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Abstract: In the last decade 3D printing (3DP) technology has gained increasing interest in the pharmaceutical field addressing several novel challenges such as on-demand manufacturing at the point of need, customization of drug release profiles and combination of several APIs in one dosage form. Therefore, 3DP become a new and promising path to drug product development and manufacturing, able to support specific therapies and improve compliance, safety and effectiveness. The aim of this work was to partially coat tablets with a glyceride using a 3D printer as an approach for tuning the release of two Active Pharmaceutical Ingredients (APIs), one of which was hydrophilic and the other lipophilic. Various parameters of the 3DP coating process were purposefully modified using experimental design techniques in order to customize the selected APIs release profile, without affecting the core composition of the formulation.

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Highlights

- 3D printing as a coating technology for customizing the release rate of drugs
- Experimental design as a tool for a 3D process characterization
- 3D printing as a tool for fine tuning critical quality attributes

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Partial Tablet Coating by 3D Printing

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Abstract

In the last decade 3D printing (3DP) technology has gained increasing interest in the pharmaceutical field addressing several novel challenges such as on-demand manufacturing at the point of need, customization of drug release profiles and combination of several APIs in one dosage form. Therefore, 3DP become a new and promising path to drug product development and manufacturing, able to support specific therapies and improve compliance, safety and effectiveness. The aim of this work was to partially coat tablets with a glyceride using a 3D printer as an approach for tuning the release of two Active Pharmaceutical Ingredients (APIs), one of which was hydrophilic and the other lipophilic. Various parameters of the 3DP coating process were purposefully modified using experimental design techniques in order to customize the selected APIs release profile, without affecting the core composition of the formulation.

Keywords: 3D Printing, Tablet Coating, Design of Experiments

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1. Introduction

Three-dimensional printing (3DP) is a layer-by-layer production of 3D objects from digital designs. The general term 3DP includes a range of different printing technologies according to the raw materials used or the way layers are deposited in order to create the objects. Fused Deposition Modeling (FDM), inkjet printing, stereolithography (SLA) or semisolid extrusion are some examples of 3DP. According to Ventola (Ventola, 2014), “3DP or Additive Manufacturing (AM) or Solid Free-Form (SFF) or Rapid Prototyping (RP) is a manufacturing method in which objects are created by fusing or depositing materials in layers to produce a 3D object”. All these approaches, despite the type of the 3DP technology, the various operating conditions, the materials used or the differences in speeds and resolution, can construct any 3D model derived from a computer-aided design software (CAD). In other words, 3DP is an additive technology where an object is built according to a digital model through which commands are given to the printer to build the set object layer after layer (Mills, 2015). In a basic setup, a rapid prototyping stereolithography (.stl) file format is created defining the surface geometry of the 3D object (Jonathan and Karim, 2016). Subsequently, through a computer software, a machine specific code (.gcode) is generated from the previously created .stl file, which is read and followed by the 3D printer. This file describes the size of the parts to be build and gives commands to the printer, which constructs the object layer by layer by moving the print head along the x-y axis and vertically along the z-axis, as guided by the CAD (Giannatsis et al., 2016; Gibson et al., 2015).

Since its introduction, 3DP has evolved rapidly and is currently being used along a wide range of industries, such as automotive, architecture, construction and aerospace

(Bak, 2003; Berman, 2012; Joshi and Sheikh, 2015; Liu et al., 2016; Perkins and Skitmore, 2015). It is highly flexible, robust, multilateral, cost effective, precise and fast; These attributes draw the attention of the researchers and industries in the pharmaceutical field opening new possibilities to product development and manufacturing (Attaran, 2017). 3DP allows the production of personalized dosage forms meeting the patient's unique needs (Skowyra et al., 2015) challenging the 'one-size fits-all' approach (Lamichhane et al., 2019). Within this context, complex geometries unable to be produced with the traditional techniques (Lamichhane et al., 2019; Norman et al., 2015) designs requiring dose accuracy for narrow therapeutic index drugs (Vakili et al., 2015), which could be also combined with additional active ingredients with tailored release profiles (Goyanes et al., 2017) or the potential of production at the point of need (Araújo et al., 2019) provide a much better outcome in terms of compliance, safety and effectiveness (Alhnan et al., 2016).

Attaran (Attaran, 2017) reported the rapid growth of 3DP market, which has grown from \$3.07 billion in 2013 to \$5 billion in 2016 and it is expected to exceed \$21 billion by 2020. The introduction of 3DP in the pharmaceutical world is relatively new and might be proved revolutionary. In the last five years, there has been a burst of published research articles on 3D printed formulations, reaching the number of 55 publications only in 2018, while the respective number was below 10 in 2014 (Gioumouxouzis et al., 2019).

Among its many advantages, agility, speed and precision are the ones challenging the traditional manufacturing technologies. This was realized by the recent FDA approval of Spritam[®], the first 3D printed, instantaneously disintegrating formulation

(Aprecia Pharmaceuticals, 2015). Many reviews have been published emphasizing the characteristics of each 3DP technology (Jonathan and Karim, 2016; Lamichhane et al., 2019; Norman et al., 2015), the manufacturing of personalized dosage forms (Drăgănescu et al., 2019; Giannatsis and Dedoussis, 2009; Gioumouxouzis et al., 2019), the development of new delivery systems with complex geometries (Goyanes et al., 2015b, 2015c) or the combination of different active ingredients in one dosage form (Khaled et al., 2015; Pereira et al., 2019). However, the literature on the use of 3DP for the coating or partial coating of solid dosage forms is limited while the materials used consist of a specific range of polymers (Konta et al., 2017). For example, Okwuosa et al. (Okwuosa et al., 2017), fabricated a shell-core delayed release tablet using dual-nozzle FDM 3DP and polymers, in which the inside core includes the API, while the outside shell serves as an enteric coating. In the same manner, Wand et al., fabricated cube core-shell structures using a powder-based 3PD (Wang et al., 2008). On the other hand, Goyanes et al. (Goyanes et al., 2015a), combined three different technologies for the fabrication of controlled-release tablets. Hot Melt Extrusion (HME) was used for the filament creation, FDM 3DP for the fabrication of tablets, while for the coating, a bottom spray fluidized bed coater was employed. Payumo et al. (Payumo et al., 2011), described an oral dosage form fabricated by 3DP, which encapsulates a toxic or potent API in the core which then coated, providing protection and isolation of the core.

Partial coating of tablets is reported by various research teams. Katstra et al. (Katstra et al., 2000) and Yu et al. (Yu et al., 2007) for example, fabricated controlled release tablets with a powder-bed 3D printer and polymeric materials. The printed tablets consisted of placebo coating layers on top and bottom of the tablets, while the core

contained the API and the polymer, leaving the lateral surface uncoated. The API's release was controlled by the polymer content in the core of the tablet. Melocchi et al. (Melocchi et al., 2016), demonstrated the potential of creating filaments from different solubility grade polymers. These filaments can be employed by FDM 3DP and construct immediate or modified release coating layers at tablets or whole capsules. Partial coating by 3DP was also applied in drug loaded implants for modifying the release profile of the API. Huang et al. (Huang et al., 2007), constructed cylindrical implants of API and polymer matrix material with 3D inkjet-printing. The API was either encapsulated in the core of the implant surrounded by the polymeric matrix without any free sides or in the same manner encapsulated with an additional bottom region of API. Finally, Wu et al. (Wu et al., 2014), constructed different drug delivery implants with the use of a powder-bed 3DP system.

These examples demonstrate the implementation of 3DP for the construction of dosage forms which include drug-free coated sides. The literature review indicated a range of materials used, mainly consisting of polymers, including Polyvinylpyrrolidone (PVP), Hydroxypropyl Methylcellulose (HPMC), Eudragit®, Polyvinyl Alcohol (PVA), Polyethylene Oxide (PEO), Polycaprolactone (PCL) and Polylactic Acid (PLA). On the contrary, a very limited number of studies reported the manufacture of lipid-based drug delivery systems with 3DP (Boyd et al., 2019). Vithani et al. (Vithani et al., 2019) for example, used 3DP technology for the preparation of solid self-micro emulsifying drug delivery systems. On the other hand, Kyobula et al. (Kyobula et al., 2017) used beeswax as a carrier to produce drug-loaded solid dosage forms. Finally, İçten et al. (İçten et al., 2017) developed a dropwise 3DP technique for preparing amorphous self-emulsifying

drug delivery systems based on lipids. Nevertheless, no publications were found demonstrating the use of glycerides for the coating of tablets with 3DP.

The objective of this work was to demonstrate the feasibility of employing the 3DP technology for the partial coating of matrix tablets with glycerides, where the API's release would be precisely regulated by controlling the coating characteristics only, without modifying the core formulation. More specifically, two model APIs were chosen and formulated as tablets, which were then partially coated by a picked glyceride with 3PD. Experimental design was used as a statistical tool to characterize the effects and possible interactions of selected parameters of the printing-coating process on the release profiles of the two APIs. The feasibility of the proposed technology was shown by modifying the geometry of the coating and acquiring knowledge on which of these parameters and/or their interactions affect the release profile of the APIs and thus achieving personalized drug release rates according to the patient's needs.

2. Materials & Methods

2.1. Tablet Formulation

For the purpose of this project two APIs were formulated in two different 11mm flat surface tablets of 280mg total weight. The model drugs selected were the hydrophilic methyl-levodopa hydrochloride (Melevodopa, $C_{10}H_{13}NO_4$ HCl) and the lipophilic Acyclovir ($C_8H_{11}N_5O_3$). The tablets were formulated according to the composition shown in Table 1 and were directly compressed with a single punch tableting machine (Styl'One Evolution, MEDELPHARM SAS, France) using a compression force of 20 kN.

Table 1.

Tablet Core Formulation (%w/w).

Component	Content	Supplier
		Fidia S.p.A. (Italy, Lot. 010100)
Acyclovir or Melevodopa	30%	Chiesi Farmaceutici S.p.A. (Italy, Lot. MNTTF004)
Hypromellose	30%	Methocel E3 Premium LV Colorcon® (UK, Lot. IF10023)
Lactose Monohydrate DC	20%	RetaLac®, Meggle (USA, Lot. L1004A4020)
Microcrystalline Cellulose	19%	Avicel PH-102 ACEF S.p.A. (Italy, Lot. H2622003)
Magnesium Stearate	1%	ACEF S.p.A. (Italy, Lot. C1402005)

2.2. Coating Material

The glyceride used was glyceryl distearate (Precirol® ATO 5, Gattefossé SAS France, Lot. 161841). It consists of esters of palmitic (C₁₆) and stearic (C₁₈) acids with the diester fraction being predominant. It has a melting range of 50-60 °C and a Hydrophilic-Lipophilic Balance (HLB) of 2 (Gattefosse, 2019). Precirol® ATO 5 functions mainly as a coating agent for protection and taste masking, as a lipid matrix former for modified and sustained release tablets and as a lubricant and flow aid for capsule filling with powders (Ash and Ash, 2007; Gattefosse, 2019). It is also suitable for use in melt

processing techniques such as hot melt extrusion, coating and granulation (Becker et al., 2015; Gattefosse, 2019). Finally, Precirol® ATO 5 has been generally recognized as safe (GRAS) by the FDA and has been used in approved pharmaceutical products (Gattefosse, 2019).

2.3. 3D Printing

Tablet coating was carried out using a lab scale 3D printer for semi-solids, designed and constructed at the Dpt. of Mechanical Engineering, University of Parma, Italy. The printer consisted of a rectangular glass printing table and a print head equipped with a 2.5 ml syringe, a G26 needle and a heating system. On top of the printing table, a support structure was printed and attached in order to keep the tablets at the same position while the coating was printed (Fig. 1A). The syringe was loaded with Precirol® ATO 5 powder and was placed in a metal cylinder filled with water, which was constantly heated throughout the printing process above the material's melting point in order to maintain the glyceride in its liquid form (Fig. 1B). The material was then extruded on the tablet surface at room temperature to form the coating in a rectilinear layout and a standard layer height of 0.3 mm. The 3D model of the coating (.stl file) was created with the software OpenSCAD (v.2015-03-2) and the parameters of the 3D printer affecting the coating characteristics (.gcode file) were controlled with the software Slic3r (v.3).

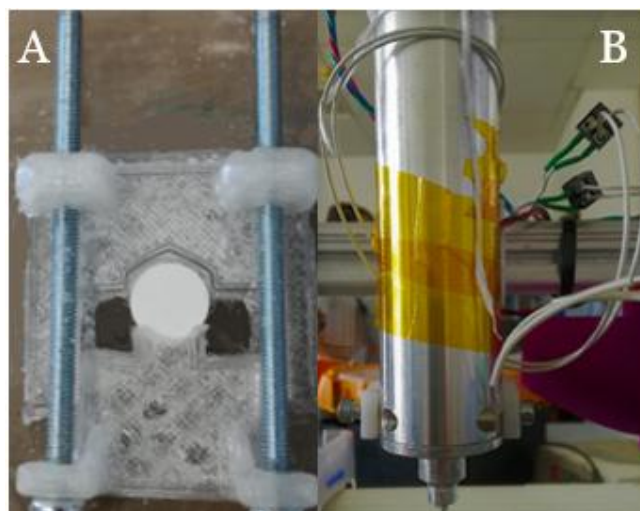


Fig. 1. Parts of the semi-solid 3D printer. A) Tablet support construction attached to the printing table in order to keep the tablet at a constant position. B) Heating system of the syringe keeping the material in liquid form.

2.4. Design of Experiments (DoE)

Two factors at four different levels were chosen to control the coating characteristics, namely Surface Coverage (Factor A) and its Thickness (Factor B). Factor A describes the percentage of the tablet surface covered by the coating, meaning how densely or sparsely the tablet surface is covered by the coating material, while factor B expresses the number of coating layers printed on top of the tablet. For each factor and level, the tablets were coated either on one or both sides, while the lateral surface was always left uncoated. Table 2 shows the combination of factors and levels chosen, while examples of the CAD drawings of the coatings are shown in Fig.2. A custom design (Design-Expert® v.11, Stat-Ease Minneapolis, USA) was employed using all possible combinations of the two numeric factors, at the four levels chosen, allowing for the

estimation of the main effects and factor interactions. For each API, two different designs were performed, corresponding to the one and the two-sided coated tablets. The Mean Dissolution Time (MDT) (Podczeck, 1993) was chosen as the response factor and each experiment was performed in triplicate.

Table 2.

Factors and Levels of the experimental design for each coated tablet side and each API.

Factor	Units	Level				Response
A (Surface Coverage)	%	25	50	75	100	MDT (min)
B (Thickness)	N Layers	2	4	6	8	

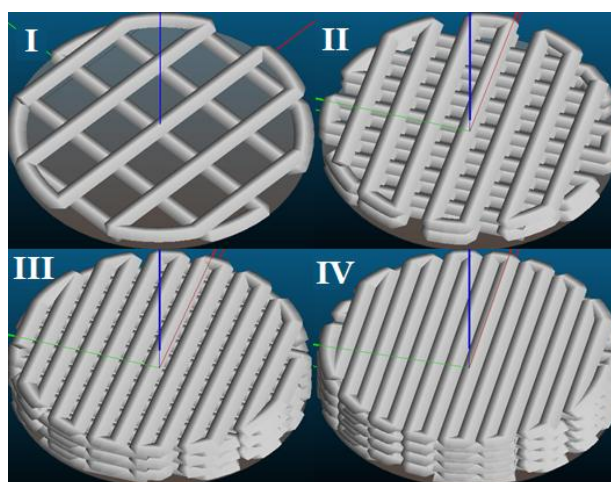


Fig. 2. CAD drawings of coating with the levels of factors A and B increasing from I to IV. I) Factor A was set at 25% and factor B at two layers. II) Factor A was set at 50% and factor B at four layers. III) Factor A was set at 75% and factor B at six layers. IV) Factor A was set at 100% and factor B at eight layers.

2.5. Dissolution Studies

Dissolution studies were performed for the uncoated and coated tablets in two different media. Initially, 750 ml of HCl 0.1N at pH 1.1 was used for 1 h followed by the addition of 250 ml phosphate buffer (0.3 M Na₂HPO₄) to achieve a final pH 5.5 and volume of 1000 ml. The dissolution system used (Varian 705 DS, Varian Inc., California, USA) was equipped with an automated sampling pump (IPC, Ismatec®, Cole-Parmer GmbH, Wertheim, Germany) and a UV/Vis spectrophotometer (PerkinElmer Co., Waltham, Massachusetts, USA). Baskets with rotation speed of 100 rpm were used and the samples solutions of Acyclovir and Melevodopa were measured at 256nm and 280nm respectively. For comparison purposes the data were expressed with MDT, which can be calculated according to the following equation (Podczeck, 1993):

$$MDT = ABC/M_0 \quad (1)$$

where M_0 is the asymptote of the amount of drug dissolved and ABC is the area between the dissolution curve and M_0 can be calculated according to the following equation:

$$ABC = \sum_{i=1}^{n-1} ABC_i = \sum_{i=1}^{n-1} [(t_{i+1} + t_i) \cdot (M_{i+1} - M_i)/2] \quad (2)$$

Where i is the sample number, n is the number of dissolution sample times, M is the amount of drug dissolved at the corresponding sample time.

2.6. Statistical analysis

For all the performed experiments, the obtained results are expressed as mean \pm standard deviation of three replications. The design space was constructed and analyzed using the Design-Expert® Software, v.11 (Stat-Ease Minneapolis, USA).

3. Results and Discussion

The hydrophilic Melevodopa and the lipophilic Acyclovir tablets were partially coated with the glyceride Precirol ATO5 using the semi-solids 3D printer according to the experimental design. Subsequently, the dissolution profiles were recorded and analyzed in order to identify the effect and/or interactions of the selected coating parameters on the API release according to the design matrices shown in Table 4 to Table 7. Examples of the actual partially coated tablets are shown in Fig. 3.



Fig. 3. Examples of partially coated tablets with 3DP with the four levels of factor A increasing from left to right.

Uncoated Tablets

The dissolution parameters of the uncoated core tablets expressed in terms of MDT are shown in Table 3.

Table 3.

MDT of uncoated-core Melevodopa and Acyclovir tablets.

API	MDT (min)
Melevodopa	65.50±1.64
Acyclovir	112.67±6.11

As expected, the hydrophilic API Melevodopa showed a faster release, as depicted by its lower MDT compared to the lipophilic compound.

Design I: Melevodopa one-side coated tablets

The first experimental design performed was for the hydrophilic API in a tablet coated on one side only. 16 runs with different combinations of factor A and B at four levels were performed and the results are depicted in Table 4.

Table 4.

Experimental design for Melevodopa tablets coated on one side. Factor A: Surface Coverage (%), Factor B: Thickness (N. Layers), Response: MDT (min)

Run	Factor A: Surface Coverage (%)	Factor B: Thickness (N. Layers)	Response: MDT (min)
1	25	4	63.39 ± 1.27
2	50	8	65.71 ± 1.75
3	75	6	84.79 ± 4.27
4	100	6	94.87 ± 3.55
5	25	8	69.23 ± 1.89
6	50	2	67.94 ± 3.56
7	75	8	89.12 ± 6.07
8	25	2	65.11 ± 1.27
9	50	6	81.42 ± 5.92
10	75	2	71.29 ± 7.48
11	75	4	79.10 ± 8.28
12	25	6	70.73 ± 1.79
13	50	4	75.71 ± 3.36
14	100	8	89.89 ± 3.67
15	100	4	84.90 ± 3.14
16	100	2	68.04 ± 9.33

The statistical analysis showed that the factors A and B were significant ($p < 0.05$), while their interaction AB was marginally not significant. The results are depicted in detail in Fig. 4. Not surprisingly, the increase of factors A and B resulted in an increased MDT. Regarding the AB interaction, the effect of factor B on MDT is more pronounced when factor A is at its highest level. This means that the effect of the number of layers on the selected response is more pronounced when the surface coverage is higher. The equation describing this relationship is as follows:

$$MDT = +76.33 + 9.05 \cdot A + 5.75 \cdot B + 4.12 \cdot AB \quad (3)$$

where, MDT is expressed in min, A: Surface Coverage, B: Thickness and $-1 < A, B < 1$. The high levels of the factors are coded as +1 and the low levels are coded as -1.

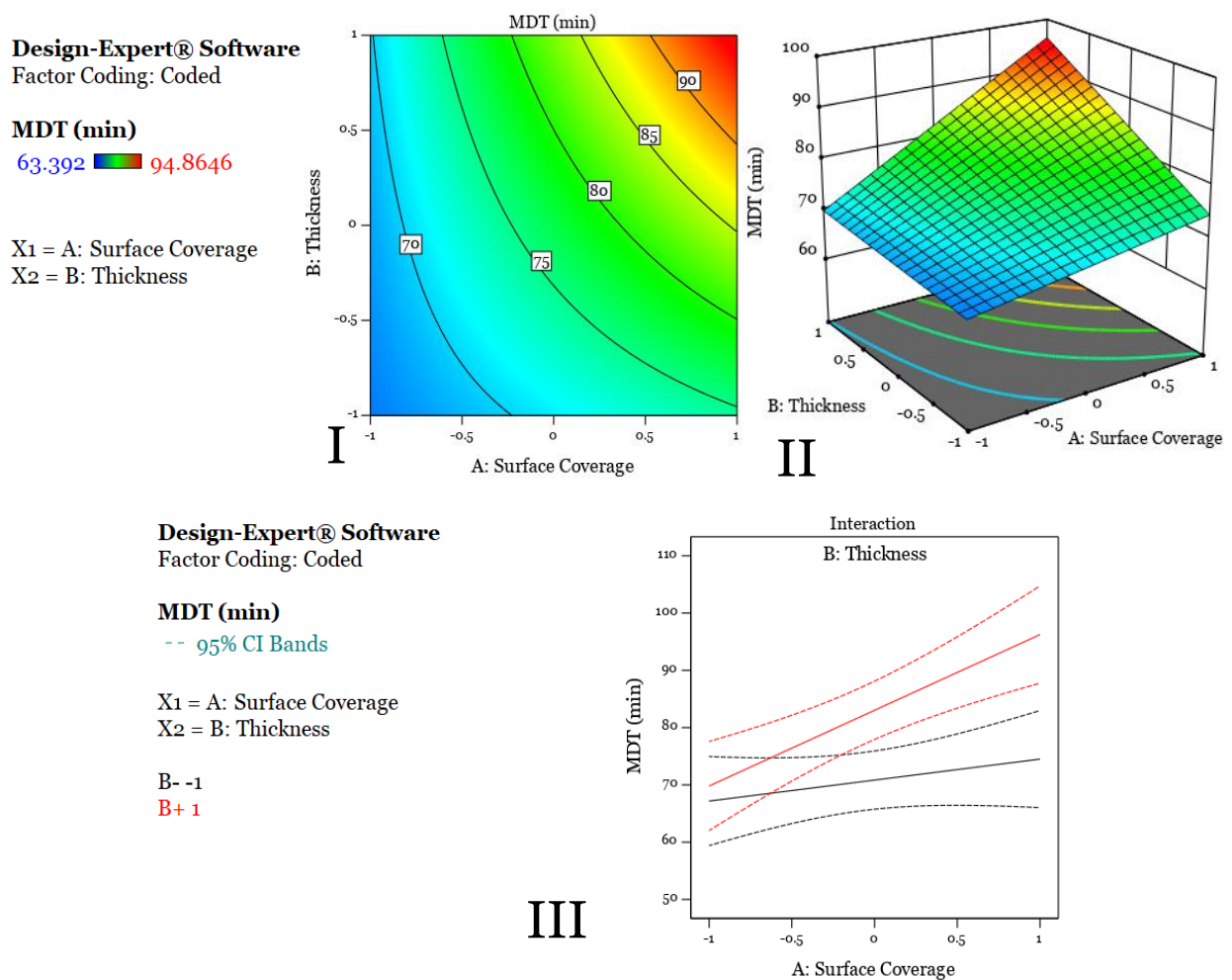


Fig. 4. Plots for Melevodopa One-sided coated tablets. Both factors are expressed in a coded scale from -1 to +1, with -1 being the lowest level and +1 being the highest. I) Contour plot, Surface Coverage vs Thickness. II) 3D Surface plot, Surface Coverage and Thickness vs MDT. III) Interaction Plot, Surface Coverage and Thickness vs MDT.

Design II: Melevodopa two-sides coated tablets

The second design performed for the hydrophilic API corresponds to the two-sided coated tablets. The combinations of factors A and B along with the selected response are presented in Table 5.

Table 5.

Experimental design for Melevodopa tablets coated on two sides. Each run is coded by a unique name.

Factor A: Surface Coverage (%), Factor B: Thickness (N. Layers), Response: MDT (min)

Run	Factor A: Surface Coverage (%)	Factor B: Thickness (N. Layers)	Response: MDT (min)
1	50	6	79.85 ± 1.14
2	100	4	100.62 ± 5.06
3	50	4	74.53 ± 1.18
4	100	2	89.31 ± 2.78
5	25	2	65.02 ± 4.28
6	75	2	84.98 ± 5.43
7	75	6	100.08 ± 1.19
8	25	4	69.30 ± 3.11
9	100	6	111.22 ± 1.12
10	50	8	85.54 ± 2.46
11	50	2	66.57 ± 1.96
12	100	8	111.38 ± 4.48
13	25	6	69.84 ± 2.07
14	25	8	71.22 ± 2.11
15	75	8	107.76 ± 0.77
16	75	4	91.07 ± 1.12


For the two-sided coated Melevodopa tablets the same pattern was identified as with the one-side coated tablets. Fig. 5 illustrates the results in detail. However, coating of

tablets on both sides resulted in more extended MDT values when compared with the ones of the one-sided tablets. The ANOVA analysis showed that factors A, B and AB were significant ($p < 0.05$). The increase of factors A and B resulted in an increased MDT. For the interaction AB, the effect of factor B on MDT is more pronounced when factor A is at its highest level. Meaning that when the surface coverage is higher, the effect of the number of layers on MDT is more pronounced. In other words, as the coating becomes thicker and denser, MDT is affected in a greater extend compared to a thinner coating even if the surface coverage increases in the same manner. The equation describing this relationship is as followed:

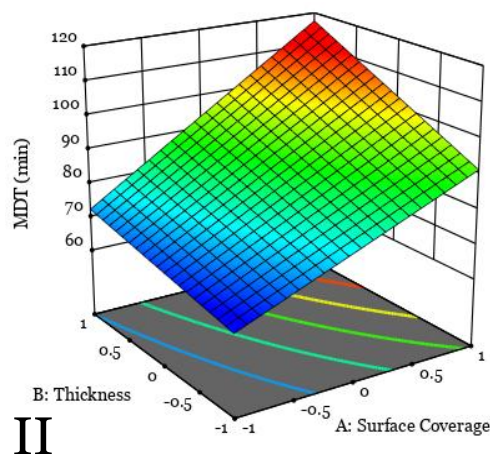
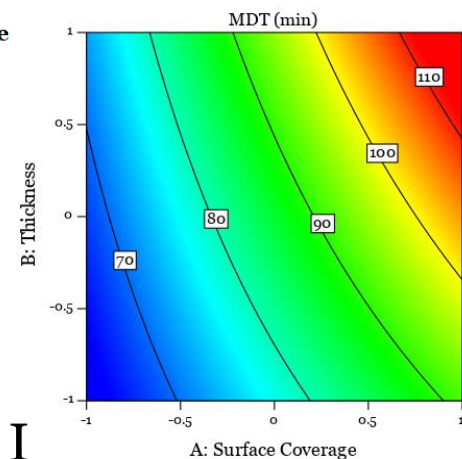
$$MDT = +86.14 + 18.33 \cdot A + 8.83 \cdot B + 4.23 \cdot AB \quad (4)$$

where, MDT is expressed in min, A: Surface Coverage, B: Thickness and $-1 < A, B < 1$.

Design-Expert® Software
Factor Coding: Coded

MDT (min)
65.02  111.384

X1 = A: Surface Coverage
X2 = B: Thickness



Design-Expert® Software
Factor Coding: Coded

MDT (min)
-- 95% CI Bands

X1 = A: Surface Coverage
X2 = B: Thickness

B- -1
B+ 1

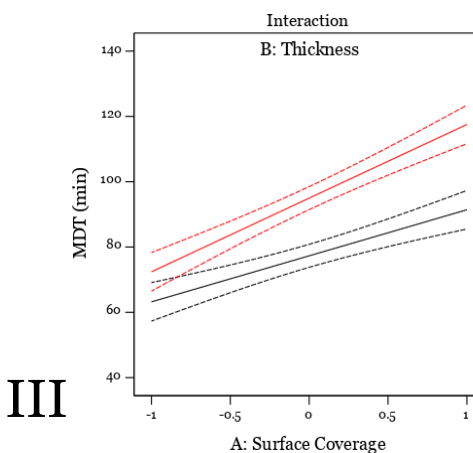


Fig. 5. Plots for Melevodopa Two-sided coated tablets. Both factors are expressed in a coded scale from -1 to +1, with -1 being the lowest level and +1 being the highest. I) Contour plot, Surface Coverage vs Thickness. II) 3D Surface plot, Surface Coverage and Thickness vs MDT. III) Interaction Plot, Surface Coverage and Thickness vs MDT.

Design III: Acyclovir one-side coated tablets

As for Melevodopa, the first design performed for the lipophilic API corresponds to the core tablets being coated on one side. The combinations of factor A and B at four levels are depicted in Table 6.

Table 6.

Experimental design for Acyclovir tablets coated on one side. Each run is coded by a unique name. Factor A: Surface Coverage (%), Factor B: Thickness (N. Layers), Response: MDT (min)

Run	Factor A: Surface Coverage (%)	Factor B: Thickness (N. Layers)	Response: MDT (min)
1	50	8	128.13 ± 2.31
2	50	6	121.49 ± 8.13
3	100	4	125.12 ± 9.45
4	75	6	115.35 ± 2.66
5	25	6	128.53 ± 5.20
6	100	6	120.12 ± 6.42
7	25	2	135.78 ± 8.95
8	50	2	128.73 ± 5.05
9	100	2	137.20 ± 4.25
10	50	4	113.12 ± 1.62
11	75	4	121.29 ± 6.15
12	25	8	129.27 ± 4.51
13	75	8	115.54 ± 9.61
14	25	4	113.87 ± 5.30
15	100	8	120.82 ± 6.51
16	75	2	134.25 ± 4.04

The analysis of results for the lipophilic API one-side coated tablets revealed some remarkable differences compared the hydrophilic API. The results are depicted in detail

in Fig. 6. In this case, ANOVA analysis revealed the quadratic model as significant and the terms which affect the MDT were B, AB and B² (p<0.05).

$$MDT = +116.19 - 0.6606 \cdot A - 4.30 \cdot B - 4.87 \cdot AB + 4.61 \cdot A^2 + 9.96 \cdot B^2 \quad (5)$$

where, MDT is expressed in min, A: Surface Coverage, B: Thickness and -1<A, B<1.

For the lipophilic Acyclovir one-side coated tablets, the AB interaction revealed that the effect of factor B on MDT is more pronounced when factor A is at its highest level. This means that the effect of the number of layers on the selected response is more pronounced when the surface coverage is high. In other words, when the coating is thin and as it becomes denser, MDT is affected to a greater extent than a thicker coating even if the surface coverage increases in the same manner.

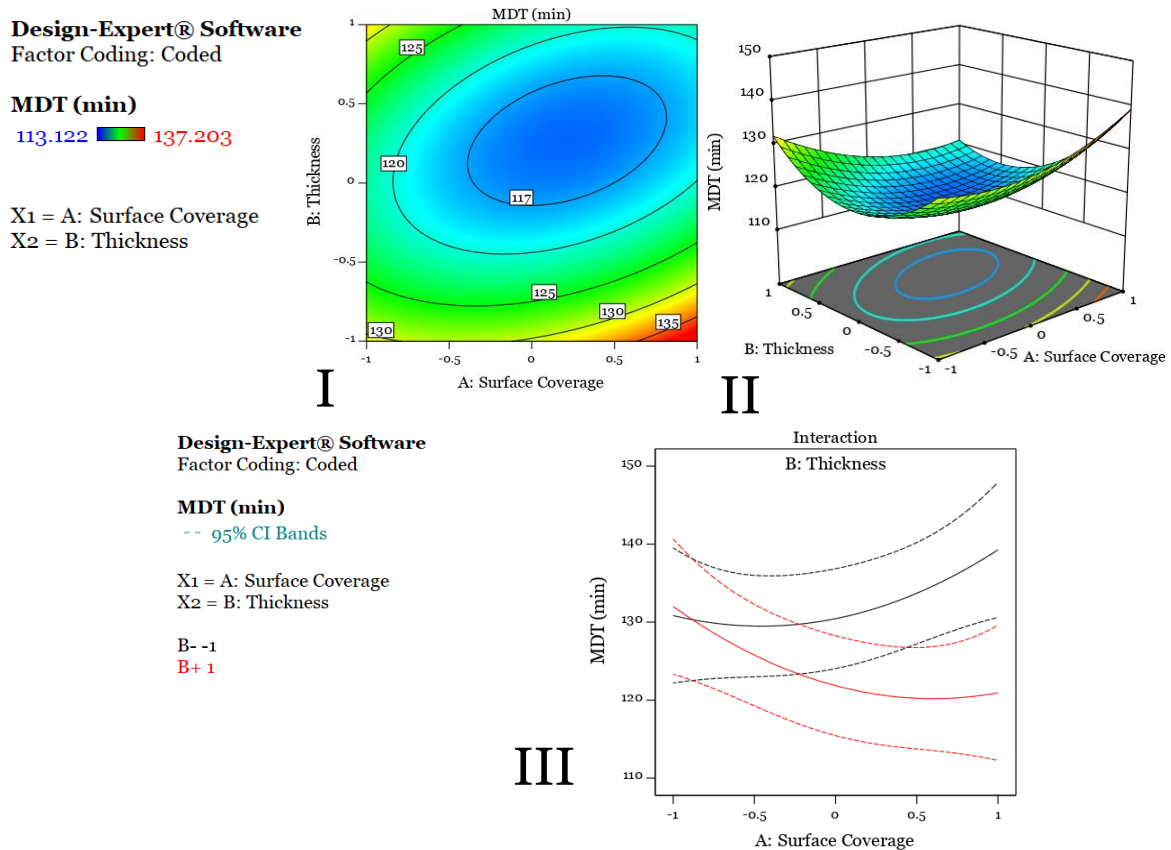


Fig. 6. Plots for Acyclovir One-side coated tablets. Both factors are expressed in a coded scale from -1 to +1, with -1 being the lowest level and +1 being the highest. I) Contour plot, Surface Coverage vs Thickness. II) 3D Surface plot, Surface Coverage and Thickness vs MDT. III) Interaction Plot, Surface Coverage and Thickness vs MDT.

Design IV: Acyclovir two-sides coated tablets

The second design performed for Acyclovir corresponds to the tablets coated on both sides. The combinations of factors A and B along with the selected response are presented in Table 7.

Table 7.

Experimental design for Acyclovir tablets coated on two sides. Each run is coded by a unique name.

Factor A: Surface Coverage (%), Factor B: Thickness (N. Layers), Response: MDT (min)

Run	Factor A: Surface Coverage (%)	Factor B: Thickness (N. Layers)	Response: MDT (min)
1	75	6	131.67 ± 4.37
2	50	6	115.44 ± 8.45
3	100	2	125.61 ± 9.87
4	50	4	116.41 ± 6.54
5	50	2	106.21 ± 5.14
6	25	8	121.10 ± 4.51
7	100	6	139.37 ± 3.96
8	100	4	125.09 ± 2.53
9	25	4	110.90 ± 10.08
10	75	2	118.76 ± 8.23
11	25	6	111.68 ± 3.34
12	75	4	126.92 ± 6.93
13	75	8	128.05 ± 2.51
14	25	2	111.06 ± 4.00
15	100	8	128.96 ± 3.72
16	50	8	124.06 ± 4.14

The two-sides coated Acyclovir tablets showed a similar but not identical behavior with the hydrophilic API as factors A and B were found significant but not their

interaction. The results are depicted in detail in Fig. 7.. Like the hydrophilic API, the increase in factors A and B result in an increased MDT, meaning that as the surface of the tablet is covered with a thicker coating, the release of the API is lower. The model describing the relation of the MDT as a function of factors A and B is presented in the following equation:

$$MDT = +121.33 + 8.86 \cdot A + 5.27 \cdot B \quad (6)$$

where, MDT is expressed in min, A: Surface Coverage, B: Thickness and $-1 < A, B < 1$.

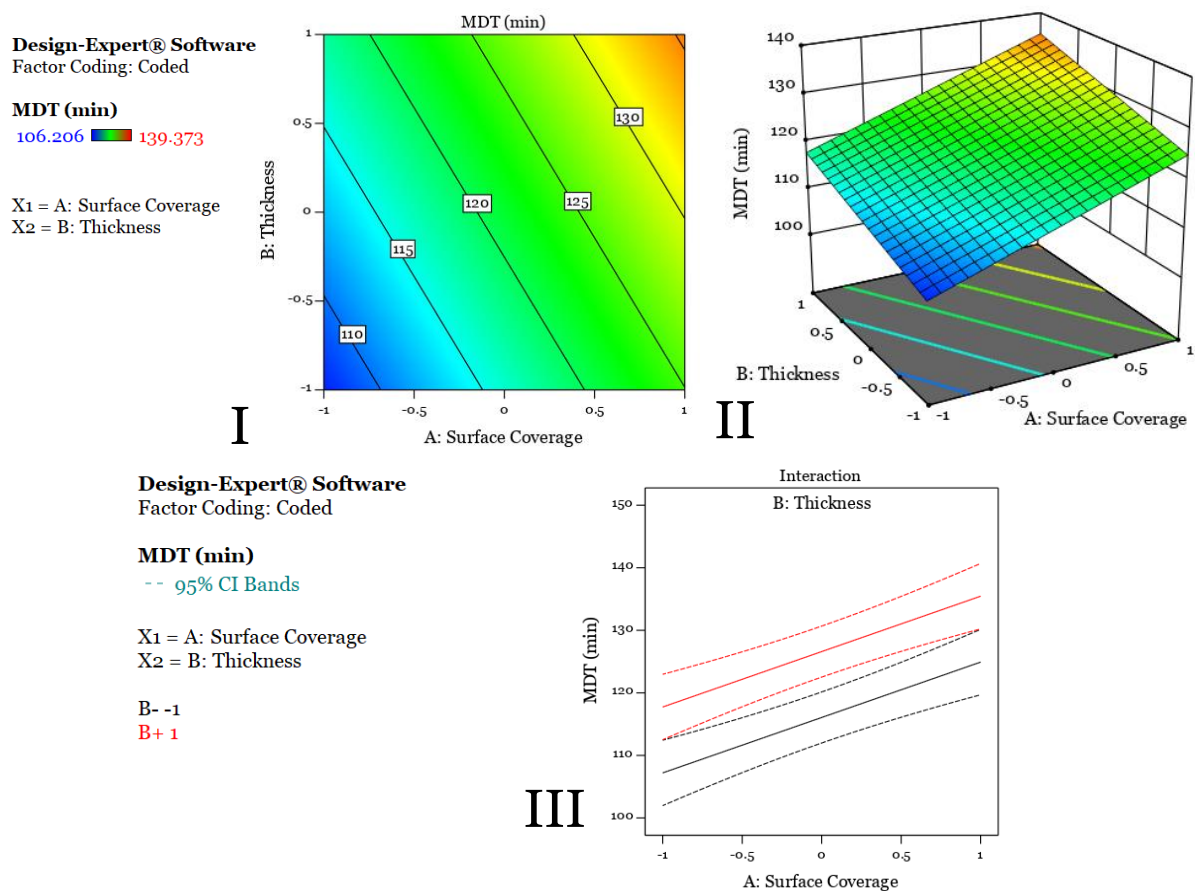


Fig. 7. Plots for Acyclovir Two-side coated tablets. Both factors are expressed in a coded scale from -1 to +1, with -1 being the lowest level and +1 being the highest. I) Contour plot, Surface Coverage vs Thickness. II) 3D Surface plot, Surface Coverage and Thickness vs MDT. III) Interaction Plot, Surface Coverage and Thickness vs MDT.

The significant terms and interactions which affect the MDT of both APIs are depicted in Table 8. It can be concluded that factors A, B and their interaction AB proved significant in most of the cases. For the one side coated Acyclovir tablets the model describing the relation of the MDT as a function of the selected factors was quadratic and factor A did not prove to be significant, while for the two-sided coated

tablets the model was linear, and the significant terms were only factors A and B. For the one-side coated Melevodopa tablets, the interaction AB was marginally not significant. In all cases however, factor B was found significant regardless of the API and the number of coated sides.

Table 8.

Terms with significant effect on the MDT. A: Surface Coverage , B: Thickness, S: Significant, NS: Non-Significant.

Tablet	Terms				
	A	B	AB	A ²	B ²
Melevodopa (One-side coating)	S	S	NS	-	-
Melevodopa (Two-sides coating)	S	S	S	-	-
Acyclovir (One-side coating)	NS	S	S	NS	S
Acyclovir (Two-sides coating)	S	S	-	-	-

Kinetic Model and statistical analysis

In order to identify any possible changes in the drug release kinetics when applying the partial glyceride coating to the different APIs, the Korsmeyer-Peppas equation (Eq. 7) was applied (Korsmeyer et al., 1983).

$$M_t/M_\infty = k \cdot t^n \quad (7)$$

where, M_t is the amount of drug released at time t , M_∞ is the total mass of drug loaded into the device, t is the release time, k is the release rate constant, and n is the diffusional exponent characteristic of the release mechanism.

This equation is only valid for the first 60% of the fractional release and the values expressed by the n exponent represent the release kinetics. In particular, if $n \leq 0.5$ then a Fickian diffusion mechanism occurs, if $0.5 < n < 1.0$ an anomalous (non-Fickian) transport, if $n = 1.0$ a Case II (relaxational) transport and if $n > 1.0$ a super case II transport (Dash et al., 2010; Korsmeyer et al., 1983; Vlachou et al., 2017).

In both APIs, regardless of the levels of the coating parameters, the release kinetics were found to be non-Fickian. For the uncoated Melevodopa tablets the exponent n was found 0.51 ± 0.04 , while for the uncoated Acyclovir tablets was 0.61 ± 0.004 . The one and two-sided coated Melevodopa tablets exhibited an exponent n which varied between 0.52-0.60 and 0.59-0.73 respectively. For the lipophilic API, all exponent values were found between 0.61-0.70, for the one-side and between 0.62-0.74 for two-sided coated tablets. In conclusion, regardless of the type of API, number of coated sides and the levels of the surface coverage-layers applied, n exponents fall within the non-Fickian transport range, which showed that the dissolution profiles can be controlled without affecting the kinetic mechanism.

4. Conclusions

The present work demonstrated the applicability of lipid excipients to 3D printing technology for partial coating of tablets for modifying the release rate of the two selected drugs, without altering the core composition of the formulation. For both the hydrophilic and lipophilic APIs, different dissolution profiles can be achieved by simply tuning three coating parameters, namely the surface coverage, number of the applied layers and the number of the coating sides. Regardless of the API used and the levels of the coating parameters, a non-Fickian release profile was evident.

3D printing technology can be successfully used in addressing the challenging demands for designing dosage forms with release profiles customized to each patient unique needs and/or production at the point of need. In combination with Design of Experiments, a major tool for the implementation of statistical thinking and Quality by Design in pharmaceutical development, 3D printing proved a simple and reliable tool for fine-tuning such a critical quality attribute.

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Athens, 03 December 2019

Dear colleagues,

We would like to submit the manuscript entitled “***Partial Tablet Coating by 3D Printing***” for publication in the “*International Journal of Pharmaceutics*”.

In this work we present the feasibility of employing 3D printing technology for the partial coating of tablets in order to precisely regulate the release of the active ingredient and achieve personalized drug release rates according to the patient’s unique needs. This was made feasible through a 3D printing process employing alternative coating materials, glycerides, and by controlling the coating characteristics only, without modifying the core formulation of the tablet. Experimental design was used as a statistical tool to characterize the effects and possible interactions of selected parameters of the printing-coating process on the release profiles of the two model active ingredients. Finally, the drug release kinetics and any possible changes were defined when applying the partial glyceride coating.

3D printing or Additive Manufacturing or Rapid Prototyping has evolved rapidly in the past decade and is currently being used along a wide range of industries, such as automotive, architecture, construction and aerospace. Among its attributes, the flexibility, robustness and precision were the ones that draw the attention of the researchers and industries in the pharmaceutical field challenging the traditional manufacturing technologies. The recently FDA approved first 3D printed dosage form along with the

opportunity of producing personalized dosage forms meeting the patient's unique needs, open new possibilities to product development and manufacturing. Within this context, complex geometries, designs requiring dose accuracy for narrow therapeutic index drugs, combinations of several active ingredients in one dosage form with tailored release profiles or the potential of production at the point of need, provide a much better outcome in terms of compliance, safety and effectiveness.

Semi-solid 3D printing in combination with a picked glyceride was selected in order to demonstrate the application of the proposed technology and the use of alternative materials as coating agents. The results were surprisingly promising, not only personalized drug release rates without altering the core formulation of the tablet were achieved, but also the drug release kinetics were unaffected regardless the coating geometry or the nature of the active ingredient. This could be regarded as a major advance on the field, as the challenging demands for designing dosage forms with release profiles customized to each patient unique needs and/or production at the point of need can be addressed with a simple and reliable tool.

To our knowledge, this is the first time that 3D printing in combination with glycerides have been utilized in the pharmaceutical field for the improvement and production of personalized dosage forms. We do believe that the present study complies with the spirit of International Journal of Pharmaceutics, as it shows the possibility of implementing novel technologies and statistical thinking in pharmaceutical development.

Looking forward to hearing from you.

Yours sincerely,

Eleni Tsintavi

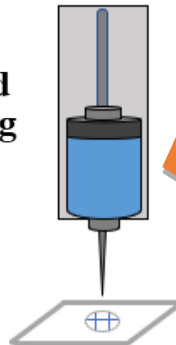
Core Tablets



Coating material



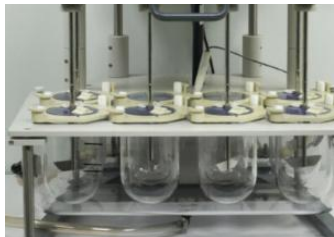
**Semi-Solid
3D printing**



Coated Tablets



Dissolution



**Statistical
Analysis**

