"Click" to "Print": A Novel Technology to Design and Manufacture Pharmaceutical Drug Products

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This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

Presentation Outline

- Introduction: History
- 3D printing: current status of drug, device, biologics & research in 3DP
- What is 3D printing in pharmaceuticals
- Why 3D printing
- How is it different than other drug product manufacturing
- Different 3D printing platforms
- Manufacturing challenges
- Regulatory challenges
- Conclusion

History: Evolution of Pill

According to history, the oldest known pills can be traced back to 140 BC, first compressed tablets were prepared by Dr. Robert Fuller in 1878*

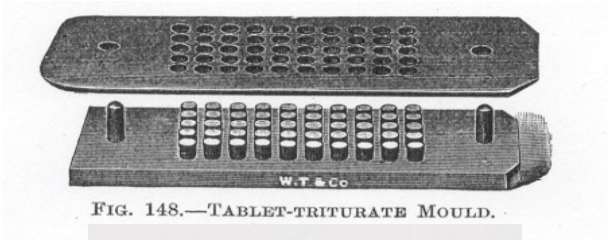
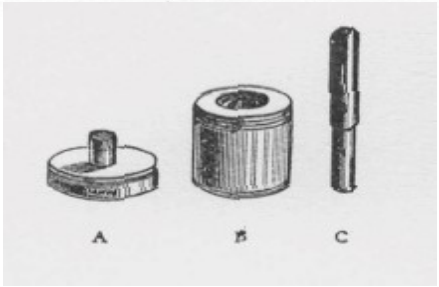


FIG. 148.—TABLET-TRITURATE MOULD.



Picture from the Museum of the Royal Pharmaceutical Society

* ***Ref***. S. Anderson. *A Brief History of Pharmacy and Pharmaceuticals, Pharmaceutical Press, London, 2005.)*

History: Evolution of Pill

- Numerous advancement in manufacturing solid oral dosage forms over a century: continuous manufacturing (API to DP), robots in pharm mfg., real time release, PAT, QbD and multiple unit operations for SODF
- Orally disintegrating, effervescent, micro, multi layered, tablet within a tablet, caplet, sublingual, floating, chewable, muco-adhesive, buccal and vaginal tablet. *Formulation driven.*
- All use some sort of compression force or mold to form a tablet

How 3D Printing Technology Came into Pharmaceutical Field?

The first 3D printed object, a tiny cup for eye wash Invented by Chuck Hilll in 1984

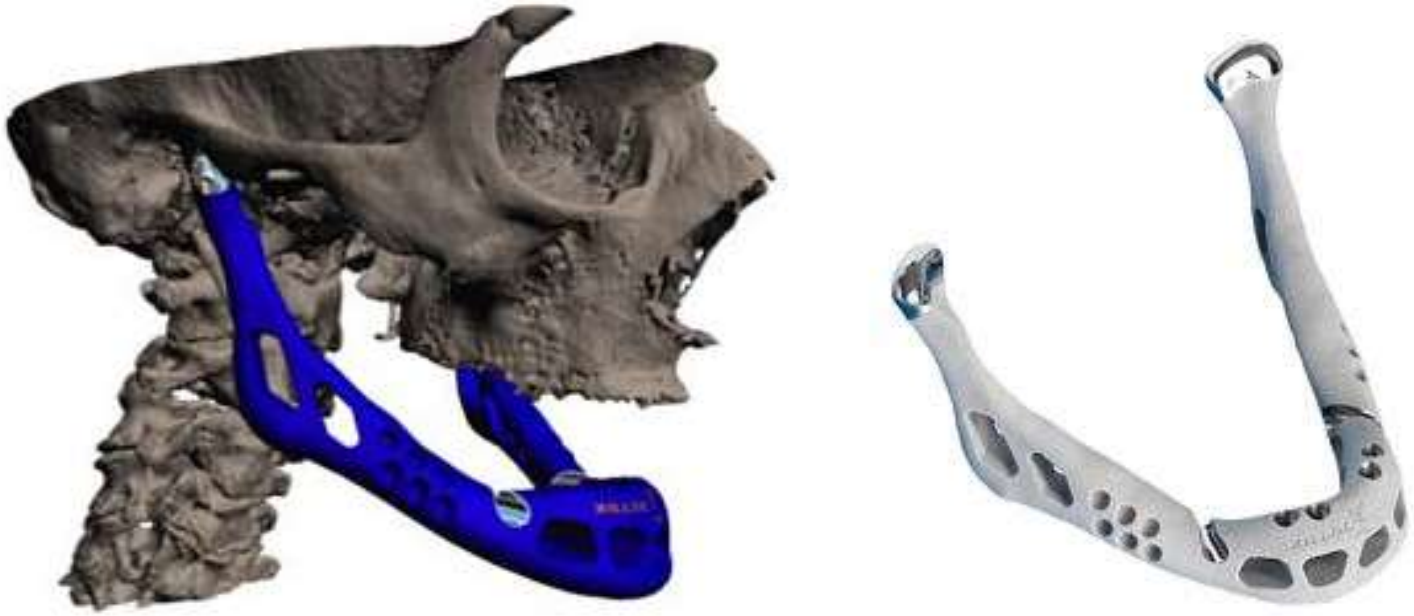
Source: CNN Interview, US Patent 4,575,330

Continuing Evolution of 3DP

- Food
- Fashion, toys
- Automobile industry
- Computer parts
- Architectural industry
- Medicine
- Pharmaceuticals, first reported 3D pill in 1996

A 3D Printed Human Skull Implanted in a 22 year old women in Netherland in 2014.

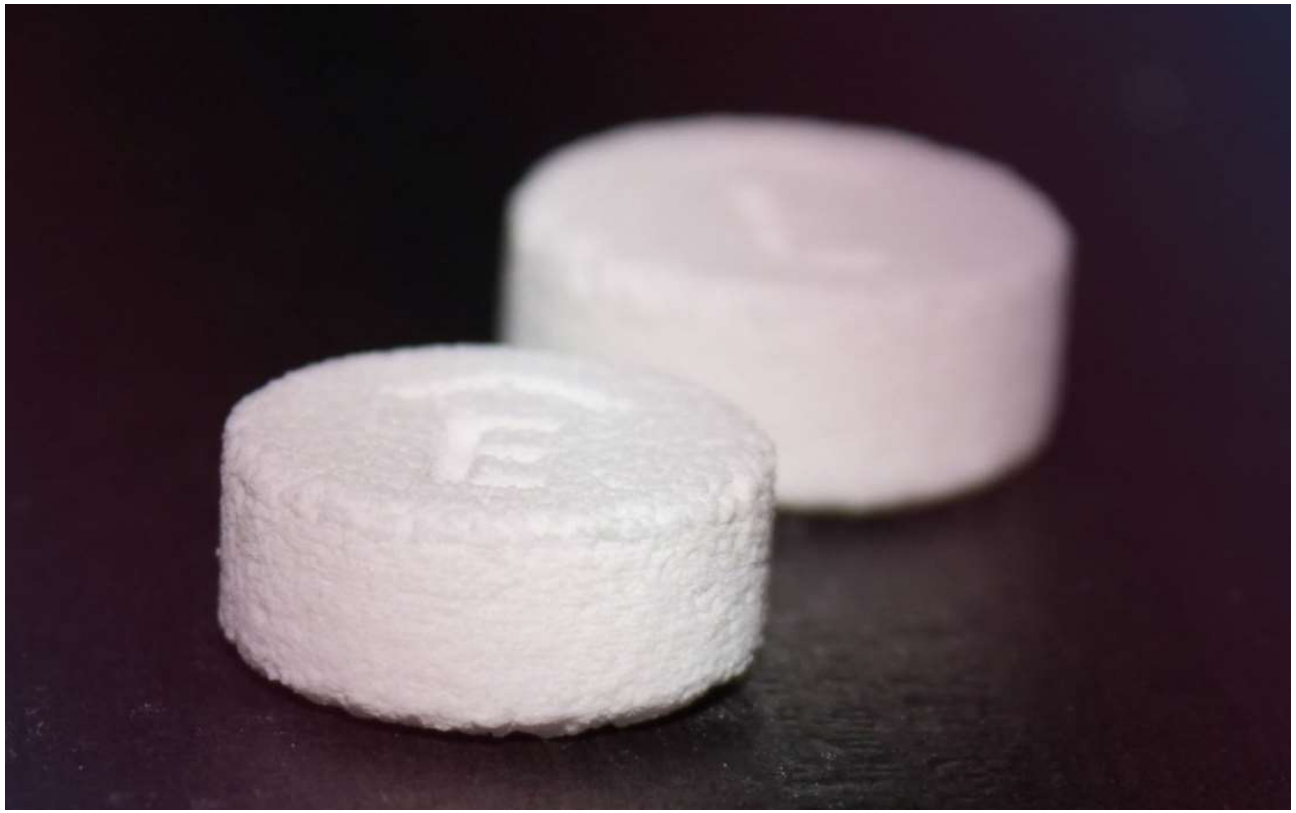
Source: Science, March 2014



A 3D printer-created lower jaw that has been fitted to an 83-year-old woman's face. Source: BBC News, 2012

A 3D printer-created human ear: Nature, Apr' 2015

3DP Kidney, Liver, Heart



SPRITAM *(levetiracetam) tablets, for oral use:*

FDA's first approved 3D printed drug product

3D Printing: Current Status

- 3D Printing begun with genomic revolution in early1990s with a concept of a possible platform for personalized medicine.
- There are major achievement in 3D printed medical device, FDA's Center for Device and Radiological Health (CDRH) has reviewed and cleared 3DP medical devices for over 10 years
- So far, 85 3D-printed devices already have been brought to market in the United States (Ref. Med Device, 2015)

3D Printing: Current Status

- No biological products manufactured by additive manufacturing yet for FDA approval.
- FDA's CDER has approved the first 3D printed solid oral dosage form in the month of August, 2015.
- President Obama launched the National Additive Manufacturing Innovation Institute in August 2012, in an effort to foster collaboration and provide support for 3D printing technologies and products.

  Source: http://www.manufacturing.gov/nnmi_pilot_institute.html

3D Printing: Current Status, Research

3DP Technology	Dosage Forms	API
Desktop 3DP	Tablet	Guaifenesin
Lab Scale 3DP	Capsule	Pseudoephedrine HCl
Fused Deposition Modelling (FDM)	Tablet	5-ASA & 4-ASA
Thermal Inkjet Printing	Oral Film	Salbutamol
Extrusion Based 3DP	FDCP: Multilayered, multicomparment Tablet	Nifedipine, Glipizide, Captopril
Inkjet 3DP	Nanosuspension	Rifampicin
Inkjet 3DP	Implant	Levofloxacin
3D Printing	Multi drug implant	Rifampicin & Isoniazid
Extrusion Based 3DP	Capsule containing PLGA microsphere	Dexamethasone

Ref. *A. H. Jassim-Jabbori & M. O. Oyewumi, 3D Printing Technology in Pharmaceutical Drug Delivery: Prospects and Challenges., Biomolecular Research & Therapeutics., 2015*

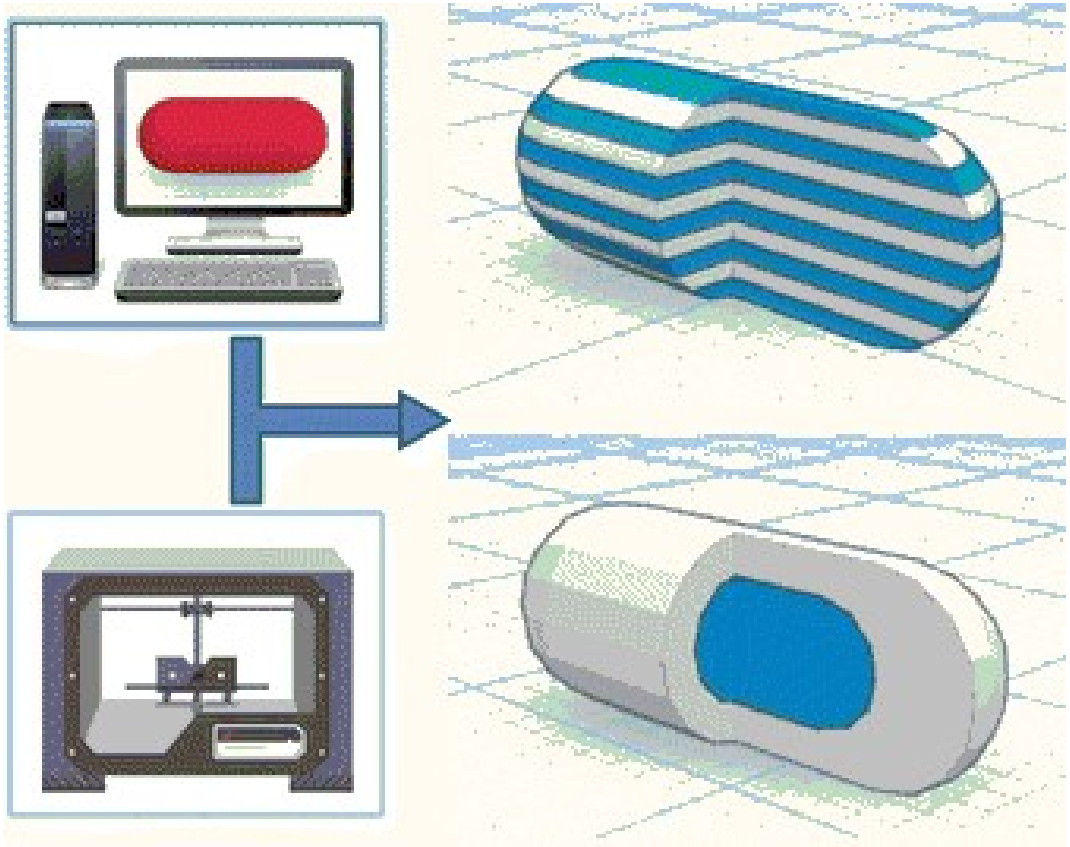
What is 3D Printing?

Definitions

- 3D printing is layer-by-layer production of 3D objects from digital designs.
- It is also known as “additive manufacturing”, “rapid prototyping” and “solid free form fabrication”
- 2D Printing : simply use inkjet paper printing technology with the exception of a polymeric film instead of paper and drug instead of ink.

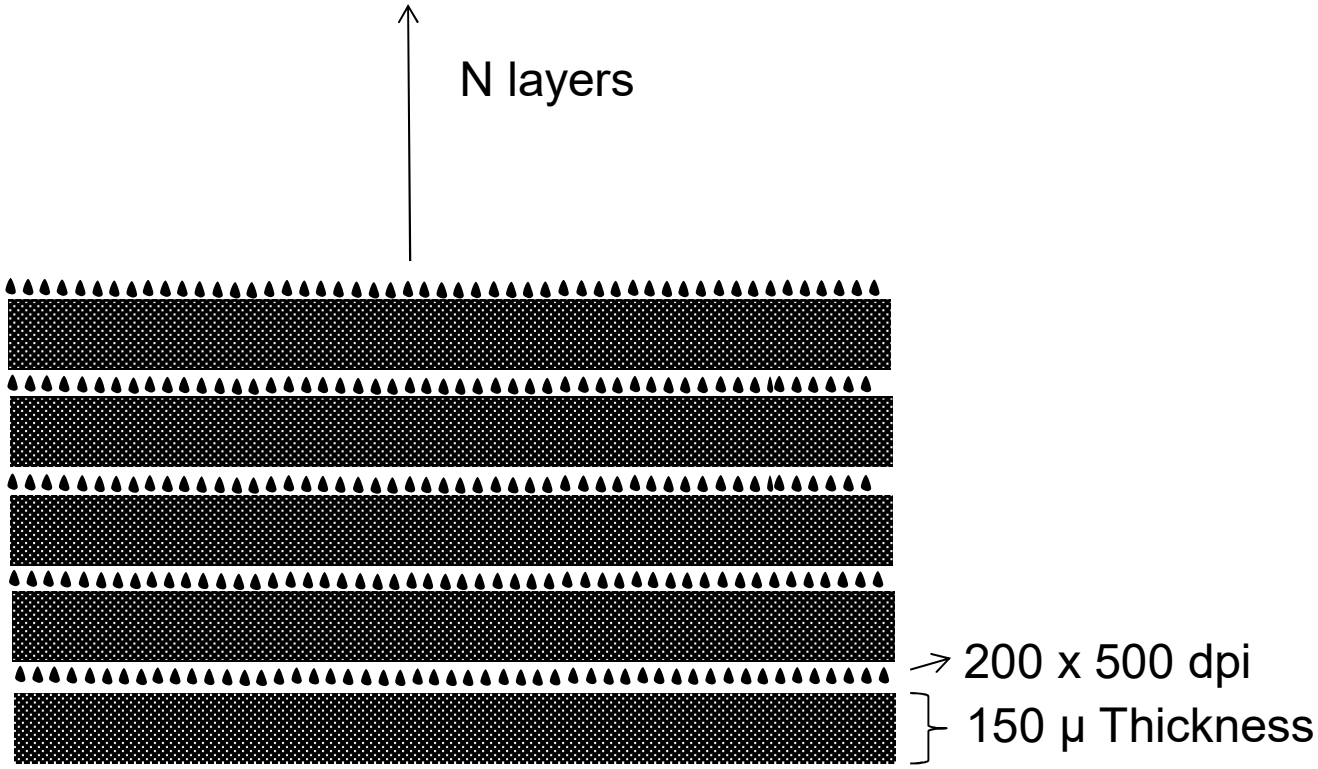
How Does It Work?

- First, the pharmaceutical product is designed in three dimension (or 2D) with computer aided design (CAD)
- Conversion of the design to a machine readable format, which describes the external surface of the 3D tablet
- The computer program then slice these surface into several distinct printable layers and transfer that layer-by-layer instruction to the machine
- This represent the major types of 3D printing

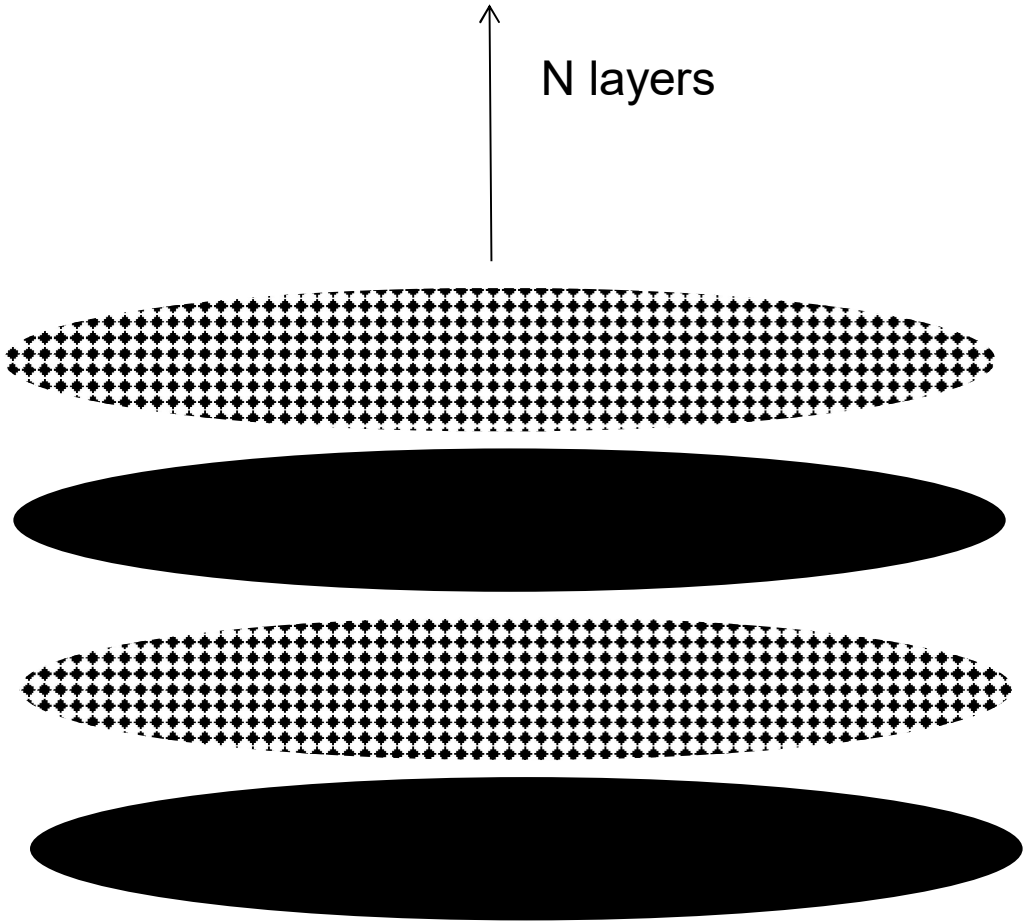


Ref. A. Goyanes et. al., 3D Printing of Medicines: Engineering Novel Oral Devices with Unique Design and drug Release Characteristics., Mol. Pharm. 2015

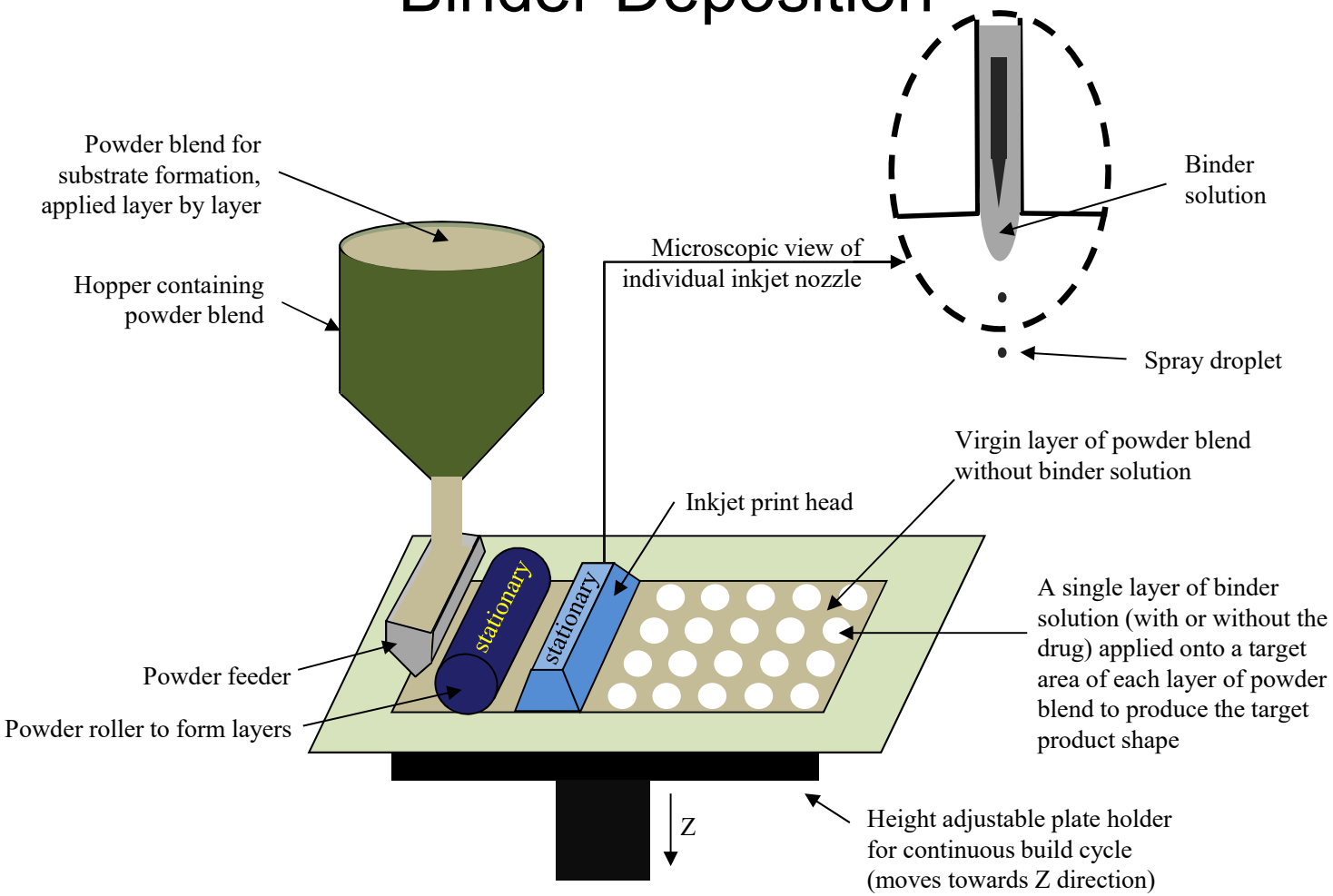
3 DP Product Design: 2 D Cross Sectional View



3 DP Product Design: 2 D Horizontal View



Electrostatic Inkjet Dispenser: 3D Printing Process Binder Deposition



Ref. J. Norman, R. Madurawe, C. Moore, M.A. Khan, ***A. Khairuzzaman***., A new chapter in pharmaceutical manufacturing: 3D-printed drug products., ***Advanced Drug Del. Rev***. March 2016. Vol. 99.

3DP Types for SODF

- Binder deposition
- Material jetting
- Extrusion
- Powder bed fusion
- Photo polymerization
- Pen-based 3D printing
- 3DP Molds
- Others not yet used for drug product manufacturing: e.g. electrospinning,

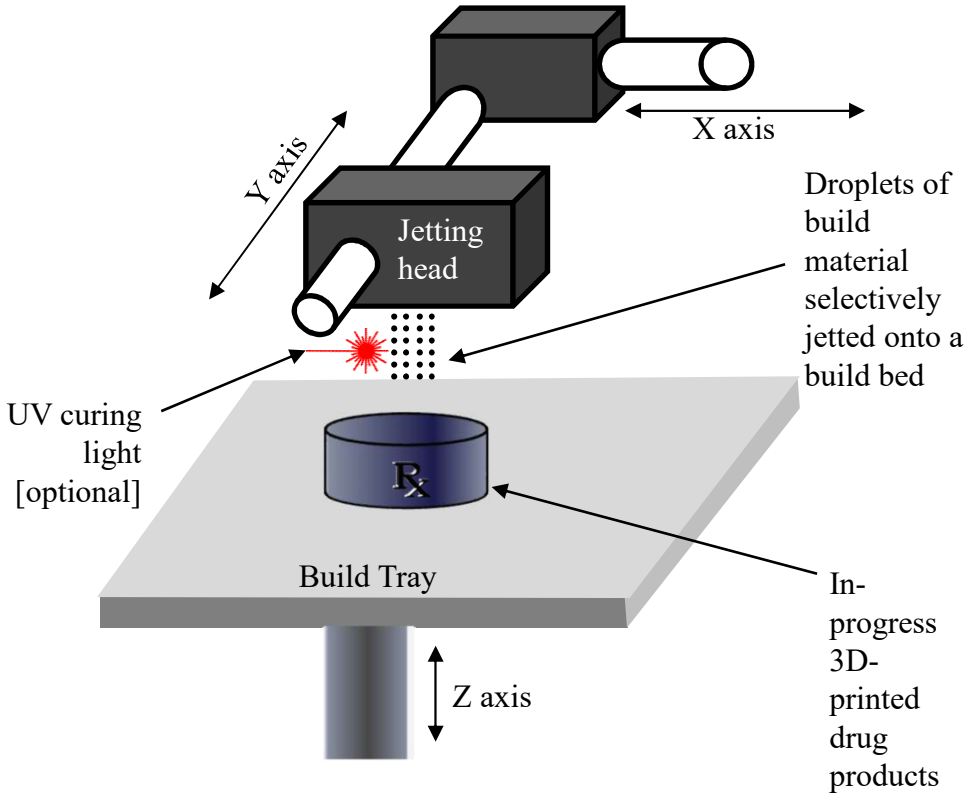
3DP Types for SODF: Binder Deposition

- Inkjet printers. It spray formulations of drugs or binders in small droplets at precise speeds, motions, and sizes onto a powder bed. Solidification mechanism for binder is identical to that of the drying

  Inject printing category:

  - Thermal/roof shooter (applies heat to ink)
  - Piezoelectric (deformation of a piezoelectric material upon application of voltage)- three types (squeeze mode, bend and push mode and shear mode)
  - Electrostatic (electric voltage applied in between two electrode to crate target liquid droplet size)
  - Acoustic inkjet (use ultrasound)

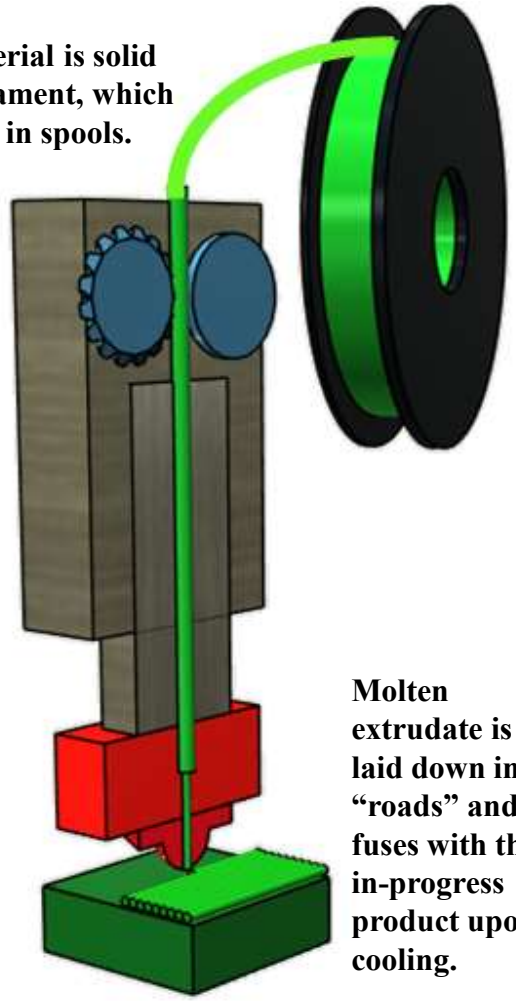
3DP Types for SODF: Material Jetting



- A powder bed is not necessary
- Inkjets can print freeform structures that solidify drop-by-drop
- Commonly jetted materials are molten polymers and waxes, UV-curable resins, solutions , suspension, & complex multi-component fluids
- The entire formulation needs to be formulated for jetting and rapid solidification
- High resolution: inkjet droplets are ~100 micron

Ref. J. Norman, R. Madurawe, C. Moore, M.A. Khan, ***A. Khairuzzaman***., A new chapter in pharmaceutical manufacturing: 3D-printed drug products., ***Advanced Drug Del. Rev***. March 2016. Vol. 99.

3DP Types for SODF: Extrusion, FFF



- Fused Filament Fabrication
- No powder bed as well
- Widely used in other fields
- RM: polymers, pastes, silicones, other semisolids
- Simple equipment
- Requires heat, difficult to reprocess, slow printing speed, highly viscous
- Suitable for implants, drug device

Ref. J. Norman, R. Madurawe, C. Moore, M.A. Khan, ***A. Khairuzzaman***., A new chapter in pharmaceutical manufacturing: 3D-printed drug products., ***Advanced Drug Del. Rev***. March 2016. Vol. 99.

Comparison of 3D Printing to Other Pharmaceutical Processes

Manufacturing Method	Example Product	Throughput	Dimensional Tolerance	Mechanical Integrity	Product Complexity	Potential for Personalization	On Demand Capability
Compression	Tablet	High	Medium	Medium	Low	Low	Low
Encapsulation	Capsule	High	High	Medium	Low	Low	Medium
Molding	Suppository	High	High	High	Medium	Low	Low
Extrusion	Ocular implant	High	Medium	High	Low	Low	Low
Laser machining	Absorbable stent	Medium	High	Medium	Low	Medium	Low
Coating	Coated stent	Medium	Medium	Low	Low	Low	Low
Lyophilization	ODT*	Medium	Medium	Low	Low	Low	Low
3D Printed Drug Products		Low	Low	Low	High	High	High

Ref. J. Norman, R. Madurawe, C. Moore, M.A. Khan, ***A. Khairuzzaman***., A new chapter in pharmaceutical manufacturing: 3D-printed drug products., ***Advanced Drug Del. Rev***. March 2016. Vol. 99.

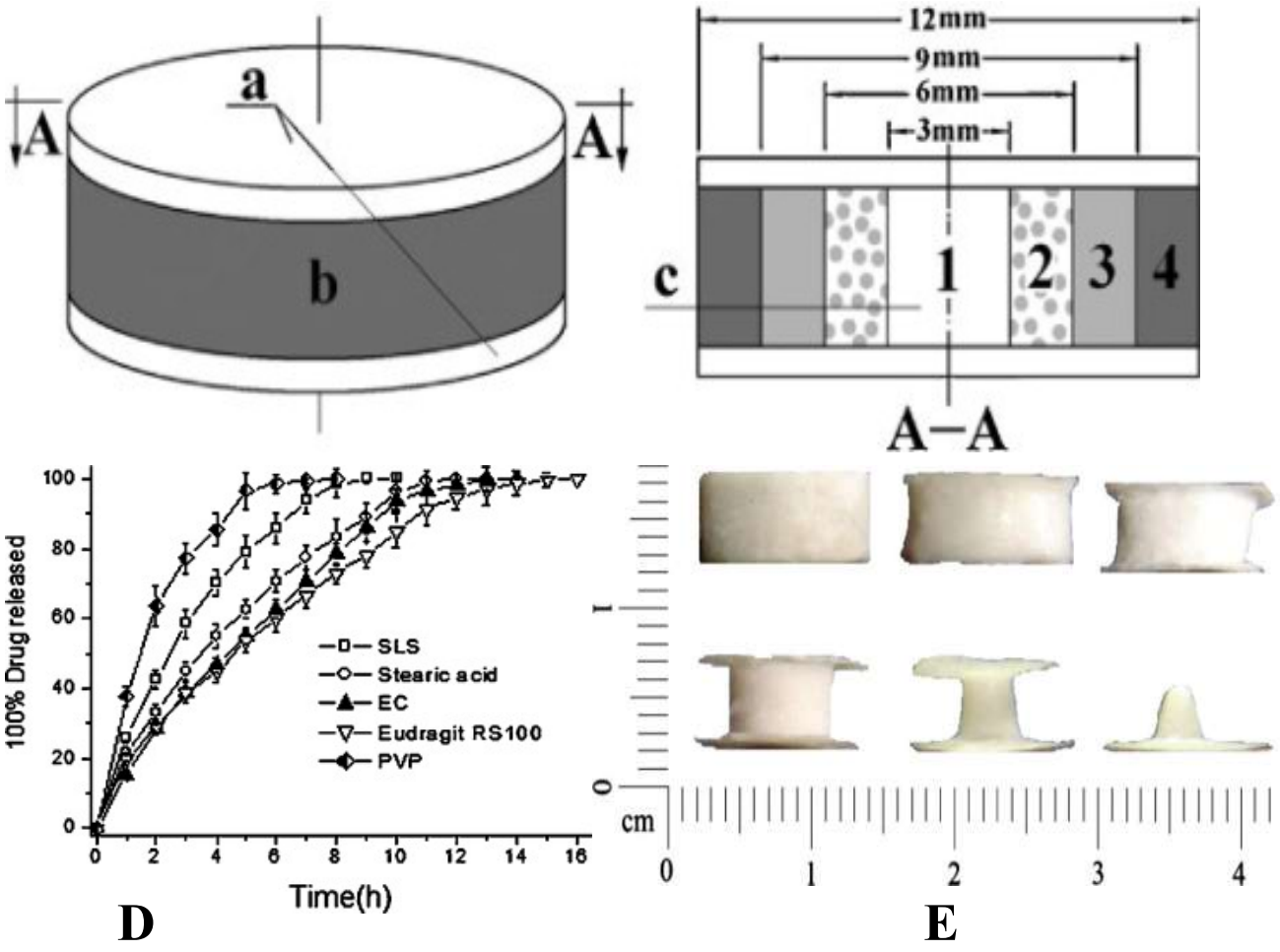
Why 3D Printing?

What is the Motivation?

Why 3D Printing?

- **Increased product complexity:**
  - Complex MR Products: multilayered, tablet within a tablet, osmotic, multilayered multiparticulate system and others. Batch process with some variability.
  - Advanced drug release profile
  - Alternate for oral powder, high dose ODT
  - Printing amorphous dispersions by hot melt extrusion
  - Delivery of extremely low dose drugs (as low as 3 ng)
  - MR products: Creating radial gradients of diffusion-controlling excipients
  - Complex drug device design

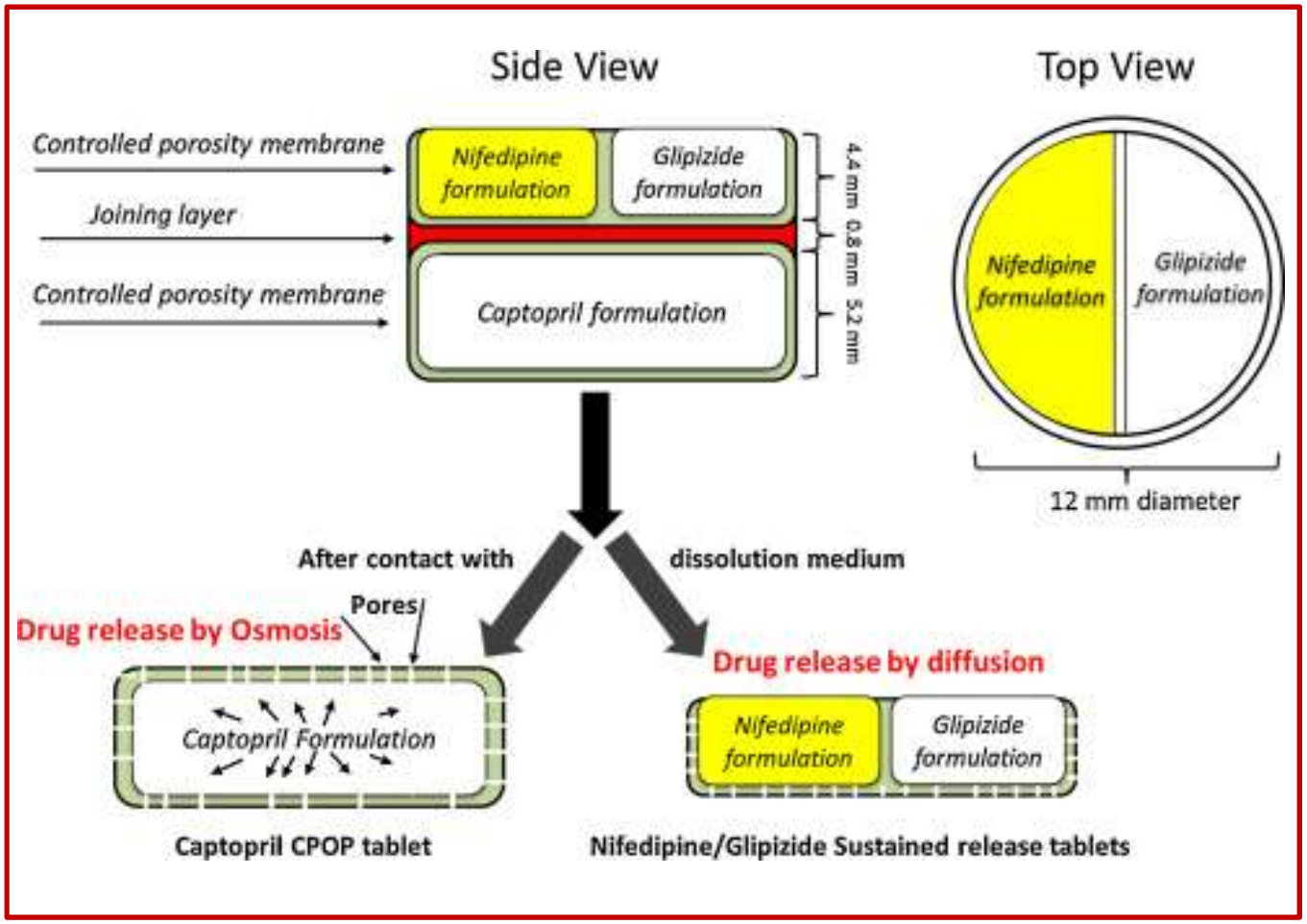
Increased Product Complexity



Digitally controlling arrangement of matters: A schematic diagram of the tablet with material gradients, (a) barrier layer; (b) drug-containing region; (c) gradients of release-retardation material (d) Release profiles of Acetaminophen from tablets with different material gradients (e) Photographs of tablets at different time points

Ref. Deng Guang Yu et al., Tablets With Material Gradients Fabricated by Three-Dimensional Printing, *Journal of Pharmaceutical Sciences*, Volume 96, Issue 9, 2007

Increased Product Complexity

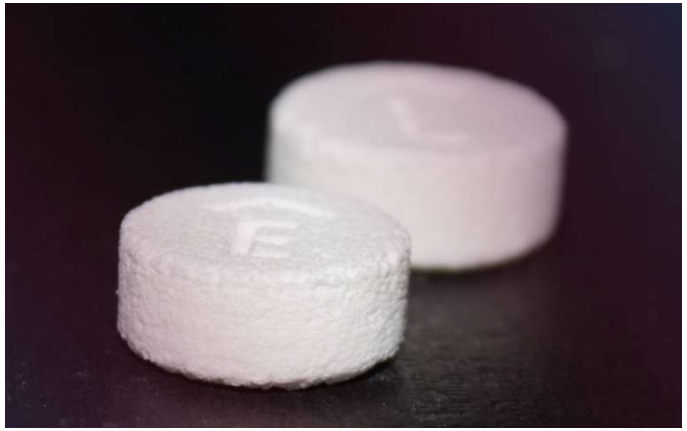


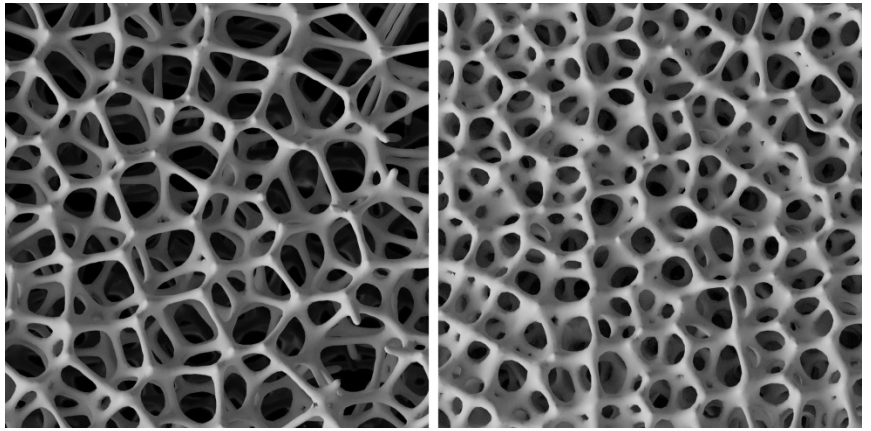
A bilayer multi-compartmental fixed dose combination products of captopril, nifedipine and glipizide sustained release tablet.

Bi-modal release mechanism in built: osmotic pressure controlled and diffusion controlled

Ref. Clive Roberts et al., 3D printing of tablets containing multiple drugs with defined release profiles, *Intl Journal of Pharmaceutics., V*ol 494, Oct' 2015.

Increased Product Complexity



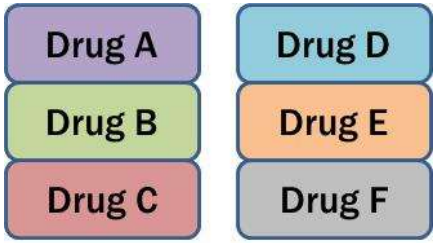


3D Printed Drug Product Design for Oral Use: High Porosity offering High Tortuosity, Better Mechanical Strength

A compressed ODT does not have high porous structure, relies on super-disintegrant. Typically has hardness issues. Dose limit: 500 mg dose.

Why 3D Printing?

- **Personalized Use:**
  - Accurate dosing, lower side effects, low cost, better pediatric adherence .
  - Manufacture as per need and preference: strength, size, flavor, color, precision. Just select recipe on computer and then click.
  - No need for long shelf life
  - Individualized multi drug polypills
  - On demand mfg. e.g. Drug shortage, emergency



Manufacturing Challenges

Process Consideration for 3D Printing

- **Raw material control:** printability, physicochemical characteristics, thermal conductivity, viscoelastic property, Print fluid characteristics (Viscosity, Surface tension, Density, Rheology/ Viscoelastic property)
- **Process control:** Identify high risk steps which may impact identity, appearance, assay, content uniformity, drug release, impurity level, hardness, friability, crystallinity, and API polymorphic form. Example of such steps could be: printing, solidification, recycling, controlling mass & energy transport. PAT can be used for control.

Ref. (1)*United States Food and Drug Administration. Additive Manufacturing of Medical Devices Public Workshop – Transcript for October 8th (2014) Available from.*
Ref. (2) *B. Meyer, Accuracy in Additive Manufacturing, in Machine Design. 84 (2012) 56-62*

Risks and Potential Control Strategies for 3D-Printing Processes

3D printing method	Some Unique Risks	Potential Controls
General, applicable to most 3D printing methods	Inability to print a given design with a given printer	Software controls
	Variability in layer thickness	Real-time layer thickness monitoring
	Variability in the quality of recycled materials	In-process tests for assay, purity, blend uniformity, water content, and particle size distribution. Restrictions on how many times a material can be recycled
	Improper layering due to environmental conditions	Temperature and humidity of the printing environment
	Inaccurate positioning during printing	Print head height, Print head speed
	Compositional variation, thermal variation, etc.	Various types of PAT

Ref. J. Norman, A. Khairuzzaman., R. Madurawe, C. Moore, M.A. Khan, ***A. Khairuzzaman***., A new chapter in pharmaceutical manufacturing: 3D-printed drug products., ***Advanced Drug Del. Rev***. March 2016. Vol. 99.

Risks and Potential Control Strategies for 3D-Printing Processes (Cont'd…)

3D printing method	Some Unique Risks		Potential Controls
Binder Deposition	Raw material risks	Uneven layers	Powder water content Powder particle size distribution
		Print head clogging	Suspension particle size distribution Real time monitoring of inkjet flow
		Inconsistent binding / agglomeration between layers	Binder viscosity Binder surface tension
	Process parameter risks	Uneven layers	Powder deposition rate Roller speed relative to the powder
		Inconsistent binding / agglomeration between layers	Jetting rate Jetting temperature Liquid fill height in the print head Print head speed relative to the powder Drying time between layers

Ref. J. Norman, A. Khairuzzaman., R. Madurawe, C. Moore, M.A. Khan, ***A. Khairuzzaman***., A new chapter in pharmaceutical manufacturing: 3D-printed drug products., ***Advanced Drug Del. Rev***. March 2016. Vol. 99.

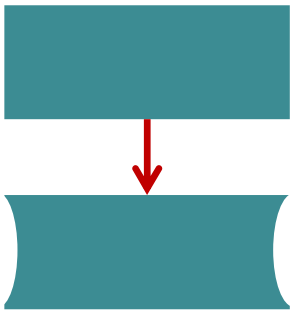
Risks and Potential Control Strategies for 3D-Printing Processes (Cont'd…)

3D printing method	Some Unique Risks		Potential Controls
Fused filament fabrication	Raw material risks	Inconsistent extrusion patters due to variability in raw material rheology	Water content Polymer molecular weight distribution, T_g, composition Melt viscosity, Filament uniformity
		Friability after printing	Polymer toughness
	Process parameter risks	Inconsistent extrusion during printing	Extrusion pressure / gear speed Extruder temperature, Print head speed
Fusion	Raw material risks	Uneven layers	PSD, Particle shape distribution
		Incomplete fusion, Unintentional fusion across layers	Raw material rheological properties at relevant heating rates and temperatures
	Process parameter risks	Uneven layers	Powder deposition rate Roller speed relative to the powder
		Inconsistent fusion, Laser-induced degradation	Laser energy Laser duty cycle Raster pattern and raster speed

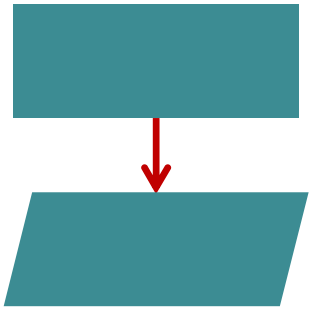
3DPrinted Drug Products: Typical Quality Defects

- Banding: ripples on a product's sides caused by vibration in the x-y plane during printing
- Leaning: off-axis products caused by drift in the x-y plane during printing
- Warping: product distortion caused by thermal expansion or contraction
- Shifting: First few layers were shifted because of base line shift during printing
- Collapse: loss of porosity caused by sagging layers or excessive mass/energy input
- Residuals: unbound powder or uncrosslinked monomer caused by incomplete printing

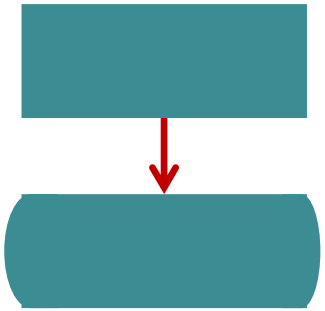
3DPrinted Drug Products: Typical Quality Defects



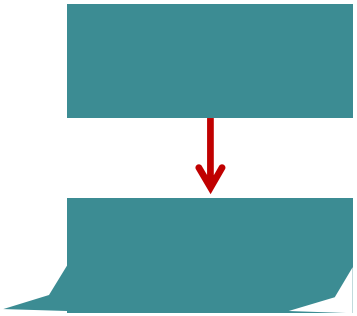
Banding



Leaning



Warping



Shifting

3DP: Some Limitation for SODF

- Not well known in pharmaceuticals
- Regulatory risk is unknown if being persued for personalized used such as in compounding or in hospital compounding facility
- For commercially distributed pharmaceutical products, and batch manufacture speed could be an issue, ~4000 tablet/5-6 min
- Technology is protected by several intellectual property
- Materials: API and Excipient selection suitable for inkjet technology
- Ease of use for commercial purpose: requires considerable skills to operate and understand the process and the anatomy of the equipment

Regulatory Challenges

3DP: Regulatory Challenges

- What do we call a 3D printed drug product?
- What is the appropriate regulatory pathway?
- Can we use 3D Printing technology in compounding?
- Can 3D print cartridges loaded with drug be regulated?
- Should FDA regulate 3D printers?

3DP: Regulatory Challenges

- Currently, there is no regulatory framework or guidance for 3D printed drug products (SODF)
- FDA Draft Guidance on "Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base Guidance for Industry", December 2015
  - Guidance for IND, NDA, ANDA & BLAs
  - A brief description of the proposed new technology
  - A brief description why the proposed technology could modernize pharm. mfg.
  - A summary of the development plan
  - A timeline for a submission

3DP: Regulatory Challenges

- 3D printed drug product must also be manufactured in accordance with current CMC standards as set forth in the 21 CFR 200s & 300s and other relevant guidance for 505 b(1), 505 b(2) type of submission
- Personalized drug products may not align with any of these pathways – 505(b)(1), 505(b)(2), or 505(j) – because products submitted by these pathways need to have consistent quality
- FDA regulates 3D printed drug product rather than 3D printers that manufacture the drug products

Conclusion

- This technology has proven commercial feasibility through the FDA approval of a 3D product in August of 2015
- It is continually evolving in pharmaceuticals for complex formulation and for better safety & efficacy
- Potential use in personalized pharmaceutical products manufacturing and compounding

Thank You

Acknowledgement

James Norman
Rapti Madurawe
Bob Iser

Back-Up Slides: SPRITAM

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SPRITAM® safely and effectively. See full prescribing information for SPRITAM.

SPRITAM (levetiracetam) tablets, for oral use
Initial U.S. Approval: 1999

INDICATIONS AND USAGE

SPRITAM is indicated for adjunctive therapy in the treatment of:

- Partial onset seizures in patients with epilepsy 4 years of age and older weighing more than 20 kg (1.1)
- Myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy (1.2)
- Primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy (1.3)

DOSAGE AND ADMINISTRATION

Administer whole SPRITAM tablets with a sip of liquid; the tablet should be swallowed only after it disintegrates (2.1)