primarily answer the safety aspect of the device, and can also provide preliminary information on the dose of drug to be used. After the sponsor proves appropriateness