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Research Paper

Effect of polymer microstructure on the docetaxel release and stability of polyurethane formulation

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ABSTRACT

PurSil®AL20 (PUS), a copolymer of 4,4′-dicyclohexylmethane diisocyanate (HMDI), 1,4-butane diol (BD), poly-tetramethylene oxide (PTMO) and poly-dimethyl siloxane (PDMS) was investigated for stability as a vehicle for Docetaxel (DTX) delivery through oesophageal drug eluting stent (DES). On exposure to stability test conditions, it was found that DTX release rate declined at 4 and 40 °C. In order to divulge reasons underlying this, changes in DTX solid state as well as PUS microstructure were followed. It was found that re-crystallization of DTX in PDMS rich regions was reducing the drug release at both 4 °C and 40 °C samples. So far microstructural features have not been correlated with stability and drug release, and in this study we found that at 40 °C increase in microstructural domain sizes and the inter-domain distances (from ~85 Å to 129 Å) were responsible for hindering the DTX release in addition to DTX re-crystallization.

1. Introduction

Non-vascular self-expanding metallic stents (SEMS) are used to avoid malignant obstructions of various organs such as esophagus, gastrointestinal tract, pulmonary and urinary tract. But unrestricted growth of tumour often leads to re-occlusion of the passageway [1,2]. To avoid re-occlusion drug eluting stents (DES) have been investigated as a drug delivery vehicle. Non-biodegradable polymers have been utilized in the manufacture of non-vascular stents [3–5] as a film covering. Paclitaxel [6,7] and gemcitabine [1,8] loaded polyurethane (PU) film covered SEMS has been investigated as a palliation therapy for unresectable malignant obstructions of gastro-intestinal tract.

PUs are one of the most important groups of biomedical polymers. Since the 1960s they have been utilized in the preparation of medical devices, implants and prostheses. Over the years, a concerted effort from researchers in understanding the structure property relationship have widened the application of this polymer class into more sophisticated devices such as orthopaedic implants, neurostimulation devices, blood contacting implants and drug delivery devices [9]. Poly-dimethyl siloxane (PDMS) based PUs are composed of aromatic/aliphatic isocyanate and a PDMS (i.e silicone). An additional diol (chain extender) is included to increase the length of the hard segment and allow microphase separation in the microstructure. The isocyanate portion, along with a chain extender forms the hard segment while the PDMS is the soft portion of the PU. These hard and soft segments are thermodynamically incompatible. Although lack of compatibility (causing phase separated microstructure) is generally considered to improve mechanical properties, PDMS based PUs have reduced tensile strength, extensibility and toughness caused by poor interfacial adhesion between hard and soft domains. To reduce this incompatibility, soft segment diols are generally added in mixed fashion which allows hydrogen bonding interaction between hard and soft segments and reduce the microphase separation [10–12]. Hard segments contain hydrogen bonded urethane groups which provide strength to the polymer while the soft segments provide the elasticity.

Stability testing of pharmaceutical products provides information on the quality of product under the influence of different conditions of temperature and humidity. It also provides an evidence of the shelf life and storage condition. In the present paper, we focus on the stability aspect of the drug delivery application of PurSil® AL20 TSPU (PUS) for Docetaxel (DTX) delivery to the esophagus through a DES. PUS is a non-biodegradable PDMS based PU

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and has a tendency to re-orient over the period to a thermodynamically stable microstructure. This property of phase re-organization could potentially change the release behaviour of the DTX over the period under stress (i.e. stability test condition). Drug diffusion especially in the case of phase separated PUs takes place through the tortuous path provided by the soft segments while the hard segments hinder the diffusion physically or chemically by forming a hydrogen bond with the diffusant [13]. Similarly, polymer cross linking [14,15] and increase in hard segment content [16–18] have been shown to affect microstructure and diffusion. Strikingly, we found no literature report covering the phase re-organization and its impact on drug release. In addition to the general tests used for the stability assessment *viz*., physical, chemical and solid state properties we analysed the microstructural changes in PUS using SAXS to elucidate the likely effect of it on the DTX release.

2. Experimental methods

2.1. Materials

DTX was obtained from Shanghai Jinhe Bio-Technology Co., Ltd. (Shanghai, China) and PurSil® AL 20 75A TSPU (Fig. 1) was provided by DSM (Biomedical Berkeley, CA, USA). The PUS contains 4,4′-dicyclohexylmethane diisocyanate (HMDI) and chain extender 1,4-butane diol (BD) which together constitute 35% of the total weight. Poly-tetramethylene oxide (PTMO) and PDMS form the mixed soft segment, contributing 44.5% and 20% of the total weight, respectively. PUS is further surface-modified with 0.5% of PDMS. Tetrahydrofuran (THF) was purchased from Chem-Supply Pty. Ltd. (Adelaide, SA, Australia). HPLC grade acetonitrile was purchased from Merck (Melbourne, VIC, Australia). All other reagents were of analytical grade.

3. Experimental section

3.1. Formulation preparation and stability studies

3.1.1. Film preparation

Using a Petri plate, blank films were casted [19] from a 5% w/v THF solution of PUS (thickness ~90 μm). DTX loaded films (F) were prepared by adding 4.76% by weight of DTX. The blank PUS layer was prepared from 5% and 10% w/v THF solution. Thickness of 10% w/v solution film was ~180 μm. Formulations of the DTX were also prepared in bilayer configuration by agglutinating the blank PUS layer (180 μm thick) to DTX loaded layer using THF. The bilayer configuration facilitates unidirectional release of DTX towards the esophagus. Films were dried in an oven at 60 °C for 24 h. For DMA, additional films were prepared at 5%, 10%, 20%, 40% and 60% w/w DTX loading.

3.1.2. Stability studies and in vitro release

Stability studies were performed as per the conditions prescribed under Q1A (R2) of The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines. Stability conditions and packaging are summarized in Table 1. Sample of PUS and DTX loaded films was stored in the refrigerator in polyethylene bags. Samples were also exposed to 25 °C – 65%RH (relative humidity) and 40 °C – 75%RH in a stability chamber by packaging in polyethylene bag and heat-seal Alu–Alu foil, respectively. For each temperature and humidity condition, a PUS film sample was also kept as a blank control. The control samples of PUS and DTX films (Table 1) stored in a desiccator were used as standard references to compare the SAXS and XRD results. Stability samples were stored for 3 months and analysed for chemical stability using a HPLC method [19] as described under S1 in supplementary information. Stable samples were then subjected to *in vitro* release studies. The drug release experiments were performed in 15 mL of 0.1 M, pH 6 phosphate buffer with 0.1% v/v tween 80 at 37 °C [19]. Unidirectional release was studied by attaching films to 3 mm thick acrylate sheet using double sided tape. Release medium was replaced completely after each sampling point to maintain sink conditions.

3.1.3. Dynamic Mechanical Analysis (DMA)

DMA was performed on a TA-Q800 instrument with a tensile grip. Film samples (4 cm × 0.3 cm) were heated at 3 °C/min from −145 to 150 °C at 1 Hz frequency.

3.1.4. X-ray Diffraction (XRD)

XRD analysis was performed on a Bruker D8 Advance at room temperature. Cu Kα (1.542 Å) X-rays were used after passing through a nickel filter. Data were collected in continuous mode between 5° and 40° 2θ at a step size of 0.02°.

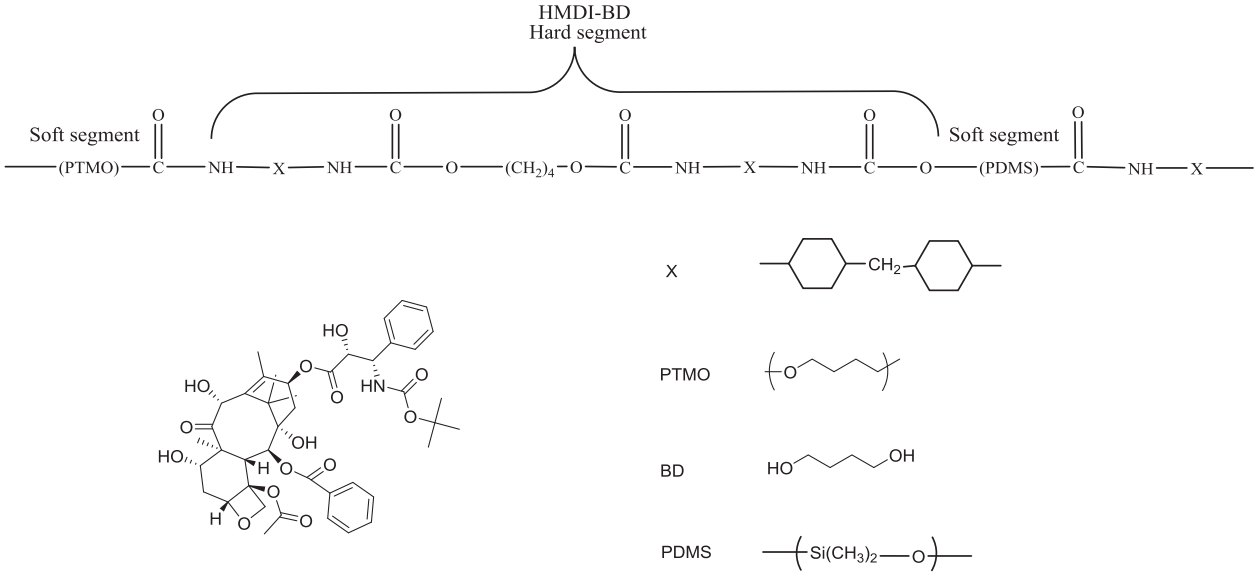

Fig. 1. Chemical structure [12] of PurSil® AL 20 75A TSPU (PUS) and Docetaxel (DTX). PTMO – Poly-tetramethylene oxide, PDMS – Poly-dimethylsiloxane, BD – Butane diol and HMDI – 4,4′-dicyclohexylmethane diisocyanate.