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

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Keywords

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**Abstract**

In the past decade, prescriptions for opioid medicines have been exponentially increasing, instigating opioid abuse as a global health crisis associated with high morbidity and mortality. In particular, diversion from the intended mode of opioid administration, such as injecting and snorting the opioid, is a major problem that contributes to this epidemic. In light of this, novel formulation strategies are needed to support efforts in reducing the prevalence and risks of opioid abuse. Here, modified release tramadol printlets (3D printed tablets) with alcohol-resistant and abuse-deterrent properties were prepared by direct powder extrusion three-dimensional printing. The printlets were fabricated using two grades of hydroxypropylcellulose (HPC). Both formulations displayed strong alcohol-resistance and had moderate abuse-deterrent properties. Polyethylene oxide (PEO) was subsequently added into the formulations, which improved the printlets' resistance to physical tampering in nasal inhalation tests and delayed their dissolution in solvent extraction tests. Overall, this article reports for the first time the use of direct powder extrusion three-dimensional printing to prepare drug products with both alcohol-resistant and abuse-deterrent properties. These results offer a novel approach for the safe and effective use of opioids that can be combined with the advantages that 3D printing provides in terms of on-demand dose personalisation.

## 1. Introduction

Misuse and addiction to drugs is a global crisis, affecting 27 million people worldwide and contributing to the global disease burden (Degenhardt et al., 2014; WHO, 2018a). In particular, opioids are commonly abused for their strong analgesic effects and ability to relieve pain (Cohen and Raja, 2006; Fine et al., 2009). An example of such is tramadol, which is commonly prescribed for the relief of moderate to severe pain (Hollingshead et al., 2006; Subedi et al., 2019). However, due to its abusive potential (Lanier et al., 2010) ~~has~~and on recommendation of The Advisory Council of the Misuse of Drugs (ACMD), the United Kingdom (UK) Parliament has reclassified Tramadol from a Schedule 5 ~~been conferred~~to a class C Schedule 3 Controlled Drug ~~status in the United Kingdom since~~in 2014. Based on the U.S. Food and Drug Administration (FDA), a drug's abusive potential can be defined as "*its use in nonmedical situations, repeatedly or even sporadically, for the positive psychoactive effects it produces* (FDA, 2010; Joranson et al., 2000). Such psychoactive effects include euphoria, hallucinations, and mood alteration. Notably, long-term use of opioids can lead to drug addiction, which often leads to high-risk side effects including, respiratory depression, coma, and even death (BNF, 2016). In 2014, the cost of drug addiction was estimated at £15.5 billion a year (NHS, 2014), heightening regulatory concerns. The high morbidity and mortality associated with long-term opioid drug usage renders them as dangerous tools, outweighing their benefits (Manchikanti and Singh, 2008). Nevertheless, opioids are key components of the World Health Organisation (WHO) analgesic ladder (WHO, 2018b). Therefore, strategies to minimise the risks associated with opioid abuse are essential to safeguard their continued use.

To support these efforts, there is a need for novel formulations with abuse-deterrent properties (FDA, 2015; FDAVoice, 2013). Such formulations aim to decrease the abusive potential of drugs by preventing their tampering or rendering them less attractive to abusers. Strategies towards abuse-deterrence include the use of physical barriers, viscosity enhancement, sorption processes and solubility modification. Usually, the use of a single approach is insufficient in deterring all forms of abuse; therefore, a combination of several approaches is often recommended. In addition to the conventional modes of abuse, such as injection and nasal inhalation, simultaneous alcohol and drug use is also a practice frequently observed in drug abusers (Midanik et al., 2007). The presence of alcohol can lead to considerable variations in the absorption and performance of the medication upon administration. As some drugs and excipients possess higher solubility in organic solvents such as ethanol compared to water, accelerated drug release is observed (Walden et al., 2007) . This is known as alcohol-induced dose-dumping (Meyer and Hussain, 2005), which often bears negative

implications on drug safety and efficacy, and is potentially life threatening. The detrimental outcomes are more potent in modified-release formulations compared to their immediate-release counterparts as the former commonly employ larger drug concentrations, thus rendering them more attractive to abusers.

An abuser will try different ways to manipulate a medicine physically and chemically (Xu et al., 2016). As such, a strategy to mitigate the negative effects of opioid abuse is the development of drug products with abuse-deterrent and alcohol-resistant properties. In this regard, three-dimensional printing (3DP) offers a novel manufacturing tool to fabricate such products. 3DP is an additive manufacturing technology (Trenfield et al., 2020), which in the ~~arena of~~ pharmaceutical field has the benefit of providing accurate dosing individualised to the patient (Awad et al., 2018a; Gioumouxouzis et al., 2018; Goyanes et al., 2019b; Goyanes et al., 2017; Peak et al., 2019; Pietrzak et al., 2015; Scoutaris et al., 2018; Trenfield et al., 2019a; Xu et al., 2020). Currently, the most commonly used 3DP technology in the preparation of pharmaceuticals is fused deposition modelling (FDM) (Awad et al., 2018b; Solanki et al., 2018). FDM 3DP involves the melting of a filament, passing it through a nozzle, and depositing on a build plate. The printer's nozzle head moves in a raster pattern, depositing layers of molten filaments over one another, thus, forming the desired shape (Goyanes et al., 2014; Melocchi et al., 2019; Sadia et al., 2018; Skowyra et al., 2015). Recently, 3D printed formulations made with polyvinyl alcohol (PVA), the most common ~~used~~ pharmaceutical excipient used in 3DP, have been reported to show abuse deterrent properties (Nukala et al., 2019). Nonetheless, as aforementioned, the negative impacts of abuse are more pronounced in modified-release formulations and necessitate greater concern.

Favourably, most FDM 3D printed medicines (printlets) have stronger mechanical properties compared to tablets made using conventional compression processes (Zhang et al., 2017) , enabling them to resist higher external forces. As such, we hypothesised that this manufacturing technique might be suitable for the production of abuse-deterrent and alcohol-resistant formulations. We have previously reported a novel single-step printing process to produce printlets directly from powdered material, obviating the need for the hot melt extrusion step that precedes FDM, thereby making the technology more accessible for research and clinics (Goyanes et al., 2019a). Moreover, this novel technology produces printlets with breaking force values comparable to those prepared by conventional FDM. Therefore, the aim of this work was to utilise direct powder extrusion 3DP to fabricate printlets containing the opioid analgesic tramadol with alcohol-resistant and abuse-deterrent characteristics.

## 2. Materials and Methods

### 2.1 Materials

Tramadol hydrochloride (HCl) HPLC grade was purchased from Sigma-Aldrich, UK (MW 299.84 Da). Hydroxypropylcellulose (HPC-SL, MW 100,000 Da and HPC-L, MW 140,000 Da) was sourced from Nisso Chemical Europe, Germany and polyethylene oxide (PEO) (MW 8,000,000 Da) was purchased from Sigma-Aldrich, UK. D-Mannitol (purchased from Sigma-Aldrich, UK) was used as a plasticiser and magnesium stearate (Sigma–Aldrich Co. Ltd., UK) was used as a lubricant. The salts (listed ~~below~~in section 2.2.3) used for the preparation of the buffer dissolution medium were purchased from VWR International Ltd., Poole, UK.

### 2.2 Methods

*2.2.1 Preparation and 3D printing of drug-loaded dosage forms*

For each batch, a 10 g blend of drug and excipients was prepared. The matrix polymers, plasticisers and lubricant were mixed in a mortar and pestle with the drug to obtain a homogenous mixture. The compositions of the formulations evaluated in this study are listed in Table 1. The prepared mixture was then added to the hopper of a M3DIMAKER™ pharmaceutical 3D printer (FabRx, London, UK) with a direct powder extruder nozzle as previously reported (Goyanes et al, 2019). AutoCAD 2014 (Autodesk Inc., USA) was used to design the templates of the printlets, exported as a stereolithography (.stl) file into a 3D printer software (Repetier host v. 2.1.3, Germany). The selected 3D geometry was a cylindrical printlet (10 mm diameter × 3.6 mm height). The printer settings in the Repetier Host software were as follows: Feed 2100 steps/mm, infill 100%, high resolution with brim, without raft and an extrusion temperature of 170 °C, speed while extruding (20 mm/s), speed while travelling (90 mm/s), number of shells (2) and layer height (0.20 mm). 16 printlets were p~~rinte~~repared in each batch.

**Table 1.** Compositions of all the formulations investigated in this study.

| Formulation | HPC-SL (%w/w) | HPC-L (%w/w) | PEO (%w/w) | Mannitol (%w/w) | Printing Temperature (°C) |
|---|---|---|---|---|---|
| HPC-SL | 50% | - | - | 40% | 170 |
| HPC-L | - | 50% | - | 40% | 170 |
| HPC-SL/PEO | 60% | - | 20% | 10% | 170 |
| HPC-L/PEO | - | 60% | 20% | 10% | 170 |

Note: All formulations included 5% tramadol HCl and 5% magnesium stearate.

### 2.2.2 Determination of Printlets Morphology

The physical dimensions of the printlets were measured using a digital caliper, wherein 10 printlets from each formulation were assessed.

### *2.2.3 In Vitro Dissolution Studies*

The drug release profiles of the printlets were evaluated using a USP-II paddle apparatus (Model PTWS, Pharmatest, Hainburg, Germany). The speed of the paddle was set at 50 rpm with a temperature of 37 ± 0.5 °C (n=3). To mimic fasting GI tract conditions, modified dissolution settings were used (Fadda and Basit, 2005; Goyanes et al., 2015). The tablets were dropped in 750 mL of 0.1 M HCl for 2 h, thus simulating gastric conditions. This was followed by 950 mL of modified Hanks based dynamic dissolution media (136.9 mM NaCl, 5.37 mM KCl, 4.17 mM $NaHCO_3$, 1.26 mM $CaCl_2$, 0.812 mM $MgSO_4.7H_2O$, 0.441 mM $KH_2PO_4$ 0.337 mM $Na_2HPO_4.2H_2O$) for 35 min (pH 5.6 - 7). Afterwards, the volume was increased to 1000 mL by adding 50 mL of pre-Krebs solution (400.7 mM $NaHCO_3$, 6.9 mM $KH_2PO_4$). The mixing of modified Hanks buffer media with pre-Krebs solution resulted in the generation of an in-situ modified Kreb's buffer (pH 7 - 7.4, then 6.5) (Liu et al., 2011). The initial 3.5 h dissolution in the bicarbonate buffer media (Hanks and Krebs buffers, pH 5.6 - 7.4) mimics the transit time in the small intestine, while the subsequent drop in the pH of the buffer to 6.5 mimics the transit time in the colon. Both conditions, along with the change in the pH values, simulate fasting GI tract conditions. The buffers' compositions were prepared to mimic the composition of the human intestinal fluids (Goyanes et al., 2015; Hatton et al., 2015; Liu et al., 2011).

To control the pH of the media, an Auto pH System™ was used. The system mainly comprises a pH probe linked to sources of carbon dioxide ($CO_2$) and helium. The flow of gases was controlled using a control unit, which provides a dynamically adjustable pH that is maintained at a uniform value throughout the experiment, thus providing dynamic conditions. The bicarbonate buffer mainly consists of two ions, bicarbonate ($HCO_3^-$) and carbonic acid ($H_2CO_3$), that co-exist in equilibrium. To decrease the pH of medium, $CO_2$ (g) was purged into the solution, thus stimulating the formation of carbonic acid, whereas, to increase the pH of the medium, Helium was used to displace the dissolved $CO_2$ from the solution. The percentage of drug released was obtained using an in-line UV spectrophotometer (Cecil 2020, Cecil Instruments Ltd., Cambridge, UK) at 270 nm and the data were analysed using Icalis software (Icalis Data Systems Ltd, Berkshire, UK).

To evaluate the printlets' alcohol-resistant properties, supplementary dissolution studies were carried out using 750 mL 0.1 M HCl with an ethanol concentration of 40% (v/v) for 2 h followed by the normal set up in bicarbonate buffer (as aforementioned). The dissolution profiles in the alcoholic and non-alcoholic media were compared using an $f_2$ similarity test. The similarity factor $f_2$ is a logarithmic reciprocal square root transformation of the sum of the squared error and is calculated using equation (1) (Moore, 1996).

(1)

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-\frac{1}{2}} \times 100\right\}$$

Where *n* refers to the number of dissolution time points considered. $R_t$ and $T_t$ are the release profiles of the reference and test formulations at time point t respectively (Gohel et al., 2009). The $f_2$ value ranges from 0 to 100, where the release profiles are considered to be alike when the value exceeds 50, and identical if the value is equal to 100 (Shah et al., 1998). Moreover, as the $f_2$ value decreases, the variation between the dissolution profiles increases, indicating that the formulation lacks the alcohol-resistive properties and is more prone to alcohol-induced dose-dumping.

*2.2.4 Solvent Extraction*

The ability of different solvents to chemically extract the drug from the intact printlets was assessed. Four solvents were used, including water, absolute ethanol, 0.1 M HCl (pH 1.2), and 0.1 M NaOH (pH 12.4). A printlet (*n*=3) was transferred into a beaker containing

100 mL of each solvent, where the solution was stirred using a magnetic stirrer at a speed of 100 rpm throughout the test. Samples were withdrawn at 5, 15, 30, 60 min and 24 h to calculate the amount of drug that was extracted. All samples were diluted 10 times before analysis using high performance liquid chromatography (HPLC). The water and ethanol samples were diluted using deionised water, whereas, the HCl and NaOH samples were diluted using phosphate buffer (pH 6.0) to neutralise the samples (Xu et al., 2016).

A Hewlett Packard 1050 Series HPLC system (Agilent Technologies, UK), equipped with an online degasser, quaternary pump, column heater, autosampler and UV/Vis detector, was used. All samples were filtered using 0.45 µm filters (Millipore Ltd., Ireland) prior to their analysis. The assay entailed injecting 20 µL of sample into an Eclipse plus C18 3.5 µm column, 4.6 × 150 mm (Zorbax, Agilent technologies, Cheshire, UK). The compounds were separated using a mobile phase consisting of 70% of water with 0.1% trifluoroacetic acid (TFA) and 30% of acetonitrile, which was pumped at a flow rate of 1 mL/min. The temperature was maintained at 40°C and the eluents were assessed at a wavelength of 220 nm.

### *2.2.5 Syringeability Test*

The purpose of this test was to simulate an abuser's attempt to prepare a drug solution suitable for intravenous injection. A vial containing 5 mL of deionised water was heated on a hot plate until ~~a~~ the temperature of the deionised water reached 100 ±1 °C ~~was reached~~. One printlet was then dropped into the vial and left to boil for 5 min. The mixture was drawn up a 5 mL syringe attached to a 21-gauge needle and a cigarette filter (5 mm, Swan, UK) (Grünenthal, 2016). Figure 1 shows images of the setup. The amount of drug withdrawn into the syringe was analysed using HPLC (as described previously). Prior to HPLC analysis, all solution samples ($n$=3) were diluted 10 times using deionised water.

Insert Figure 1.

**Figure 1**. Images on the steps followed in performing the syringeability test.

### *2.2.6 Nasal Insufflation Test*

To study the abusive potential of the manipulated drug to be snorted, the particle size distribution following the milling of the printlets was determined. A printlet ($n$=3) was

milled using a Tefal coffee grinder (Model GT203840, 200 watts; Tefal, UK) for 2 min. The particle size distribution of the milled powder was determined by sieve analysis, where five sieve sizes were used, including 1 mm, 710 µm, 500 µm, 355 µm, and 250 µm (Grünenthal, 2016). Particles with sizes ~~less~~ smaller than or equal to 500 µm were considered small enough to be snorted.

### *2.2.7 X-ray Powder Diffraction (XRPD)*

Discs of 23 mm diameter × 1 mm height were 3D printed from the mixtures of drugs and excipients and analysed. Samples of the drug, excipients and powder mixtures were also analysed. The X-ray powder diffraction patterns were obtained in a Rigaku MiniFlex 600 (Rigaku, Wilmington, MA, USA) using a Cu Kα X-ray source (λ = 1.5418 Å). The intensity and voltage applied were 15 mA and 40 kV, respectively. The angular range of data acquisition was 3–40° 2θ, with a stepwise size of 0.02° at a speed of 2°/min.

### *2.2.8 Thermal Analysis*

Differential scanning calorimetry (DSC) was used to characterise the powders and the drug-loaded printlets. DSC measurements were performed with a Q2000 DSC (TA instruments—Waters LLC, New Castle, DE, USA) at a temperature range of 0°C to 200 °C and a heating rate of 10 °C/min. Calibration for cell constant and enthalpy was performed with indium (Tm = 156.6 °C, ΔHf = 28.71 J/g), according to the manufacturer's instructions. Nitrogen was used as a purge gas with a flow rate of 50 mL/min for all the experiments. Data were collected with TA Advantage software for Q series (Version 2.8.394) and analysed using TA Instruments Universal Analysis 2000 (TA instruments—Waters LLC, New Castle, DE, USA). All melting temperatures are reported as extrapolated onset unless otherwise stated. TA aluminium pans and lids (Tzero) were used with an average sample mass of 3–5 mg.

### *2.2.9 X-ray Micro Computed Tomography (Micro-CT)*

A high-resolution X-ray micro computed tomography (Micro-CT) scanner (SkyScan1172, Bruker, Kontich, Belgium) was used to three-dimensionally visualise the internal structure and calculate the density of the printlets. The printlets were scanned with a resolution of 2000 × 1048 pixels. 3D imaging was performed by rotating the object through 180º with steps of 0.4 º and four images were recorded for each. Image

reconstruction was performed using NRecon software (Version 1.7.0.4, Bruker-microCT) and 3D model rendering and viewing were performed using the associate program CT-Volume software (Version 2.3.2.0). The collected data were analysed using Analyzer (Version 1.16.4.1), where maps of different colours were used to represent the density of the printlets.

## 3. Results and discussion

Direct powder extrusion 3DP was successfully utilised to create printlets (Figure 2). HPC-SL and HPC-L were selected as the main polymeric matrix, mannitol as a plasticiser, and tramadol as the active pharmaceutical ingredient. The time needed to print one batch of 16 printlets was ~45 min. The printlets were white in colour and were produced with high consistency in weight and physical dimensions (Table 2).

**Table 2.** The average weight and dimensions of HPC-SL & HPC-L printlets

| Formulation | Weight (mg) (Mean ± SD) | Width (mm) (Mean ± SD) | Diameter (mm) (Mean ± SD) |
|---|---|---|---|
| HPC-SL | 323.7 ± 4.8 | 3.9 ± 0.4 | 9.8 ± 0.1 |
| HPC-L | 314.1 ± 2.3 | 3.6 ± 0.3 | 10.4 ± 0.3 |

Insert Figure 2.

**Figure 2**. Images (from left to right) of the HPC-SL and HPC-L printlets (scale is in cm).

X-ray micro-CT was used to three-dimensionally visualise the internal structure and calculate the density of the printlets (Figure 3). ~~Indeed, both the HPC-SL and HPC-L printlets appeared to have smooth, molten strtuctures, where~~Results have shown that the HPC-SL printlets showed ~~more~~less dense regions as compared to the HPC-L printlets.

Insert Figure 3.

**Figure 3**. X-ray micro-CT images of the (A) HPC-SL and (B) HPC-L printlets.

DSC and XRD analysis of the drug, polymers and powder mixtures prior to printing, and of the printlets, were performed to determine the physical state of the drugs and the degree of their incorporation within the polymers (Figures 4 and 5). DSC data show that ~~pure~~ tramadol hydrochloride melts at ~187°C. The thermograms of the powder mixtures and printlets show sharp melting peaks at ~163°C corresponding to the melting of

mannitol. The absence of tramadol melting peaks indicate that tramadol is either molecularly dispersed within the polymers or dissolved within them as the temperature increases during the DSC process. Corroborating with the results obtained by DSC, the X-ray diffractograms of the powder mixtures and printlets show that mannitol is in the crystalline state. Whereas, there are no crystalline peaks corresponding to tramadol.

Insert Figure 4.

**Figure 4**. DSC thermograms of the HPC-SL and HPC-L formulations, the drug, excipients and powder mixtures prior to printing.

Insert Figure 5.

**Figure 5**. X-ray diffractograms of the HPC-SL and HPC-L formulations, drug, excipients and powder mixtures prior to printing.

The abuse-deterrent properties of the printlets were subsequently assessed. In general, the most common way of abusing opioids is through the ingestion of large amounts of tablets. However, as the frequency of drug abuse increases, some users start to build tolerance to the abusive agent (Young et al., 2010). In turn, to achieve the desired euphoria, abusers turn to alternative routes of administration. Moreover, as most opioids are fabricated as modified release formulations, abusers often try to achieve an accelerated onset of action and intensified psychoactivity by attempting to manipulate the intact formulation. As such, it is recommended to test abuse-deterrent formulations for abusive potential through different routes of drug administration (Pergolizzi et al., 2018).

The printlets' abuse potential via the intravenous route was assessed by simulating an abusers' attempt to prepare drug solution suitable for intravenous injection in 5 mL of boiling water. Results have shown that only 21.9% ± 6.9 and 20.0% ± 4.2 of the drug can be abused from HPC-SL and HPC-L printlets, respectively. These results suggest that HPC-SL and HPC-L printlets are already moderately resistant against abuse via the intravenous route.

The printlets' abuse potential via the intravenous route was further assessed by dissolving them in 100mL of different solvents for drug extraction. When extraction is conducted in water, results have shown that 49.3% and 52.5% of the drug can be directly

extracted after 1 hour from the HPC-SL and HPC-L printlets, respectively. This can be explained by the formation of a viscous gel when HPC is in contact with water, causing it to resist passage through a hypodermic needle. This was followed by attempts to extract the drug using different solvent, under prolonged conditions. A summary of the results is shown in Table 3.

**Table 3**. Summary of the drug percentage that could be extracted from the HPC-SL and HPC-L formulations using 100mL of different solvents at different time intervals.

| Formulation | Time | Solvent | | | |
|---|---|---|---|---|---|
| | | **Water** (%Mean ±SD) | **Ethanol** (%Mean ±SD) | **0.1 M HCl** (%Mean ±SD) | **0.1 M NaOH** (%Mean ±SD) |
| HPC-SL | **5 min** | 12.0 ± 1.4 | 5.6 ± 2.3 | 23.3 ± 11.2 | 3.7 ± 0.8 |
| | **15 min** | 19.6 ± 2.3 | 12.7 ± 3.5 | 40.2 ± 16.8 | 6.3 ± 0.7 |
| | **30 min** | 32.5 ± 9.0 | 23.1 ± 10.7 | 55.5 ± 23.5 | 9.4 ± 0.7 |
| | **60 min** | 49.3 ± 12.3 | 34.0 ± 12.8 | 83.7 ± 17.0 | 22.9 ± 15.2 |
| | **24 h** | 93.6 ± 2.1 | 98.0 ± 2.5 | 108.2 ± 13.3 | 102.4 ± 1.8 |
| HPC-L | **5 min** | 15.7 ± 6.5 | 6.6 ± 0.6 | 14.1 ± 2.4 | 5.8 ± 1.2 |
| | **15 min** | 28.4 ± 14.1 | 12.1 ± 2.4 | 26.4 ± 8.8 | 8.6 ± 1.8 |
| | **30 min** | 35.3 ± 14.3 | 18.0 ± 3.8 | 43.5 ± 24.4 | 11.2 ± 1.7 |
| | **60 min** | 52.5 ± 20.8 | 30.3 ± 8.8 | 68.5 ± 32.6 | 14.9 ± 1.8 |
| | **24 h** | 94.4 ± 1.0 | 97.8 ± 11.6 | 109.7 ± 12.0 | 102.0 ± 2.6 |

The printlets abusiveness through the nasal route was assessed following their milling for 2 min and the cumulative % undersize (500 µm) was calculated. Results have shown that 92.0% and 93.7%, of the drug could be abused through the nasal route from HPC-SL and HPC-L printlets, respectively due to the particle size distribution (Table 4). However, due to the gelling properties of HPC, it has the tendency to induce nasal distress, acting an aversion agent. Thus, abuse through the nasal route may be deterred. An aversion agent refers to an agent that results in an unpleasant feeling or unintended effect when the drug has been tampered with and/or used through an unintended route of administration (Carinci, 2020; Loeser and Rodriguez, 2019). Examples of such include substances that cause nausea, vomiting, mucosal irritation, laxative effect, cutaneous vasodilation or those having severe bitter tastes or unpleasant smells (Hale et al., 2016; Mastropietro and Omidian, 2015a).

**Table 4.** The particle size distribution of the HPC-SL and HPC-L printlets following their milling for 2 min.

| Formulation | <250µm (%Mean ±SD) | 250-355µm (%Mean ±SD) | 355-500µm (%Mean ±SD) | 500-710µm (%Mean ±SD) | 710µm-1mm (%Mean ±SD) | >1mm (%Mean ±SD) |
|---|---|---|---|---|---|---|
| HPC-SL | 60.2 ± 3.0 | 18.5 ± 1.0 | 13.3 ± 1.5 | 4.7 ± 1.8 | 1.9 ± 0.6 | 1.4 ± 0.9 |
| HPC-L | 61.2 ± 1.2 | 19.4 ± 1.5 | 13.1 ± 0.2 | 3.9 ± 0.6 | 1.4 ± 0.4 | 1.1 ± 0.9 |

Due to the strong correlation between alcoholism and drug abuse, it is advantageous to formulate abuse-deterred printlets with alcohol-resistant properties. The printlets' alcohol-resistant properties were evaluated using a dynamic, in vitro model, which simulates fasted conditions of the GI tract (Figure 6). For the acid phase, the studies were conducted in two different media; (a) 750 mL 0.1 M HCl and (b) 750 mL 0.1 M HCl with an ethanol concentration of 40% (v/v). The results from the alcoholic and non-alcoholic media were similar and showed that the printlets even had slightly slower drug release rate in the medium containing ethanol. The $f_2$ similarity value has shown that both the HPC-SL and HPC-L printlets exhibited similar drug release profiles in the presence and absence of alcohol, wherein $f_2$ similarity values of 71 and 63 were obtained respectively ($f_2$ values between 50-100 indicate parity). As such, it was concluded that both formulations display strong alcohol-resistant properties.

Insert Figure 6.

**Figure 6**. Drug dissolution profiles of the HPC-SL and HPC-L printlets, in the presence and absence of alcohol. The red line shows the pH values of the medium.

In an attempt to enhance their abuse-deterrence whilst retaining their strong alcohol-resistance, the printlets were re-formulated to include PEO. PEO is a non-ionic thermoplastic polymer that has been previously used to deter abuse by forming a viscous gel (Meruva and Donovan, 2019; Tocce et al., 2019; Zhang and McGinity, 1999). The PEO formulations showed good printability with high consistency in weight and physical dimensions (Table 5 and Figure 7). X-ray micro-CT images indicated that both, the HPC-SL/PEO and HPC-L/PEO printlets, had more dense regions when compared to the HPC-SL and HPC-L printlets (Figure 8).

**Table 5.** The average weight and dimensions of HPC-SL/PEO and HPC-L/PEO printlets

| Formulation | Weight (mg) (Mean ±SD) | Width (mm) (Mean ±SD) | Diameter (mm) (Mean ±SD) |
|---|---|---|---|
| HPC-SL/PEO | 298.1 ± 1.7 | 3.4 ± 0.02 | 10.1 ± 0.07 |
| HPC-L/PEO | 290.4 ± 3.2 | 3.4 ± 0.05 | 10.1 ± 0.2 |

Insert Figure 7.

**Figure 7**. Images (from left to right) of the HPC-SL/PEO and HPC-L/PEO printlets (scale is in cm).

X-ray micro-CT images indicated that both, the HPC-SL/PEO and HPC-L/PEO printlets, had ~~more~~less dense regions when compared to the HPC-SL and HPC-L printlets (Figure 8).

Insert Figure 8.

**Figure 8.** X-ray micro-CT images of the (A) HPC-SL/PEO and (B) HPC-L/PEO printlets.

DSC data show that PEO melts at ~63°C (Figure 9). The thermograms of the printlets also show sharp melting peaks at ~63°C, indicating that PEO remains in its crystalline state after printing. Unlike the HPC-SL and HPC-L printlets, the HPC-SL/PEO and HPC-L/PEO printlets do not show melting endotherms at ~163°C, which could be due to the lower mannitol content. Validating the results obtained by DSC, the X-ray diffractograms of the HPC-SL/PEO and HPC-L/PEO printlets do not show any peaks, indicating that the drug/excipients are in the amorphous state (Figure 10).

Insert Figure 9.

**Figure 9**. DSC thermograms of the HPC-SL/PEO and HPC-L/PEO formulations, drug, excipients and powder mixtures prior to printing.

Insert Figure 10.

**Figure 10**. X-ray diffractograms of the HPC-SL/PEO and HPC-L/PEO formulations, drug, excipients and powder mixtures prior to printing.

With regards to the printlets' abuse potential via the intravenous route, syringeability test results have shown that only 13.4% ± 2.8 and 14.7% ± 1.3 of the drug can be abused from the HPC-SL/PEO and HPC-L/PEO printlets, respectively. These results further support the abuse-deterrent properties of the printlets, as only a fraction of tramadol can be extracted through conventional methods employed by drug abusers. The printlets' abuse potential via the intravenous route was also assessed by dissolving them in different solvents under prolonged conditions, as previously described. A summary of the results is shown in Table 6. The lower percentage of drug extracted in printlets containing PEO is likely due to PEO's inherent modified release properties. In particular, its high solubility in water due to 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 (Externbrink et al., 2019). It was noted that a higher percentage of drug can be extracted when 0.1M HCl is used, due to acid hydrolysis of HPC. Nevertheless, the relatively large volume of solvent used in this extraction cannot be feasibly injected into an abuser, supporting the abuse-deterrent properties of the printlets. Overall, the combination of HPC and PEO has shown stronger abuse-deterrent properties compared to the use of HPC alone.

**Table 6**. Summary of the drug percentage that could be extracted from the HPC-SL/PEO and HPC-L/PEO formulations using 100mL of different solvents at different time intervals.

| **Formulation** | **Time** | **Solvent** | | | |
|---|---|---|---|---|---|
| | | **Water (%Mean ±SD)** | **Ethanol (%Mean ±SD)** | **0.1 M HCl (%Mean ±SD)** | **0.1 M NaOH (%Mean ±SD)** |
| HPC-SL/PEO | **5 min** | 5.0 ± 2.2 | 4.0 ± 1.2 | 6.3 ± 1.8 | 3.6 ± 0.2 |
| | **15 min** | 9.7 ± 4.2 | 8.7 ± 1.8 | 14.3 ± 3.6 | 8.6 ± 2.4 |

| | | | | | |
|---|---|---|---|---|---|
| | **30 min** | 13.1 ± 3.9 | 13.3 ± 3.0 | 22.8 ± 6.3 | 14.3 ± 5.4 |
| | **60 min** | 19.2 ± 3.7 | 19.6 ± 3.4 | 36.9 ± 11.8 | 20.5 ± 6.1 |
| | **24 h** | 94.7 ± 0.9 | 98.6 ± 31.7 | 99.7 ± 1.5 | 101.8 ± 0.6 |
| HPC-L/PEO | **5 min** | 6.8 ± 4.4 | 4.3 ± 0.8 | 6.3 ± 1.4 | 1.3 ± 0.2 |
| | **15 min** | 10.0 ± 3.8 | 9.0 ± 1.1 | 12.3 ± 4.1 | 3.8 ± 0.3 |
| | **30 min** | 14.6 ± 5.6 | 13.9 ± 2.7 | 19.9 ± 7.1 | 6.7 ± 0.5 |
| | **60 min** | 22.4 ± 6.9 | 20.7 ± 4.5 | 31.2 ± 11.9 | 12.1 ± 1.7 |
| | **24 h** | 98.1 ± 31.1 | 93.2 ± 10.8 | 101.0 ± 2.7 | 101.8 ± 2.9 |

The printlets abusiveness through the nasal route was assessed and results have shown that 68.5% and 59.5% of the printlets particles are small enough to pass through the nasal airway from HPC-SL/PEO and HPC-L/PEO printlets, respectively (Table 7). This shows that the addition of PEO significantly improves the mechanical properties of the printlets, making them more resistant to physical tampering in comparison to the HPC formulations. Moreover, as PEO is a gelling agent, it has the tendency to gel upon its contact with the mucous membrane in the nasal airway, thus resulting in nasal distress and discouraging nasal insufflation (Maincent and Zhang, 2016; Mastropietro and Omidian, 2015b). As such, due to the high content of PEO, abuse through the nasal route will be averted. Application of heat, such as during the printing process, also changes the physical state of PEO, resulting in high mechanical strength, thereby making its use favourable for abuse-deterrence~~. Thus, it can be concluded that printlets containing PEO are more resistant to abuse through the nasal route when compared to heat-treated PEO tablets previously reported by Muppalaneni et al.~~ (Muppalaneni et al., 2016).

**Table 7.** ~~The percentage of printlet particles obtained from the nasal inhalation tests~~The particle size distribution of t SL/PEO and HPC-L/PEO printlets following their milling for 2 min.

| Formulation | **<250µm (%Mean ±SD)** | **250-355µm (%Mean ±SD)** | **355-500µm (%Mean ±SD)** | **500-710µm (%Mean ±SD)** | **710µm-1mm (%Mean ±SD)** | **>1 (%Mea** |
|---|---|---|---|---|---|---|
| **HPC-SL/PEO** | 25.8 ± 3.8 | 16.8 ± 3.4 | 25.0 ± 3.1 | 15.7 ± 3.3 | 12.7 ± 4.4 | 3.0 |
| **HPC-L/PEO** | 22.2 ± 3.0 | 13.6 ± 1.2 | 23.7 ± 2.6 | 19.2 ± 2.9 | 15.8± 1.4 | 5.4 |

In vitro dissolution studies show that despite the addition of the PEO, the formulations still retained their alcohol-resistant properties, wherein $f_2$ similarity values of 87 and 84 were obtained from the HPC-SL/PEO and HPC-L/PEO printlets, respectively (Figure 11). In fact, due to PEO's insolubility in alcohol, the formulations containing PEO had higher $f_2$ similarity values when compared to the formulations without PEO. Moreover, due to the gelling properties of PEO, the formulations containing PEO had slower drug release properties when compared to the formulations without PEO.

Insert Figure 11.

**Figure 11**. Drug dissolution profiles of the HPC-SL/PEO and HPC-L/PEO printlets, in the presence and absence of alcohol. The red line shows the pH values of the medium.

In principal, the use of opioid printlets provides the advantage of ~~efficient~~effective treatment whilst preventing harms associated with their abuse and/or misuse. Although previous studies have shown that abuse-deterrent formulations made using injection moulding are successful at deterring drug abuse (Smith et al., 2016), this production method is limited to large-scale production due to the high cost of producing small batches (Awad et al., 2018b; Hopkinson and Dicknes, 2003). Due to its ability to produce printlets in a short time frame, 3DP is an attractive concept for the on-demand fabrication of medications. As such, it could provide the benefit of limiting the amount of drug available for abuse, while avoiding the use of bulky machineries or complex processes. Moreover, due to the ease of coupling 3DP with anti-counterfeiting methods, the transparency and tracking of opioids usage across the supply chain could be enhanced and their illicit abuse could be restricted (Trenfield et al., 2019b). This could even be extended to cover specific patient subgroups, such as those with visual impairment, enabling the identification of medications even when taken out of their original packaging (Awad; et al., 2020).

Recently, Nukala et al. successfully fabricated abuse-deterrent immediate release egg-shaped tablets using FDM (Nukala et al., 2019). Nonetheless, in comparison to immediate-release formulations, modified-release tablets contain higher doses of the drug and consequently pose a greater safety risk when abused. Whilst many consider abusing prescription opioids to be less harmful than illegal counterparts (Simon et al., 2015), in some cases prescription opioids may be easier to procure. Therefore, controlling the number of prescribed opioids alone is insufficient to quell the drug abuse

epidemic. Instead, small-scale production of opioid formulations personalised to individual patient's needs might provide higher control over opioid use.

## 4. Conclusions

Direct powder extrusion 3DP was successfully utilised as a novel technique for the fabrication of abuse-deterrent and alcohol-resistant formulations with modified drug release properties. The use of direct powder extrusion 3DP with HPC polymers resulted in the fabrication of printlets with alcohol-resistant properties and moderate abuse-deterrent characteristics. The further incorporation of PEO strengthened the printlets abuse-deterrence whilst maintaining their alcohol-resistant properties. Moreover, as 3DP strives to offer more accurate and personalised therapy, the on-demand dispensing of opioid formulations could limit the amount of drug available for abuse.

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