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Drug Loaded Biodegradable Polymer Microneedles Fabricated by Hot Embossing

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Key Words: Microneedles, transdermal, drug delivery, hot embossing, poly- ε-caprolactone (PCL)

Abstract

This study demonstrates a fast low temperature method for fabrication of drug loaded polymer microneedles (MNs). First, arrays of tapered pillar MNs with a length of 275 ± 3 µm (mean ± SD) and a diameter of 84 ± 1 µm were fabricated in Si with a three-step deep reactive ion etching (DRIE) process. The Si MNs were used as a template for fabrication of polydimethylsiloxane (PDMS) stamps. The stamps were applied for replication of the MNs in spin coated poly-ε-caprolactone (PCL) films by hot embossing at 60°C and a pressure of 1.4 MPa for 3 min. The resulting PCL MNs perfectly resembled the Si MNs and had a length of 270 ± 5 µm and a diameter of 84 ± 3 µm. The MNs had sufficient mechanical strength to penetrate the surface of a 10 w/w% gelatine gel without deformation. Finally, PCL MNs containing 20 w/w% of furosemide were fabricated and drug release by diffusion was demonstrated.

1. Introduction

In the late 90's, microneedles (MNs) were introduced as a novel method for (trans)dermal drug delivery [1]. A large number of different types of MNs were reported, such as dissolvable polymer MNs [2], hollow silicon MNs for drug injection [3] or coated biodegradable MNs for vaccine delivery [4]. MNs are less invasive and less painful compared to traditional hypodermic needles [5]. Arrays containing hundreds of MNs can be fabricated on a footprint area of a few mm^2. Drug loaded polymer MNs are in most cases fabricated by solution casting methods [6-9]. In this case, small amounts of drug-polymer solutions are cast on moulds typically made of silicones such PDMS. Alternatively, spray coating was used to deposit drug polymer solutions into PDMS MN moulds [10]. Furthermore, drawing lithography techniques or electro drawing from droplets at ambient temperature were introduced for fabrication of dissolvable MNs [11, 12]. Most of these methods have the drawback that they are time consuming and not suitable for large-scale production.

In comparison, hot embossing is a versatile micro moulding process for the fast replication of polymer microstructures with high aspect ratio [13]. Typically, hot embossing only requires a short polymer flow allowing lower moulding temperatures compared to other micro moulding techniques [14]. Hot embossing of MNs has been demonstrated using polylactic acid (PLA) [15], poly(methyl methacrylate) (PMMA) [16, 17], polycarbonate (PC) [18-20] and cyclic olefin copolymer (COC) [19]. However, none of these MNs were loaded with drug. A major drawback in all of these studies is a long cycle time at high processing temperatures above 150°C. Those conditions will affect a considerable range of drugs and prevent that active pharmaceutical ingredients can be pre-loaded in the polymer film.

PCL is a biodegradable polymer with a low melting temperature of 59-64°C [21]. This facilitates micro moulding processes and identifies PCL as a potential matrix for drugs that are unable to withstand high temperatures, such as proteins and peptides. Additional advantages of PCL are high permeability for many drugs and good biocompatibility [21]. Here, we demonstrate the direct fabrication of drug loaded MNs in a single step of hot embossing at low