BIODEGRADABLE, MRI VISIBLE AND DRUG-ELUTING POLYMERIC STENT ENABLED BY METAL-ORGANIC FRAMEWORKS

8th UFGNSM TEHRAN-IRAN NOVEMBER 2021

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ABSTRACT

The development of stents has been a major advancement in the treatment of obstructive vascular disease since the introduction of balloon angioplasty. However, the occurrence of neointimal hyperplasia, resulting in in-stent restenosis, remains a major obstacle in the long-term success of the percutaneous coronary intervention. Many advancements have been made in developing new materials for drug-eluting stents. However, biodegradability, sensitivity to medical imaging, and preventing re-stenosis remain major concerns in developing an ideal polymeric stent material. Metal-Organic Frameworks (MOFs) as advanced nanomaterials are utilized for applications in numerous fields. As nanoscience revolutionizes many existing biomedical devices, the development of MOF-based 'theranostic' macro-scale devices is reported here which is not achieved before. In this work, stent visualization with magnetic resonance imaging (MRI), controlled release of immunosuppressive and anticoagulant drugs, and long-term biodegradation are obtained in a MOF-based 'theranostic' stent. For this purpose, PCL and MOF-based polymeric composite films are prepared by combining a solution of a polymer (matrix phase) and a dispersion of a MOF or MOF containing Rapamycin (Rap@MOF, filler phase just for MOF composites) in dichloromethane. Then, thin films of composites with a thickness of 120 µm are cut using a laser cutter (Universal Laser Systems X-600, USA, power 45%, and speed 25%) for the fabrication of the stents based on a stent AutoCAD design. Finally, two sides of the laser engraved films were partially heated to be adhered for making 3D Rap@MOF reinforced PCL stent. To investigate the interactions between MOFs and polymeric chains, extensive physicochemical characterizations such as ATR-FTIR, XRD, ssNMR, DSC, TGA, SEM, and DMA were used to characterize stents composed of pure polycaprolactone (PCL), MOF@PCL, and Hep-(Rap@MOF)@PCL. The results demonstrated a proper interface between MOFs and the polymeric matrix. Blood coagulation tests were also performed to study the effects of MOF incorporation and heparin coating on interactions with blood. The susceptibility effect caused by iron inside the MOF structure (1.11% Wt of the stent) leads to an additional signal loss which can be observed with the T2-weighted GRE sequence, which makes in vivo MRI visualization of the reinforced stents possible. The stents by the instability of MOFs were revealed to be highly biodegradable following degradation tests under various conditions (28% weight loss in 32 weeks compared to 5% weight loss of neat PCL in vitro).*

KEYWORDS: *METAL-ORGANIC FRAMEWORKS, DRUG-ELUTING STENT, THERANOSTIC, NANOTECHNOLOGY, BIODEGRADABLE*

INTRODUCTION

The advent of drug-eluting stents (DES) is considered a major breakthrough in interventional cardiology [1]. Numerous clinical studies are being conducted to understand the safety and efficacy of these agents [2]. As a result of these investigations, biodegradation is considered a critical factor in establishing the efficiency of these stents [3].

Metal Organic Frameworks (MOFs) as advanced materials in nanoscience are known for their unique features such as high surface area, tunable pore size, and adjustable internal surface properties [4]. The combination of the two components of a MOF, the metal ion or cluster and the organic linker, provides endless possibilities with diverse applications including catalysis and biomedicine [5]. Many advancements have been made. However, the development of MOF-based macro-scale theranostic devices has not yet been achieved. Both in vitro and in vivo tests carried out on MOFs (mainly Fe-based) have confirmed their biocompatibility, biodegradability, and their control over drug release [6]. Currently, MRI is a leading imaging technique for clinical diagnosis, characterization, and treatment monitoring in the body. As MOFs are commonly used in the development of T2-weighted contrast agents for magnetic resonance imaging (MRI) [7]. their polymeric composites can be appealing for use in complex cardiac procedures by providing soft-tissue contrast without the use of ionizing radiation [8].

MATERIALS AND METHODS

Synthesis of NH2-MIL-101(Fe)

To prepare amino-functionalized MIL-101(Fe), a solution of 0.225 g (1.242 mmol) of NH2-H2bdc in DMF (7.5 mL) was added to a solution of 0.675 g (2.497 mmol) of FeCl3·6H2O (2.50 mmol) in DMF (7.5 mL) and the resulting mixture was transferred to an stainless steel autoclave (30 mL total volume) and heated at 110 °C for 24 h. The solid was recovered by centrifugation, double-washed with DMF and ethanol and dried under vacuum at room temperature. Scanning Electron Microscopy (SEM) image of as-synthesized MOFs is shown in Fig. 1.

Rapamycin encapsulation and release experiments

Microcrystalline bulk materials of NH2-MIL-101(Fe) are dried in vacuum oven at 100 °C overnight. Then, 100 mg of heat activated MOFs were dispersed in ethanolic solution of rapamycin (0.250 µg/ml). After 24 h of magnetic stirring at dark room, the particles were collected and washed through ethanol and water centrifuging cycles, after which Rap@MOFs were dried at room temperature under vacuum.

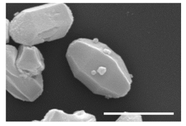

Figure 1: SEM image of as-synthesized MOFs. Scale bar represents 1µm.

Preparation of composites

Briefly, PCL and MOF based polymeric composite films are prepared by combining a solution of a polymer (matrix phase) and a dispersion of a MOF or rap@MOF (filler phase just for MOF composites) in dichloromethane using magnetic stirring for 12 h, followed by solution casting the polymeric film and solvent evaporation for 12 h at vacuum to achieve a free-standing membrane.

Fabrication of stents

Then, thin films of composites with thickness of 120 µm are cut using a laser cutter (Universal Laser Systems X-600, USA, power 45%, and speed 25%) for the fabrication of the stents based on a stent AutoCAD design. Then, two sides of the laser engraved films were partially heated to be adhered for making 3D Rap@MOF reinforced PCL stent. should present materials, methods, instrumentations, software, and experimental procedures briefly. Please identify the suppliers' complete name (companies) which provided the materials and equipment.

RESULTS AND DISCUSSION

Here, we develop heparin (hep, an anticoagulant)-coated polymeric MOF 'theranostic' stents, where NH2-MIL-101(Fe) encapsulates and releases rapamycin (rap, an immunosuppressive drug) (Fig. 2a,b). Firstly, in order to investigate the interactions between MOFs and polymeric chains, extensive physico-chemical characterizations such as ATR-FTIR, XRD, ssNMR, DSC, TGA, SEM, and DMA were used to characterize stents composed of pure polycaprolactone (PCL), MOF@PCL, and Hep-(Rap@MOF)@PCL. The results demonstrated proper interface between MOFs and the polymeric matrix. For example, there was no compromise of PCL mechanical strength or flexibility in MOF/PCL composites (Fig. 2c). The obtained release patterns of heparin (on the surface of the composite) and rapamycin (within the pores of MOFs) can ensure a type of programmed model to deal with both blood coagulation and restenosis (Fig. 2d). We then demonstrated the efficacy for inhibition of human umbilical vein endothelial cell (HUVEC) proliferation through the release of rapamycin in vitro (Fig. 2e). Blood coagulation tests were also performed to study the effects of MOF incorporation and heparin coating on interactions with blood. The susceptibility effect caused by iron inside the MOF structure (1.11% Wt of stent) leads to an additional signal loss which can be observed with the T2*-weighted GRE sequence, which makes in vivo MRI visualization of the reinforced stents possible (Fig. 2a). The stents by virtue of instability of MOFs were revealed to be highly biodegradable following degradation tests under various conditions (28% weight loss in 32 weeks compared to 5% weight loss of neat PCL in vitro) (Fig. 2f). In vivo experiments are currently being explored to further evaluate the potential of these MOF-polymer composite medical devices.

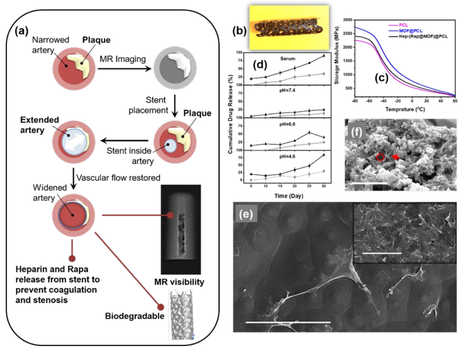

Figure 2: a) Capabilities of Hep-(Rap@MOF)@PCL stent. b) Theranostic MOF/polymer stent. c) Dynamic Mechanical Analysis (DMA) of samples. d) Release patterns of Rap from stents with (gray), and without heparin coating (black) in different conditions. e) SEM image showing the inhibition of HUVECs proliferation through release of Rap compared to the proliferation of HUVECs on a PCL stent (scale bar is 200 µm). f) SEM photograph of degraded theranostic stent for 32 weeks in vitro, red arrow shows a MOF which is being degraded and the circle depict the pore which is formed due to the MOF degradation (scale bar is 5 µm).

CONCLUSIONS

Developing advanced materials for noninvasive imaging is rapidly progressing. The risk of vascular disease is on the rise and therefore there is a critical need to develop novel materials for biodegradable drug eluting stents with detectability using MRI. Nanotechnology promises to revolutionize manufactured materials, creating a vast array of new products, drug delivery devices, and monitoring mechanisms. Here, we have designed and fabricated the first MOF-based theranostic macro-scale medical device. We have shown that the seemingly weak point of MOFs, which is its instability, can be used to accelerate the biodegradation of stents over a prolonged period of time. Rapamycin was loaded into MOFs, and its further release from stents in vitro prevented proliferation and migration of HUVECs. The covalent linkage of a heparin coating on (Rap@MOF)@PCL stents was effective in reducing blood coagulation, while also influencing the drug release patterns. These patterns are further indicative of the expected engineered release profiles for inhibition of clotting and stenosis in vivo. The biodegradable polymeric components also demonstrated feasible visibility utilizing MRI while placed in a pig carotid artery ex-vivo. This study promises an exciting future where the advent of new chemistries such as MOFs, in combination with engineered macro-scale medical devices, may change the way the physicians work.

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