PLA-PCL Microsphere Formulation to Deter Prescription Opioid Abuse via Smoking

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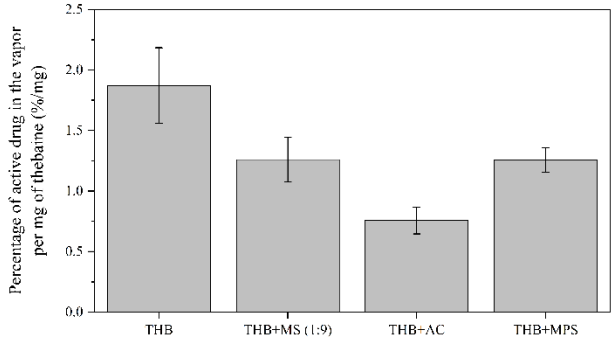
Statement of Purpose: Opioids are routinely prescribed across the US for pain relief, despite the alarming prevalence of their abuse that often leads to addiction and overdose deaths. Abuse deterrent formulations (ADFs) for prescription opioids are aimed at making nonmedical use of these drugs more challenging and less satisfying. Typical abuse routes for prescription opioids are ingestion, injection, and inhalation, including snorting and smoking.[1] Despite the fact that more than 30% of surveyed abusers in the US reported smoking opioids[2], to our knowledge, there is currently no ADF to prevent this particular route of abuse. Here, we show a novel approach to deter smoking of a model prescription opioid drug, thebaine (THB). We mix THB with polylactic acid (PLA) and polycaprolactone (PCL) microspheres (MS) to limit the escape of vaporized drug. Our data indicate that, at a 1:1 mass ratio, the microspheres function as a sink for the active drug and its volatile degradation products formed during heating.

Methods: PLA-PCL MS with varying (1:9, 5:5 and 9:1) molar ratios of PLA to PCL were prepared by a single emulsion-solvent evaporation method, freeze-dried for 48 hours, and characterized by scanning electron microcopy (SEM). The ability of PLA-PCL MS to deter smoking of THB was assessed based on the analysis of drug content in the vapor by high-performance liquid chromatography (HPLC) and the remaining mass by thermogravimetric analysis (TGA). The abuse-deterrent performance of PLA-PCL MS was compared to that of activated carbon (AC) and mesoporous silica (MPS), two materials with excellent and well-established drug-adsorbing properties.

Results: SEM image analysis showed that PLA-PCL MS had an average diameter of less than 5 µm. According to the HPLC data, among the three MS formulations with varying molar ratios of PLA to PCL, PLA-PCL MS (1:9) reduced the amount of active drug in the vapor most, with a statistical difference from the negative control (THB alone) group ($p=0.033$); therefore, this formulation was selected for further testing. PLA-PCL MS (1:9) entrapped significantly less active drug than AC ($p=0.005$) but showed no statistical difference from MPS ($p=1.000$) (**Fig.1A)**. According to the total area under the curve (AUC) per mg of THB, which indicates total amount of vaporized THB and its degradation products, PLA-PCL (1:9) MS significantly reduced the amount of thermal degradation products of THB in the vapor compared to negative control (THB alone) ($p<0.001$), to the extent comparable to MPS ($p=0.184$) (**Fig. 1B)**. These findings were validated by the use of TGA, which was utilized to quantify the mass loss of the drug alone, as well as drug in the presence of PLA-PCL MS (1:9), AC and MPS upon heating.

A



B

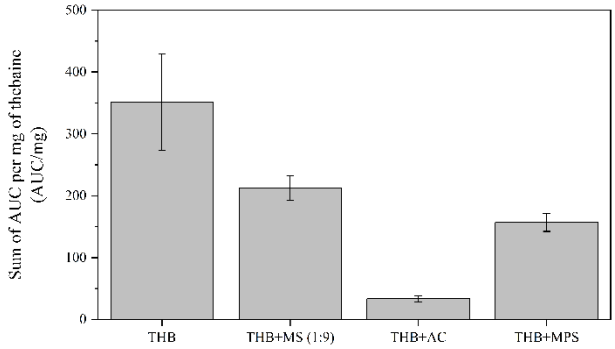


Figure 1. Analysis of active drug (A) and its degradation products (B) entrapment by PLA-PCL MS (1:9) in comparison to negative (THB alone) and positive (AC and MPS) controls.

Conclusions: Our study showed that PLA-PCL MS with 1:9 molar ratio of PLA to PCL effectively reduced the amount of active drug and thermal degradation products in the vapor generated by heating of THB. The abuse-deterrent performance of the microspheres was comparable to that of mesoporous silica. Our data indicate that PLA-PCL microspheres can potentially be used to create an ADF against smoking for common prescription opioids.

References:

1. Gasior M. Postgrad Med. 2016; 128:85-96.
2. Vietri J. Pain Med. 2014; 15:2064-2074.