Research paper

Laser-cutting: A Novel Alternative Approach for Point-of-Care Manufacturing of Drug in Polymer Matrix

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**Abstract**

A novel laser cutting subtractive manufacturing method to produce structures with immediate and extended drug release is presented. The first report on applying fusion laser cutting is presented to produce bespoke frusemide dosage forms based on pharmaceutical-grade polymeric carriers. Tablets of the cylindric structure of different sizes were produced by controlling the two-dimensional design of circles of the corresponding diameter. Immediate and extended drug release patterns were achieved by modifying the composition of the polymeric matrix. Thermal analysis and XRD indicated that furosemide was presented in an amorphous form. The tablets produced by the novel approach demonstrated no significant drug degradation (<2%) nor the formation of impurities were identified. Multi-linear regression was used to quantify the influences of laser-cutting process parameters (laser energy levels, scan speed, and the number of laser applications) on the depth of the laser cut. The utility of this approach was exemplified by manufacturing tablets of accurate doses of furosemide. Unlike additive or formative manufacturing, the reported approach of subtractive manufacturing avoids the modification of the structure of the matrix e.g., drug physical form or matrix density of the tablet during the production process. Hence, fusion laser cutting is less likely to modify critical quality attributes (CQAs) such as release patterns or drug contents. In a point-of-care manufacturing scenario, laser cutting offers a significant advantage of simplifying quality control (QC) and a real-time release of laser-cut products such as solid dosage forms and implants.

*Keywords***:**CNC; Early phase clinical trials; Subtractive manufacturing; Patient-specific; Personalized; Small batch.

1. **Introduction**

Creating personalised medicines, medical devices, and implants necessitates precise, quick, and adaptable qualities and the ability to manufacture customised dosage forms at the point of care (PoC). In the past decade, additive manufacturing technologies such as semi-solid extrusion 3D printing [9], and fused deposition modelling 3D printing [10–12]. Powder bed fusion [13] and inkjet printing [14] were heavily researched. These technologies permit the creation of patient-specific medical devices and dosage forms in small batches at or near medical facilities, such as hospital pharmacies [15]. Nevertheless, 3D printing technologies have several limitations such as low output, thermal post-treatment steps, drug degradation, and long manufacture time-per-tablets [16] In addition, both formative (powder compression or injection moulding) and additive (3D printing) manufacturing induce significant changes to the starting material such matrix density and the formation of amorphous form of the drug [17,18].

Laser-cutting technology is a form of subtractive manufacturing that is widely used in the production of biomedical devices built from biodegradable polymers [19,20], with examples including magnesium stents, and intraocular lenses [21]. It offers several advantages such as the ability to create small and precise cuts and to minimise dust and waste formation [22]. In the process, laser power, cutting speed, nozzle diameter, and focus point position can influence the kerf width and the edge quality of the cut. The process has been used to curve polymethacrylate [23] and polycarbonate [24], and to process 3D printed structures [25]. Yet, there have been no previous reports on applying laser cutting to produce dosage forms or drug-eluting implants.

Children undertaking cardiac surgery or suffering from heart failure are prescribed diuretics such as furosemide [1]. The standard furosemide dose for children with normal renal function is 1 to 2 mg/kg. Due to the extended half-life of the medicine in the infant body, accumulation may occur and a recognised adverse effect is sensorineural hearing loss [2]. Moreover, an overdose of furosemide in children may increase other risks including hypovolemia, gallstones, and hypercalciuria [2]. Therefore, providing children with individualised precise dosing is highly beneficial. Solid dosage forms such as oral tablets and implants are mainly manufactured using a formative manufacturing method such as powder compression in a metal die or injection moulding [3]. These methods for manufacturing solid dosage forms are well-established and economical [4]. However, the process is geared toward mass production and the process is too rigid and expensive for manufacturing bespoke doses [5].

In this work, we evaluate for the first time using laser cutting as a suitable method for the on-demand manufacturing of oral solid dosage forms, and its potential to overcome some challenges associated with 3D printing and powder compression technologies. To achieve this, specially designed prefabricated drug-polymer castings were used as a substrate, to be cut *via* the laser cutting process. Furosemide, a molecule liable to light and temperature degradation, was used as a model drug to investigate the impact of laser on drug degradation. To demonstrate the suitability of the produced tablet for small-batch manufacturing, tablets were laser cut to provide precise dose adjustment solutions to the clinical needs of individual patients. Finally, the impact of the laser-cutting process on drug integrity, the formation of impurities and the potential of laser cutting in comparison with other manufacturing methods have been evaluated.

**2. Materials and methods**

*2.1 Materials*

Furosemide (>97%), and polyethene glycol 400 (PEG 400) and 6,000 (PEG 6,000) were purchased from Alfa Assar (Massachusetts, USA). Kolliphor® P188 Geismar was a donation from BASF (Ludwigshafen, Germany). Glyceryl monostearate (GMS) (Imitators K900) was donated by Oleo GmbH (Hamburg Germany). Cindering® Gold sheen, Blue Shimmer and Silver Sheen were provided by Merck (Darmstadt, Germany). All other materials were of a reagent grade.

*2.2* *Design of the 3D printing template for drug-polymer casts*

The supporting templates (83 x 83 x 8mm) with 25 (8 x 8 x 5mm) cross-shaped support pistons were specially designed to accommodate the casting (77 x 77 x 3mm) template (Supplementary data, Fig. S1). All templates were manufactured using stereolithography 3D printer Form2 (Formlabs, Massachusetts, USA) and a flexible photo-polymeric methacrylate resin (Flexible80A).

*2.3 Preparation of drug-polymer casts*

To facilitate the absorption of laser light by the substrate, different light absorbents, including sodium chloride, Blue Shimmer, Silver Sheen, and Gold Sheen, were added to PEG 6000 at 5% (w/w). The concentration of the selected light absorbent was optimised using lower concentrations (1%, 2% or 3% w/w), and 1% w/w of Gold Sheen was used as the optimal light absorbent concentration. Poloxamer K188 and GMS were added as a hydrophilic binder and lubricant to enhance matrix solidification at 3% [26], respectively. Table 1 provides a summary of the composition of 6 drug-polymer casts to provide immediate and extended-release formulation. A drug-polymer cast (60 g) with dimensions (length x width x height = 77 x 77 x 3 mm) was prepared as detailed in Fig. 1. Firstly, glass plates and 3D printed templates were placed in an oven at 40°C to prevent the molten material from rapid cooling. Then, PEG 6000, GMS, and Poloxamer K188 were co-melted and blended at 75°C using a magnetic stirring hot plate. Furosemide powder was added to the blend under continuous stirring at 75°C and stirred for an additional 5 min. Gold Sheen was then added under consistent stirring to the molten blend prior to casting. Finally, the mixture was slowly poured into the pre-warmed 3D printed casting template.

**Table 1.** The composition of six different dosage forms.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Formulation** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** |
| **Drug** | 5 | 5 | 5 | 5 | 5 | 5 |
| **PEG400** | 0 | 20 | 20 | 20 | 20 | 20 |
| **PEG6000** | 84 | 74 | 71 | 70 | 65 | 67 |
| **K188** | 7 | 0 | 0 | 0 | 0 | 0 |
| **Gold Sheen** | 1 | 1 | 1 | 1 | 1 | 1 |
| **GMS** | 3 | 0 | 3 | 4 | 8 | 10 |

A picture containing diagram

Description automatically generated**Fig. 1.** (**a**) The setup of the laser cutting station: a specially made drug-polymer cast (workpiece) is placed in 3D printed template holder. The setup is enclosed in a confined chamber equipped with high-performance filtration unit. (**b1, b2**) Top and (**c1, c2**) side views of 3D printed template to support the polymerics casts during laser cutting process, each tablet will be supported by a cross-shaped pistol that allows the discharge of the molten casts. Yellow circles show the position of the tablets (**b2, c2**). (**d1-d3**) Steps of laser cutting process of furosemide loaded cast: (**d1**) setting origin (starting point); (**d2**) tablets cutting; (**d3**) the end the of the cutting process. (**e1**) Rendered image of blank support template and following laser cutting. Batch of laser-cut the ablets placed in the supporting template: **e2**) before and **e3**) after removal of out-cut frame.

*2.4* *Optimisation of the laser cutting process parameters*

The prepared drug-polymer casts were directly placed in an Emblazers 2 benchtop laser cutter (Darkly Labs, Melbourne, Australia). To optimise the process of laser cutting, four parameters were assessed: speed, power, counts of laser cutting, as well as margin distance between the tablets. Firstly, the laser power was set at 2.25 Watts for this study to find the ideal laser speed. The cutting speed was adjusted to 10, 50, 100, 200, 500, or 1000 mm/min for one cutting turn. For optimal laser power, the laser power was adjusted to 1.5, 1.75, 2, 2.25, 2.5, 2.75, or 3 Watts, where cutting counts and speed were set at 25 rounds and 1000 mm/min, respectively. Thirdly, the number of repeated laser path were optimised by adjusting the number of cutting counts to 1, 5, 10, 20, or 50 rounds under constant laser power of 2.25 Watts and a cutting speed of 1000 mm/min. Finally, to determine the optimal margin between the two tablets, the laser power and cutting speed were fixed at 2.25 Watts and 1000 mm/min, while the distance between the two tablets was adjusted to 0, 1, 2, 3, or 4 mm.

*2.5 Tablet design and laser cutting*

The Lightburn software (Darkly Labs, Melbourne, Australia) enabled the control of the weight of the tablets by changing the diameter of the laser cutting circle and the production of four tablet batches. The target weight of the tablets could be determined based on the percentage of furosemide loading of the casting, the volume of the cut cylinder, and the target dose of the furosemide. Emblaser 2 benchtop laser cutter (Darkly Labs, Melbourne, Australia) was loaded with furosemide casts, and tablets were cut at 2 Watts, 1000 mm/min and 50 rounds (Fig. 1b1-b3). A batch of 25 tablets was produced. The diameter of the laser cutting circle was set at 7.6, 8.8, 10, or 11.5 mm to achieve tablets of the approximate diameter of 5, 7.5, 10, and 15 mg, respectively. The engravement on the surface of the tablets was achieved by applying the following settings: 5 rounds, laser energy of 2.25 Watts, and laser speed of 1000 mm/min.

*2.6 Thermogravimetric analysis (TGA)*

The thermal degradation of the raw materials, physical mixes, and laser-cut tablets were analysed by scanning samples in platinum pans one run per sample with a TGA Q500 (TA Instruments, Elstree, Hertfordshire, UK). Samples were heated from 20 to 275°C at a rate of 10°C/min with a nitrogen purge of 10:90 mL/min for the furnace: sample, respectively. TA Universal analysis software (v 4.5A, TA Instruments, Elstree, UK) was used to analyse the data.

*2.7 Differential scanning calorimetry (DSC)*

Thermal measurement was conducted using a differential scanning calorimeter DSC Q2920 (TA Instruments, Elstree, UK). All samples and raw materials were separately sealed between an aluminium hermetic pan and lid and heated from 10 to 255 °C at 10 °C/min. All measurements were conducted with nitrogen as the purge gas with a flow rate of 60 mL/min. The analysis was performed by TA Universal analysis software (v 4.5A, TA Instruments, Elstree, UK).

*2.8 X-Ray Diffractometry (XRD)*

The physical form of the drug and excipients within the laser-cut tablets was assessed using a powder X-ray diffractometer, Miniflex 600 (Rigaku Corporation, Japan). Samples were scanned from 2Theta = 3° to 35° using a 1.25 sec time count and 0.01° step width. The divergence slit was 1 mm, and the scatter slit was 0.6 mm. The filament emission was 10 mA with a scan type coupled with a theta/theta scintillation counter over 60 min. The wavelength was 0.154 nm using Cu2+ source and a voltage of 30 kV.

*2.9* *Drug content of laser-cut tablets*

The contents of furosemide were quantified with an Agilent 1260 series UV-HPLC (Agilent Technologies, Germany) equipped with Kinetex Biphenyl column (50 × 4.6 mm, 2.6 μm particle size) at a temperature of 25°C. The used mobile phase was a 50:50 (v/v) mixture of ammonium acetate buffer (50 mM) and acetonitrile, and the injection volume was 20 μL. The flow rate is maintained at 1mL/min with a running time of 6 min and a detector wavelength of 254 nm. To determine the level of furosemide impurities following casting and laser cutting processes, an additional HPLC method using Inertsil™ ODS-2 column (250 × 4.6 mm, 5μm particle size, GL Sciences, Japan) was applied. Potassium dihydrogen phosphate and cetrimide buffer BP: propanol mixture 7:3 (v/v) was used as a mobile phase. The following settings were used: an injection volume of 20 μL, a flow rate of 1 mL/min, a temperature of 25°C, a running time of 35 min, and a detector wavelength of 238 nm.

*2.10* *Characterization of the laser-cut tablets*

a. Tablet dimensions and weight

The diameter and thickness of laser-cut tablets (n=20) were measured using a digital calliper (eSynic, China) with a resolution of 0.01 mm. The tablet thickness measurements were performed by taking the average values of the thickness at a circle inscribes on the four corners of a square and the centre of the tablets. The weight uniformity of laser-cut tablets was assessed by weighing all tablets in the batch (n = 25 tablets).

b. Mechanical properties of laser-cut tablets

The mechanical properties of the laser-cutting tablets (n = 6) were assessed by measuring tablet hardness using C50 Tablet Hardness & Compression Testing Machine (Engineering Systems, Nottingham, UK). The friability of laser-cut tablets was assessed by accurately weighing (n = 10) and rotating at 25 rpm for 4 min using Friabilator FT2 (Sotax AG, Switzerland).

c. Surface morphology

The surface morphology of the laser-cut tablets was characterised by Phenom Pro Desktop scanning electron microscope (ThermoFisher Scientific, Paisley, UK) at 10kV. Tablets were laser cut and attached to a sample holder with double-sided carbon adhesive tape to obtain images of the cross-section and outer surface. The images were generated using SW software (version 4.6.4).

*2.11 In vitro disintegration and dissolution*

To evaluate the disintegration time of laser-cut tablets, a pharmacopoeia disintegration apparatus (Copley ZT2, Euweka Apparatus GMBH, Heusenstamm, Germany) was used.

Using the USP I dissolution instrument (708-DS dissolution apparatus, Agilent, USA) equipped with inline a UV/VIS spectrophotometer (Cary 60 UV-Vis, Agilent, USA), the *in vitro* furosemide release from laser-cut tablets was determined. Each experiment was conducted in triplicates at 37 ± 0.5 °C and 100 rpm with a rotating basket. The dissolution medium was 900 mL of 0.1M HCl (pH 1.2) for 2 hours at 37 ± 0.5°C. The samples were measured at 5 min intervals at a 274 nm wavelength and a UV path length of 10 mm. For extended release tablets (F4-F6), USP pH-change method was applied 2 hours in pH 1.2 (750 mL of 0.1 M HCl) followed by 4 hours pH 6.8 ( the addition of 250 mL of 0.215M tri-basic sodium phosphate solution to the medium of the gastric phase) and 6 hours pH 7.4.

*2.13 Statistical analysis*

Standard multiple linear regression using SPSS Software Version 22.0.0.2 (SPSS Inc., Chicago, IL) was conducted to predict the kerf width and the cut depth from laser energy, laser travel speed, and counts. The assumptions of linearity, multicollinearity and homoscedasticity were assessed and no violation for these were found. One-way ANOVA was employed using SPSS Software (22.0.0.2) to analyse the results. Differences in results less than the probability level (*p* < 0.05) were considered significant.

# **3. Results and discussion**

* 1. *Optimisation of polymeric cast for laser-cutting*

Laser cutting is theorised to be achieved through fusion, vaporisation, or chemical degradation [27,28]. In this work, the cutting of material was achieved through the fusion of thermoplastic polymer by elevating the local temperature at the cutting path above the melting point of the cast (>75°C). The addition of a light absorber permits the laser to permeate through the polymeric matrix and melt the polymer [29]. Initially, the same concentration of light absorber (sodium chloride, Blue Shimmer, Silver Sheen, or Gold Sheen) was evaluated in drug-polymer casting. The laser-cut section of the polymer casting that contained the Gold Sheen is deeper under the same cutting setting (Fig. 2).

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Description automatically generatedFig. 2** The laser cutting effect on different drug-free casts: **a1**) polymer casting without an absorbent; **a2**) with 5% sodium chloride; **a3**) 5% Blue Shimmer; **a4**) 5% Silver Sheen; **a5**) 5%, **a6**) 1%; **a7**) 2%, and **a8**) 3% Gold Sheen. **b**) Light microscope image of a laser cut of drug-free cast with 2% gold sheen showing kerf, melting and top widths. SEM images showing the impact of the speed of laser on cutting drug-polymer casts at: **c1**) 100; **c2**) 500; **c3**) 1000; **c4**) 1500; and **c5**) 2000mm/min. The impact of **d**) laser speed; **e**) laser cutting counts and **f**) laser power on kerf, melting and top widths, and depth.

Adding Gold Sheen was previously reported to facilitate SLS 3D printing [30]. In this work, increasing the concentration of Gold Sheen resulted in a deeper cut to the substrate (Fig. 3). Here, 1% Gold Sheen was selected due to its ability to produce a reproducible melting upon the projection of the laser light. The application of laser light has an impact on the surface of the cast substrate. Fig. S1 illustrates the cutting of the edges of the two tablets when the distance between their edges is 0, 1, 2, or 3 mm. Applying a margin of 0 or 1 mm led to the accumulation of molten matter at the edge of the formed tablets. However, increasing the margin to >2 mm enabled the completion of the cutting process without altering the tablet surfaces.

In many industrial settings, laser cutting is conducted through a predetermined and local melting process, and then the molten material is instantly removed by spraying gas on the substrate [31]. However, the current design did not include a spraying gas mechanism to remove the structure. Therefore, when the laser is utilised repeatedly cut the substrate straight onto the template the molten materials are retained at the bottom of the cut cleavage. Without the removal or the molten material, the cut would reseal following the cooling of the substrate (data not shown). The re-solidified molten material impedes the complete cutting of the substrate and prevents the separation of the removed part. To mitigate this risk, a specially designed template for laser cutting that supports the weight of the laser-cut tablets while allowing the drainage of the molten mater on the laser path (Fig. 1 e1-e3).

The evaluation of the interplay of cutting speed, the number of cutting circles, and the applied laser energy is essential to determine the ideal parameters [32]. Fig. 3 illustrated the influences of laser cutting speed, laser energy, and the number of laser cutting rounds on cutting depth and width using SEM imaging. To quantify the different influences, multi-linear regression was conducted, and yielded the following equation to predict the depth of the cut:

Depth = -1535 - 0.376 v + 765 p -36.3 n Equation (1)

where v is laser speed (mm/sec), p is laser energy (Watts) and n is the number of laser light application (rounds).

The depth of the cutting was increased by laser energy and the number of application and was reduced by the speed of laser. The multiple regression standardized coefficients revealed that the number of light applications (β = 1.048, *p* <0.01) was the most prominent factor in depth laser speed (standardized coefficient β = − 0.376, *p* < 0.001), while laser energy (β = 0.406, *p* < 0.01) and had smaller influences. The equation was able to describe 89% of the total variance (F (3, 47) = 138.2, *p* < 0.001).

* 1. *Thermal analysis*

TGA thermographs were performed to assess the stability of the raw materials at the casting temperature (75 °C). Fig. 4a showed a 0.48 % weight loss of the laser cut tablet up to 110 °C, which could be attributed due to moisture evaporation. In addition, GMS can be liquefied at a relatively low casting temperature (75°C) since the melting point is 58-65°C [26]. This facilitates rapid solidification of the casting at room temperature. All raw materials and laser-cut tablets demonstrated stability at 75°C showing a constant mass with no less of volatile products, indicating that the manufacture of drug-polymer cast furosemide at this temperature would not result in significant degradation of the drug.

**Diagram

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**Fig. 3 a)** TGA thermal degradation profiles, **b)** DSC thermographs, and **c)** XRD intensity patterns of furosemide, other ingredients, and laser-cut tablets.

DSC thermogram of furosemide exhibited a sharp endothermic peak at 220°C, which corresponds to furosemide melting points and demonstrates its crystalline nature [33]. The characteristic furosemide peak was not observed in the thermogram of the laser-cut tablet, confirming that furosemide was present in the amorphous state within the polymer substrate [34]. It is also possible that due to the melting of PEG 6000 during the thermal scan, the molten polymer has dissolved in drug crystals before they are able to reach their melting point [35]. DSC thermographs of the laser-cut tablets also showed an endotherm event near 62°C (Fig. 4b), which is believed to be the suppressed melting of PEG 6000, indicating the presence of a portion of PEG and GMS in a crystalline form. Therefore, the laser beam that can introduce a localised increase in temperature >70 °C was deemed necessary to liquidate GMS and PEG crystals and allow efficacious laser-cutting of the formulation.

The XRD pattern of the laser-cut tablets revealed characteristic furosemide diffraction peaks at 2(θ) =5.94°, 11.23° and 24.72° (Fig.4c). At 2(θ) = 19.57°, a subtle peak corresponding to GMS, can be observed (Fig. 4c). This indicated the presence of GMS crystals in the polymeric matrix. The absence of an intensity peak at 2(θ) =5.94° confirms the findings of the thermal analysis that no crystalline form of furosemide could be detected in the laser-cut tablets.

* 1. *Impurity analysis using HPLC*

Furosemide is labile to thermal [33] and light degradation [36]. The relative laser energy input to laser cut by fusion thermoplastic polymeric substrate might have an impact on the integrity of model molecule. A summary of HPLC analysis of furosemide impurities is presented in Table 1 and Supplementary Data Fig. S2. Furosemide concentration exceeds 99% in both a non-laser-cut corner of the drug-polymer casting as well as the laser-cut tablets. It has been demonstrated that neither the substrate manufacturing process nor the laser cutting process results in significant degradation of furosemide (*p*>0.05).

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**Fig. 4** Chromatograms of **a**) pure furosemide, **b**) laser cut tablet, and **c**) percentage of purity of furosemide, drug-polymer casts, and laser-cut tablets.

* 1. *Compendial tests of laser-cut tablets*

Figs. 5a-b shows that laser cutting can be used to engrave a logo. This feature can be used to specify the patient's details on a personalised dosage form. The laser-cut tablets have smooth surfaces with a glossy look similar to GMS-based coatings. To demonstrate the potential of the method to produce personalised tablets, four batches of laser-cut tablets (n =25) of different diameters were manufactured. Table 2 shows the dimensions, and compendial characteristics of laser-cut tablets with furosemide doses of 5, 7.5, 10, or 15 mg. While the thickness of each tablet was kept at 3 mm, the furosemide dose was controlled by digitally altering the diameter of the design (Table 2). The relationship between the tablet weight and volume was confirmed to be directly proportional (Fig. 5d). The deviation from the linear relationship could be attributed to variations in the thickness of the cast. While the surface cut for each tablet is identical, a slight variation in the thickness of the cast would result in deviation from the theoretical weight.

The content uniformity test showed that all batches of tablets met British Pharmacopoeia (BP) standards. These laser-cut tablets have a pharmaceutically acceptable degree of fragility (<1%), hence demonstrating the durability of laser-cut tablets to withstand the production, shipping, and administration processes [37]. The process also demonstrated a high degree of repeatability, as evidenced by minimal variations in tablet weight and drug content. Therefore, this highlights the potential of this laser-cutting approach as an alternative small-batch production approach.

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**Fig. 5** Laser cutting tablets with target doses: **a**) Images of the tablet containing 5, 7.5, 10, or 15 of furosemide (F3); **b**) the tablet created using laser cutting technology with engraved university logo; **c1**) SEM image of tablet edge; **c2)** SEM imagine of tablet surface. **d**) The volume-mass relationship of tablets with target doses of 5, 7.5, 10 and 15 mg.*In vitro* release of furosemide from **e**) immediate (F3) and extended release tablets (F4-F6), and **f**) immediate release laser-cut tablets (F3) of different size using USPII dissolution test, n= 3, ±SD.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Furosemide target dose (mg) | Tablet weight (mg) | Diameter (mm) | Height (mm) | Volume  (mm3) | Surface area (mm2) | Surface/mass (mm2/mg) | Surface/volume (mm-1) | Drug content (mg) | Disintegration time (min) | Tensile strength (MPa) | Friability (%) |
| 5 | 99.53 ± 2.74 | 6.15 ± 0.12 | 3.44 ± 0.12 | 101.74 ± 3.47 | 125.44 ± 2.67 | 1.26 ± 0.02 | 1.23 ± 0.03 | 4.98 ± 0.14 | 11.92 ± 1.90 | 0.83 ± 0.03 | 0.16 |
| 7.5 | 144.50 ± 6.49 | 7.26± 0.14 | 3.43 ± 0.13 | 142.00 ± 7.20 | 161.05 ± 5.01 | 1.12 ± 0.02 | 1.14 ± 0.03 | 7.22 ± 0.32 | 11.87 ± 0.71 | 0.79 ± 0.04 | 0.17 |
| 10 | 196.09 ± 9.13 | 8.41 0.12 | 3.24± 0.18 | 179.90 ± 8.34 | 196.79± 3.87 | 1.01 ± 0.03 | 1.10 ± 0.03 | 9.80 ± 0.46 | 12.10 ± 0.98 | 0.86 ± 0.08 | 0.13 |
| 15 | 279.16 ± 12.93 | 9.95 ± 0.16 | 3.26 ± 0.13 | 254.56 ± 12.21 | 258.2 ± 6.43 | 0.93 ± 0.03 | 1.12 ± 0.03 | 13.95 ± 0.65 | 9.63 ± 0.87 | 0.77 ± 0.07 | 0.34 |

**Table 2.** Measured weights, dimensions, volumes, surface area, surface/mass and surface/volume ratios, drug content, disintegrate time, tensile strength, and friability of laser-cutting furosemide tablets (n=20).

* 1. *Furosemide release from laser-cut tablets*

The disintegration times of laser-cut tablets that prepared by casting and laser cutting are reported in Table 2. The relatively short disintegration period of laser-cut tablets can be attributed to the hydrophilic nature of PEG, which promotes the passage of water into the tablet core and shortens the disintegration time [38]. Fig. 5e demonstrated that the developed drug formulation has a rapid-release profile. The tablets from different sizes (F3) released more than 75% of the drugs within 45 min, meeting the British Pharmacopoeia criteria for immediate-release dosage forms. The fast dissolution of furosemide could be attributed to the presence of furosemide in amorphous form, where little energy is needed to break the crystal lattice during the dissolution process [39]. In addition, the solubilising effect of PEG 6000 for poorly soluble drugs [40,41] has been extensively reported. Such an effect on drug release was proposed to be carrier-mediated [42].

Fig.6 provides a comparison of laser cutting compared to other tablet manufacturing technologies. Compared to standard powder compression, laser-cutting does not involve numerous processing steps and undergoes numerous phases of manufacture, including cumbersome and intricate powder processing operations, which are very operator-dependent [43,44].

The primary advantages of laser cutting are its simple and convenient operation, short production time, and ability to make one tablet in a relatively short period (< 1min), while the printing time using 3D printing was 4 min per tablet [46]. One important advantage of the laser cutting approach is avoiding the modification of the structure of the matrix during the production process. This is significantly different from additive manufacturing and powder compression, where the tablet formation process could alter the final tablet structure e.g., drug physical form or matrix density of the tablet. Hence, this approach is less likely to modify critical quality attributes (CQAs) such as release patterns or drug contents[47,48]. This is a significant advantage that can simplify quality control (QC) and a real-time release of tablet batches produced in a point-of-care manufacturing scenario. To improve process efficiency, further research is needed to determine whether the marginal materials can be recycled. While this manufacturing approach has been exemplified by producing small batches of tablets, it could be potentially applied to other drug delivery systems such as implants and wound dressing [49].

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**Fig. 6** Overview of different manufacturing methods using established formative manufacturing (powder compression), additive manufacturing (3DP) and the proposed subtractive manufacturing (CNC carving). Laser cutting offers unique features of minimal QC (major implications on batch release following manufacturing) compared to other methods.

1. Conclusion

To the best of the authors' knowledge, this research represents the first investigation into the application of laser cutting technology for on-demand tablet manufacturing. The study focused on optimizing the parameters of fusion laser cutting to achieve a precise cut of a specially formulated drug-polymer cast with minimal degradation of the active ingredient. By adjusting the digital design, the novel laser-cutting procedure enabled the production of bespoke furosemide tablets with a specific dose. The laser-cutting process induced minimal changes to the matrix structure, potentially simplifying the quality control (QC) steps required for batch release. High-performance liquid chromatography (HPLC) analysis demonstrated that furosemide degradation and impurity formation following laser cutting were minimal, and the laser-cut tablets met compendial criteria. This innovative technological approach offers a promising alternative to conventional methods for point-of-care manufacturing.

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