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3D printing in pharmaceutical technology

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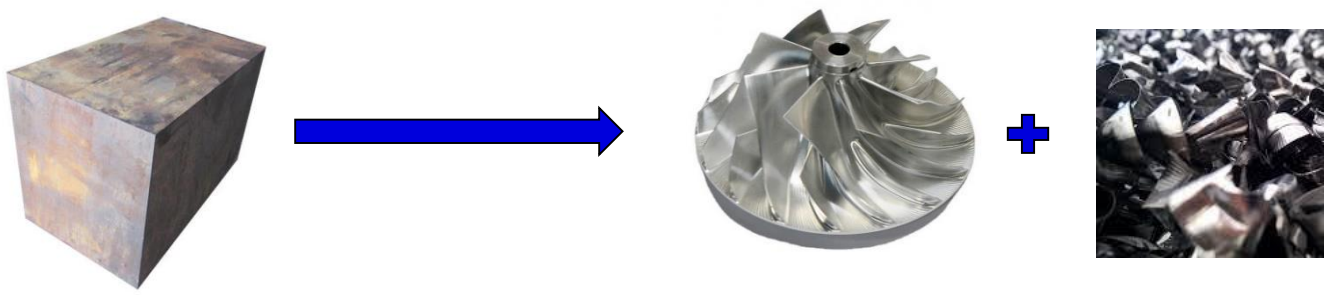
What is 3D printing?

Basic definition

- Manufacturing of 3Dimensional object according to input digital file
- Additive manufacturing:

  Technologies that, based on a geometrical representation, create physical objects by successive addition of material.

- Opposite – subtractive manufacturing (CNC machining, cutting, sawing etc.)



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Printing workflow

Model – Slicing – G-code – Printing - Product

- Preparation of digital model (*.stl; *.obj; *.amf)
  - De novo (CAD)

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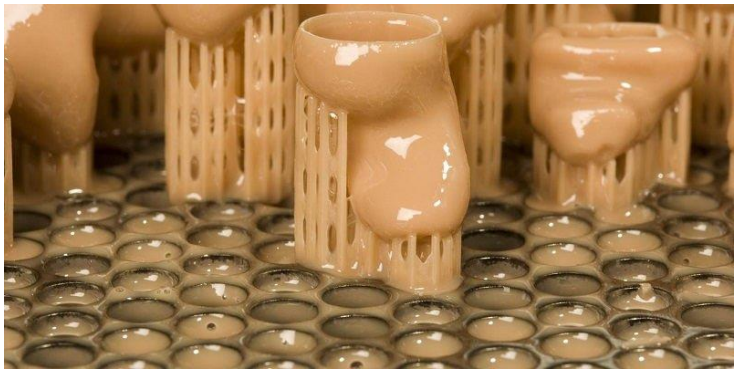
Printing workflow

Model – Slicing – G-code – Printing - Product

- Preparation of digital model (*.stl; *.obj; *.amf)
  - Scanning of readily available structure



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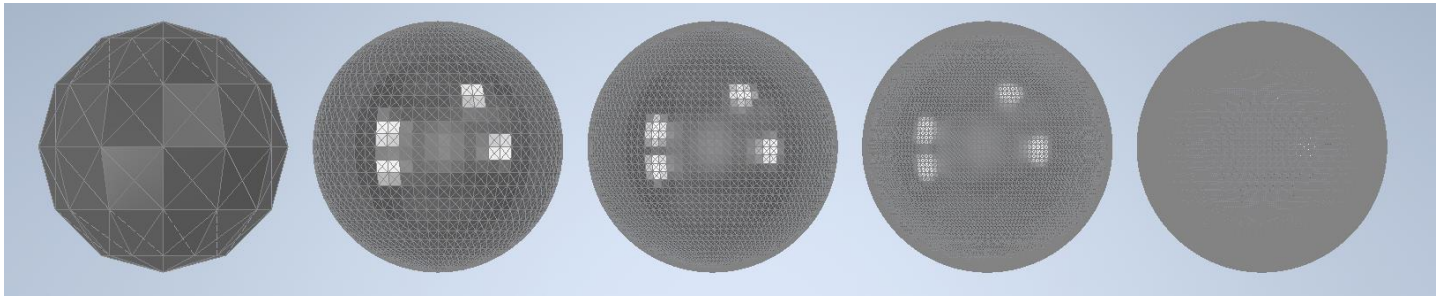
Printing workflow

Model – Slicing – G-code – Printing - Product

- It is necessary to chose optimal file format for the application!
- ***.stl**
  - keeps only surface geometry, **can´t define other properties**
  - model surface is replaced by triangular net, **positions of corner points are defined**
  - **Resolution!**
- Example:
  - Sphere of 20 mm radius has a theoretical volume of **4188.8 mm^3**
  - By setting the different output quality, volume can change radically!

3732.5 mm^3	**4169.7** mm^3	**4181.3** mm^3	**4186.3** mm^3	**4187.9** mm^3
6 kB	171 kB	441 kB	1395 kB	6940 kB



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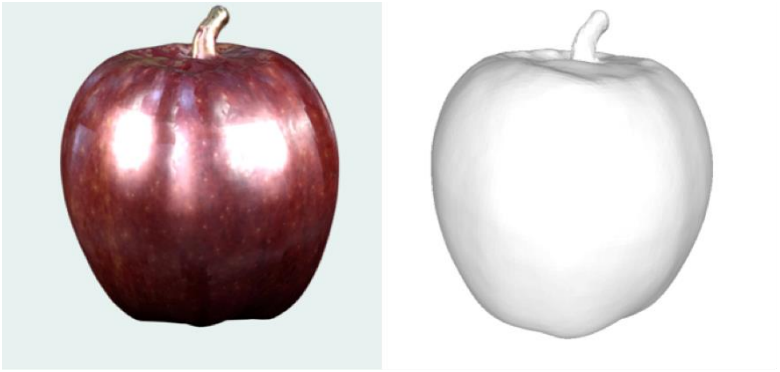
Printing workflow

Model – Slicing – G-code – Printing - Product

- ***.obj**
  - geometry is defined in the same way as in *.stl
  - properties of surfaces can be defined – type, material, color etc. – **usefull in multimaterial printing**



.obj .stl

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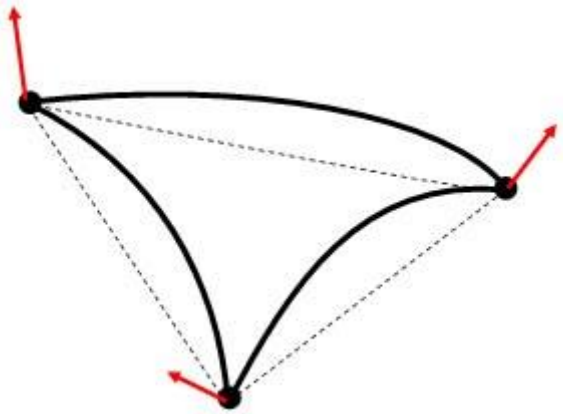
Printing workflow

Model – Slicing – G-code – Printing - Product

- ***.amf**
  - geometry is defined in the same way as in *.stl and *.obj
  - curvature of point connections can be defined – **morec precise**
  - as in ***.obj** properties of surfaces can be defined – type, material, color etc. – **usefull in multimaterial printing**



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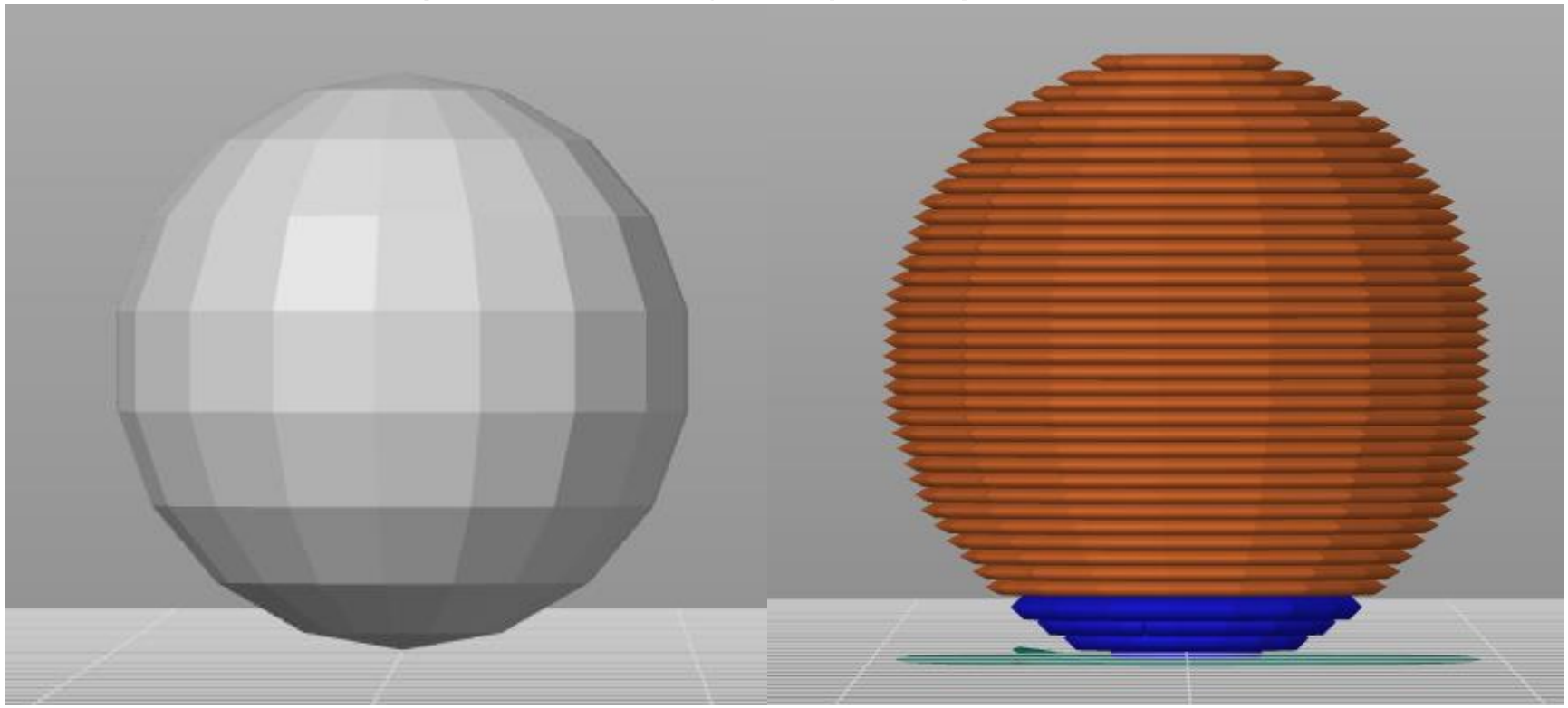
Printing workflow

Model – **Slicing** – G-code – Printing - Product

– Model is decomposed into layers (slices)



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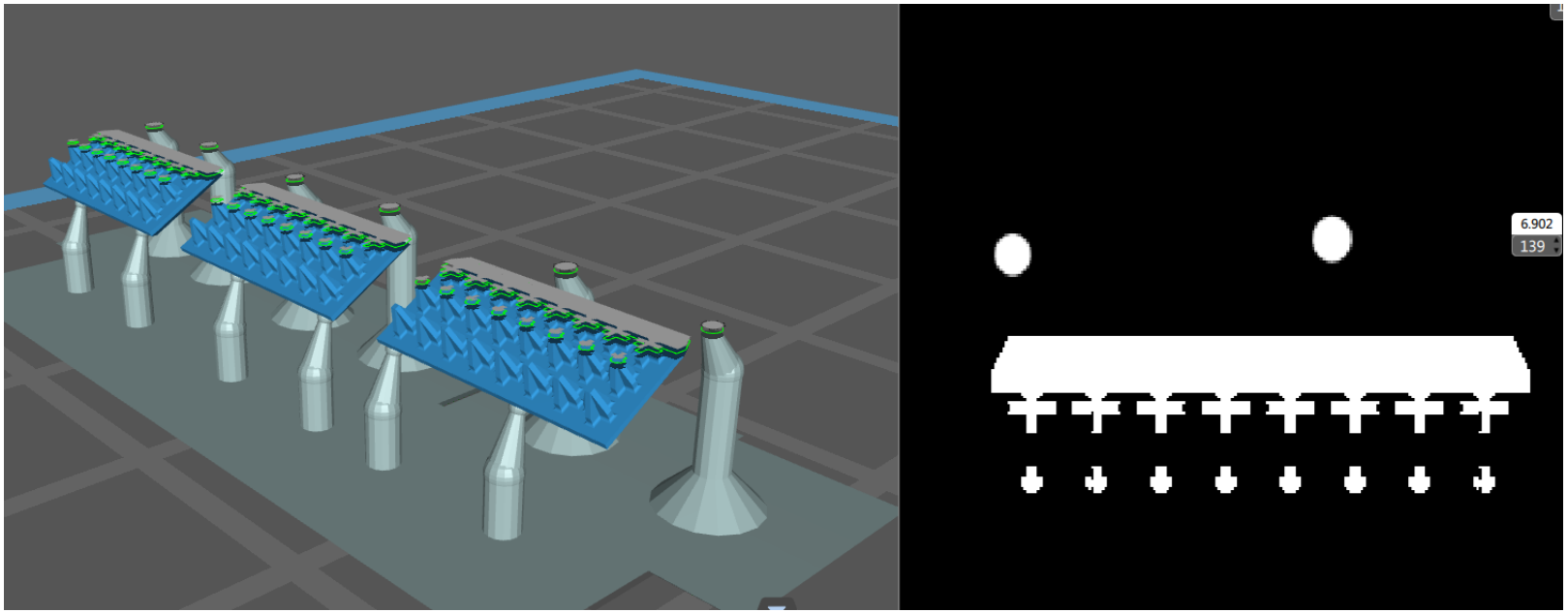
Printing workflow

Model – **Slicing** – G-code – Printing - Product

- Specific methods – SLA, binder jetting
  - Exposure time
  - Binder volume



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Printing workflow

Model – Slicing – **G-code** – Printing - Product

- Orders executable by the printer
- Defines path of print tool (nozzle, laser etc.) and print parameters
  - Temperature/Energy
  - Speed of movement
  - Amount and type of material
  - Extrusion width
  - And other – according to the print technology

CuteOcto.gcode – Poznámkový blok

Soubor Úpravy Formát Zobrazení Nápověda

```
G1 X53.844 Y129.937 E116.81200
G1 X54.280 Y128.987 E117.02180
G1 X54.481 Y128.625 E117.10474
G1 X54.707 Y128.271 E117.18904
G1 X55.305 Y127.472 E117.38941
G1 X55.585 Y127.159 E117.47364
G1 X55.951 Y126.794 E117.57722
G1 X79.175 Y105.247 E123.93289
G1 X80.028 Y104.524 E124.15719
G1 X80.842 Y103.960 E124.35601
G1 E123.85601 F2400.00000
G92 E0
G1 X120.688 Y175.747 F6000.000
G1 E0.50000 F2400.00000
G1 F900
G1 X120.583 Y175.841 E0.52265
G1 X120.410 Y175.808 E0.55102
G1 X119.484 Y175.454 E0.71039
G1 X118.849 Y175.283 E0.81603
G1 X118.336 Y175.182 E0.89999
G1 X117.782 Y175.107 E0.98988
G1 X117.478 Y175.109 E1.03878
```


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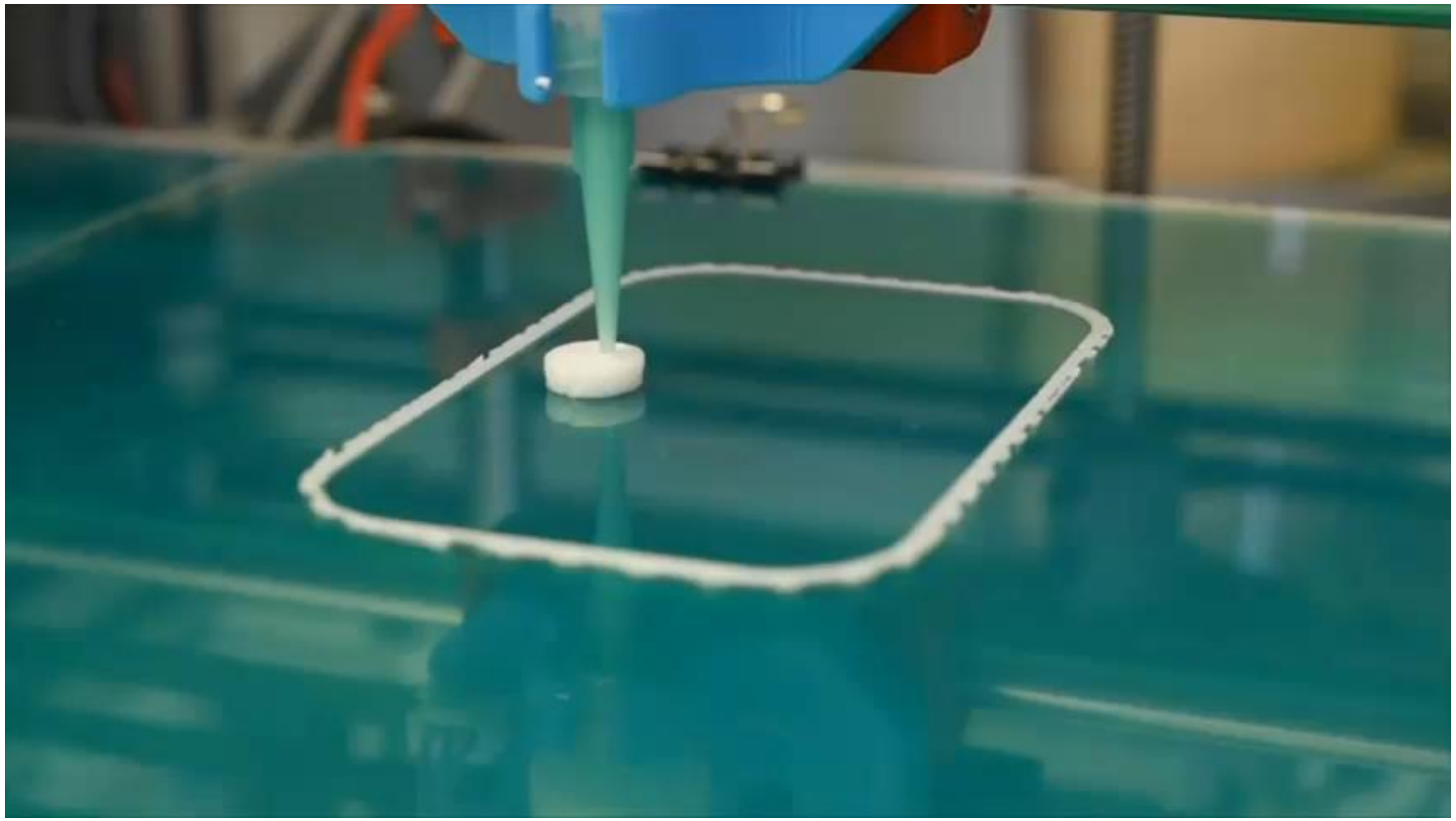
Printing workflow

Model – Slicing – G-code – **Printing** - Product

- Printer executes commands



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Printing workflow

Model – Slicing – G-code – Printing - **Product**

- Post-processing
  - Cleaning of support structures
  - Post-curing (UV in SLA)
  - Annealing (heat reatement)

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Advantages for the PT

- Quick and relatively cheap modification and tuning of product manufacturing in small batches.
- Possibility to define drug dose, release kinetics, shape, color, etc.
- Preparation of DFs having specific properties unattainable by classic manufacturing (compartmentalisation, complex shapes)

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Where to use it?

- Pre/clinical phase of drug developmenet
  - Dose, shape, stability (on-demand preparation)
  - Acceleration of **I** and **IIa** phases (**IIb**)

- Individualised therapy – DDF prepared and tuned to exact patient and his needs
  - increased compliance
  - decreasing of side effects - almost 80% of SE caused by inapropriate dosing*,**

- Life-cycle management
- Local manufacturing of DDF
  - 505(b)(2) NDA
  - Manufacturing at the location – developing countries (outbreak)
  - Hybrid 10(3) dle 2001/83/EC

*COHEN, J. S.: Tablet splitting: imperfect perhaps, but better than excessive dosing. Journal of the American Pharmaceutical Association, 2002, 42.2: 160-162.
**MA, Q.; LU, A.: Pharmacogenetics, pharmacogenomics, and individualised medicine. Pharmacological Reviews, 2011, 63.2: 437-459.

Two streams

- „Point of care“ preparation
  - Classical 3D technologies (FDM, SSE)
  - „desktop“ enclosed machines for GMP

- Industrial manufacturing
  - Heavily modified or specific 3D printing technologies
    screen printing
    binder jetting
    direct powder extrusion
  - bigger technological sections

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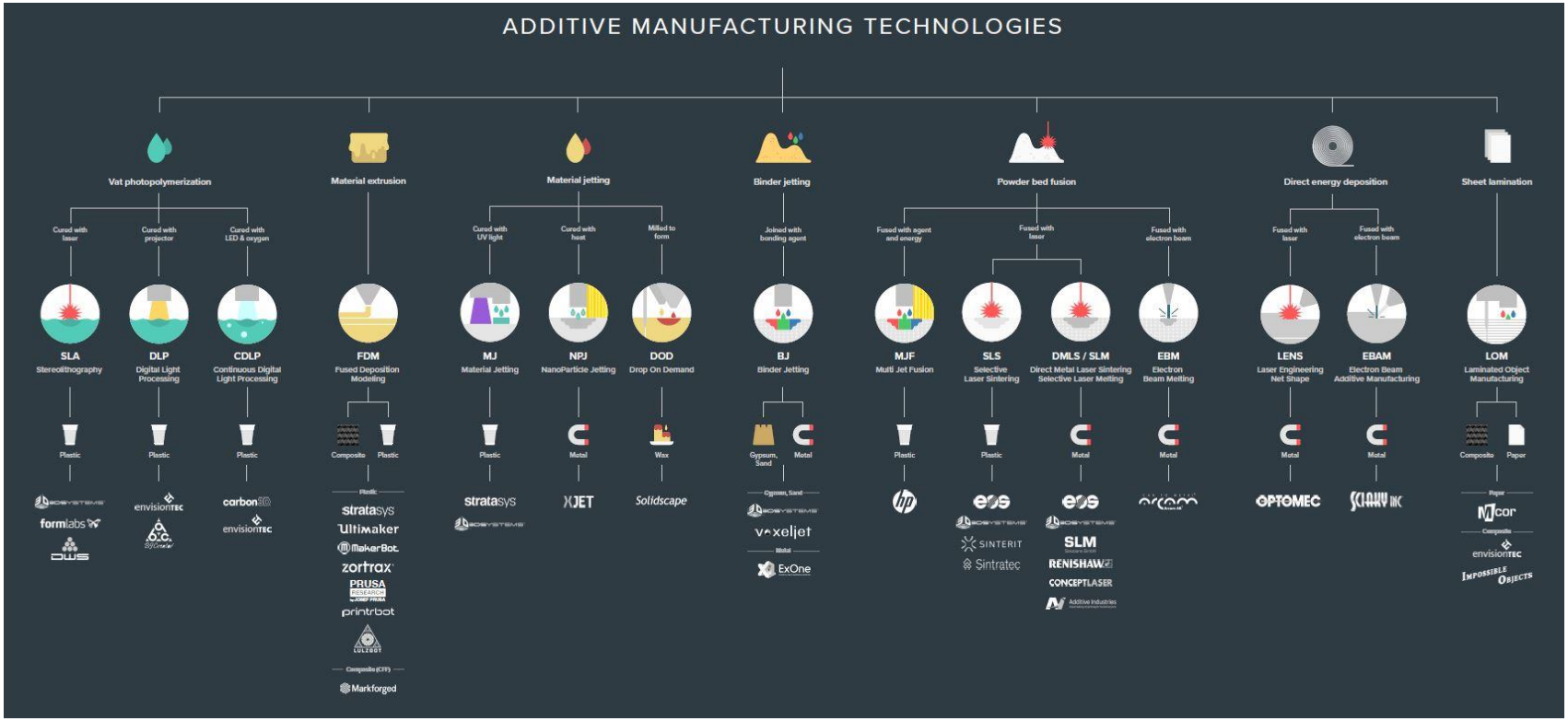
Types of 3D printing



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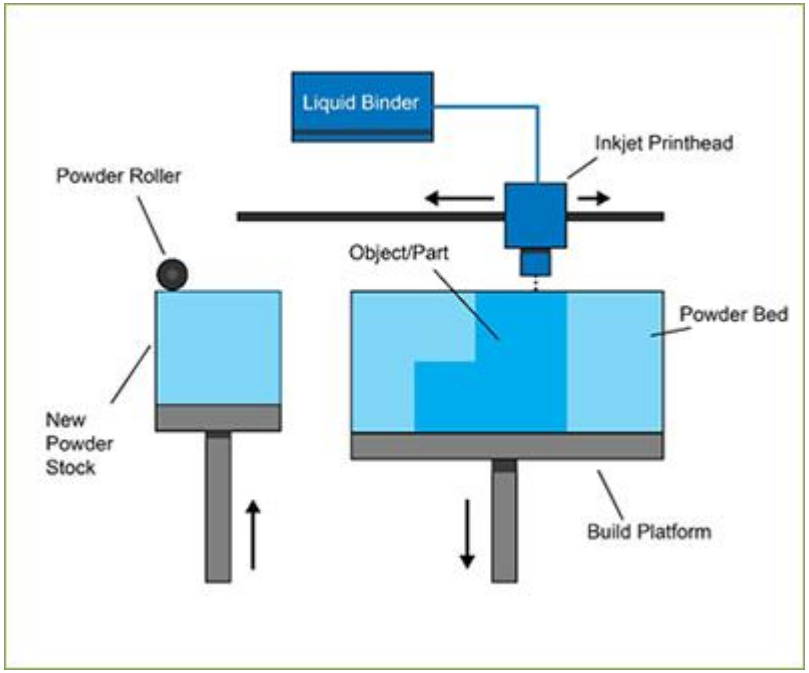
Types of 3DP appropriate for pharmacy

- **Binder jetting**
- **SLS** – selective laser sintering
- **FDM/FFF** – fused deposition modeling / fused filament fabrication
- **SSE** – semi-solid extrusion
- **SLA** – stereolitography

Binder jetting

- **Binding of thin powder layer**
  - Thin layer of powder is binded by dosed liquid (water, ethanol, glycerol)
  - New layer of powder is spread and the process is repeated
  - Product is enveloped in free powder -air claning, sieving
  - Binder may be in both – liquid or powder (sorbitol, mannitol, povidon)!
  - Excipients – surfactants (tuning of surface tension – better wetting), disintegrants, colorants etc..



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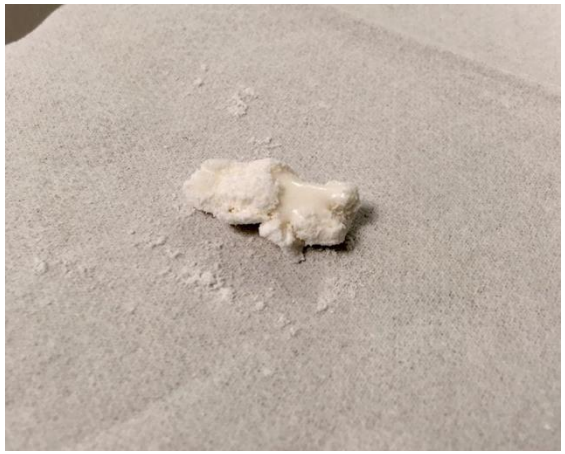
Binder jetting

- Benefits:
  - Flexibility in liquid dosing – DDF with solid surface and free-flowing powder inside
  - „**voxel**“ – 3D analogue of pixel – the smallest unit of volume, in which a liquid can be deposited
- What to watch for:
  - particle sice distribution
  - flow properties of powder
  - recycling: stray drops may bind unwanted powder → **aglomerates** (milling, sieving)
  - Inter step drying

Sometimes things just fall apart



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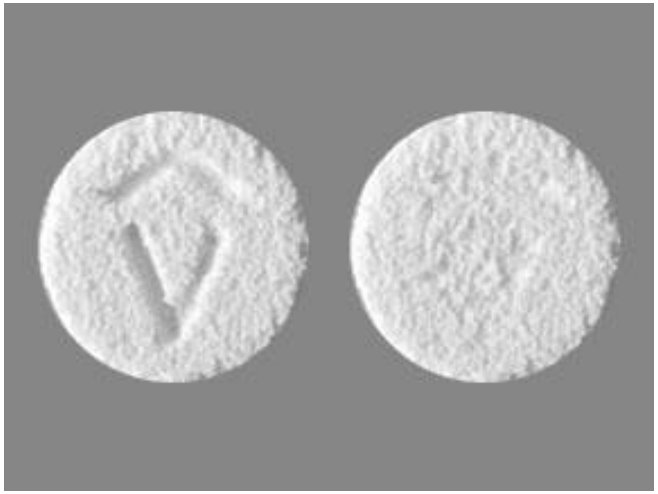
Binder jetting

- Technology **ZipDose®** (Aprecia)
- **Spritam®** ODT containing levetiracetam
  - First (and still the only) commercialy available 3D printed medicine (2015)
  - High porosity – quick disintegration in mouth, even with small amount of water
  - 250–1000 mg dose
  - practicaly still „classic“ manufacturing



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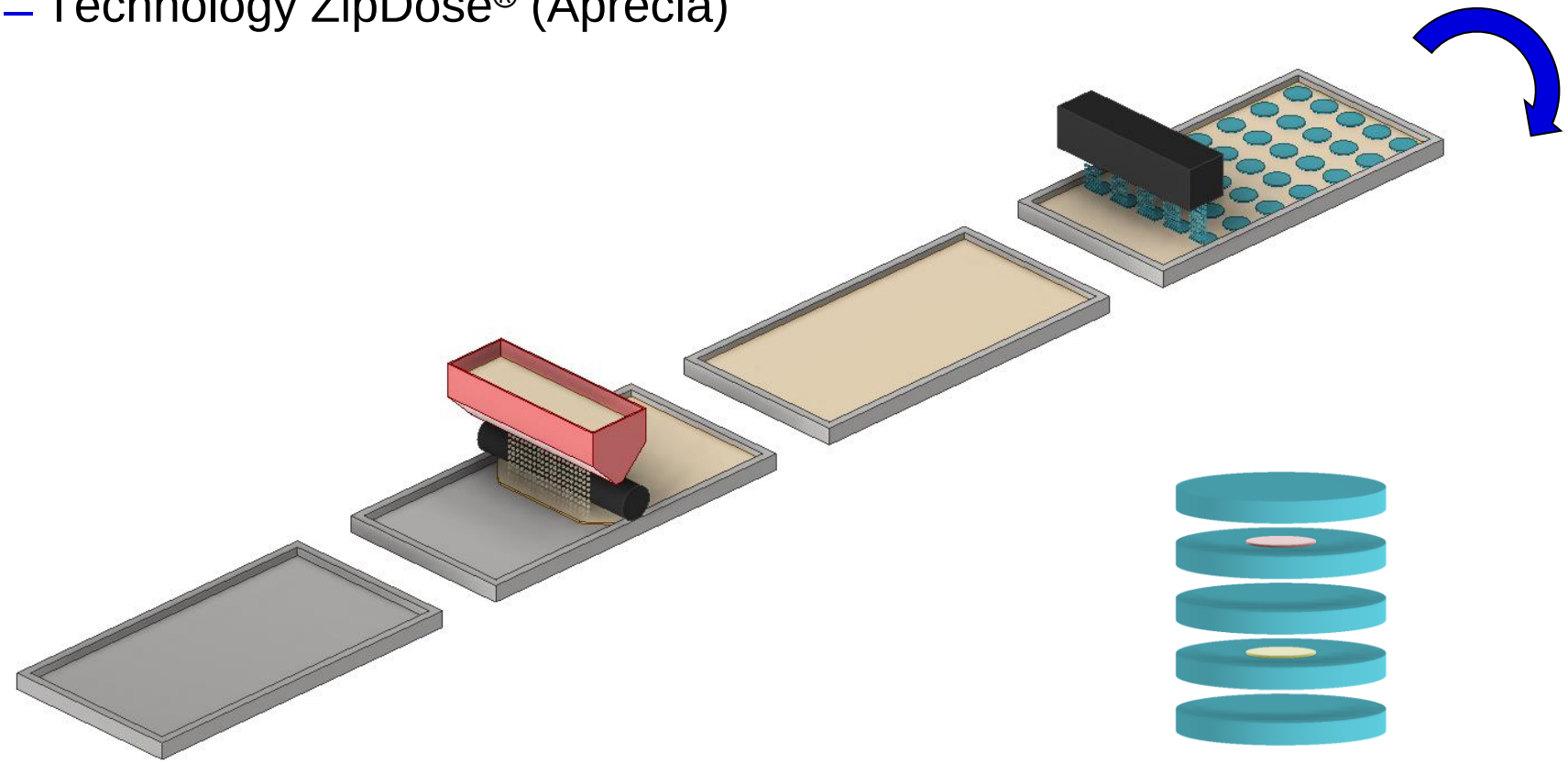
Binder jetting

– Technology ZipDose® (Aprecia)



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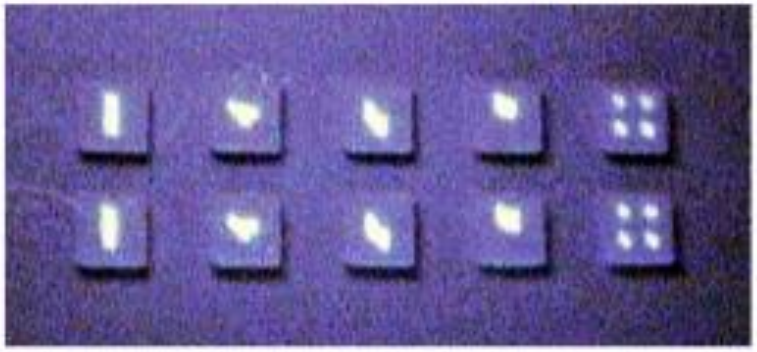
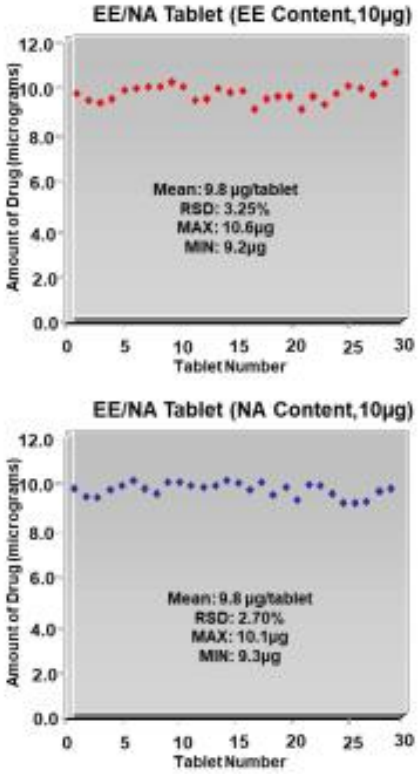
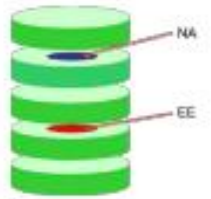
Binder jetting

- Technology ZipDose® (Aprecia)
  - Accurate deposition of small doses
  - Physical separation of drugs
  - Counterfeit measures







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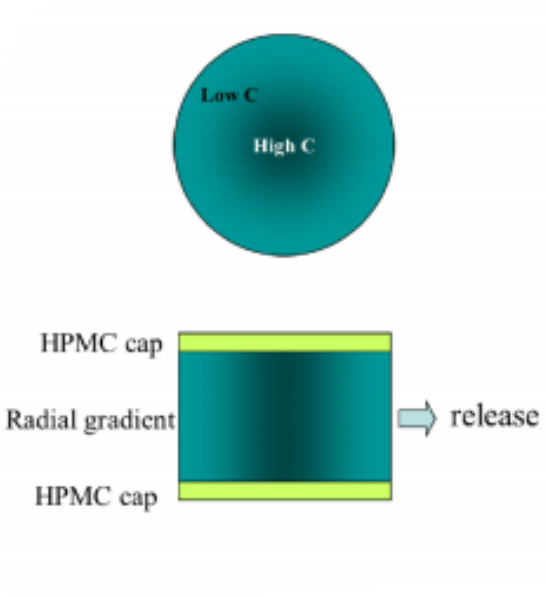
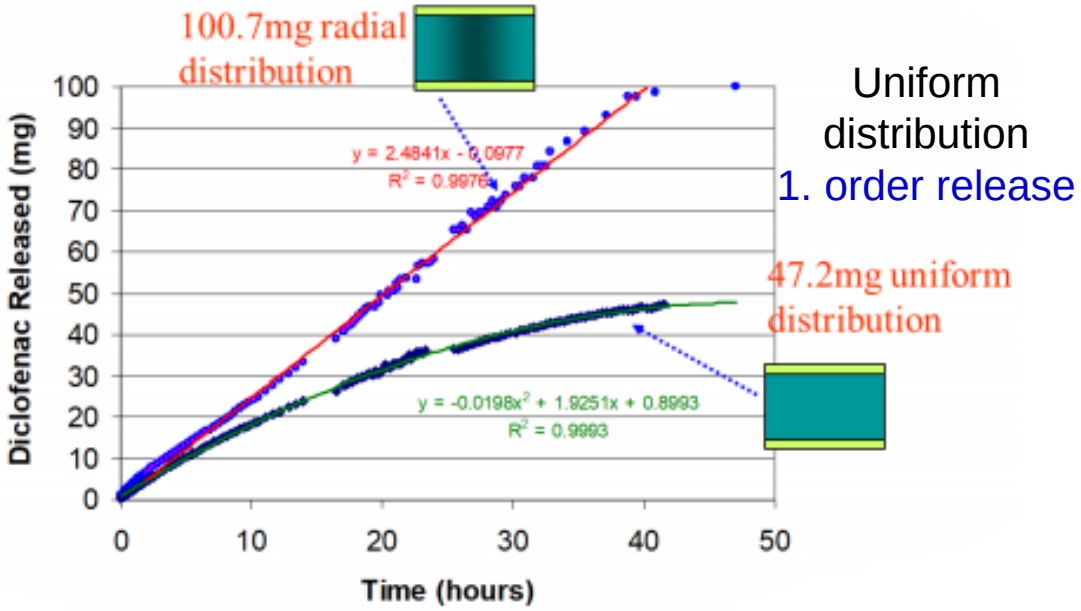
Binder jetting

- Technology ZipDose® (Aprecia)
  - Concentration gradient of drug – tuning of release kinetics



Radial distribution
0. order release



Uniform distribution
1. order release

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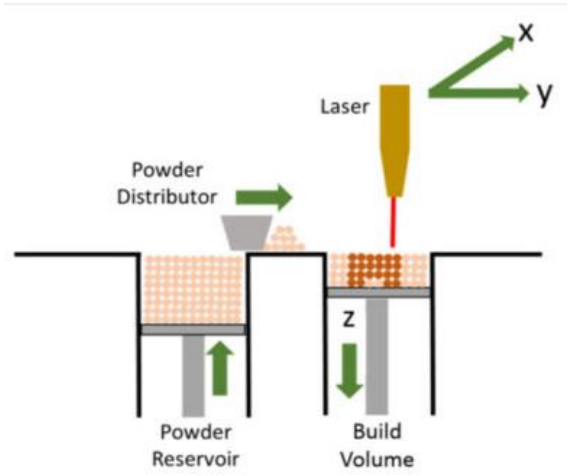
SLS – selective laser sintering

- Analogic to binder jetting
- Powder is melt-fused by laser



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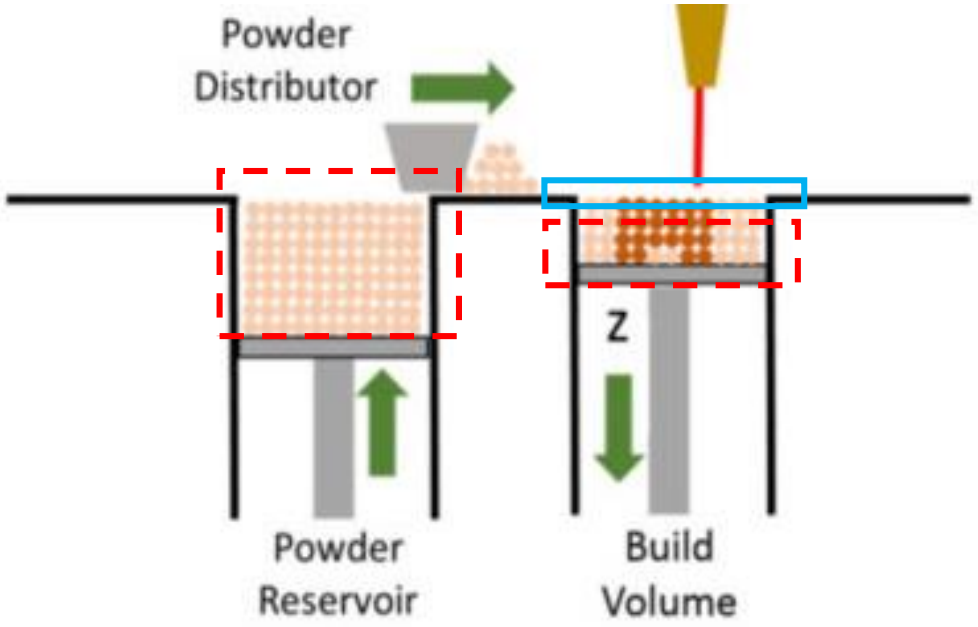
SLS – selective laser sintering

- **Possible excipients**: *waxes, polyvinylalcohol, polyethyleneglykol, methacrylates (Eudragit)*
- Good **adsorption of laser energy** is crucialll!
  - Badly adsorbing material – addition of adsorber (pigments), heating of bulk material, tuning the speed of laser
- **Unsuitable for light and thermally sensitive compounds**
- As in binder jetting – adequate **particle size distribution** and **flow properties** of powder are required

SLS – selective laser sintering

Critical parameters

- Bulk temperature - should not exceed lowest melting temp of composition
- Surface temperature – few degrees higher than Bt, IR lamps



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SLS – selective laser sintering

Critical parameters

Energy deposited (ED):

higher energy deposition leads to thourough melting, related to:

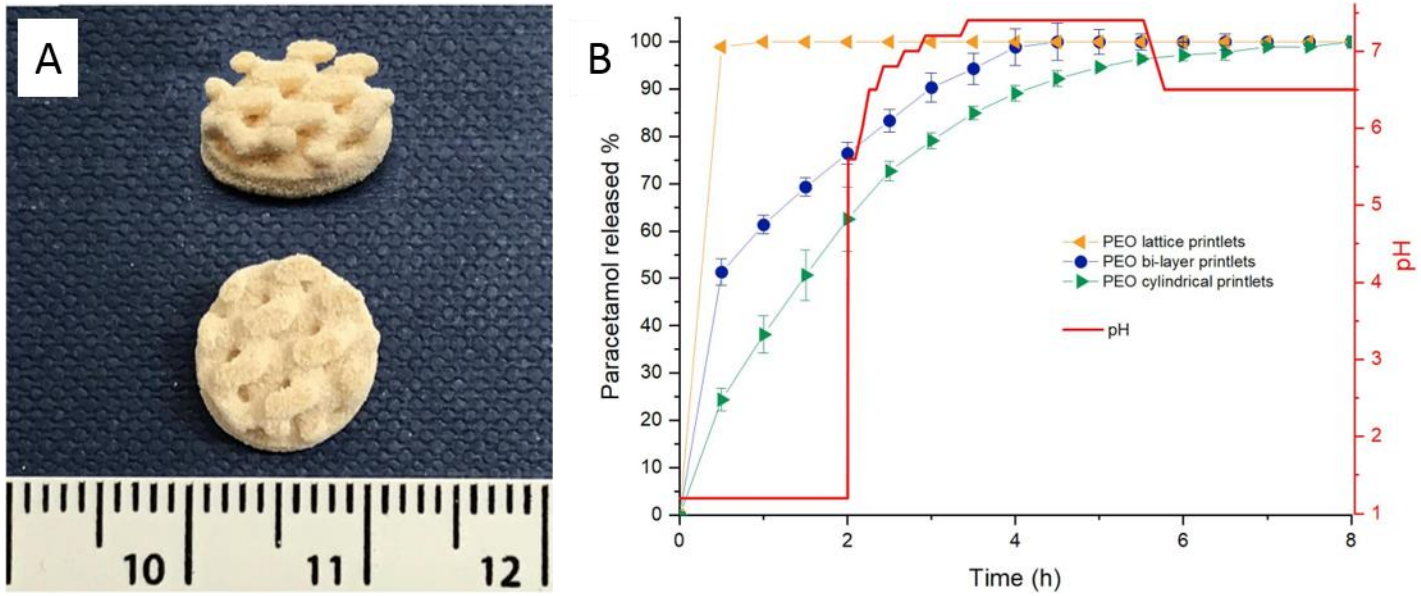
- laser speed (LS) and power (LP)
- layer height (LH)
- path distance (PD)

$$ED = \frac{LP}{LH \times LS \times PD}$$

SLS – selective laser sintering

Example of experimental use

Tablet combining immediate and prolonged release



Fina, F.; Goyanes, A.; Madla, C.M.; Awad, A.; Trenfield, S.J.; Kuek, J.M.; Patel, P.; Gaisford, S.; Basit, A.W. 3D printing of drug-loaded gyroid lattices using selective laser sintering. *Int. J. Pharm.* **2018**, *547*, 44–52, doi:10.1016/j.ijpharm.2018.05.044.

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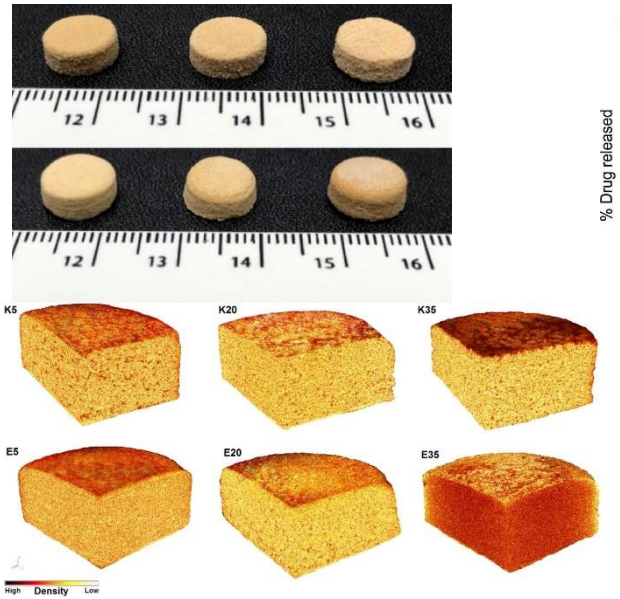
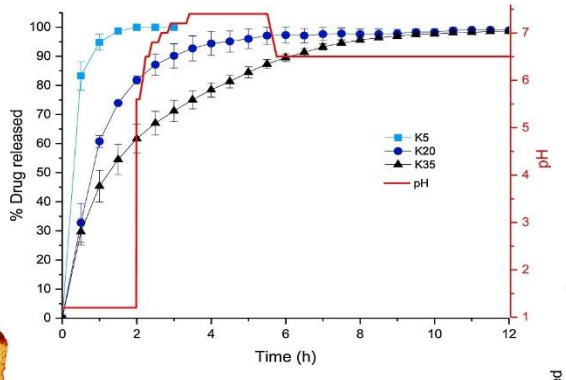
SLS – selective laser sintering

Example of experimental use

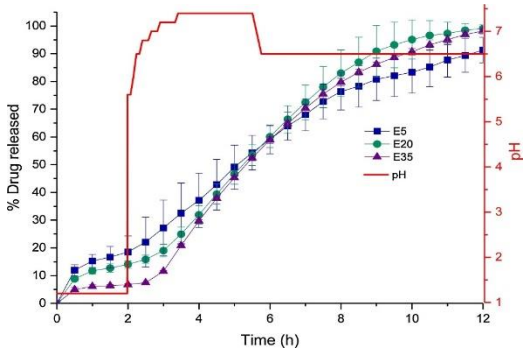
Paracetamol containing tablet – tuning of release profile by melt level





←**Kollicoat IR**

Eudragit L →



Fina, F.; Goyanes, A.; Gaisford, S.; Basit, A.W. Selective laser sintering (SLS) 3D printing of medicines. *Int. J. Pharm.* **2017**, *529*, 285–293, doi:10.1016/J.IJPHARM.2017.06.082.

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FDM – fused deposition modeling

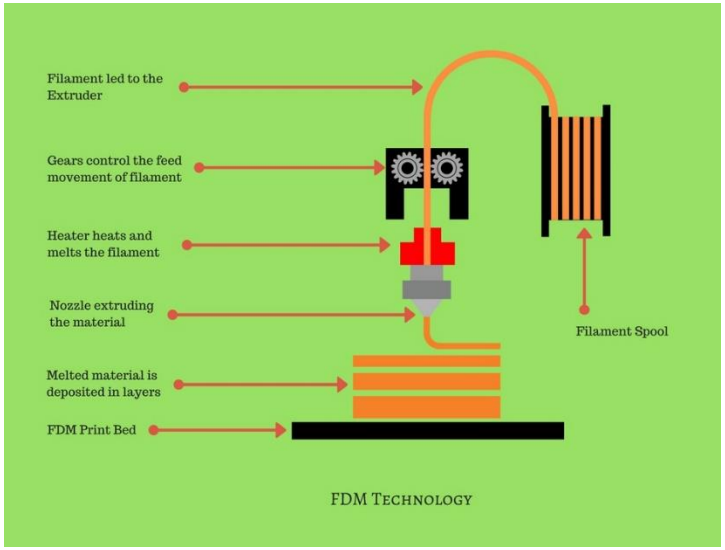
– Thermoplastic material is deposited through heated nozzle

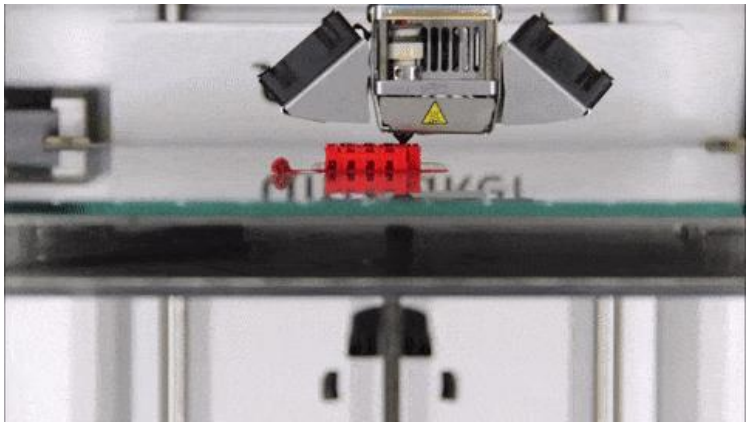
– Most commonly used type of 3D printing

\+ Flexible, low cost

\- Unsuitable for thermally sensitive compounds (low melting excipients are evaluated)

\- Material has to be in the form of filament of adequate properties for printing





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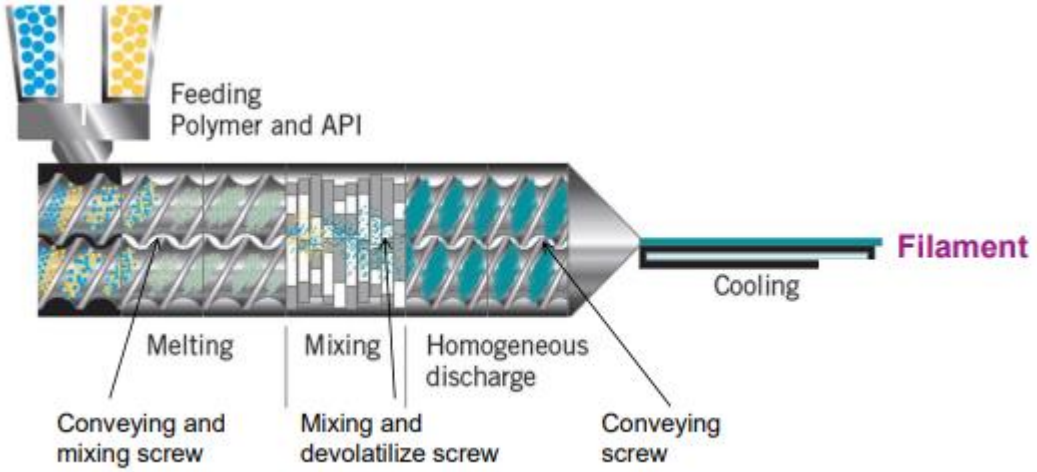
FDM – fused deposition modeling

Filament

- Filament preparation – **hot melt extrusion**
- Temperature range approx. 60-250 °C
- Solid amorphous dispersion –increasing solubility



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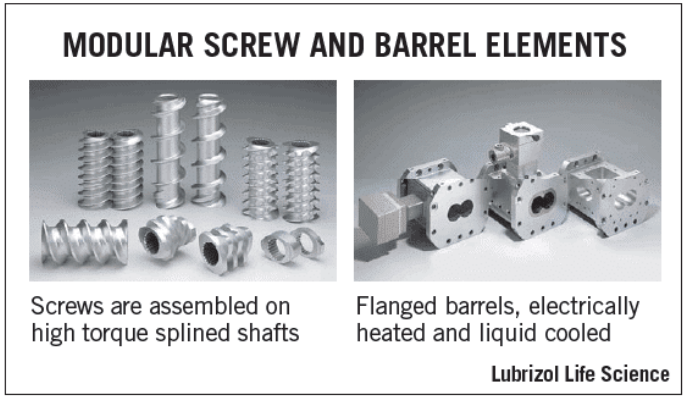
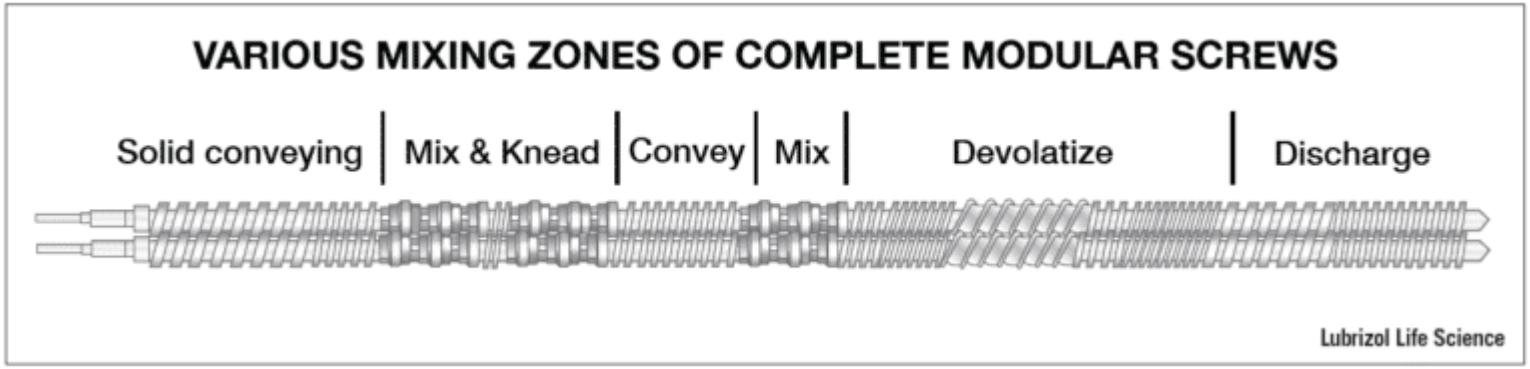
FDM – fused deposition modeling

Filament

- **Single/twin screw extruders**
- Screw geometry is defined by local function – melting, mixing, conveying, devolatilization





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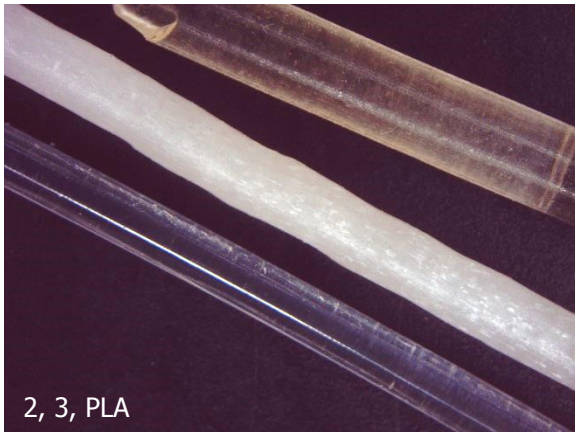
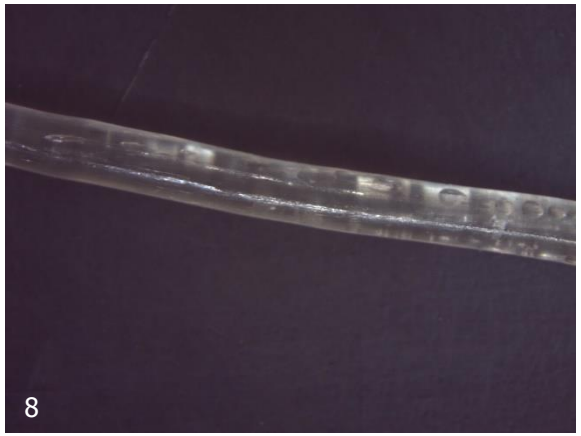
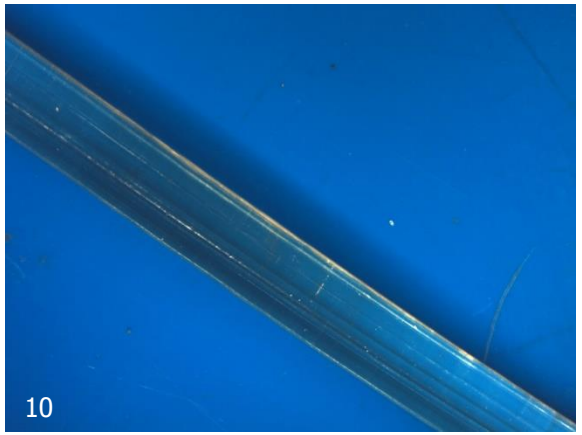
FDM – fused deposition modeling

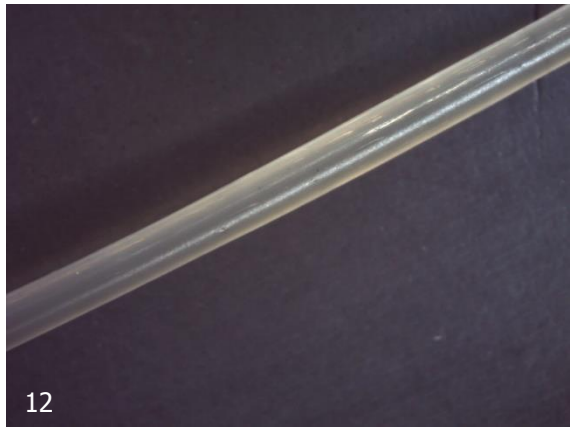
Filament







Sample	2	3	8	10	12	13	14
Eudragit® E	100		90	85	85	87	86
Kollidon® VA64		100			10	10	10
Ca stearate					2	2	2
Triethylcitrate					3	1	2
Citric acid				15			
PEG 8000			10				



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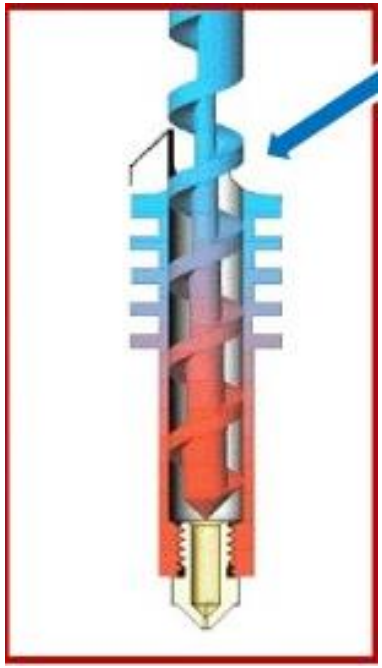
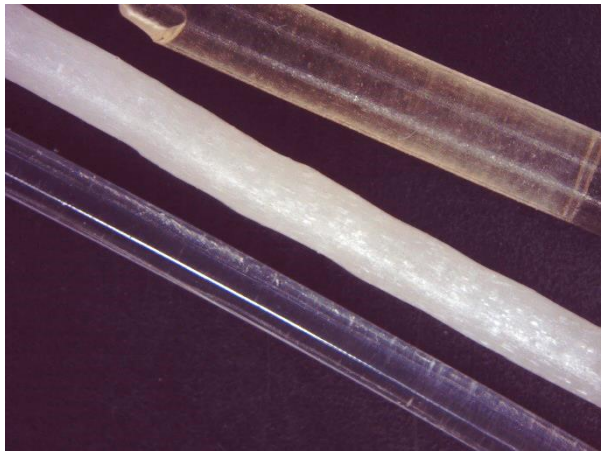
FDM – fused deposition modeling

Direct powder melting – **no need for filament!**





Goyanes, A.; Allahham, N.; Trenfield, S.J.; Stoyanov, E.; Gaisford, S.; Basit, A.W. *Int. J. Pharm.* **2019**, *567*,

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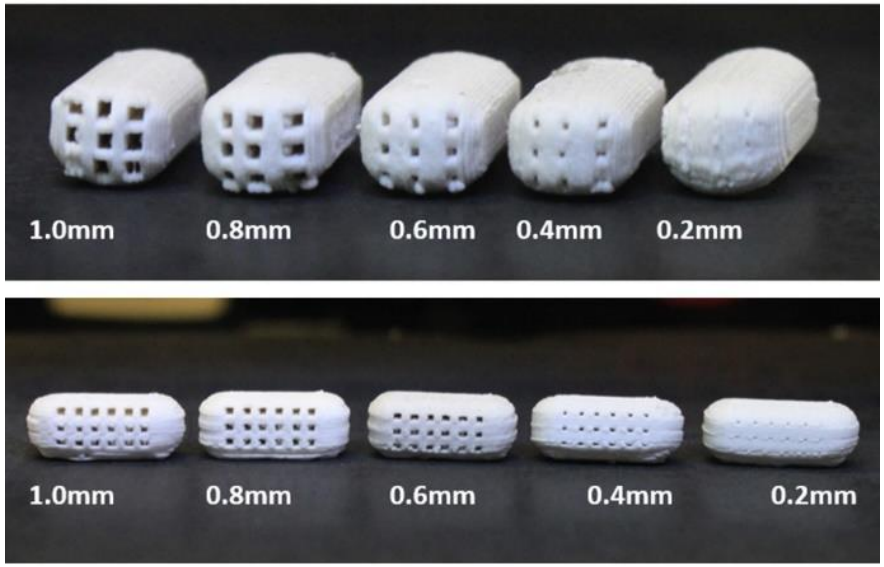
FDM – fused deposition modeling

Example of experimental use

Hydrochlorothiazide containing channeled tablets – disintegration and dissolution rate increase

Eudragit E, NaCMC, PVP

- FDM tablets have high tensile strength
- slow disintegration – limits immediate release
- solution – **geometry tuning!**
- dissolution is governed by area, length and orientation of channels



Sadia M., Arafat B., Ahmed W., Forbes R. T., Alhnan M. A.: J. Control. Release *269*, *355* (2018).

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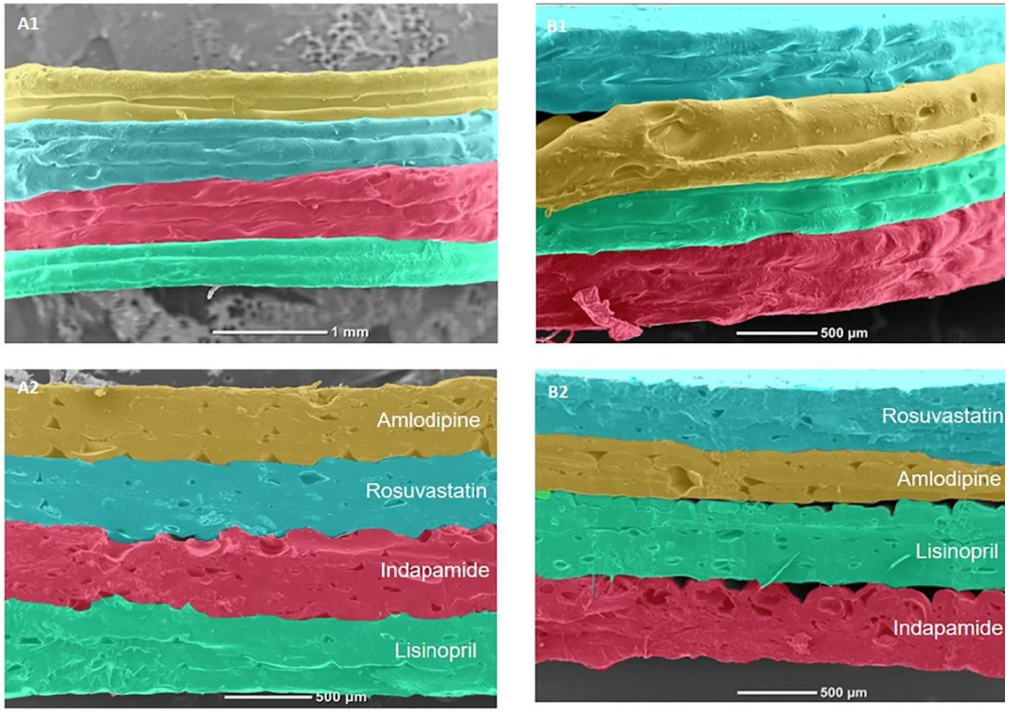
FDM – fused deposition modeling

Example of experimental use

4 drug combination and compartmenting

- PVA, Sorbitol
- *amlodipine besylate*
- *Ca rosvastatine*
- *indapamide*
- *lisinopril dihydrate*

Dissolution governed by the order of layers



Pereira, B.C.; Isreb, A.; Forbes, R.T.; Dores, F.; Habashy, R.; Petit, J.B.; Alhnan, M.A.; Oga, E.F. *Eur. J. Pharm. Biopharm.* **2019**, *135*, 94–103.

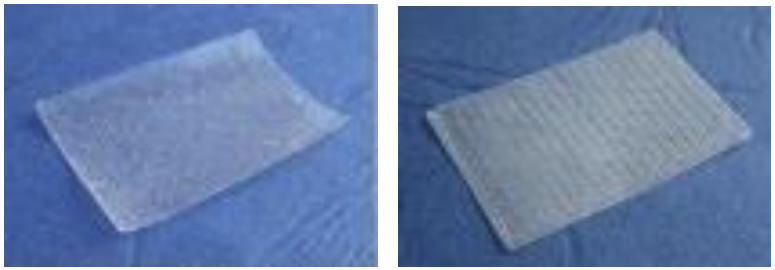
MUNI PHARM

FDM – fused deposition modeling

Example of experimental use

Aripiprazole ODF

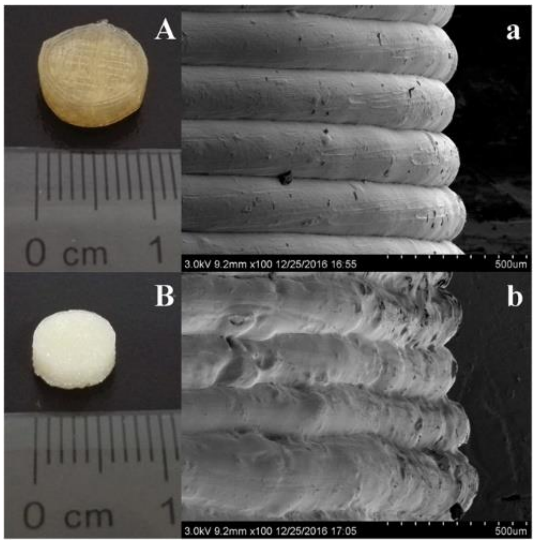
- PVA
- Dose can be tuned
- Slow disintegration (disadvantage)



Jamróz W., Kurek M., Lyszczarz E., Brniak W., Jachowicz R.: Acta Pol. Pharm. *74*, 753 (2017).

Hollow domperidon tablet

- HPC
- Prolonged release in stomach



Chai X. et all.:, Sci. Rep., 7, 2829 (2017).

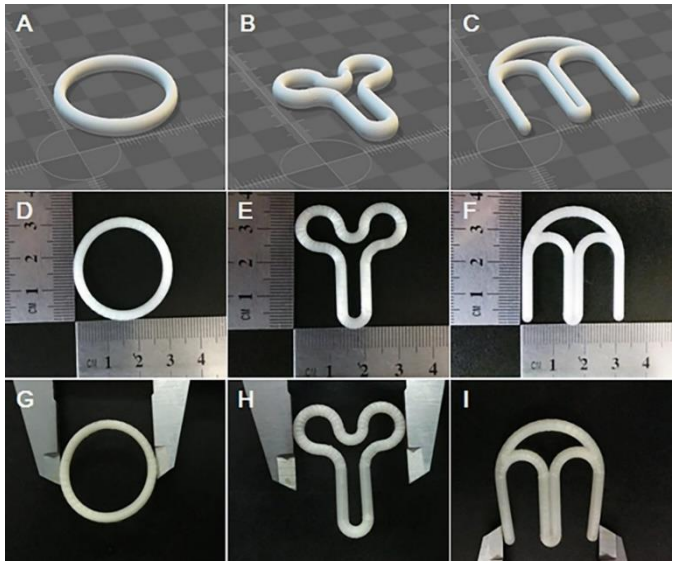
MUNI PHARM

FDM – fused deposition modeling

Example of experimental use

Progesterone vaginal inserts

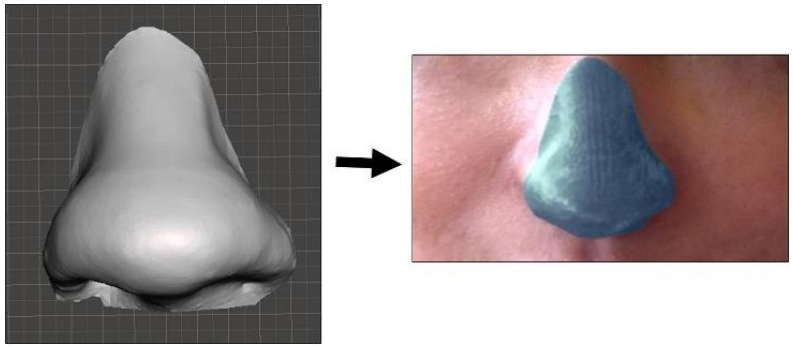
- PLA, PCL, PEG, SDS, Tween 80
- Ergonomic shaping
- Individualised dosing



Fu J., Yu X., Jin J.: Int. J. Pharm. 539, 75 (2018).

Antibacterial wound dressing

- PCL, $AgNO_3$, $CuSO_4$, ZnO
- scanning



Muwaffak Z. et all.: Int. J. Pharm. 527, 161 (2017).

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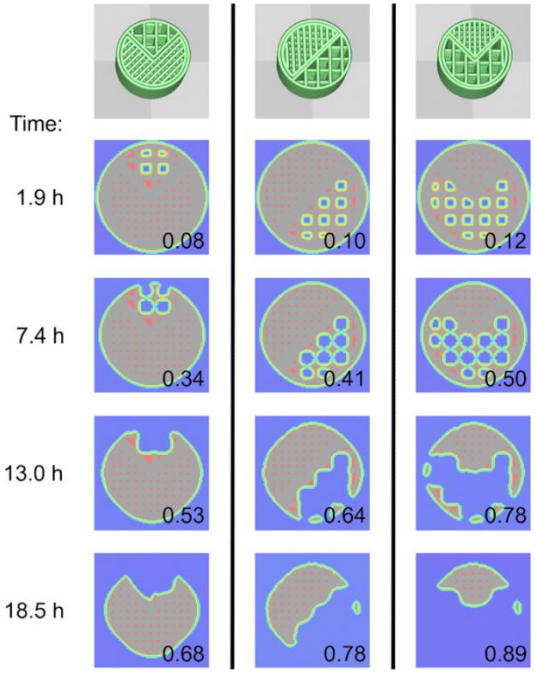
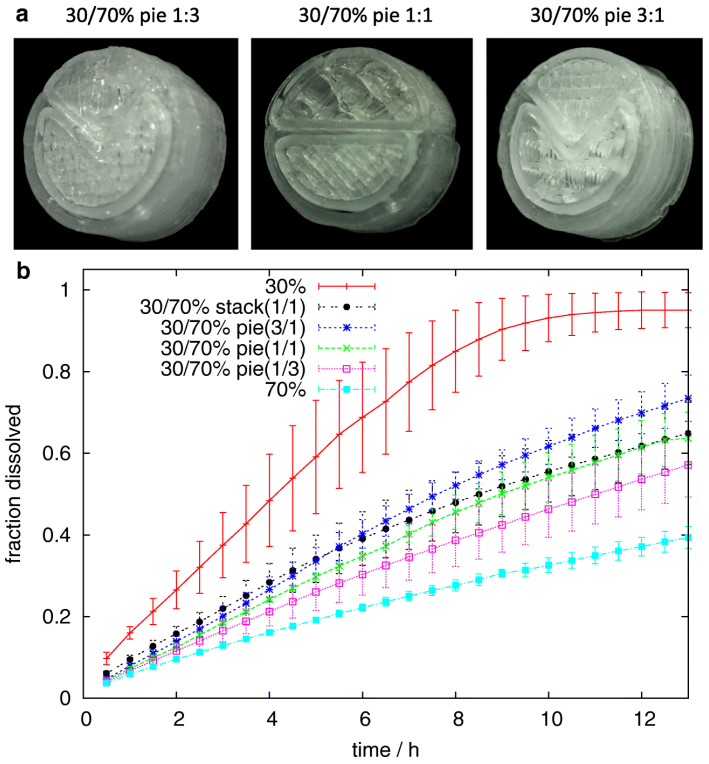
FDM – fused deposition modeling

Example of experimental use

Fine tuning of release profile by infill density





Novák, M., Boleslavská, T., Grof, Z. et al. AAPS PharmSciTech 19, 3414–3424 (2018).

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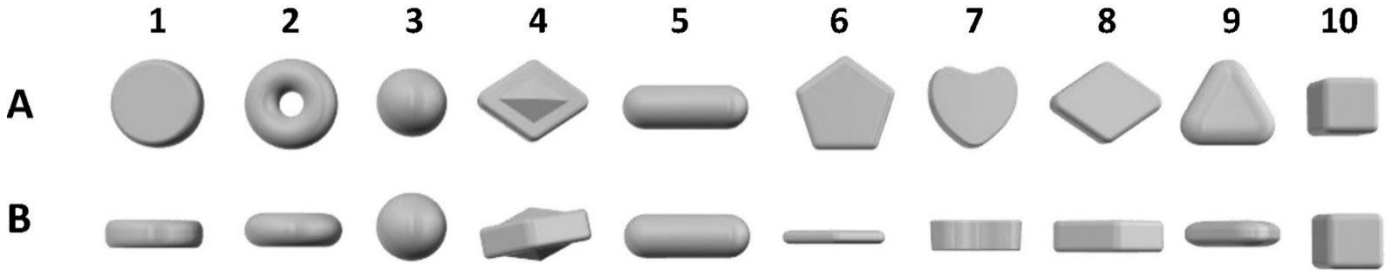
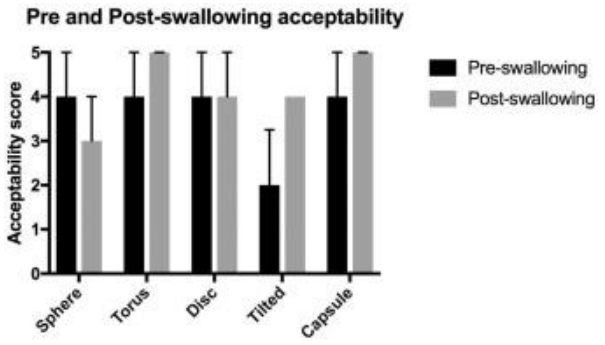
FDM – fused deposition modeling

Example of experimental use

Evaluation of tablet shape on acceptability





Goyanes et al., Int. J. Pharm., 530, 1–2, 71-78 (2017).

MUNI PHARM

SSE – semi-solid extrusion

- Analogic to FDM – no need for the heating of material
- deposition by nozzle/syringe
- pneumatic/mechanic

+ Flexible, low cost

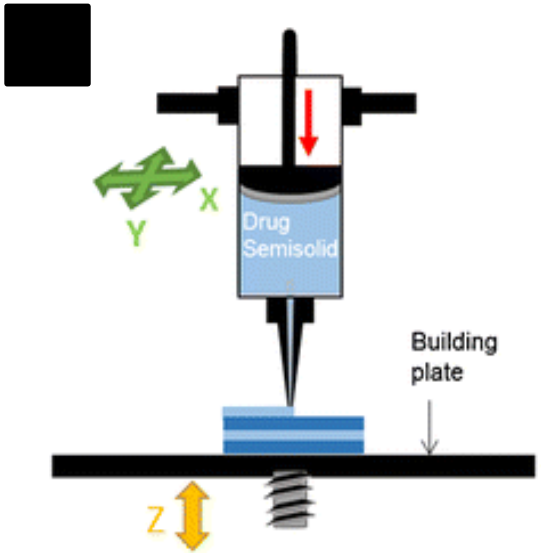
+ No filament

+ Low temperatures

- Drying is usually demanded

- Control of residual solvents (ICH Q3)

- Tuning of viscosity/surface tension of dosed material (gel, dispersion, solution)



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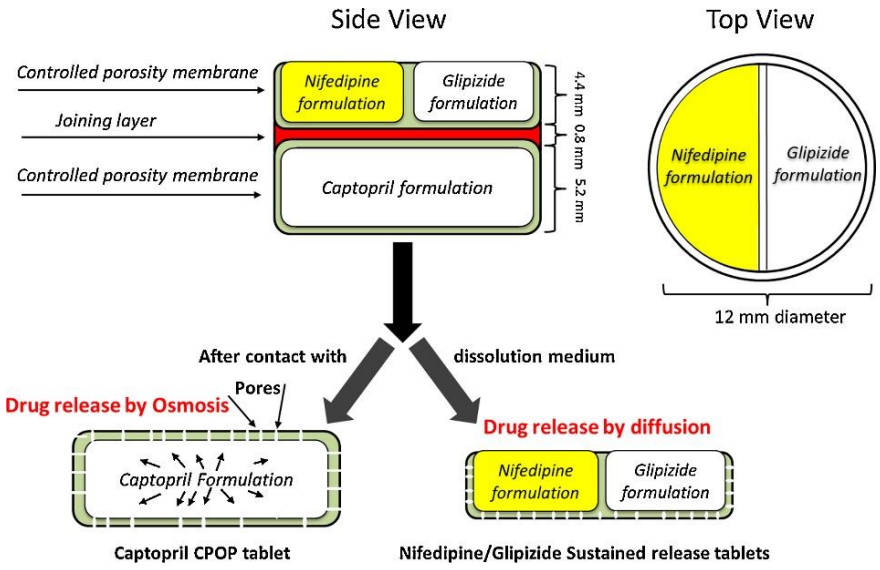
SSE – semi-solid extrusion

Example of experimental use

3 comparmtent tablet – Nifedipine/Glipizide/Captopril

- **Shell** – celullose acetate (semip. membrane), mannitol (porogen)
- Nifedipine/Glipizide - HPMC, PEG 6000, tromethamine (solub.), lactose (filler).
- Captopril - HPMC (matrix), MCC, lactose, NaCl (osmogenic)
- **Joining layer** - Na CMC, Na glycolate, starch (dezint.) PVP (binder), mannitol (filler)



Khaled S. A. et all.: Int. J. Pharm. *494*, 643 (2015).

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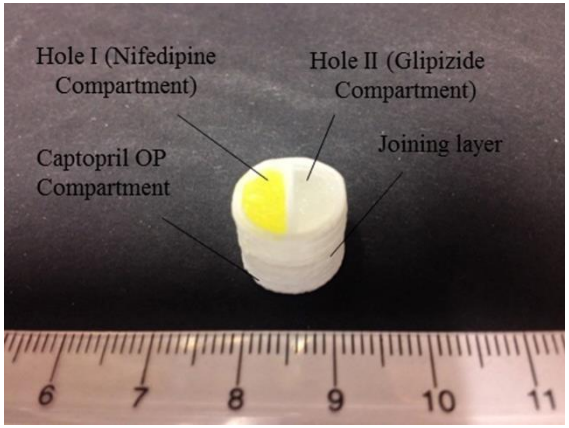
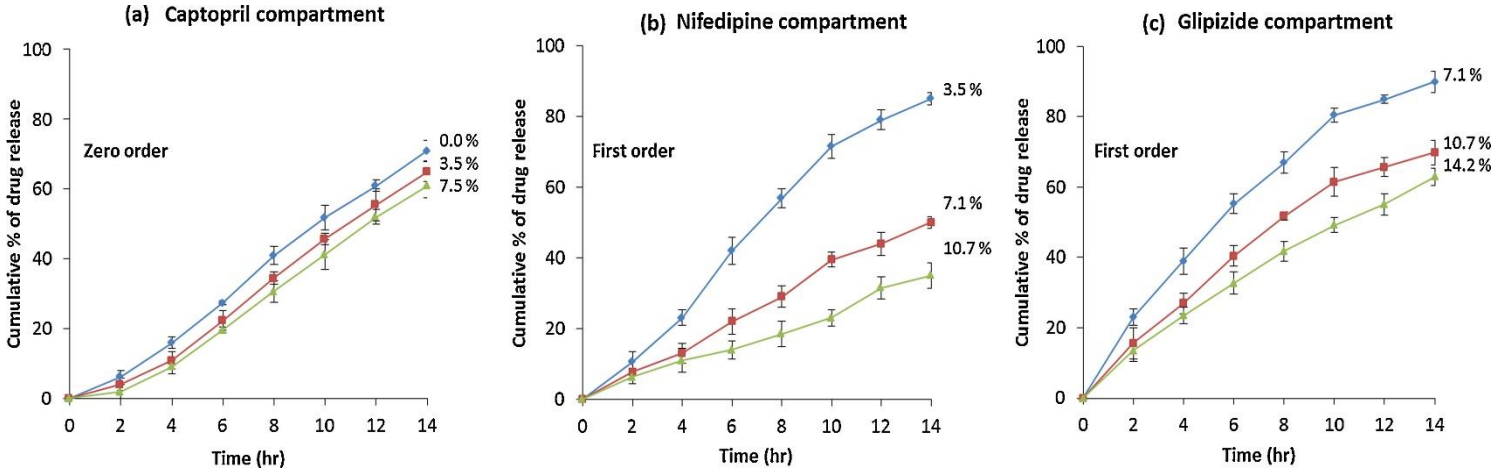
SSE – semi-solid extrusion

Example of experimental use

3 comparmtent tablet – Nifedipine/Glipizide/Captopril





Khaled S. A. et all.: Int. J. Pharm. *494*, 643 (2015).

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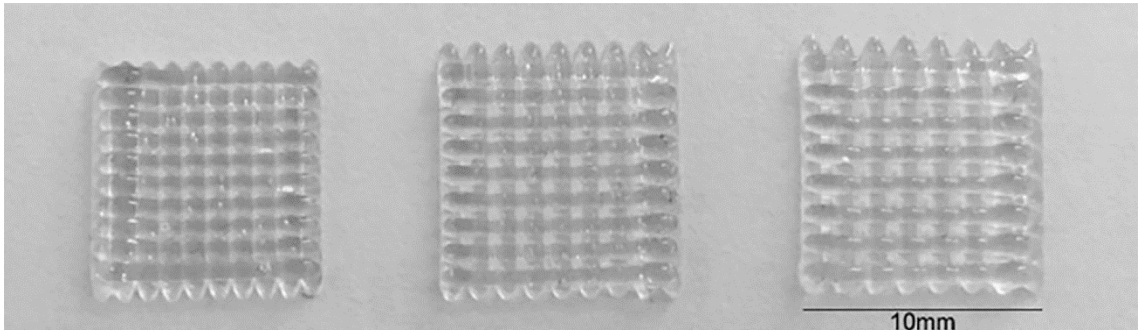
SSE – semi-solid extrusion

Example of experimental use

- **Polydimethylsiloxane (PDMS)** based DDF containing prednisolone
- PDMS – non-degradable excipient in matrix and reservoir types of inserts or implants
- slow release (weeks/months)
- can be increased by increasing the surface available - **GRID**



Holländer, J.; Hakala, R.; Suominen, J.; Moritz, N.; Yliruusi, J.; Sandler, N. *Int. J. Pharm.* **2018**, *544*, 433–442.

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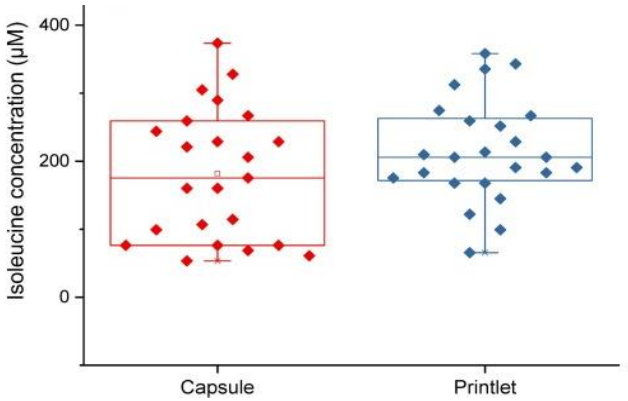
SSE – semi-solid extrusion

First clinical testing – 3D printed DDF for the therapy of LEUCINOSIS

- MSUD – „maple sirupe urine disease“ – patients body unable to break down branched aminoacids (leucine, isoleucine and valine) – accumulation of toxic products
- Incidence: 1:185 000 newborns
- Chewable tablets containing individualised dose of izoleucine
- Better control of plasmatic isoleucine concentration againts manually prepared capsules



Goyanes et. al., Int. J. Pharm., 567 (2019).

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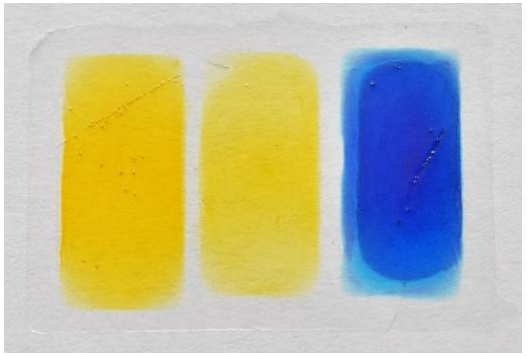
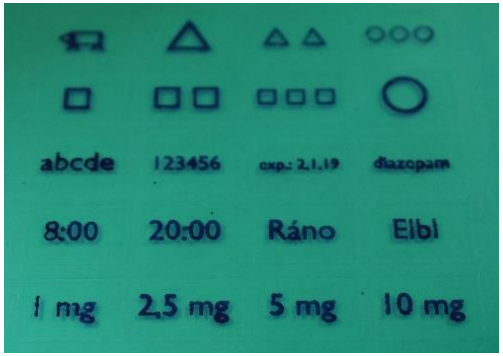
SSE – semi-solid extrusion

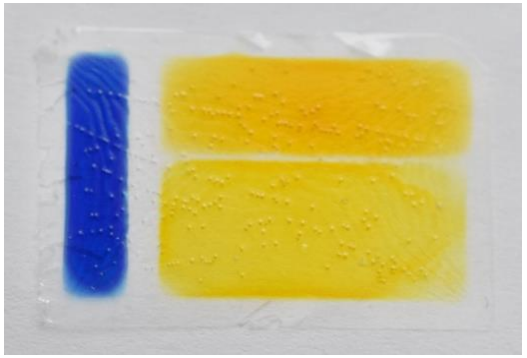
First clinical testing – 3D printed DDF for the therapy of LEUCINOSIS

Orally disintegrating films

- Labeling (for pharmacist/patient)
- Taste masking layers
- Unusuall shapes







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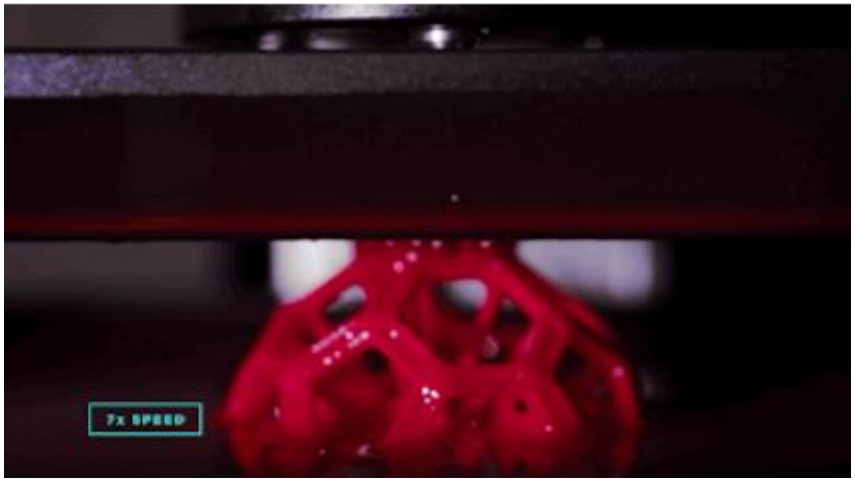
SLA - stereolitography

- Liquid photopolymer is solidified by UV light/laser of appropriate wavelength
- Liquid polymer forms thin layer between plate and bottom a light is emmited through the bottom.
- Plate is lifted and retracted after each layer exposure, forming new uncured layer.



+ High doses of API may be incorporated

– Unsuitable for UV sensitive APIs

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SLA - stereolitography

Appropriate polymers

- **Photopolymers** – API is trapped inside crosslinked matrix
- Free radicals/ionic polymerisation
- Both systems use PHOTOINICIATORS to create reactive species

Riboflavine (B2)

diphenyl(2, 4, 6-trimethylbenzoyl)phosphineoxide

- Limited selection of GRAS photopolymers – mainly methacrylates or acrylates

PEGDA - polyethylene glycol diacrylate

PEGDMA - poly(ethylene glycol) dimethacrylate

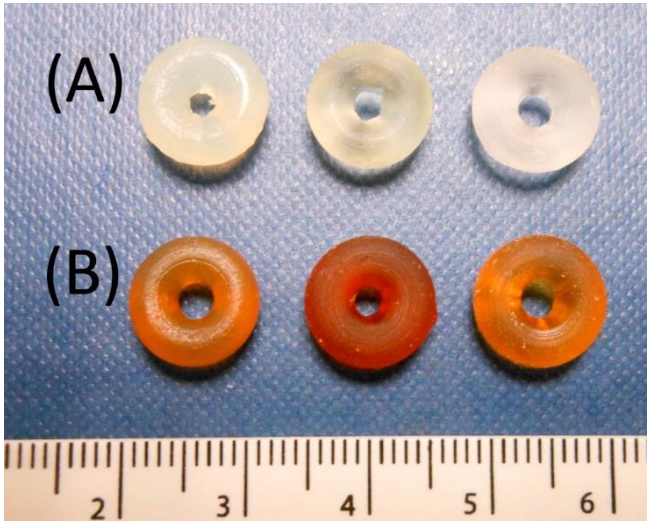
HEMA - hydroxyethyl methacrylate

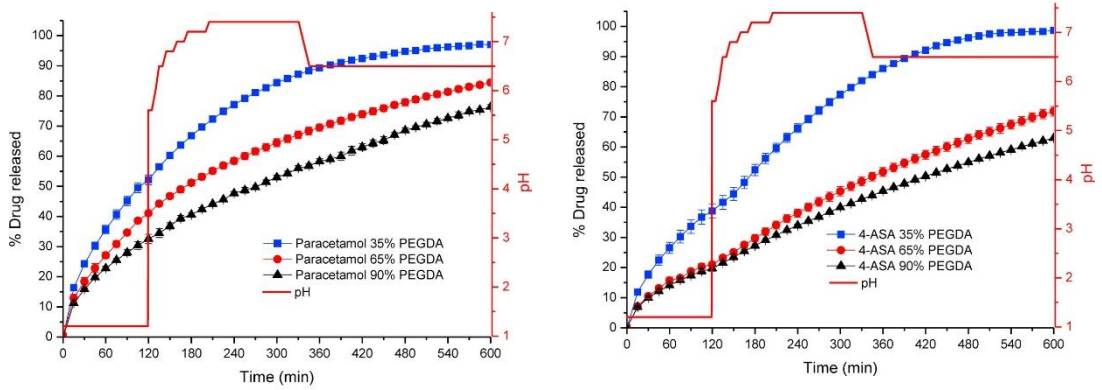
PPF/DEF - poly(propylene fumarate) / diethyl fumarate

SLA - stereolitography

Example of experimental use

- Toroidal tablets
- Increased surface/volume ratio, relatively stable throughout dissolution
- PEGDA, PEG 300
- diphenyl-(2,4,6-trimethylbenzoyl)phosphineoxide
- paracetamol or 4-ASA





Wang J., Goyanes A., Gaisford S., Basit A. W.: Int. J. Pharm. *503*, 207 (2016).

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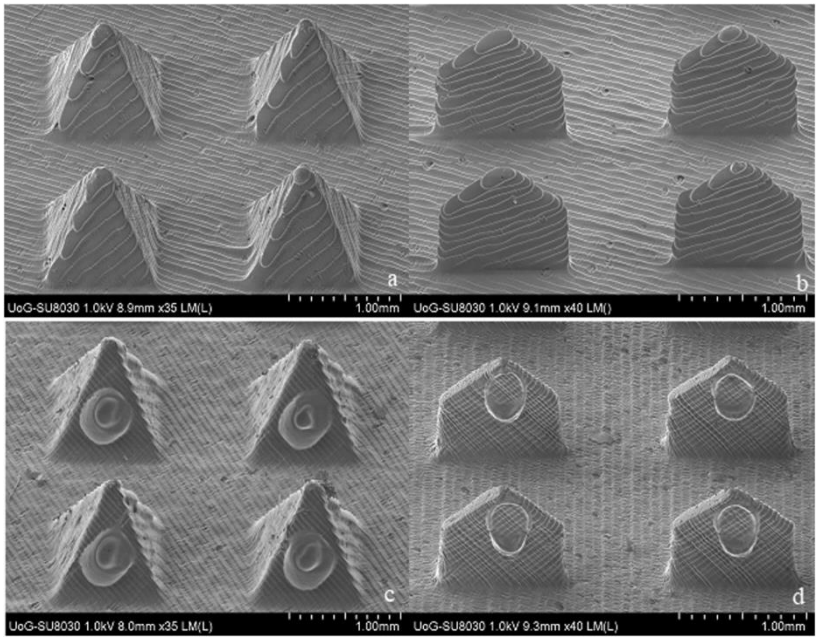
SLA - stereolitography

Example of experimental use

- Microneedle patch for transdermal **insuline** application
- array of small (µm sized) needles – almost „non-invasive“ application
- 3D printed carrier
- drop on demand Insuline
- **Longer control of glucose blood level, compared to subcutaneous administration of equal insuline dose**



Economidou, S.N.; Pere, C.P.P.; Reid, A.; Uddin, M.J.; Windmill, J.F.C.; Lamprou, D.A.; Douroumis, D. *Mater. Sci. Eng. C* **2019**, *102*, 743–755,

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Regulatory framework

Virtually non-existent

- **FDA** - Spritam ® (2015) – almost classical manufacturing
- **Emerging Technology Programe** – dialogue with manufacturers planning on using new innovative technologies (e.g. 3D printing, continuous manufacturing of APIs/DDF, continuous aseptic spray drying etc.)

- **Technical Considerations for Additive Manufactured Medical Devices** (2017) – compendium of considerations for the additive manufacturing of **helthcare devices**

EMA – 2022 **Quality Innovation Group** (QIG) – new technologies

- **DCM** – decentralized manufacturing (POC) – reacts to new treatements and trends
  - Highly personalised
  - Short shelf-life (products of blood derivatives, ATMP – gene therapies and such)

POC applications

FabRx – M3DIMAKER Mk II

- GMP
- 3 swappable extruders
  - FDM
  - Direct powder extrusion
  - SSE
- Scales incorporated
- NIR sensor for PAT (process analytical technology)

~ €100 000

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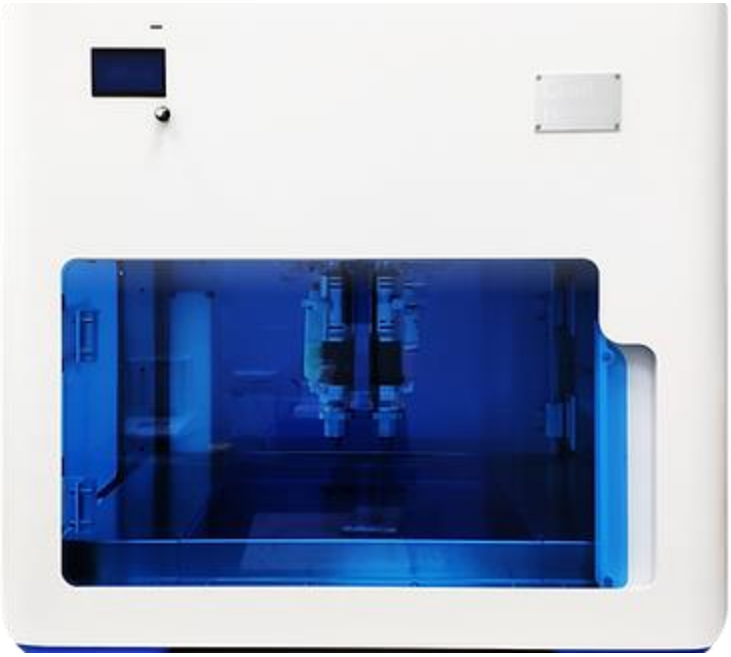
POC applications

Craft Health

- SSE
- integrated HW a SW systéem
- only proprietary excipient blends
- GMP ready
  - Enclosed system
  - Stainless steel
  - Process repeatability
  - Audit trail



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POC applications

DiHeSys - FLEXDOSE

- Direct powder/granulate extrusion
- Inkjet 2D print – on un-medicated substrates
- DiHeSys aims to create closed-loop system with feedback from health monitoring devices (wereables and such) to printer

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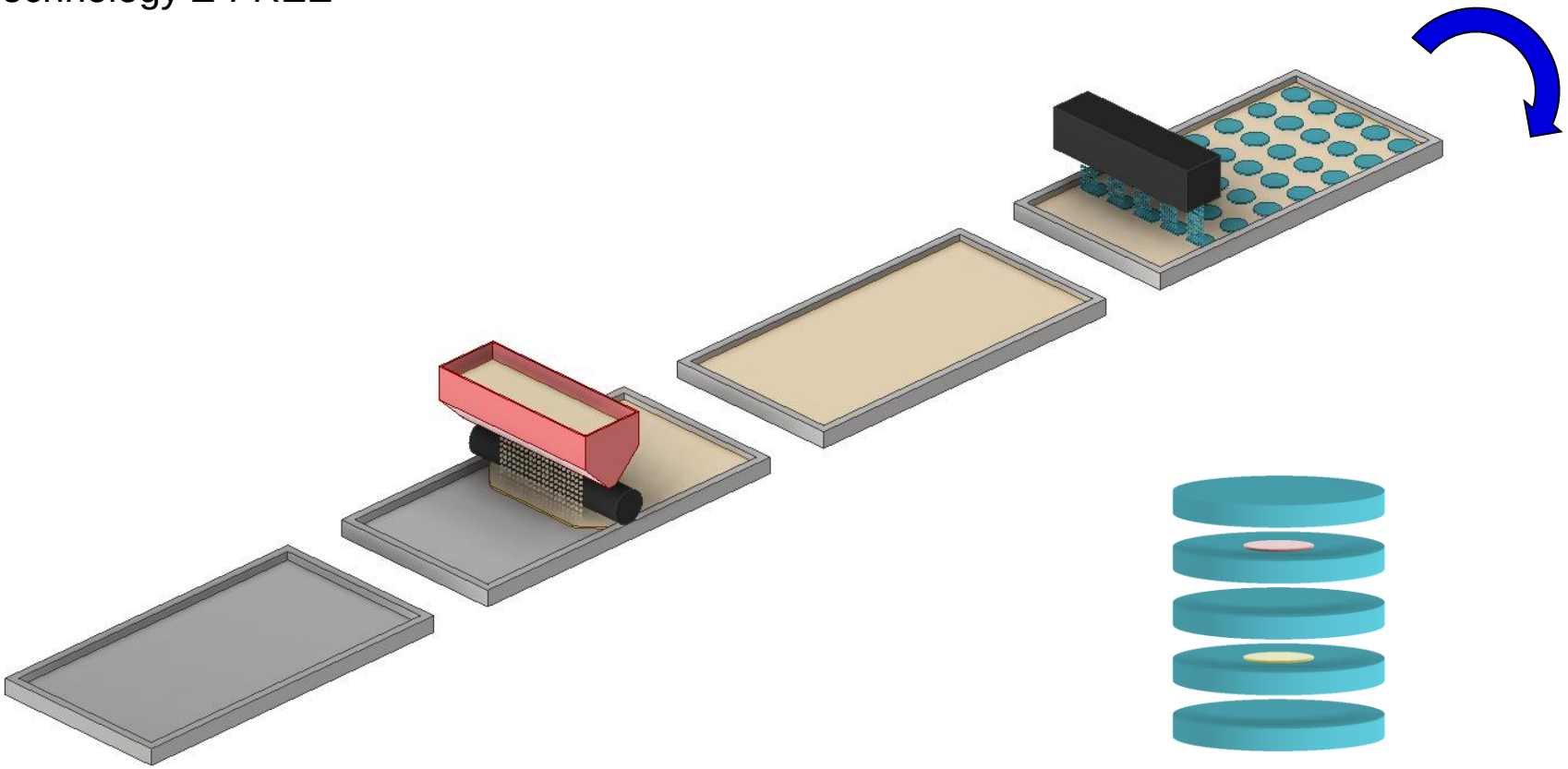
Industrial applications

Apprecia – Zip Dose ®

– Technology Z-FREE®



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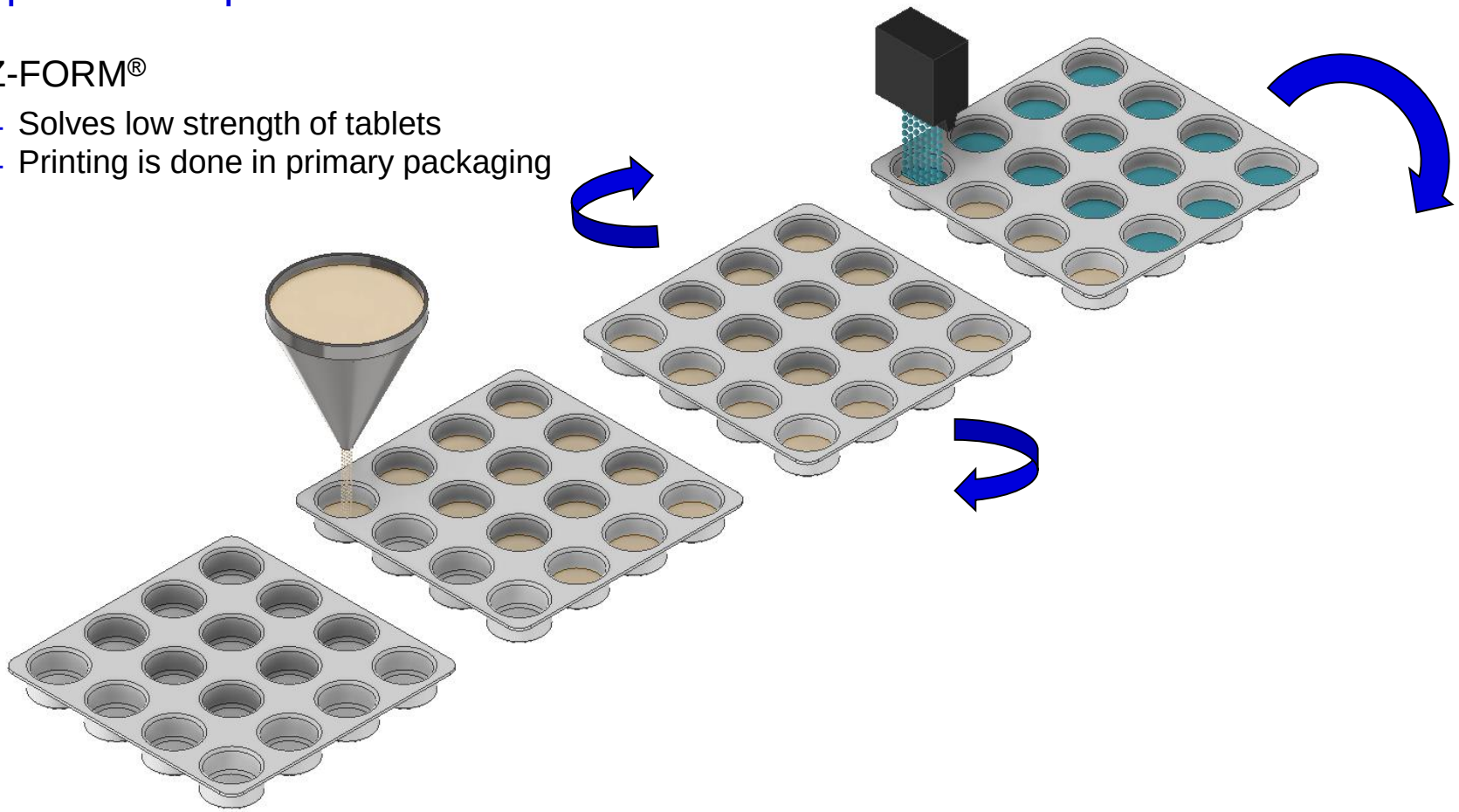
Industrial applications

Apprecia – Zip Dose®

- Z-FORM®
  - Solves low strength of tablets
  - Printing is done in primary packaging



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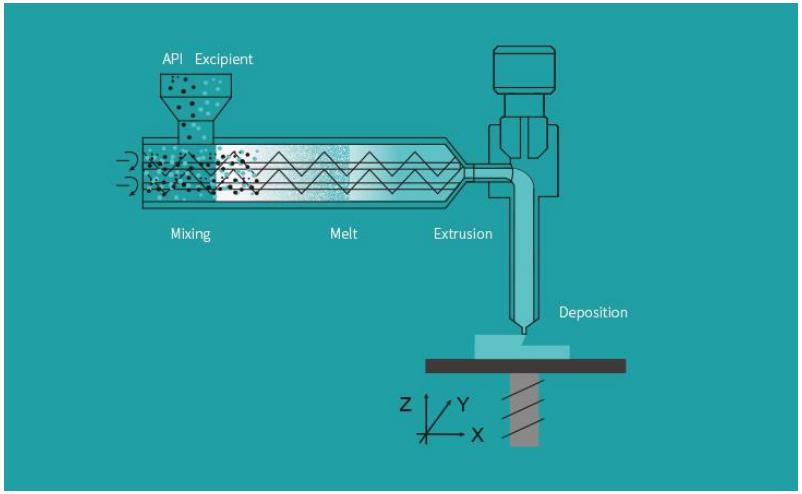
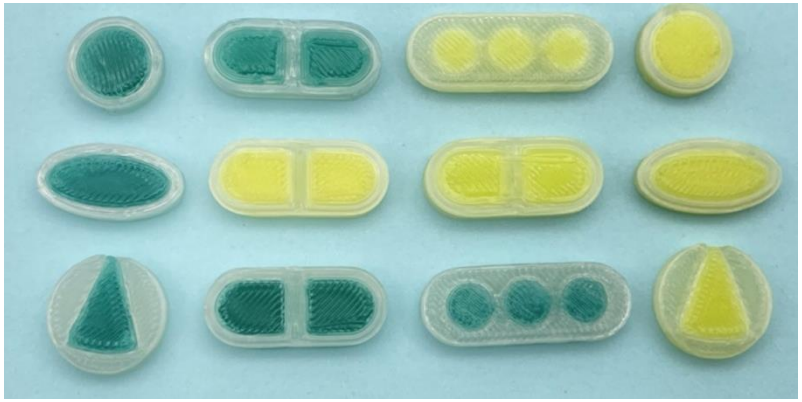
Industrial applications

Triastek – MED® (Melt-Extrusion Deposition)

- Direct powder extrusion
- 3 products in clinical phase of testing
  - T19 rrheumatoid arthritis
  - T20 clotting disordes
  - T21 ulcerative colitis – *tofacitinib* (iJAK)
    8/23 promising results from FIH





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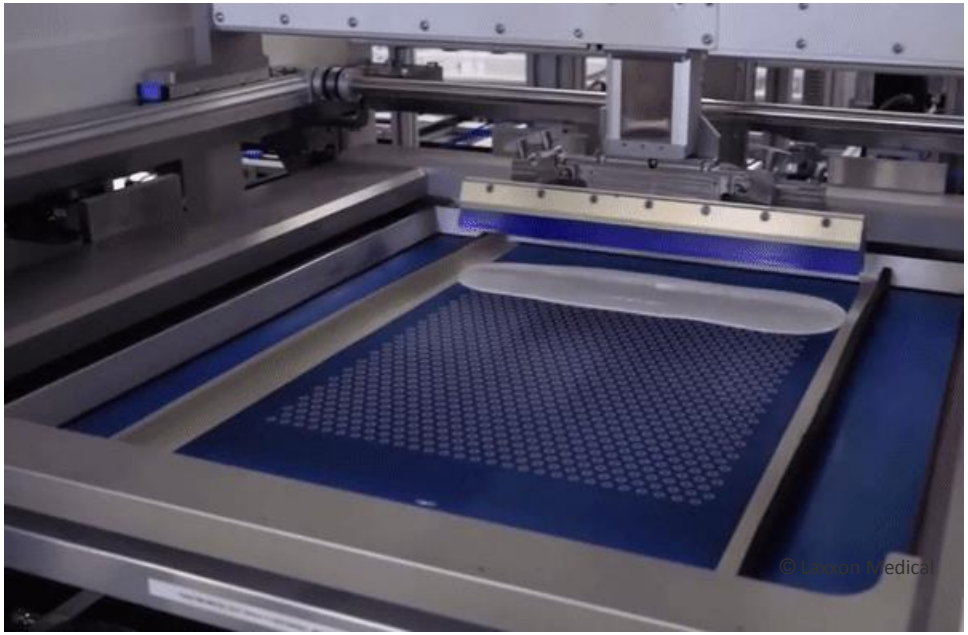
Industrial applications

Laxxon Medical – SPID® (screen 3D printing)

- Based on screen printing
- Suspension of API/excipients is transferred through mesh and stencil
- Multiple stencils may be combined
- Hundreds of tablets in one batch - quick



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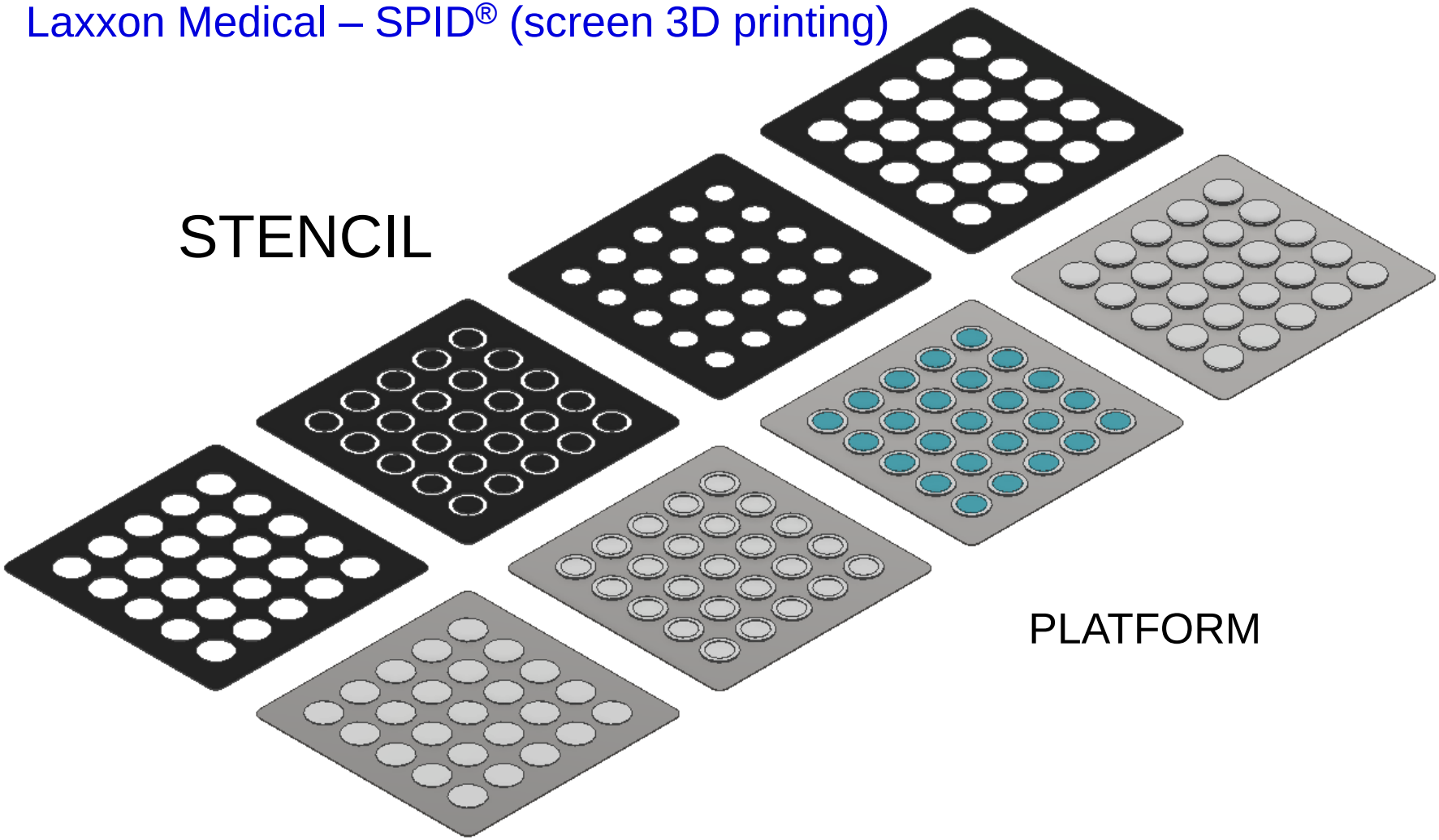
Industrial applications

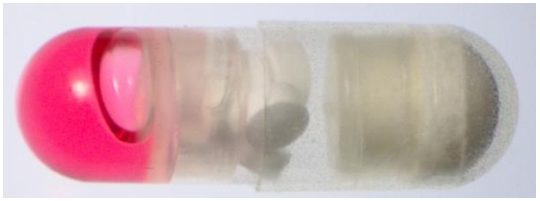
Laxxon Medical – SPID® (screen 3D printing)

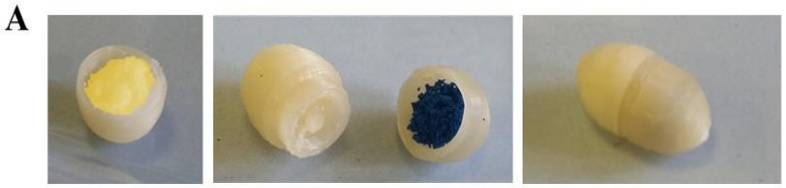


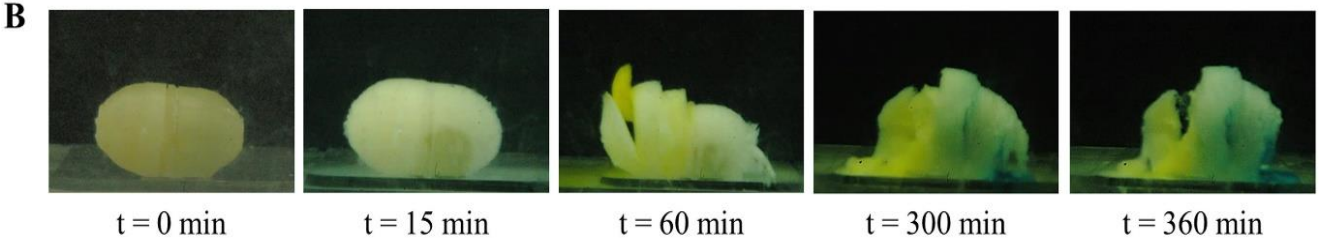
Industrial applications

Early birds

- **MultiplyLabs** – multicompartment capsules made from HPC
- time/place control of release by wall thickness tuning
- nutraceuticals







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Industrial applications – do we still need pharmacists?

– **MultiplyLabs –** 3D printed capsules in combination with automated preparation

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And that´s all….

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