PROCEEDINGS OF THE 33rd European Symposium on Computer Aided Process Engineering (ESCAPE33), June 18-21, 2023, Athens, Greece

Innovative process for manufacturing pharmaceutical mini-tablets using 3D printing

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Abstract

Providing drug products for pediatric patients is a challenging problem for the pharmaceutical industry. Children often require flexible low-dose medication with features like taste-masking and ease of swallowing. In recent years, mini-tablets have emerged as an attractive dosing solution that can meet these requirements. They are small form oral dosages around 2-4 mm in diameter that can be dispensed individually or in combination. Conventionally, they are made using methods like direct compression and hot melt extrusion. This study introduces a new technique to make mini-tablets: drop-on-demand 3D printing. Here the active ingredient is suspended in a liquid excipient, the formulation is printed as droplets and each drop is solidified to yield a mini-tablet. An optimal solvent bath that can uniformly capture mini-tablets is designed and dosages of Atorvastatin (active ingredient) are produced as a test case. Quality of these dosages is determined by measuring their content uniformity.

Keywords: pharmaceuticals, mini-tablets, 3D printing, drop-on-demand, low dose high precision drug products

1. Introduction

Pediatric medicines make up less than 10% of the overall drug market. Serving this patient group however poses a major challenge for the pharmaceutical industry. Factors like limited excipient compatibility, prevalence of rare diseases and smaller pediatric patient populations contribute to this (Milne & Bruss, 2008). Drug products made for children must also cater to their specific needs like having low dose strengths, taste masking and ease of swallowing etc., which in-turn make their production difficult.

Currently, two categories of drug products are popular for medicating children: liquid oral dosages and compounded dosages. Liquid oral drug products are attractive as they satisfy many of these requirements: they are flexible to dose, easy to consume and can be dispensed in low dose strengths. Compounded dosages are made in special pharmacies (called compounding pharmacies) where drug products are made at non-commercial specifications, by either altering the dose or changing the ingredients, to meet the needs of the patient. Both these products, however, face some limitations: 1) many active pharmaceutical ingredients (APIs) are unstable in aqueous media and prone to degradation 2) liquids are also susceptible to inaccurate dosing leading to adverse drug reactions. 3) In compounded dosages, achieving drug content uniformity and release profile matching commercial products is difficult (Zuccari et al., 2022).

In recent years, mini-tablets have emerged as an attractive alternative for pediatric medication. These are small-size solid oral drug products (2-4 mm in diameter) that are easy to swallow and can be dispensed individually or in combination in flexible doses. Two broad categories of techniques have been used to make them: powder based and 3D printing based. Powder based techniques include conventional methods like granulation

and direct compression (Stoltenberg & Breitkreutz, 2011). Here the API is blended with excipient powders to yield a powder formulation. In granulation this formulation is processed into coarse aggregates. Each granule aggregate is then dispensed as a mini-tablet. In direct compression the powder formulation is compacted using small dies into mini-tablets. These methods rely on existing process technology and thus are easy to implement. They also can achieve high production rates. However, manufacturing low dose drug products is challenging for poorly flowing API powders. The second category of techniques is 3D printing, this is a manufacturing process in which the product is made in a layer-wise fashion. Hot melt extrusion is the most used 3D printing method for making mini-tablets (Krause et al., 2021). Here the API-excipient blend is extruded into a thin filament which is then melted and formed into the desired shape. Drug loading in the dosage can be easily customized by varying the number of printed layers. A key limitation of this method is the need for high operating temperatures which can cause degradation of the API or change its polymorphic form.

This study introduces a new method for making mini-tablets: using a drop-on-demand (DoD) inkjet printer. DoD falls under the umbrella of 3D printing methods, it processes a liquid formulation where the API is either dissolved or suspended in an excipient carrier fluid (Içten et al., 2017). The formulation is printed as droplets onto substrates like placebo tablets or capsules to make the drug product. This study aims to manufacture mini-tablets by solidifying individual drops generated by the DoD system. Printed droplets are discharged into an inert and viscous solvent bath where they settle slowly and solidify. Solid droplets are then washed and air dried to yield ready-to-use mini-tablets. The main advantage of this technique is producing dosages having low drug loadings with high precision. To develop this manufacturing route, first an optimal solvent bath is designed to uniformly capture and solidify the printed drops and next, mini-tablets for an API called atorvastatin are printed and tested for content uniformity.

2. Drop-on-demand printing of mini-tablets

As discussed before, DoD is a novel pharmaceutical 3D printing technique that builds dosages by printing multiple drops of an API containing formulation onto inert substrates. It has a versatile operation and can print a variety of formulation (melts, suspension etc.) and produce dosages with broad range of drug loadings. It can also incorporate emerging developments in pharmaceutical manufacturing like continuous processing and end-to-end operation (Sundarkumar et al., 2022).

Its working principle is as follows: the formulation ink for printing is held in the reservoir with constant agitation to ensure concentration homogeneity. Then a high-precision positive displacement pump dispenses a packet of fluid with constant volume through a nozzle in the form of a drop. This drop is then deposited on the desired substrate. The central idea in this study is to capture printed droplets and process them into individual mini-tablets. To achieve this a melt formulation is used, this formulation is then printed into an inert solvent bath (silicon oil) where the droplets self-solidify at room temperature (Figure 1). These solidified drops are then washed dried and collected as ready to use mini-tablets. Details of how the bath is designed is discussed in the results section.

Drug products have many critical quality attributes, such as, content uniformity, residual solvent content, dissolution behavior etc. For 3D printed drug products, content uniformity is an important metric as precise dosing is one of its key features. Thus, to test the quality of printed mini-tablets, uniformity in shape, weight and drug loading content across dosages are measured.

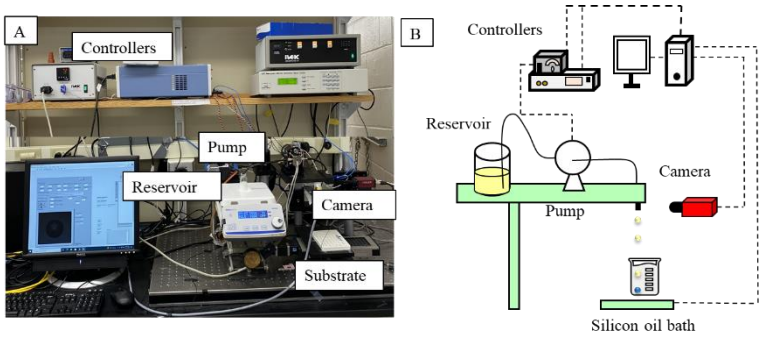

Figure 1. A] Apparatus and B] Schematic of the DoD printing system.

3. Materials

3.1. Chemicals

Atorvastatin (Dr. Reddy's Laboratories), Polyethylene glycol 2000 (PEG) (Fisher chemicals), Silicon oil (polysiloxane, PMX 200 1000 cSt, Dow Chemical Company), Hexamethyldisiloxane (HMDSO) (Fisher chemicals). Before designing the process, the excipient material needs to be selected. PEG is an excipient widely used in drug products and acts as a dissolution enhancer. It melts at ~ 65 °C and is a solid at room temperature. To solidify the printed droplets, silicon oil is used as a bath solvent as it is inert and does not interact with either the API or PEG. HMDSO is used as a washing fluid for the mini-tablets as it is a lighter inert silicon oil that can remove heavier oil adhering to the tablets.

3.2. Instruments

Nikon Eclipse E600 microscope is used to image and size mini-tablets, Waters ultra-pressure liquid chromatography (UPLC) is used to measure drug loading in mini-tablets.

4. Results

4.1. Designing the silicon oil bath

The first step in process development for this route is to design the inert solvent bath. Heat transfer (convective) due to the motion of the drop in the bath needs to be sufficient to solidify the mini-tablet. The critical process parameters here are bath viscosity and final drop temperature. Having low viscosity or high final drop temperature can lead to incomplete solidification or pooling of the droplets in the settling chamber respectively. On the other hand, high viscosities can lead to droplet aggregation (Figure 2). Optimal bath design is the one with the smallest settling chamber height (to reduce solvent amount required) and with the fastest rate of heat transfer.

To achieve this, a multi objective optimization problem can be posed with the goal of minimizing chamber height and solidification time (higher the heat transfer rate, shorter the solidification time). Decision variables here are bath viscosity η and final drop temperature T_f. Both variables are continuous: continuum in viscosity can be achieved by blending together base silicon oils (commercially available products) in required proportions. The bath is assumed to be at room temperature and thus temperature dependence of oil viscosity is ignored. To prevent pooling, an upper bound constraint is introduced on the final drop temperature; and to prevent drop aggregation, a minimum value is set for the distance between successive drops. Problem formulation is as follows:

$$min\ l_{chamber}$$
$$min\ t_{solidification}$$

$$st: \quad T_f < 35^o\,C, \quad \eta < \frac{5}{18} g d_{MT} (\rho_{MT} - \rho_{Si})$$
$$\eta \in [0.1, 10]\,Pas, \quad T_f \in [23, 35]\,^oC$$

$l_{chamber}$ and $t_{solidification}$ are calculated as follows:

1. Physical properties of the system: $d_{MT} = 4\,mm$, $\rho_{MT} = 1124\,kgm^{-3}$, $C_{p_{MT}} = 2135\,Jkg^{-1}K^{-1}$, $k_{MT} = 0.31\,Wm^{-1}K^{-1}$, $T_i = 70^oC$, $\rho_{Si} = 950\,kgm^{-3}$, $k_{Si} = 0.15\,Wm^{-1}K^{-1}$, $C_{P_{Si}} = 1250\,Jmol^{-1}K^{-1}$, $T_{bath} = 23\,C$, $\Delta H_{melt} = 100\,kJkg^{-1}$, $T_{melting} = 45^oC$
2. First, calculate terminal settling velocity of the tablets. $v_t = \frac{g d_{MT}^2}{18\eta}(\rho_{MT} - \rho_f)$.
3. Next, compute heat transfer rate (assume convection dominated). $h = Nu\frac{k}{d}$, $Nu = 2 + \left(0.4Re^{0.5} + 0.06Re^{\frac{2}{3}}\right) Pr^{0.4}$, $Re = \frac{\rho_f v_t d}{\eta}$.
4. Finally, calculate solidification time $t_s = \frac{\rho_{MT} V C_P}{hA} \ln\left(\frac{T_i - T_b}{T_f - T_b}\right) + \frac{\Delta H \rho V}{hA(T_m - T_b)}$ and $l_{chamber} = v_t * t_s$.
5. Verify if convection driven heat transfer assumption is valid, i.e., if $\frac{hd}{k} \gg 1$.

The first constraint acts as a variable bound, 35 °C is chosen because it is half the initial temperature and the formulation is fully solid at this temperature. For the second constraint, we assume that for aggregation to be arrested a gap of at least one drop diameter between successive drops is necessary $l_{inter\,drop} > d_{MT}$. As drop generation rate is constant (one every 5 sec), the constraint can be framed in terms of settling velocity: $v_t > \frac{d_{MT}}{5}$ which is equivalent to $\eta < \frac{5}{18} g d_{MT} (\rho_{MT} - \rho_{Si})$.

The problem is solved by building a Pareto front (figure 2) using the Non-dominated Sorting Genetic Algorithm II (NSGA2) available in the Python library 'pymoo'. Although this algorithm does not guarantee global optimality, it provides a quick and efficient way to generate diverse non-dominated solutions that can represent the best trade-offs between objectives. From this Pareto set, the point closest to having a bath viscosity of 0.95 Pas is chosen for operation as it is closest to the material at hand. The operating point chosen is as follows:

$$\eta = 0.95\,Pas, T_f = 34.9, l_{chamber} = 6.5\,cm\ and\ t_{solidification} = 40.8\,sec.$$

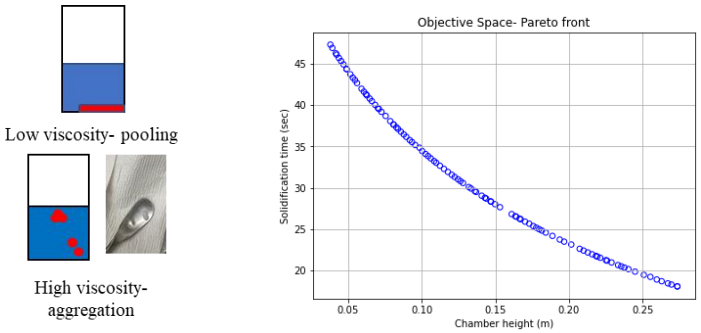

Figure 2. Design of solvent bath and settling chamber- optimization solution.

4.2. Consistency measurements for the printed mini-tablets

After determining bath viscosity, mini-tablet manufacturing is carried out. Drug products with two dose levels of atorvastatin are targeted: 0.1 and 1 mg. In each case formulation drops are printed into the bath, solidified, washed with HMDSO and air dried (figure 3).

To test whether this operation yielded consistent mini-tablets, uniformity of three parameters is measured across dosages: shape, weight and drug loading. To measure variation in shape, the diameter of each mini-tablet is determined under a microscope. Drug loading in each mini-tablet is measured by dissolved it in methanol and analyzing on an offline UPLC. 25 dosages of each dose strength are used for this analysis and the results are summarized in tables 1 and 2.

The results show that for both dose strengths highly precise mini-tablets are obtained. The variation in all three parameters is very low and is well under the regulatory threshold (5% relative standard deviation for drug loading as specified by the United States Food and Drug Administration). Drop size can be altered by changing the DoD printing conditions like ejection rate, volume per drop etc. Based on concentration of the active ingredient in the formulation, drop size can be adjusted to deliver the desired dose strengths in mini-tablets. High consistency seen in the process can be explained by two reasons: 1) it is easier to disperse API in liquid excipients compared to powder excipients leading to more uniform drug loadings; and 2) each mini-tablet is made of exactly one droplet; thus, uniformity of drop formation translates into uniformity in shape and weight of mini tablets. In this study, polymorphic transformation of the API crystals is not considered. Dissolving the API in a molten polymer like PEG and solidifying it yields amorphous solid dispersions. If polymorph control is critical then the API crystals can be suspended in an inert excipient that does not dissolve it (like triglyceride oils). This method also faces some limitations: the mini-tablets produced lack hardness which would make their transportation difficult. Manufacturing high drug loading mini-tablets is also challenging, as increasing particle loading beyond a certain concentration yields a paste-like formulation that does not generate uniform droplets.

To realize the full potential of this DoD approach (flexible dosage production rate, quick product changeovers etc.), the mini-tablet manufacturing process needs to be made entirely continuous. Currently, a part of the process (up to drop solidification) is continuous while the subsequent washing and drying steps are carried out batch-wise. Continuous operation can be achieved by integrating the DoD system with a continuous filter dryer unit. To support emerging initiatives in pharmaceutical manufacturing like digitalization and quality-by-design, sensors can be installed into the platform to track drug loading in the manufactured mini-tablets in real time. This will allow for building quality into the product during the manufacturing stage itself, and thus will mitigate the need for post manufacturing quality checks.

Table 1. Consistency results for 0.1 mg mini-tablets.

Parameter	Mean	Relative stdev
Diameter	3.14 mm	1.04 %
Weight	21.27 mg	1.54 %
Drug loading	0.107 mg	2.31 %

Table 2. Consistency results for 1 mg mini-tablets.

Parameter	Mean	Relative stdev
Diameter	2.84 mm	1.22 %
Weight	16.26 mg	2.18 %

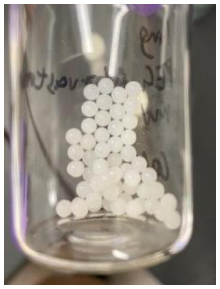

Figure 3. Printed atorvastatin mini-tablets.

Drug loading	1.01 mg	2.44 %

5. Conclusions

This study introduces a novel technique to manufacture pharmaceutical mini-tablets. API is dissolved in a molten PEG formulation and its droplets are printed and solidified in an inert silicon oil bath. These mini-tablets are seen to show a high degree of consistency in shape, weight and drug loading across dosages. To assess if these dosages are equivalent to commercial products, their dissolution behavior and long-term stability need to be determined. This technique fills an important gap in the pediatric drug market- producing high-precision low dose mini-tablets. In conjunction with the other manufacturing techniques, this method can accelerate the adoption of pharmaceutical mini-tablets.

6. Acknowledgements

The authors would like to thank the Food & Drug Administration for partially funding this work, in part, through grant (U01FD006738). Views expressed in written materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government. This material is based upon work partially supported by the National Science Foundation under Grant No. 2132142.

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