FDA U.S. FOOD & DRUG ADMINISTRATION

3D Printing in Drug Development & Emerging Health Care

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Learning Objectives

1. Identify the fundamental principles of 3D printing as it relates to design and manufacture of pharmaceutical drug products.
2. Describe the motivation driving the paradigm shift of on-demand manufacturing of personalized medicine in upcoming emerging digital health care structure.
3. Explain how various types of 3D printing platforms operate, their capability with respect to complex and precision drug design, manufacturing design and flexibility, and compare with current practice.
4. Summarize upcoming regulatory challenges of this 21st century digitalized manufacturing and its impact on health care structure.

Introduction

The Big Picture:
Patient of the Future…

Evolution of Pill

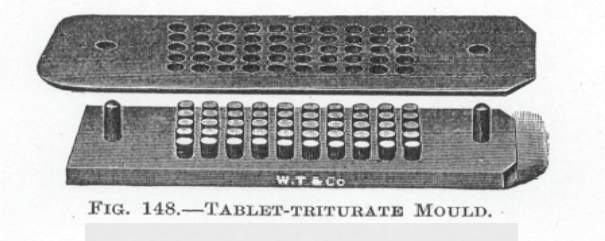
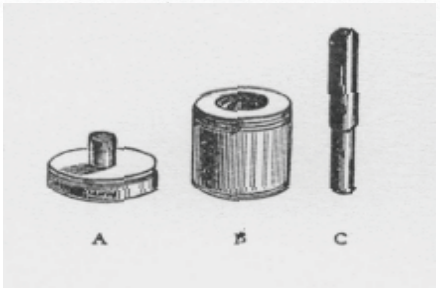


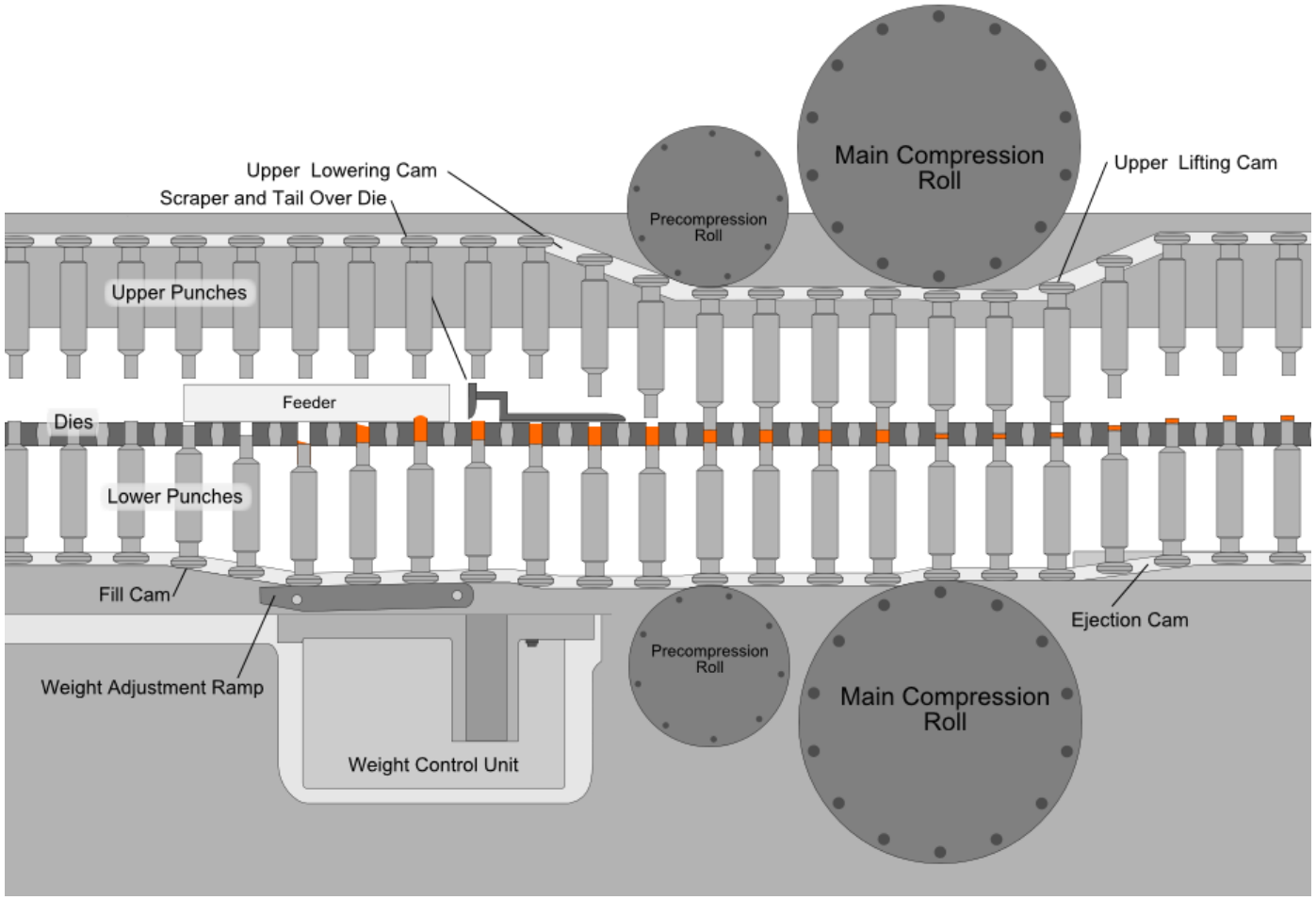
FIG. 148.—TABLET-TRITURATE MOULD.



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

Picture from the Museum of the Royal Pharmaceutical Society

Over 100 Years of Automation



21st Century Automation

- Batch Manufacturing to Continuous Manufacturing
- Robots in manufacturing
- Use of process analytical models
- Complex pill manufacturing such as pill within a pill, bi-layer/ tri-layer/multi-layer Polypill
- New dosage forms are evolved: micro tablet, sublingual tablets, muco-adhesive tablets, buccal tablets, vaginal tablets, osmotic pumps, complex extended release tablets, effervescent tablet
- All use some sort of compression force or mold to form a pill/tablet

The Digital Era…

- 21st Century is at the brink of Digital Era
- Ancient practice of medicine was very personalized
- Compounding pharmacy (~60% of medicines were compounded during 1930s and 1940s)
- Industrial revolution in Pharmaceutical Manufacturing
- Evolution of Modern Diagnostic Tests (e.g. hybrid closed-loop insulin delivery system), currently there is little or no real-time feedback from patient
- New concept of treatment: gene therapy, DNA/RNA based therapeutics and personalized medicine
- More focus on patient centric treatment and discoveries
- 3D Printing – the Disruptive Innovation

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

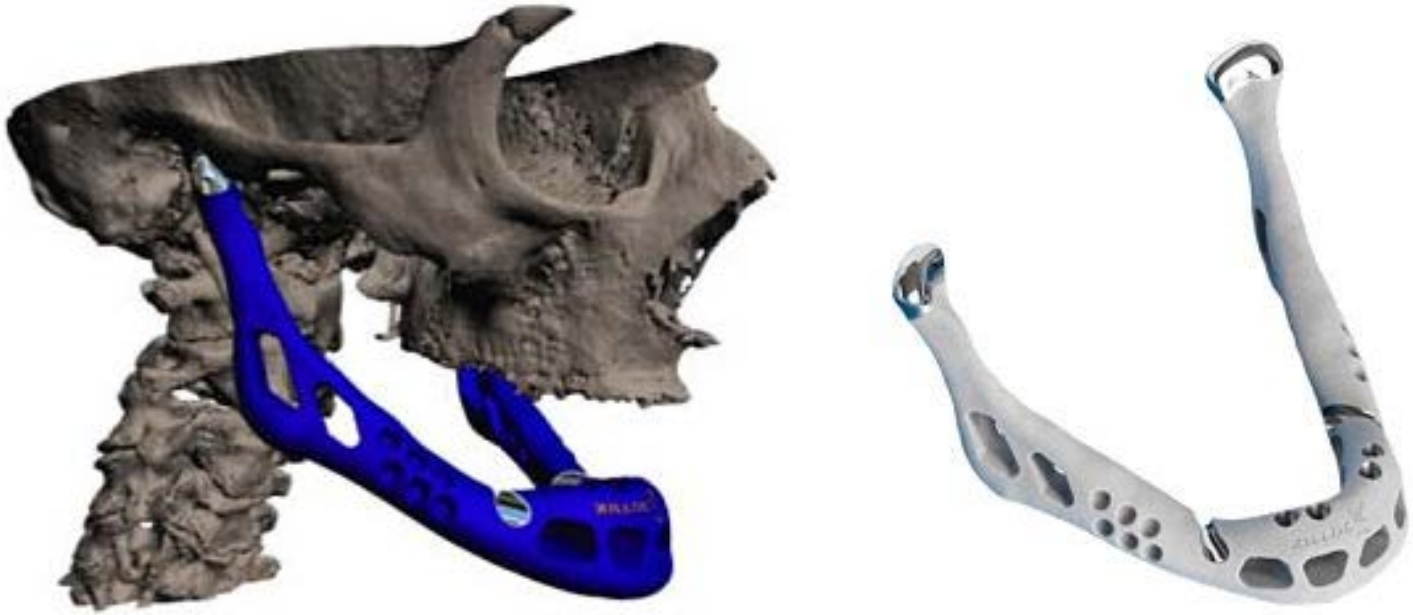
Source: CNN Interview, US Patent 4,575,330

3DP: Continuing Evolution

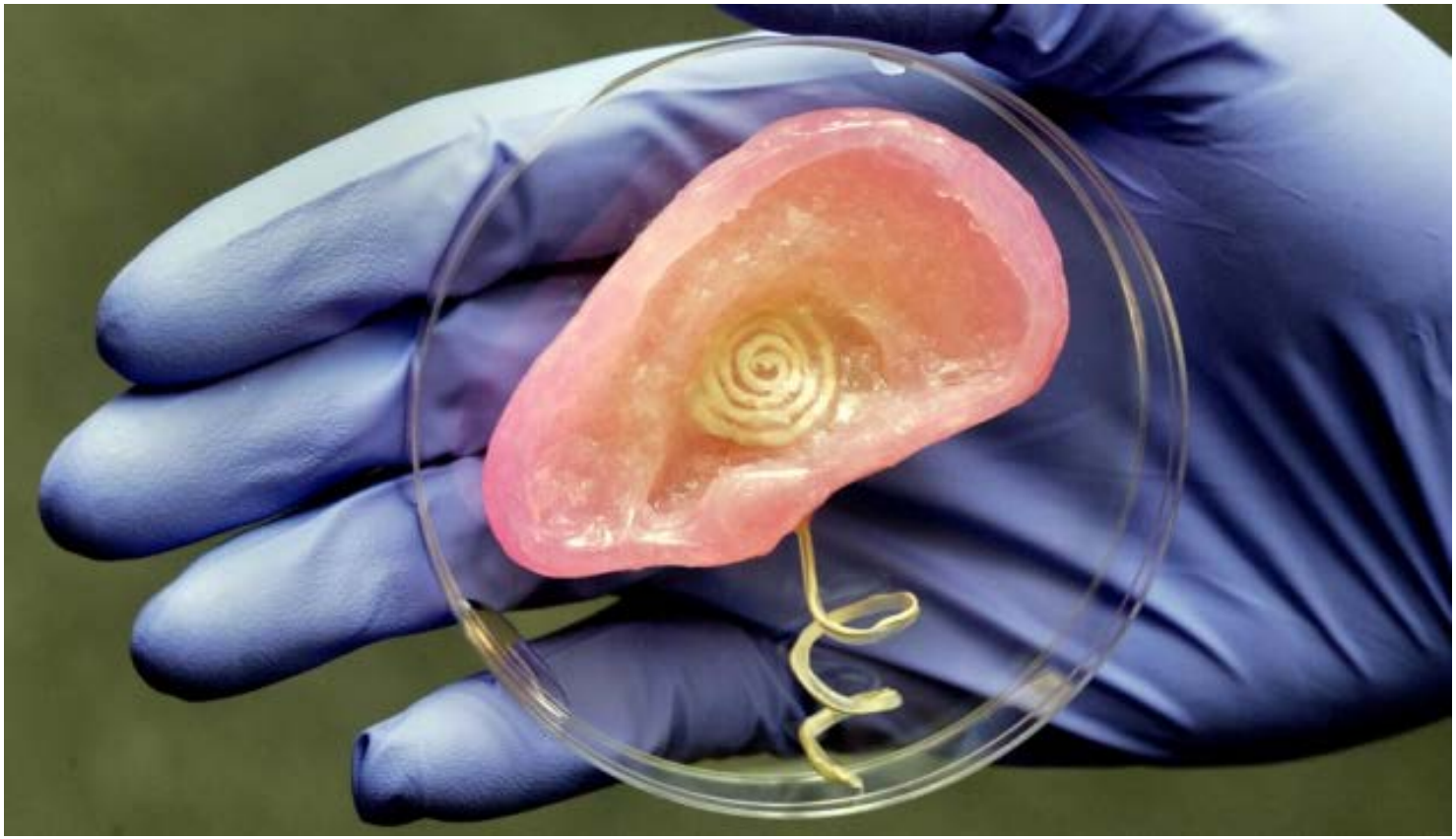
- Food
- Fashion
- Toys
- Automobile industry
- Computer parts
- Architectural industry
- Pharmaceuticals (first reported 3D pill in 1996)
- Drug Device, Medical Device & Bioprinting

A 3D Printed Human Skull Implanted in a 22 year old woman in Netherlands in 2014.

Source: Science, March 2014



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



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

3DP Kidney, Liver, Heart (Harvard News 2017)

SPRITAM *(levetiracetam) tablets, for oral use*

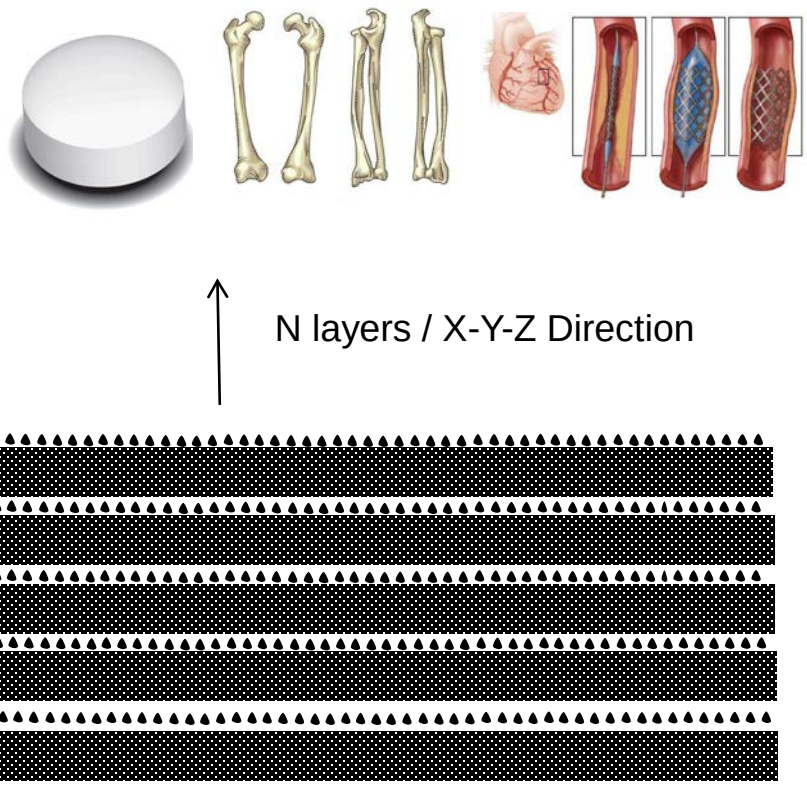
FDA's first approved 3D printed drug product

Learning Objective 1:

Identify the fundamental principles of 3D printing as it relates to design and manufacture of pharmaceutical drug products

What is 3D Printing?

- Fundamental concept from 2D paper printing
- 3DP is additive manufacturing technology – layer by layer addition of material to achieve a certain shape
- 3D printing is an umbrella term for a range of technologies (complex object and building materials)
- Objects: drug products, medical device and human organ
- Building materials: drugs and inactive ingredient, biomaterials



Typical layer thickness as low as 25 micron

Example of Biomaterials

Material	Current explored applications
Polyester textile	Vascular grafts and heart stents
Polyurethane	Pacemaker lead insulation
Silicones	Soft tissue augmentation, ophthalmological device
Poly (methyl methacrylate) PMMA	Bone cement
Carbon	Heart valves
Stainless steel	Stents and orthopedic implants
Titanium alloys	Dental implants, heart valves, spinal cages, fracture plates

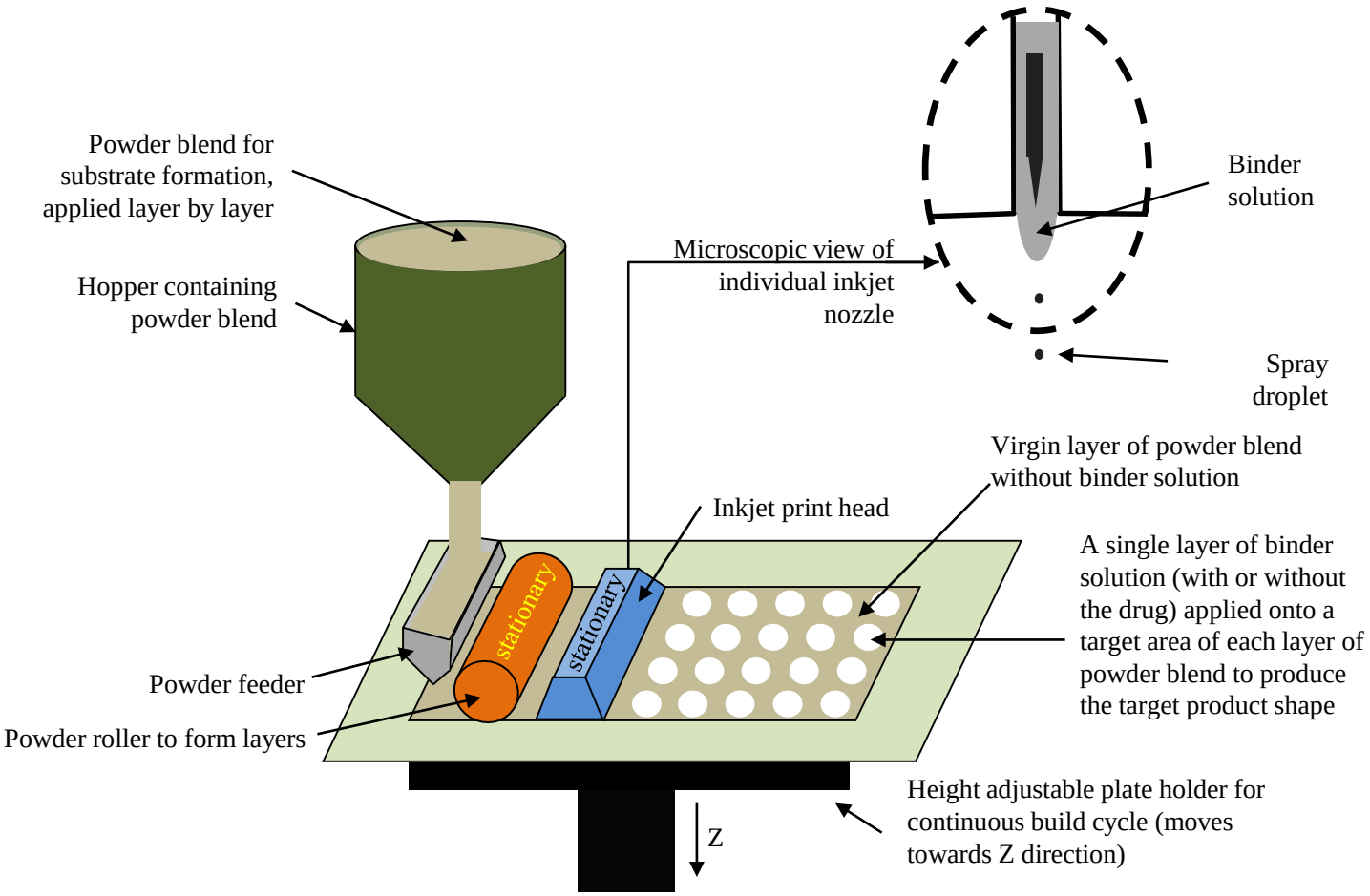
Ref. *G.B. Hatton, C.M. Madla, S. Gaisford, A.W. Basit., Medical Applications of 3D Printing, Book Chapter in 3D Printing of Pharmaceutics, Springer, 2018.*

How Does it Work

- Pharmaceutical product is designed in 3-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
- Computer program then slices the surface into several distinct printable layers and transfers layer-by-layer instructions to the machine
- This represents the major types of 3D printing

Drug in Print Fluid vs. Powder for build cycle

3D Inkjet Printing



https://www.youtube.com/watch?v=9HMENLPkftQ

https://www.youtube.com/watch?v=BsSJWqxk2Ek

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

Critical Consideration for Design

- Drug product design matching the target patient vs. target group of patients
- Specific patient needs (group or individual), e.g., localized drug delivery through 3D printed microneedle transdermal patch
- Type of the molecule, e.g., biologics may require specific formulation and process design in addition to specific regulatory requirement
- Target dose and its level of precision (e.g., ng of drug per droplet)

Critical Consideration (Cont'd…)

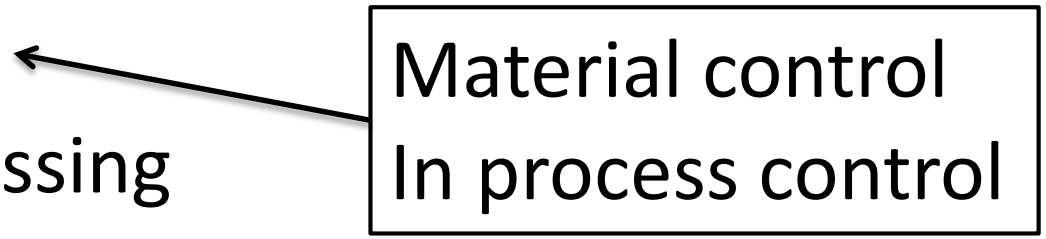
- Level of personalization
- Target delivery route
- Target *in vitro* drug release and corresponding pharmacokinetic characteristics to be achieved
- Target quality attributes
- Target packaging configuration, and
- Target shelf life

Material Understanding for Pharmaceutical Products Using Inkjet

- **Powder characteristics**: Physicochemical properties such as particle size, shape, porosity, crystallinity, water content, viscoelastic property, density, flow and uniformity of mixed material - impact on layer thickness
- **Print fluid characteristics**:
  - Print fluids can be liquids, suspensions, hot melts, contain API, contain polymers, etc.
  - Rheological/Viscoelastic properties and surface tension
  - Thermal/Isothermal properties: Thermal conductivity, specific heat capacity, T_g, etc.
- **Printability** of active pharmaceutical ingredient, and excipients

Typical 3DP Manufacturing Process

- Computer design of the product
- Software workflow to print head
- Build cycle
- Post processing
- Packaging
- Finished product testing



Manufacturing Risk & Control Strategy

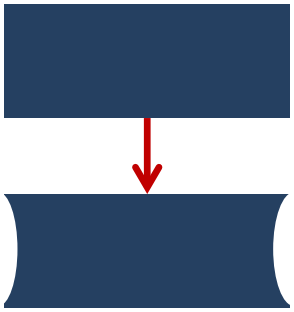
- Variable layer thickness
- Inaccurate position during printing
- Print head clogging
- Inconsistent binding between layers
- Inconsistent extrusion patterns
- Friable tablets

- Software control
- Real-time layer thickness monitoring/PAT
- Raw material control
- In process tests
- Post processing
- Real-time monitoring of inkjet flow
- Powder deposition rate, roll speed

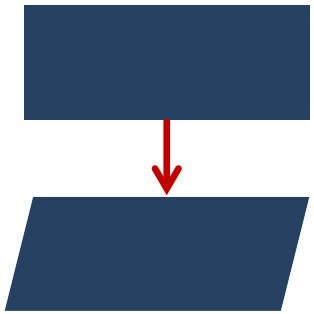
3D Printed Drug Product Quality

- Personalized medicine vs bulk manufacturing using 3D printing technology
- Identity, purity, impurity and other general quality attributes applies for all
- Strength, appearance, and drug release may vary from patient to patient in personalized medicine situations (quality attributes are specific to patient), but remain the same for bulk manufacturing
- Additional attributes are expected to be included depending on the design and performance of the 3DP product

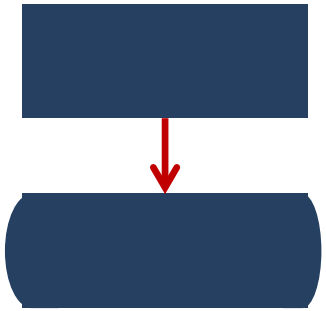
Typical 3DP Product Quality Defects



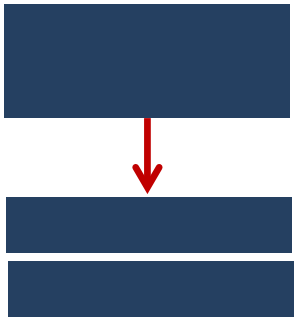
Banding ripples on a product's sides caused by vibration in the x–y plane during printing



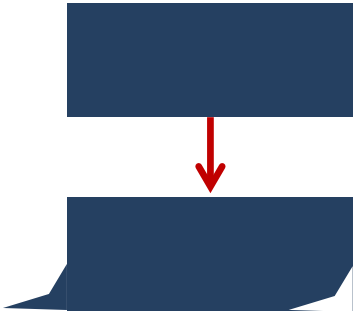
Leaning drift in the x–y plane during printing



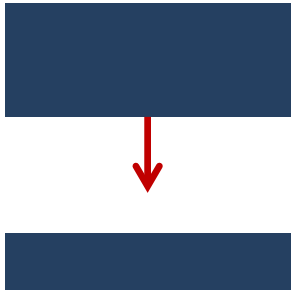
Warping product distortion caused by thermal expansion or contraction



Delamination caused by missing binder solution layers



Shifting drift in base layers



Collapse loss of porosity

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.

Learning Objective 2:

Describe the motivation driving the paradigm shift of on-demand manufacturing of personalized medicine in upcoming emerging digital health care structure

	Driver	Explanation	Advantage Within Pharmaceutical Industry
Increased Product Complexity	Complexity Is Free	Complex objects can be made with the same cost and speed as simple objects.	Potential to increase the complexity of dosage forms to improve efficacy.
	No Assembly Required	Complex parts can be fabricated at once rather than assembling many simpler parts.	3DP may enable simple manufacturing of combination products.
	Infinite Shades of Materials	Combining multiple materials into a single product is straightforward.	May enable multiple APIs to be incorporated into a single product.
	Unlimited Design Space	An infinite repertoire of shapes can be generated.	Enables production of drug products or combination products that previously could not be manufactured.
Increased Personalization	Precise Physical Replication	Existing physical objects can be scanned and replicated.	May enable combination products to be tailored to a patient's physiology or anatomy.
	Variety Is Free	A different object can be created during each production run without increasing cost.	Low production volumes are feasible, enabling personalization.
	Less Waste By Product	Less waste produced when generating structures.	Only manufacture the number of units and doses that are needed.
Point of Care Manufacturing andProcess Scale Out	Zero Lead Time	Parts can be printed on demand when needed.	Reduces need for complex supply chain and inventory.
	Compact and Portable	3D printers are more compact than traditional manufacturing lines.	May enable manufacturing of drug products at point of care.
	Zero Skill Manufacturing	Manufacturing can be performed by layman rather than trained technicians.	May enable patients or health care providers to manufacture drug products on demand.

FDA

The Ten Drivers of 3D Printing

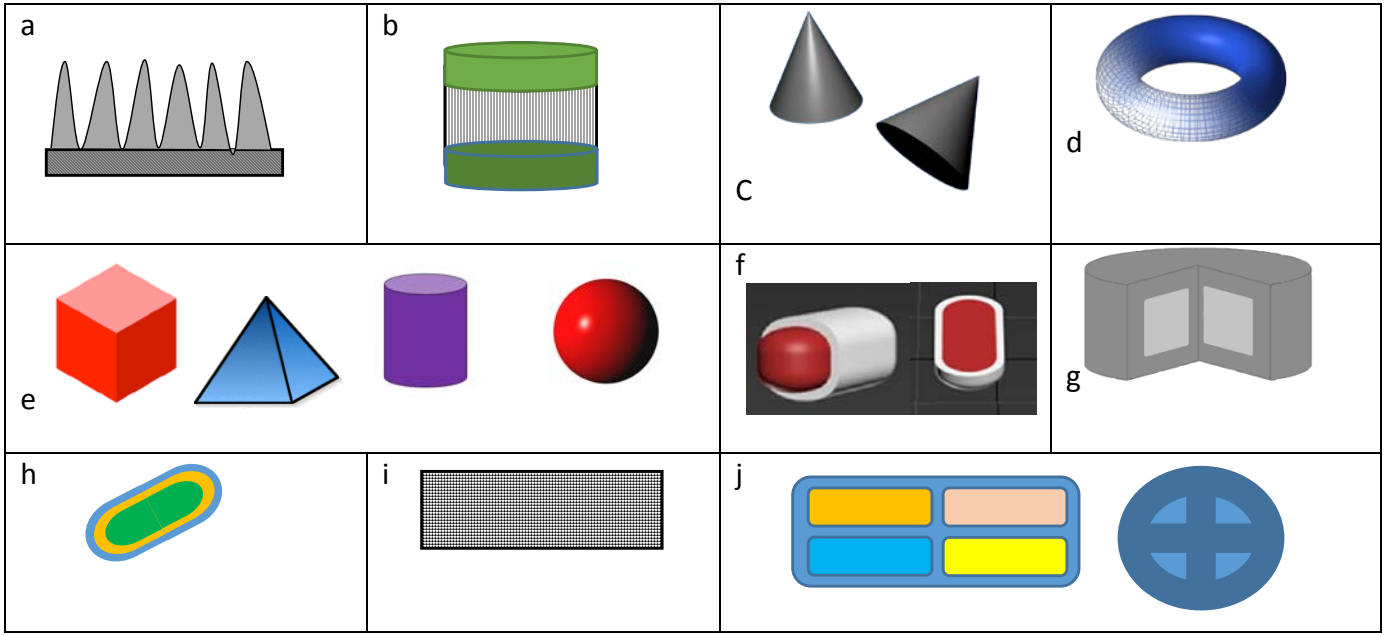
Reference:

Ashley Johnson, et al., 3D Printing in Product Development, *AAPS Magazine*, March 2017

Why Product Complexity?

- 3D Printing begun with genomic revolution in early 1990s with a concept of a possible platform for personalized medicine, introducing multidimensional product complexity
- Late 90's pharmaceutical product complexity examples - osmotic pumps, complex modified release, nanotechnology, amorphous formulations, etc.
- 21st century complexity: remedy (DNA/RNA), low dose drug with precision (e.g. nanogram), targeted complex drug release profiles, medicines are also getting digitalized for feedback to clinicians
- Personalized medical device and bioprinting

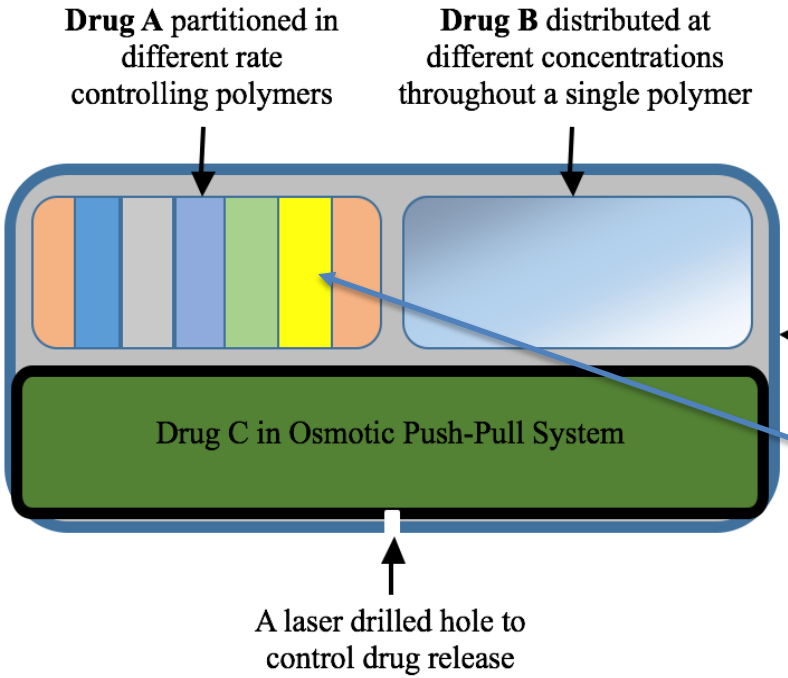
Example: Complex Product Design

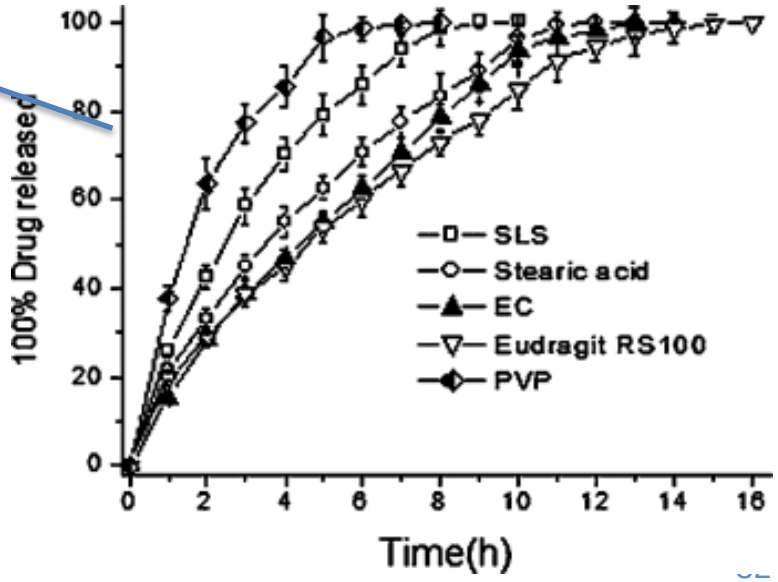


3D printed multicompartmental capsule

Ref. A. Khairuzzaman, Regulatory Perspective on 3D Printing in Pharmaceuticals, Book Chapter in 3D Printing of Pharmaceuticals, Edited by, Abdul Basit & Simon Gaisford. Springer. 2018.

Example: Complex Product Design





- Polypill with three different release mechanism
- Digitally controlling arrangement of material
- Gradients of release-retardation
- Release profiles from tablets with different material gradients

Example: Infinite Shades of Material

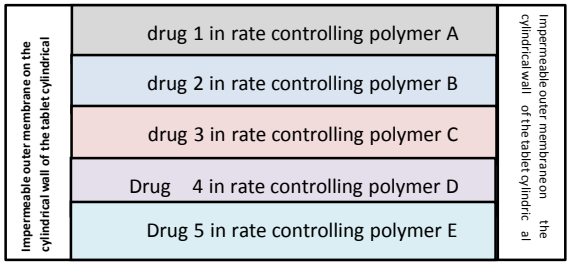


Fig I. Example of a 3D printed polypill In different layers of individual polymeri (A,B,C,D & E) offering variable release profile

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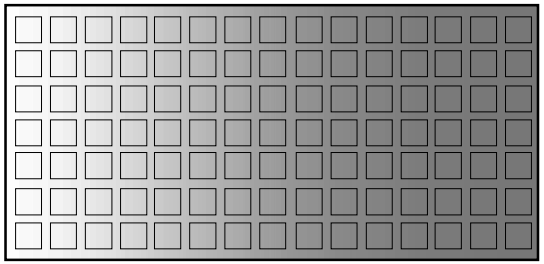


Fig II. Example of a tablet containing only one drug in a rate controlling polymer (binder solution) that is partitioned in 15 columns by varying the number of print droplets deposited in each column. Each small rectangular shape represents variable number of binder drops.

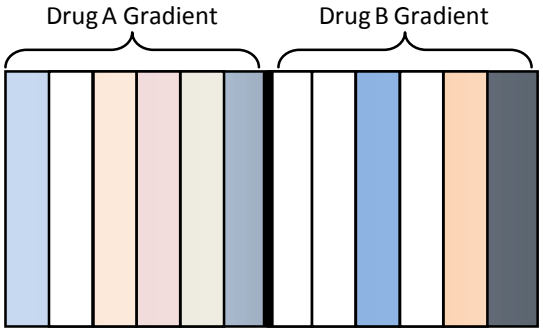
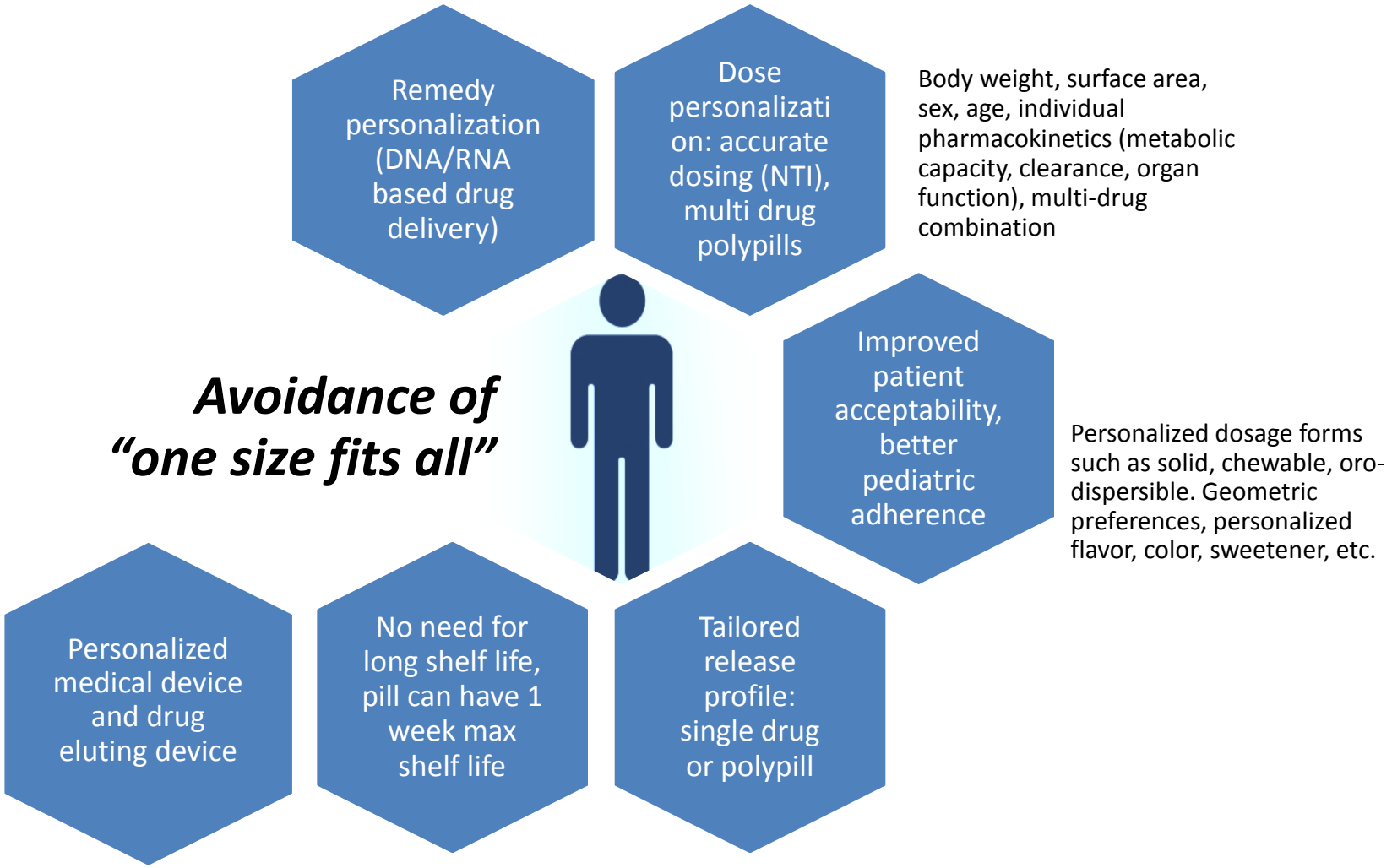


Fig III. Example of a 3D printed fixed dose tablet containing drug A & B. The left and right compartment of the tablet is designed with multiple rate controlling polymers where by the drug A & B is partitioned in different column to offer multi modal drug release.

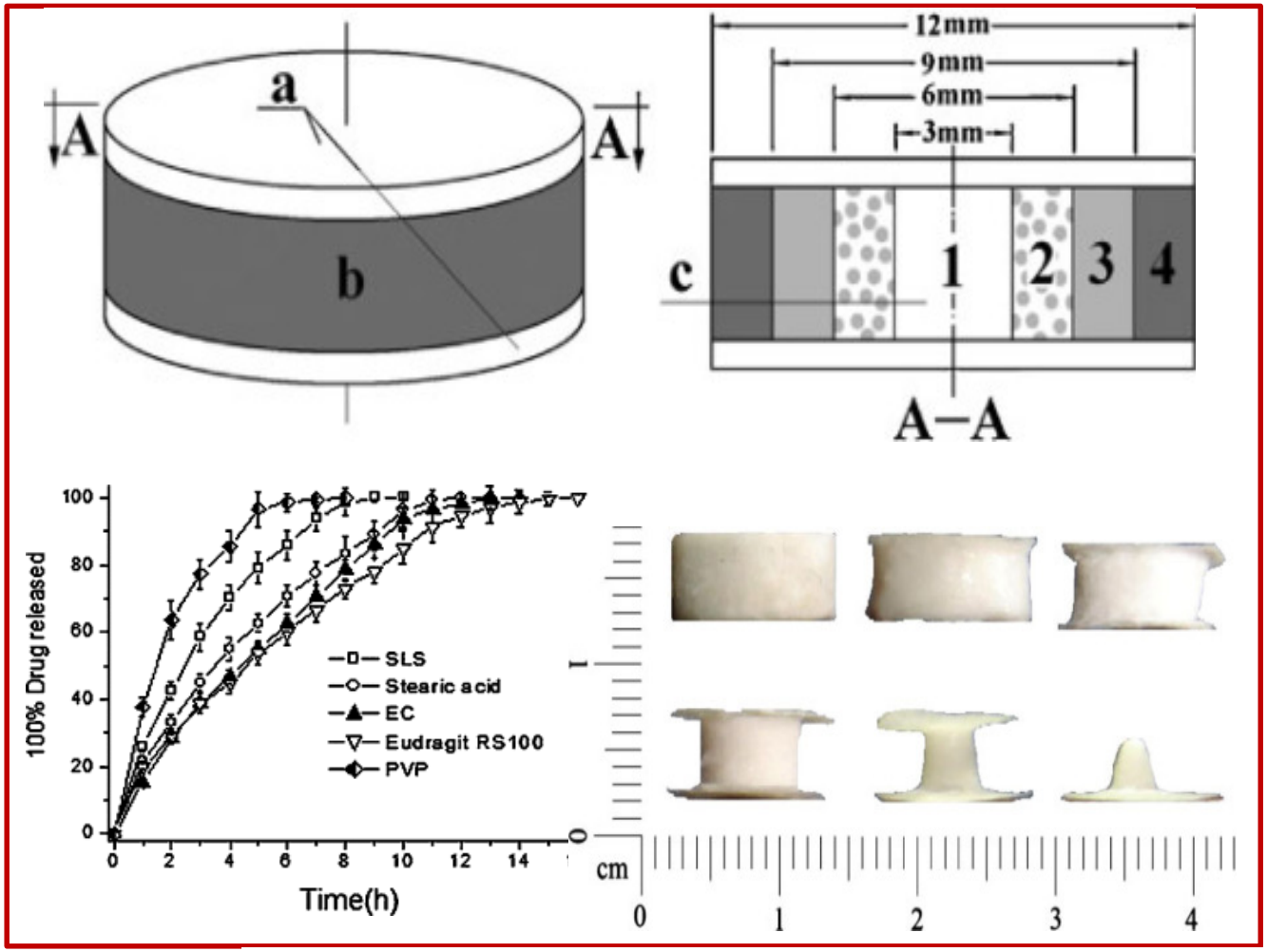
Digitally controlling arrangement of materials (drugs)

Schematic created by this presenter and presented at IFPAC-2017 meeting

Increased Personalization



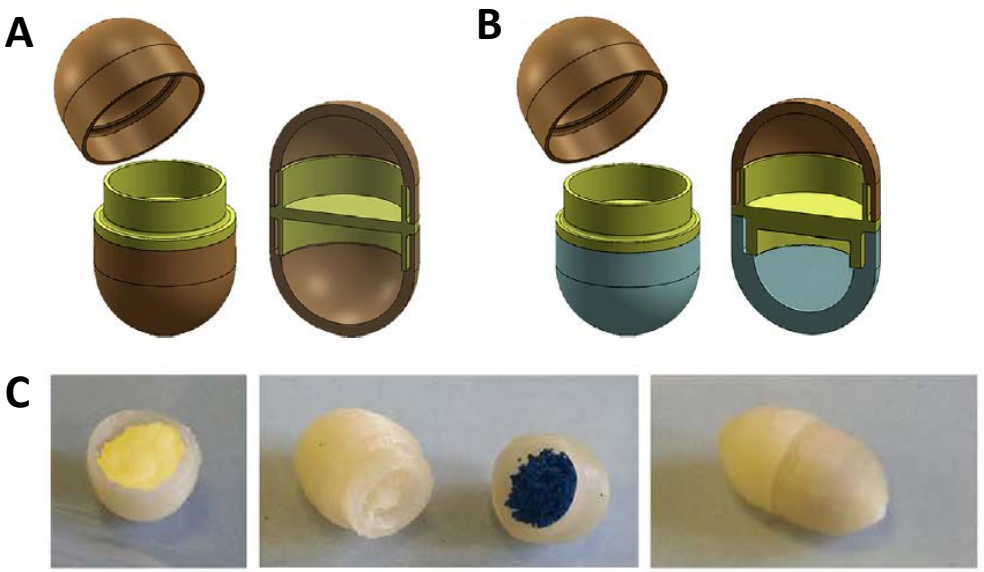
Example: Tailored Release Profile



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

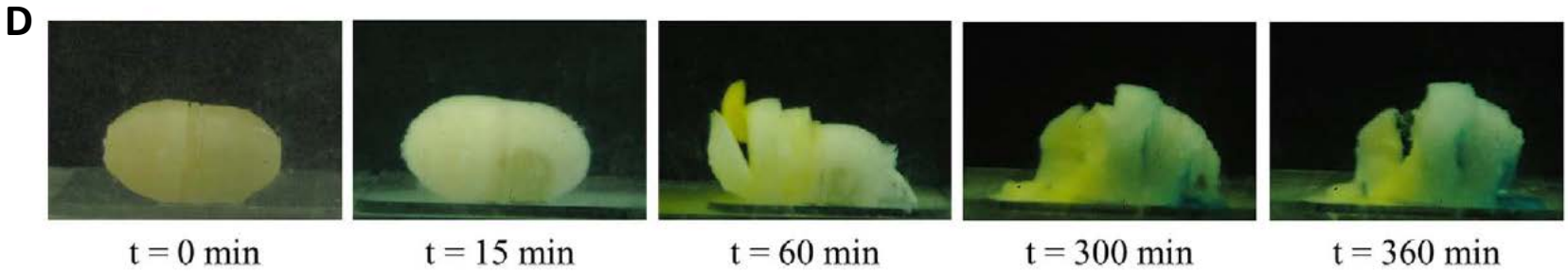
Ref. Deng Guang Yu et al., Tablets With Material Gradients Fabricated by Three-Dimensional Printing, *Journal of Pharmaceutical Sciences*, Volume 96, Issue 9, 2007

Example: Tailored Release Profile



3D Printed PVA dual compartmental device:

(A) Same material thickness
(B) Different material thickness
(C) Capsular device including two compartments with wall thickness of 600 and 1200 um filled with dye
(D) Visual release profile tailored to individual compartment (timed release for specific need)



Ref. A. Gazzaniga et al., 3D printed multi-compartment capsular device for two pulse oral drug delivery, *Journal of Control Release*, Volume 268, 28 Dec. 2017, pp 10-18.

Point of Care Manufacturing

- On demand manufacturing such as hospital compounding
- Large scale compounding pharmacy
- Printing medicine in war zone, space expedition, epidemic outbreak, and drug shortage
- Printing at home, doctor's office
- 3D printing integrated with smart health monitors, cloud based computing, so that clinician can easily access real time vital health data

Reference:

Book: 3D Printing of Pharmaceuticals, Edited by Abdul Basit and Simon Gaisford, Springer 2018.

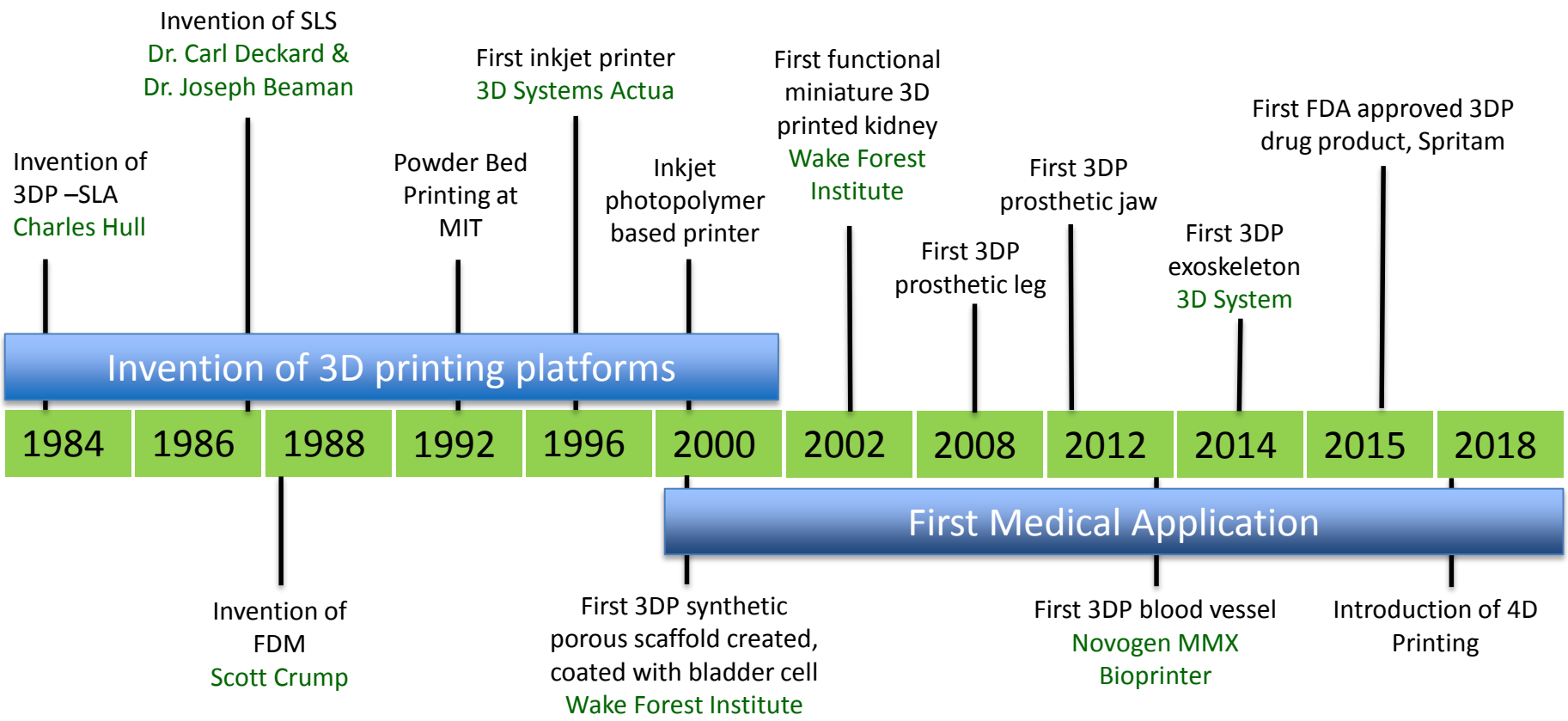
Early Phase Drug Development

- Preclinical studies – 3DP dosage forms evaluation
- First in Human Phase I clinical trial
  - Printing at clinical site for quick safety assessment
  - Dose escalation study, fast and easy
  - Dose flexibility
- Immediate manufacturing: 3DP is a small compact system easily integrated into laboratory or clinical trial set up
- Reduced resource investment
- Unique characteristics: 3DP allows ultimate designs to explore “difficult to formulate drugs” during preclinical and first in human study

Learning Objective 3:

Explain how various types of 3D printing platforms operate, their capability with respect to complex and precision drug design, manufacturing design and flexibility, and compare with current practice

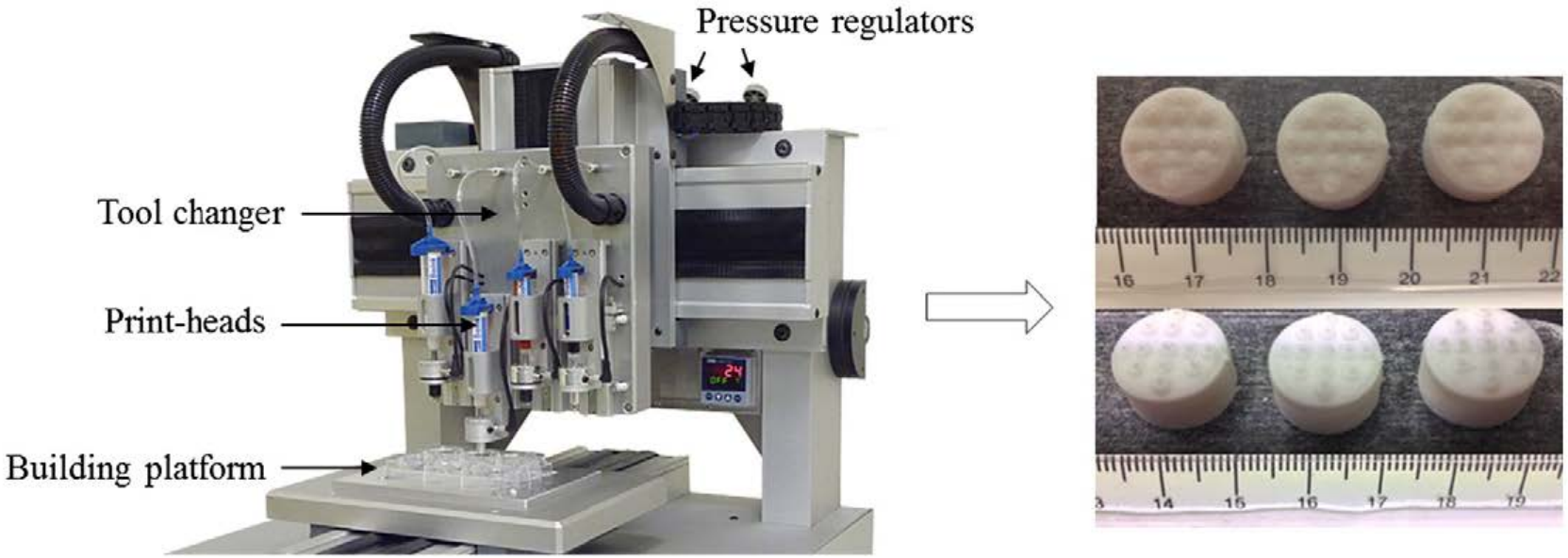
Invention of Different 3D Printing & Timeline:



SLA– Stereolithography, **SLS** – Selective Laser Sintering, **FDM** – Fused Deposition Modelling

Refence: *Book: 3D Printing of Pharmaceuticals, Edited by Abdul Basit and Simon Gaisford, Springer 2018.*

Multi Nozzle FDM for Polypill

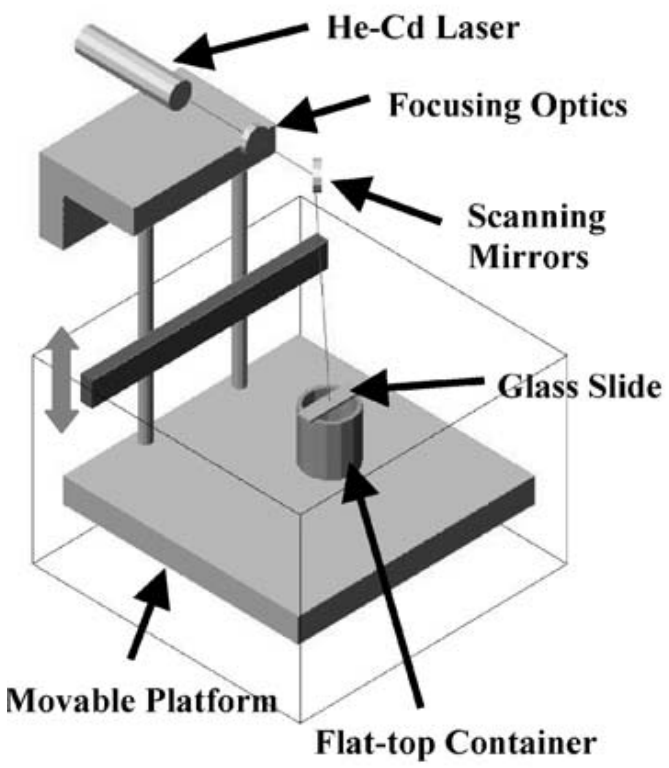


Ref. Clive Roberts et. al. 3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles. *Journal of Control Release*, 217 (2015) 308–314.

Fused Deposition Modeling

- For amorphous formulation, drugs that have poor solubility
- Suitable for implants such as vaginal ring
- Oral complex immediate release and modified release dosage form
- Polypills
- Medical devices
- Drug loaded films
- Drug loaded micro-needles

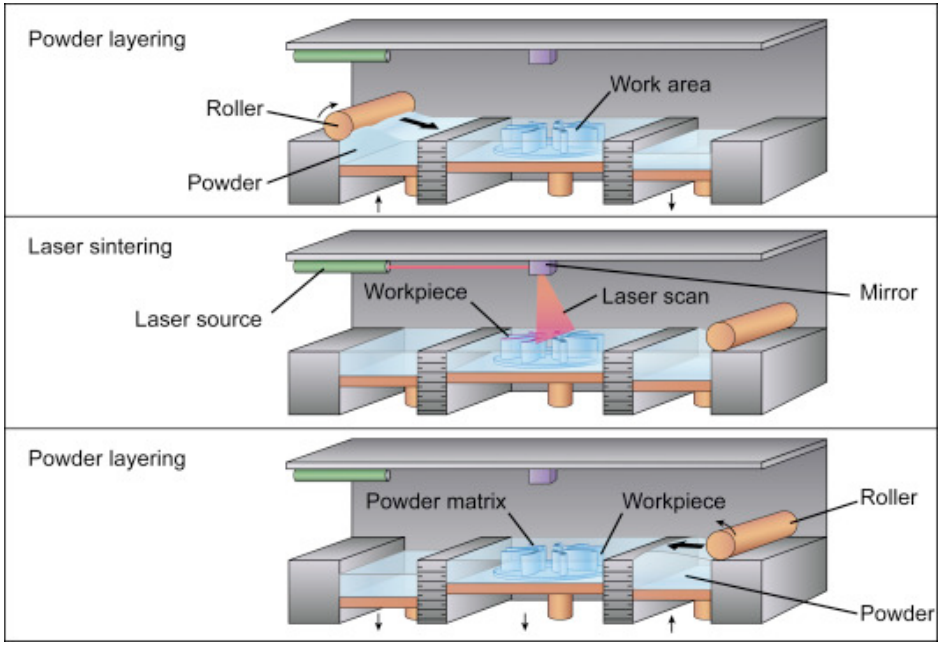
Stereolithography (SL)



- To start the fabrication, product (photopolymer solution) is added to the flat-bottom container, enough to create the target thickness
- The laser then draws the layer using the corresponding energy (UV)
- Once the first layer is created, required amount of photopolymer solution sent to the container automatically
- SL has superior precision/resolution, as low as 20 micron

Ref. Clive Roberts at. al. 3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles., *Journal of Control Release*., 217 (2015) 308–314

Selective Laser Sintering (SLS)



- It uses high power laser
- The CAD drawing of the structure is sliced in two-dimensional layers using a software → The layer thickness is set to a target → The build files are then transferred to the SL machine → To start the fabrication, powdered material is added on the base plate → The laser then fuse the material and continually build into a 3D object
- SLS is a solvent free process

Learning Objective 4:

Summarize upcoming regulatory challenges of this 21st century digitalized manufacturing and its impact on health care structure

FDA & 3D Printing

Di Prima *et al. 3D Printing in Medicine* (2016) 2:1
DOI 10.1186/s41205-016-0005-9

3D Printing in Medicine

REVIEW Open Access

Additively manufactured medical products – the FDA perspective

Matthew Di Prima[1*], James Coburn[1], David Hwang[1], Jennifer Kelly[1], Akm Khairuzzaman[2] and Laura Ricles[3,4]

- CDRH: Dozens of 3DP medical devices via the 510k pathway. Example: ear device, dental crowns, bone plates, skull plates, spinal platting system, facial implants, surgical instruments, Invisalign braces. https://www.fda.gov/medicaldevices/productsandmedicalprocedures/3dprintingofmedicaldevices/default.htm
- CBER: Has not yet approved/cleared any products (bioprinting)
- CDER: Approved Spritam® (levetiracetam) July 31, 2015, under the 505b(2) pathway

Regulatory Gaps & Challenges

- Current regulatory landscape is flexible enough for 3DP technology for mass production and distribution. However,…..
- What should be the regulatory structure if we use this technology to manufacture on-demand personalized products:
  - Printing at hospitals, pharmacies, and clinical study sites
  - Printing at home, or at the doctor's office
- Future 3DP – Bioprinting, medical devices with electronic chips, diagnostics, combination of all

Regulatory Gaps & Challenges

- Bulk manufacturing of ink cartridges containing API and excipients, and their distribution. Who and how will this be regulated?
- Who will dispense those cartridges? The doctor or pharmacist?
- Who will manufacture the 3D printers? Will they be regulated as medical devices?
- Who will monitor the manufacturing of medications at home?
- What product specifications should be applied and how should they be measured?
- What would the shelf life of the product be?
- Should the shelf life of the drug loaded print cartridges be monitored?

Conclusion

- 3D printing has already established itself as an innovative platform for the fabrication of medical devices and drug products.
- 3D printing has shown great flexibility in producing dosage forms for personalized regimens to patients.
- This technology will only grow further and shape the future of healthcare and patient-centric drug delivery.

Challenge Question 1

3D printing is a layer-by-layer addition of materials to make a 3 dimensional object, also known as additive manufacturing

A) True

B) False

Challenge Question 2

The motivation of 3D printing in medicine is as follows

A) Increased product complexity
B) Increased personalization
C) Point of care or on demand manufacture
D) A, B & C
E) None of the above

Challenge Question 3

Which one of the followings are considered as 3D printer?

A) Fused Deposition Modeling (FDM)

B) Inkjet Printer

C) Stereolithography (SL)

D) A, B & C

E) None of the above

Challenge Question 4

FDA has not yet approved 3D printed product

A) True

B) False

Thank You

Acknowledgement

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