3D PRINTING – THE LOSAN APPROACH

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4TH DRUG DELIVERY CONFERENCE, BINZEN, 2022

We make
APIs perform

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Direct Powder Extrusion (DPE)

DPE is a 3D printing technology pioneered by FabRx. It involves the extrusion of a mix of drug and excipients (blend) through a nozzle using a single screw extruder. This technology enables the production of medicines and medical devices in a single-step process to create sustained or delayed release dosage forms.

Figure: https://www.fabrx.co.uk/technologies/

Fused Deposition Modeling (FDM)

First filaments have to be prepared by hot melt extrusion, comprised of pharmaceutical-grade materials and active ingredient.

FDM 3D printers melt the filaments through a nozzle onto a build plate, to construct a dosage form layer-by-layer to create sustained or delayed release tablets, as well as multi-drug combinations (polypills).

Figure: Junhui Fu et al, Int J Pharm, **2018,** 549(1-2), 370-379.

Selective Laser Sintering

SLS is a one-step fabrication process using a laser to selectively sinter powder particles in a layered manner to form a 3D structure.

The powder to be printed is homogenously spread on the powder bed by the roller.

Once the first layer is sintered, the powder bed moves down while the reservoir bed moves up to allow for the delivery of a new layer of powder on top of the previous one.

Figure: Fabrizio Fina et al, Int J Pharm, **2018,** 541(1-2), 101-107.

Selective Laser Sintering

Advantages

- Solvent-free nature
- Availability of FDA approved thermoplastic polymer/excipients (currently used in hot melt-extrusion process)
- Minimal/no post-processing step

Major challenges

- Requirement of at least one thermoplastic component in the formulation
- Thermal stability of drug and excipients

1) Case Study 1: SLS – Ondansetron Orodispersible Tablet

Aim

- Explore selective laser sintering 3D printing technology to fabricate orodispersable 3D printed tablets
- Taste masking of ondansetron
- Be comparable to commercial ondansetron ODT product (Vonau® Flash) according to USP monograph
- Strength 8 mg

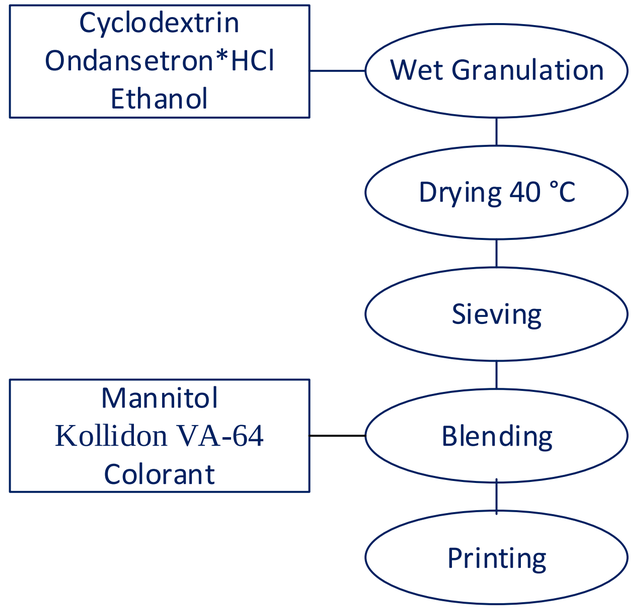
Why are Ondansetron Orodispersible Tablets interesting for 3D Printing?

- Ondansetron is an anti-emetic drug which is listed on the World Health Organisation (WHO) List of Essential Medicines
- Used as the first-line therapy for chemotherapy- and radiation-induced nausea and vomiting with a dose of 16 mg daily
- Challenges for delivering ondansetron in the mouth is its bitter taste
- Despite the high safety profile of ondansetron, one of its adverse effects is arrhythmia and dose-dependent QT-interval elongation when given with other medications, for which requires monitoring and control of the dose. QT-interval elongation is a life-threatening arrhythmia which can be induced by many drugs and lead to a sudden cardiac death. For vulnerable populations such as cancer patients or elderly taking different medicines, the use of personalised and dose-specific dosage forms is desirable.

Step 1 – Taste Masking

Different drug-cyclodextrin complexes were tested (1:1, 1:5, 1:20) to optimise the complex preparation to get the best inclusion and taste masking. The ratio 1:1 showed crystalline form of the drug, but both 1:5 and 1:20 ratios showed no crystalline form of ondansetron.

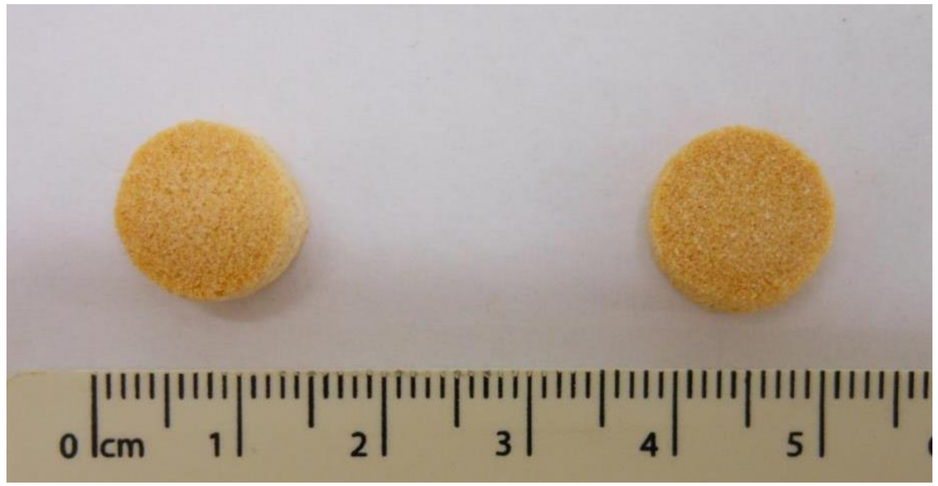
Further down processing..



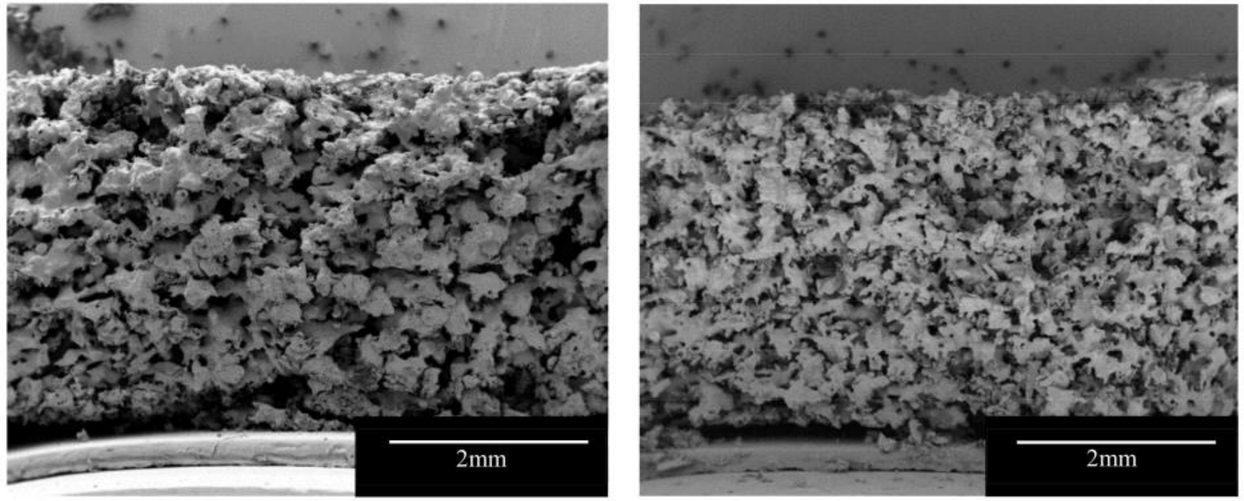
Candurin® Gold Sheen (colorant) was added to the formulations to enhance energy absorption from the laser and aid printability.
Powder mixtures were then transferred to a Desktop SLS printer (Sintratec Kit, AG, Brugg, Switzerland) to fabricate the oral dosage formulations. AutoCAD 2014 (Autodesk Inc., USA) was used to design the templates of the cylindrical printlets to obtain an ondansetron dose of 8 mg in the 3D printed formulations (12.4 mm diameter x 3.6 mm height).

Composition of the formulations (w/w)				
Formulation	1:5 ondansetron: cyclodextrin complex	Kollidon VA-64	Mannitol	Candurin® Gold Sheen
Formulation – I	22%	25%	50%	3%
Formulation – II	22%	15%	60%	3%

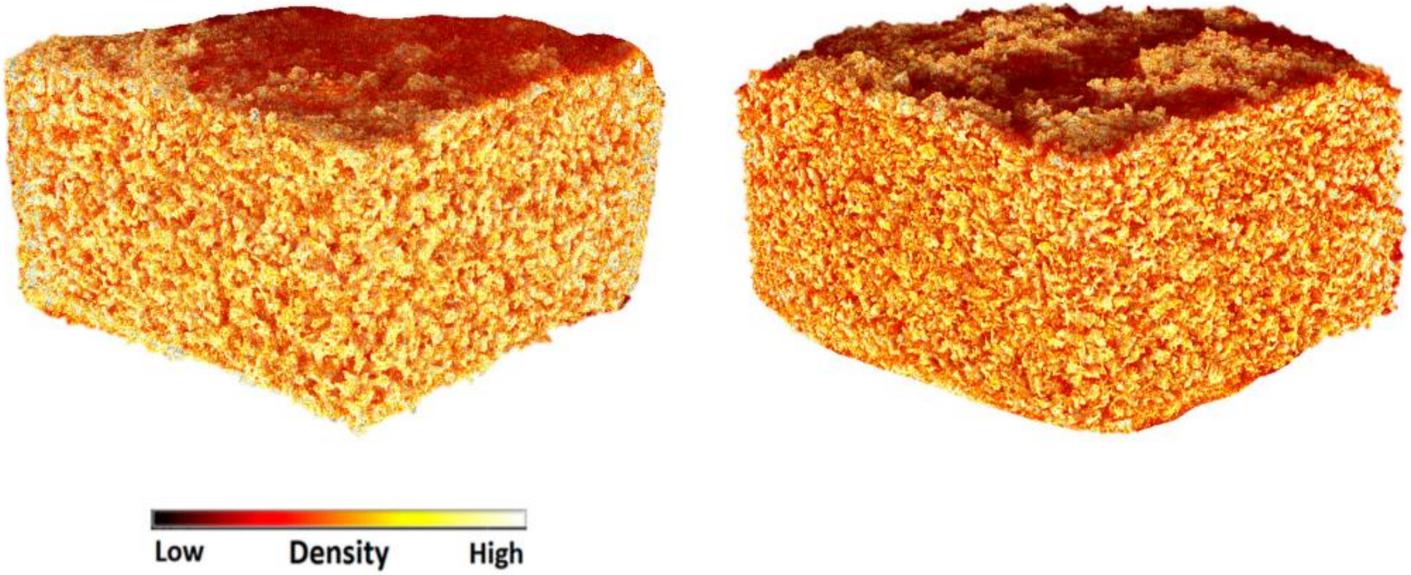
Drug Product Characterization



Images of the Formulation I (left) and Formulation II (right) (units are in cm).



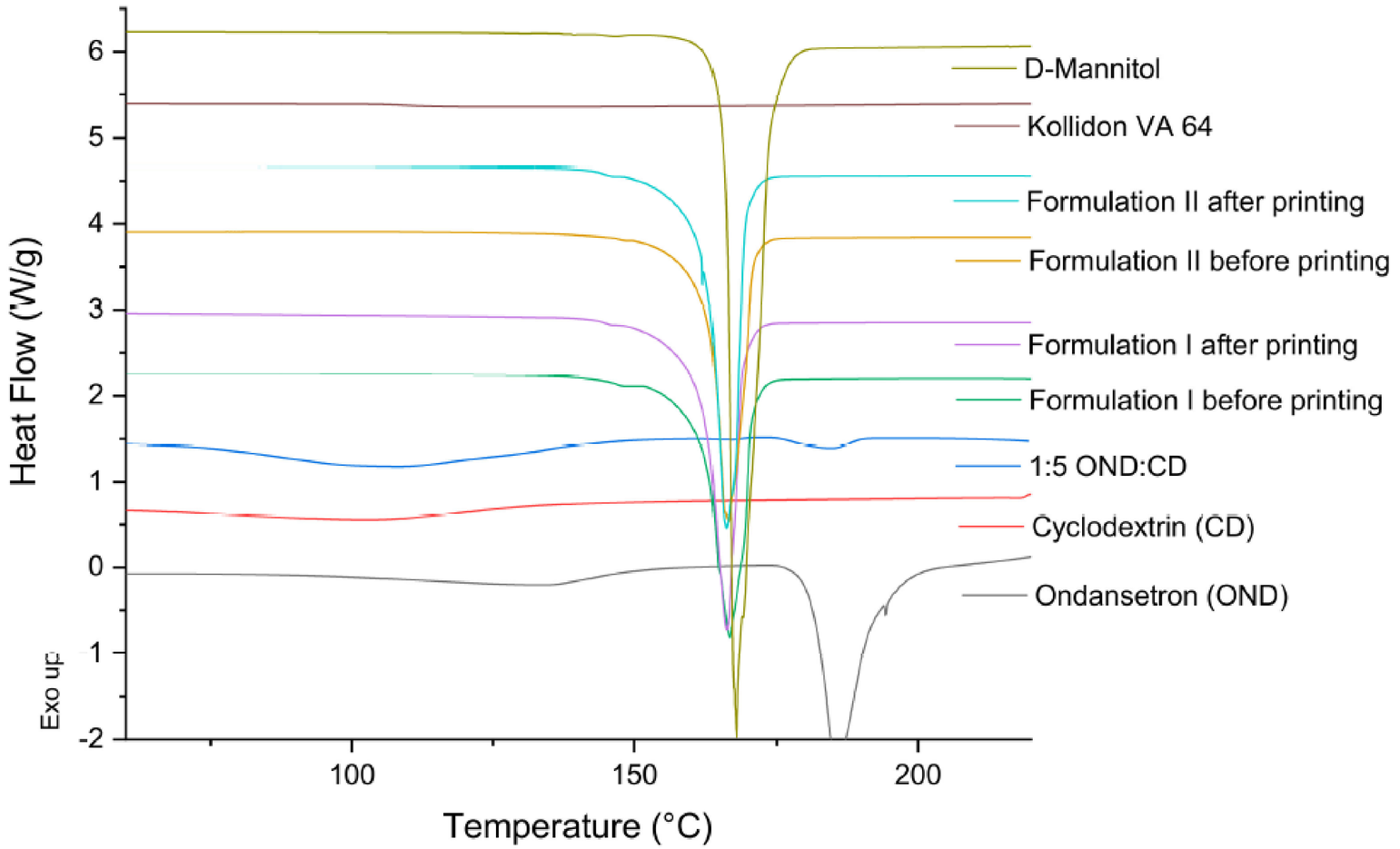
SEM Images of the Formulation I (left) and II (right)



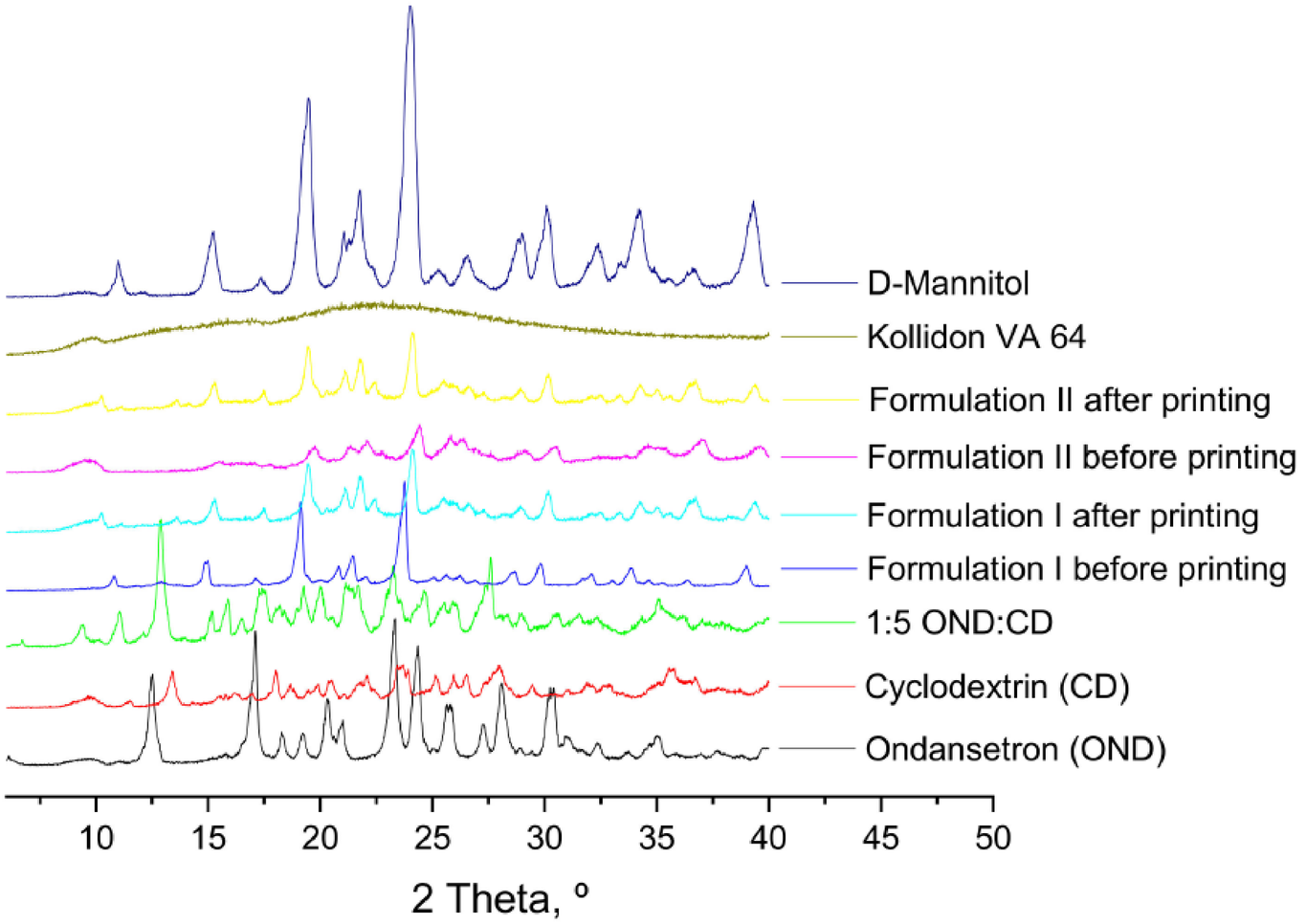
Formulation I	
Closed porosity (%)	0.4 ± 0.1
Open porosity (%)	36.3 ± 0.1
Total porosity (%)	37.2 ± 0.2

Formulation II	
Closed porosity (%)	0.2 ± 0.1
Open porosity (%)	41.3 ± 0.2
Total porosity (%)	41.5 ± 0.2

X-ray micro-CT Images of the Formulation I and II.

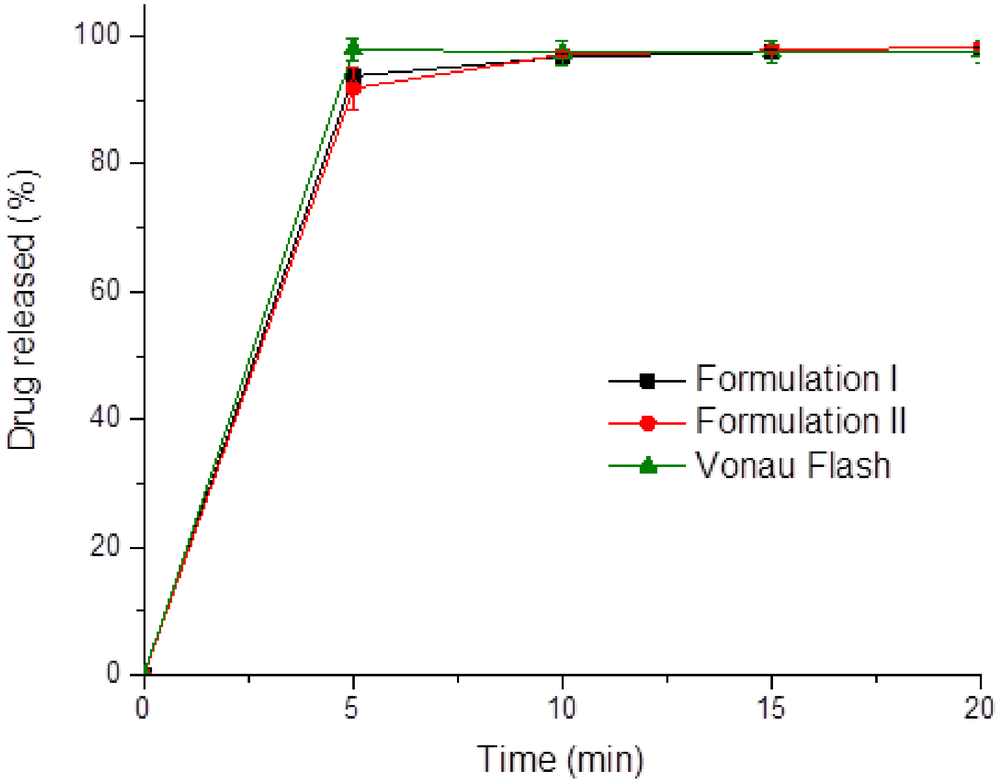


DSC thermograms of pure drug, individual polymers, powder mixtures before printing and the printlets.



X-ray powder diffractograms of pure drug, individual polymers, powder mixtures before printing and 3DP discs.

Characteristics of the formulations						
Formulation	Mean mass ±SD (mg)	Diameter ±SD (mm)	Height ±SD (mm)	Breaking force (N)	% Drug loading from theoretical content ±SD (%)	Disintegration time ±SD (s)
Formulation I	217.2 ±4.2	11.7 ±0.1	4.4 ±0.2	14.7 ±2.5	98.6 ±2.2	14.3 ±3.1
Formulation II	211.3 ±7.3	11.9 ±0.1	3.7 ±0.1	18.5 ±5.0	98.1 ±1.7	15.3 ±2.3



Dissolution profiles of the commercial and the 3D printed formulations

Summary

SLS 3D printing was used to manufacture orally disintegrating 3D printed tablets of two formulations of ondansetron. The formulations included ondansetron in drug-cyclodextrin complexes and a high percentage of mannitol (up to 60%). Proper taste masking could be achieved.

Both printlets types showed fast disintegration (~15 s) and released more than 90% of the drug in 5 min independently of the mannitol content. This work has demonstrated the potential of SLS 3DP to fabricate orodispersible printlets comparable in disintegration time and drug release rate to a commercial ODT using a manufacturing technology that would allow the preparation of personalized dose medicines.

pharmaceutics

MDPI

Article

Selective Laser Sintering 3D Printing of Orally Disintegrating Printlets Containing Ondansetron

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Received: 19 December 2019; Accepted: 20 January 2020; Published: 30 January 2020

check for updates

Thanks to

Nour Allahham
Fabrizio Fina
Simon Gaisford
Abdul W. Basit
Alvaro Goyanes

FabRx

Carmen Marcuta
Lilia Kraschew

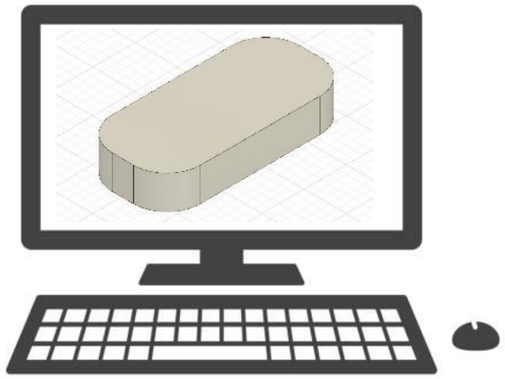
https://newsroom.losan-pharma.de/

CONCEPT OF FDM PRINTING AT LOSAN

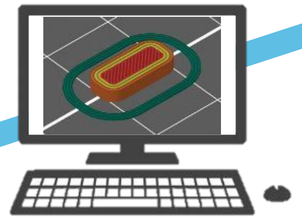
- The FDM printing uses an implemented technology platform, the HME technology, for production of the flexible and diameter controlled extrudate strands with excellent homogeneity of the included API in the polymer
- Extrudates with amorphous embedded API or dispersed, still crystalline APIs
- Our focus is on the development of immediate release tablets
- Stability evaluations will be done using specific implemented analytical systems such as XRPD, SEM beside conventional testing systems (HPLC etc.)
- Design of a special printer head (with included extrusion part for melting before printing) will be performed
- GMP set-up of printer

FDM PRINTING AT LOSAN

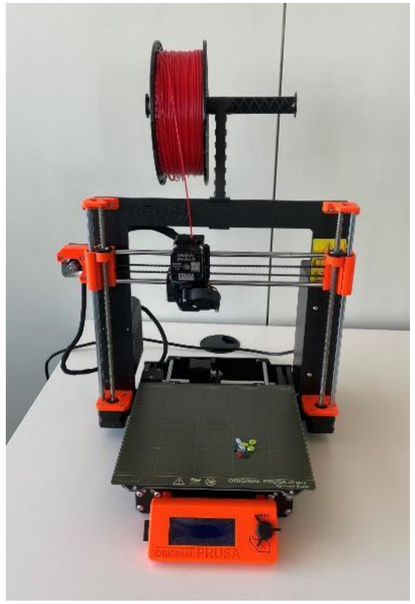
Pharma 11 Twin-screw Extruder - Thermo Fischer



CAD Software - Autodesk Fusion 360



Prusa Slicer



3D Printer - PRUSA i3

3D-printed tablet

GENERAL PROPERTIES FOR PRINTABLE STRANDS

- not brittle
- flexibel
- a certain rigidity
- of defined thickness
- smooth surface
- windable
- meltable
- storable
- …

POLYMER + PLASTICIZER + API

SUITABLE POLYMERS/ MIXTURES

POLYMER

- Methacrylic polymers (Eudragit® E, RL, RS)
- HPMC
- HPC
- PCL
- PEO (e.g. 100 K, 200 K)
- PLA
- PVP
- PVP-VA
- PVA
- Kollicoat® IR
- …

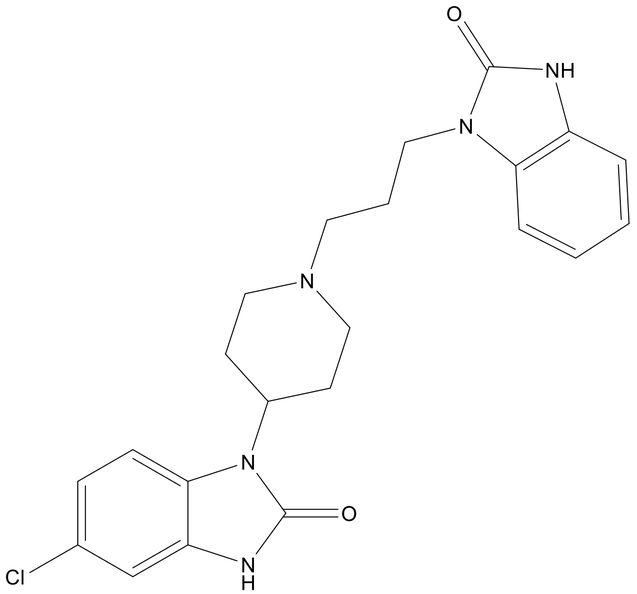
PLASTICIZER

- Triethylcitrate (TEC)
- Arabic gum
- Triacetin
- Polyethylene glycol (e.g. 1500, 4000)
- Sugar alcohols (e.g. Sorbitol)
- …

- Gelucire® (enhancer of drug release)

CASE STUDY WITH DOMPERIDONE

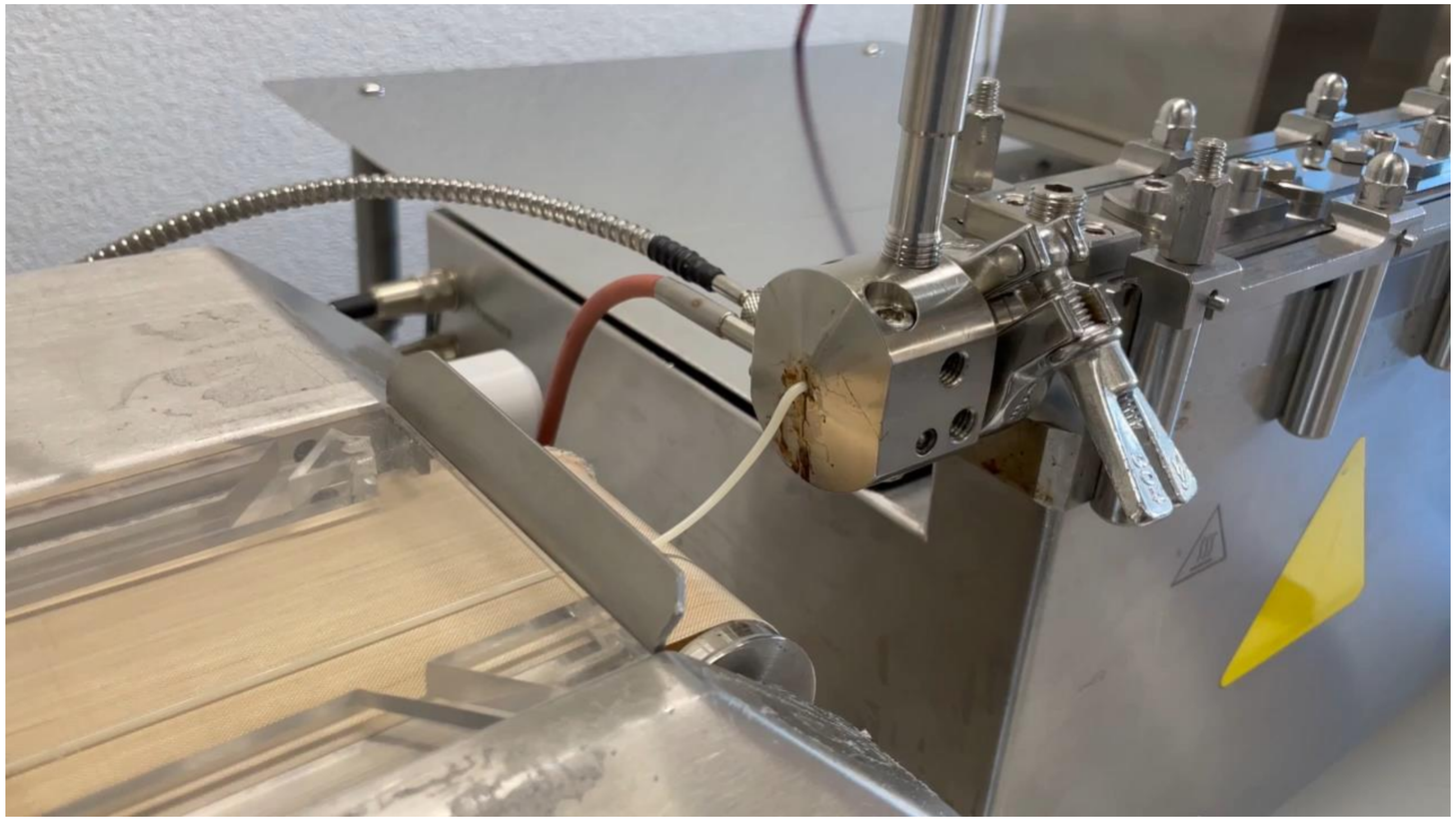
- antiemetic
- dosage: 10 mg
- M_R: 425.91 g/mol
- melting point: 242.5 °C
- insoluble in H_2O



Domperidone

CASE STUDY WITH DOMPERIDONE

- Polymer/ Plasticizer/ API ratio: 70/ 20/ 10
- Extrusion temp.: 200 °C
- „standard“ screw design: kneading/ mixing and transport zones



CASE STUDY WITH DOMPERIDONE

Printer setup:

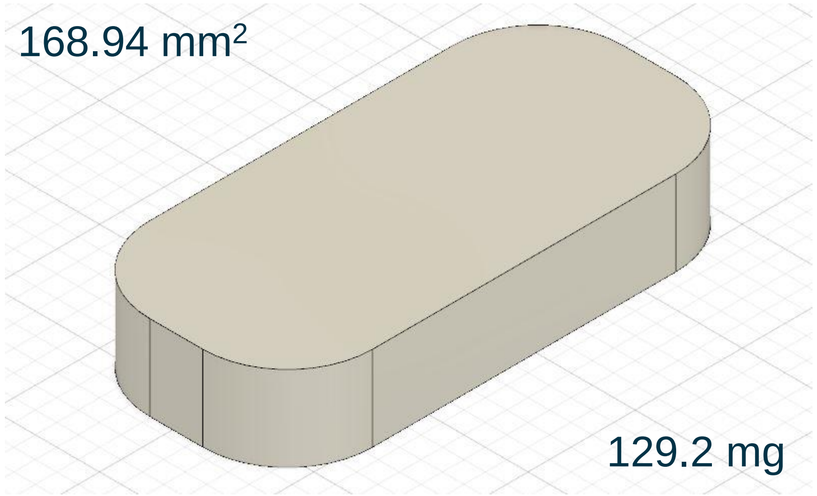
- layer height: 0.05 mm
- temperatures:
  - nozzle: 195 °C
  - printing bed: 60 °C

- diameter filament: 1.75 mm
- diameter nozzle: 0.4 mm

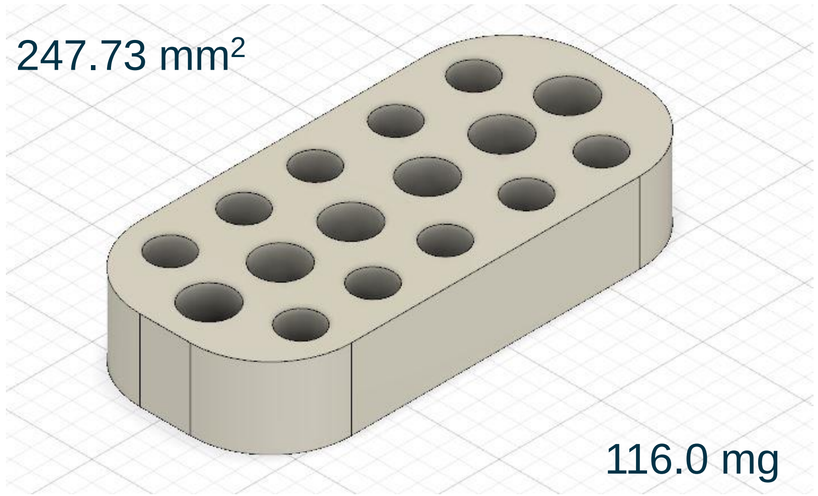
- tablet dimensions: 11.5 x 5.25 x 2 mm
- used filament: 5 cm
- printing duration: approx. 6 min

CASE STUDY WITH DOMPERIDONE

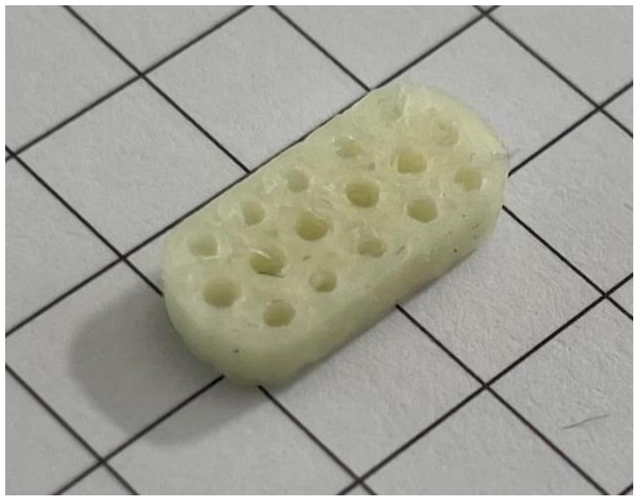
- Increase of API release by increasing tablet surface - *Infill concept*



+ 78.79 mm²



no disintegration after > 1 h



disintegration after 10 min

GMP ASPECTS

- Requirements:
  - Removal of potential foreign particle from the printing process
  - GMP compliance of the printer set-up with regard to process control and variability (temperature, pressure, flow etc.)
  - 21 CFR part 11 conform for data treatment
  - Lead times and costs
- Validation concept that covers the reproducible printing of tablets from stored strands under appropriate conditions and re-use over a defined time period (e.g. 12 months)
- Concept for primary and secondary packaging for produced tablets including quality control for direct delivery of the personalized treatments in clinical applications

SUMMARY & OUTLOOK

- Concept established and first case study started
- Definition of suitable polymers/ plasticizers ongoing for the intended future process
- Optimization of *infill concept* to reach immediate release specifications of tablets
- Process set-up for extrudates with controlled diameter - implementation of CaliCut Post-extrusion system
- Design of the printer head after definition of polymers/ plasticizers and process conditions and subsequent trials with further cases
- GMP set-up of printer (planned for end of this year)
- Manufacture of clinical trial samples for personalized medicines

Thanks to

Elena Kittel
Ramona Kopton

Matthias Rischer & Ansgar Bögershausen

THANK YOU
FOR YOUR ATTENTION