

# 3D printing of opioid medicines with alcohol-resistant and abuse-deterrent properties

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## INTRODUCTION

- Drug addiction and abuse affects 27 million people worldwide and contributes to the global disease burden [1].
- The high morbidity and mortality associated with long-term opioid drug usage renders them as dangerous tools [2].
- Novel formulation strategies are needed to support efforts in minimizing the prevalence and risks of opioid abuse.
- 3D printing (3DP) enables the fabrication of personalised doses with enhanced mechanical properties.
- This study reports, for the first time, the use of 3DP to create alcohol-resistant and abuse-deterrent tablets with modified release properties, encouraging safer use of opioids.

## METHODS

3D printed tablets (printlets) were fabricated using a direct powder extruder 3D printer (FabRx, UK) (Figure 1). SL-grade hydroxypropyl cellulose was used as the main polymer, mannitol as a plasticizer, and tramadol as the drug. Polyethylene oxide (PEO) was subsequently added to enhance abuse-deterrence. Dissolution profile of the printlets in the presence and absence of 40% ethanol was assessed using USP II apparatus (dynamic pH conditions).

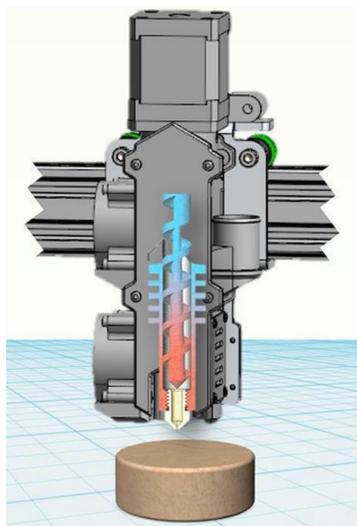


Figure 1. Design of direct powder extruder FabRx 3D printer [3]

The printlets were evaluated for abuse-deterrent properties in 3 ways:

- (1) **Syringeability:** Printlets were dissolved in 5mL of deionised (DI) water at 100°C for 5min. The mixture was drawn up a 5mL syringe attached to a 21-gauge needle and a cigarette filter. The resultant solutions were analysed using HPLC.
- (2) **Nasal inhalation test:** Printlets were milled using a coffee grinder for 2 minutes and sieved. Particles with sizes  $\leq 500 \mu\text{m}$  were considered small enough to be snorted.
- (3) **Solvent extraction:** Printlets were dissolved in 100mL of DI water, ethanol, 0.1M NaOH and 0.1M HCl for 60min. The samples were subsequently analysed using HPLC.

## RESULTS & DISCUSSION

3DP was successfully utilized to create printlets with alcohol-resistant and abuse-deterrent properties (Figure 2).

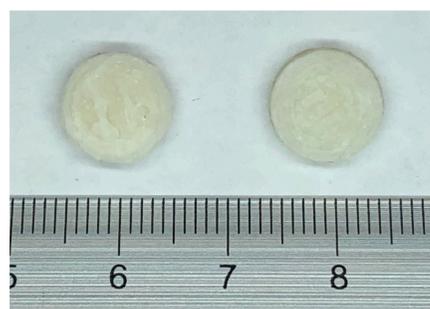


Figure 2. Images of the HPC-SL (left) and HPC-SL/PEO (right) printlets

Results from syringeability studies showed that while printlets containing HPC alone had moderate abuse deterrent properties, addition of PEO greatly enhanced their abuse deterrent properties (Figure 3a). Similarly, results from nasal inhalation tests (Figure 3b) and solvent extraction studies (Figure 4) showed that inclusion of PEO improved the printlets' abuse deterrent properties.

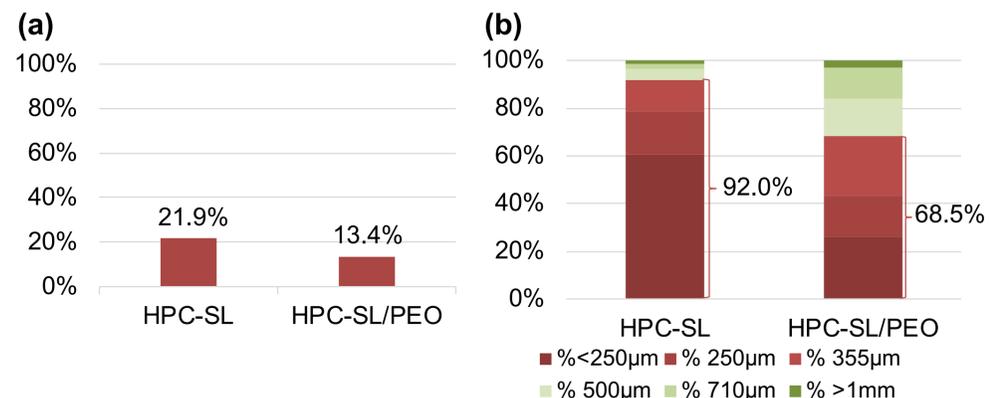


Figure 3. Summary of (a) percentage of drug obtained from syringeability studies (b) distribution of powder size after milling of printlets.

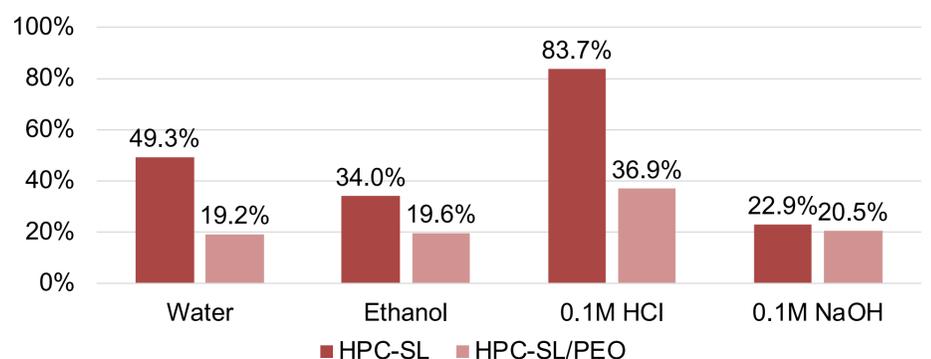


Figure 4. Percentage of drug extracted from respective different solvents after 60mins

The lower percentage of drug extracted from HPC-SL/PEO printlets is likely due to PEO's inherent modified release properties. In particular, the hydration of the oxygen group in the ether moiety results in the formation of a thick viscous gel that confers its modified release properties. Nevertheless, the large volume of solvent used in this extraction cannot be feasibly injected into an abuser.

The drug release profile of HPC-SL and HPC-SL/PEO printlets were similar in the presence and absence of alcohol, wherein  $f_2$  similarity values of 71 and 87 were obtained respectively (Figure 5). As such, ingesting alcohol with opioid-containing printlets will unlikely lead to accelerated drug dissolution rates.

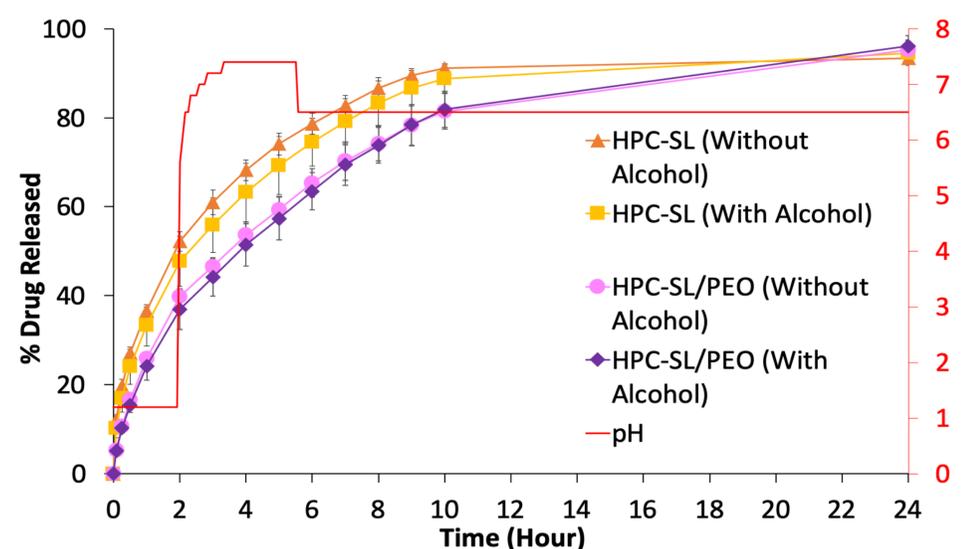


Figure 5. Drug dissolution profiles of the HPC-SL and HPC-SL/PEO printlets in the presence and absence of alcohol.

## CONCLUSION

Abuse-deterrent and alcohol-resistant formulations with modified release properties were successfully fabricated with 3DP. These novel formulations support efforts in reducing opioid misuse and adverse clinical outcomes. Given its ability to confer accurate dosing and enhanced mechanical properties, 3DP is the future of personalised pharmaceutical manufacturing.

### Reference:

1. Degenhardt, L., et al., The global epidemiology and burden of opioid dependence: results from the global burden of disease 2010 study. *Addiction*, 2014. 109(8): p. 1320-33
2. Manchikanti, L. and A. Singh, Therapeutic opioids: A ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician*, 2008. 11(2 Suppl): p. S63-S88.
3. Goyanes, A., et al., Direct powder extrusion 3D printing: Fabrication of drug products using a novel single-step process. *International Journal of Pharmaceutics*, 2019. 567: 118471