

3D Printing Technologies for Oral Drug Delivery

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Disclaimer

The presenter is co-founder of Triastek and has financial interest in Triastek, Inc.

Principles of 3D Printing Technologies

Creating objects using Computer Aided Design (CAD)

Building objects with structures layer by layer based on CAD controlled by computer

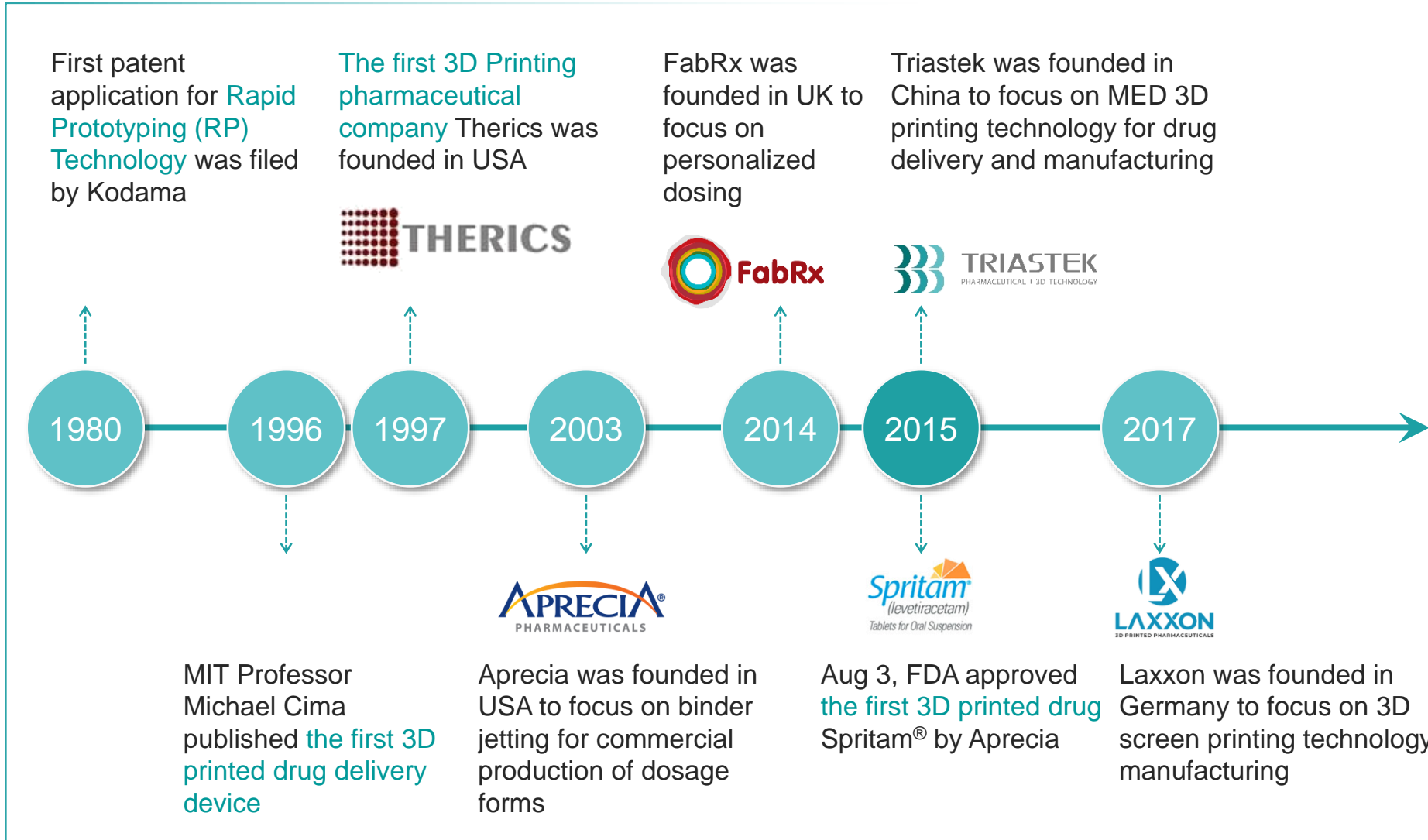
- In situ polymerization (chemical reaction)
- Melt and solidification (temperature modulation)
 - Extrusion/jetting
 - High energy beam
- Binding of powder/sheets (adhesion)
 - Binding agents
- Extrusion/jetting (solvent evaporation)

Applications of 3D Printing in Biosciences

- Creation of organ models for surgical operation planning and treatment analysis
- Tissue engineering
 - Tissue scaffolds
 - Constructing tissues and organs
- Personalized repair/restructure of tissue, organ and body parts
 - Bone, tooth
 - Transplantation
 - Artificial limb/finger
- **Pharmaceutical products**
 - Drug delivery/Product development
 - Manufacturing
 - Personalized dosing



Application of 3D Printing Technologies in Pharmaceuticals

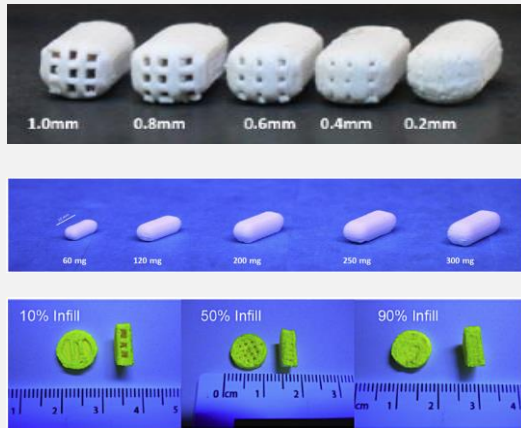


- Material Extrusion** ✓
- Binder Jetting** ✓
- Powder Bed Fusion** ✓
- VAT Photopolymerization** ✓
- Sheet Lamination** ✓
- Material Jetting** ✓
- Directed Energy Deposition**

FDM 3D-Printed Dosage Forms Reported in Scientific Literatures

Oral Tablets

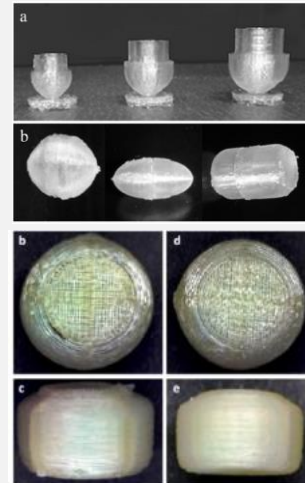
Immediate, prolonged, pulsatile, delayed release and combinations of differing kinetics



J Control Release, 269:355-363
Eur J Pharm Biopharm., 96:380-387
Int J Pharm, 476(1-2):88-92

Oral Capsules

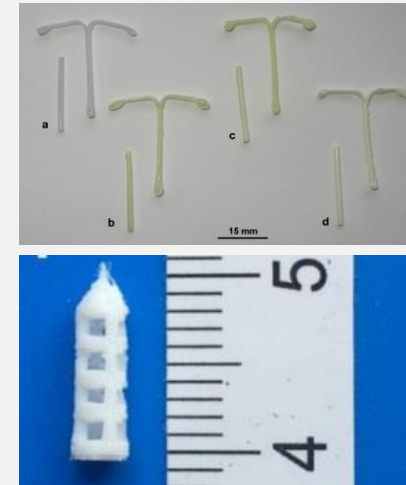
Pulsatile release, delayed release



J Drug Deliv Sci Tec, 30:360-367
Int J Pharm, 544(1):21-30

Implantable Systems/Inserts

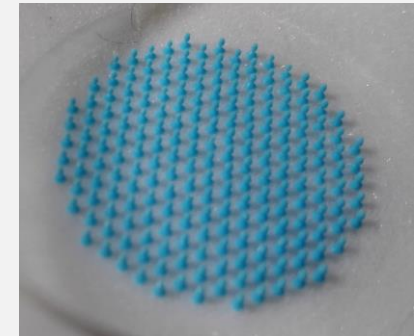
Prolonged release



J Pharm Sci, 105(9):2665-2676
Int J Pharm, 552(1-2):91-98

Dermal Patches

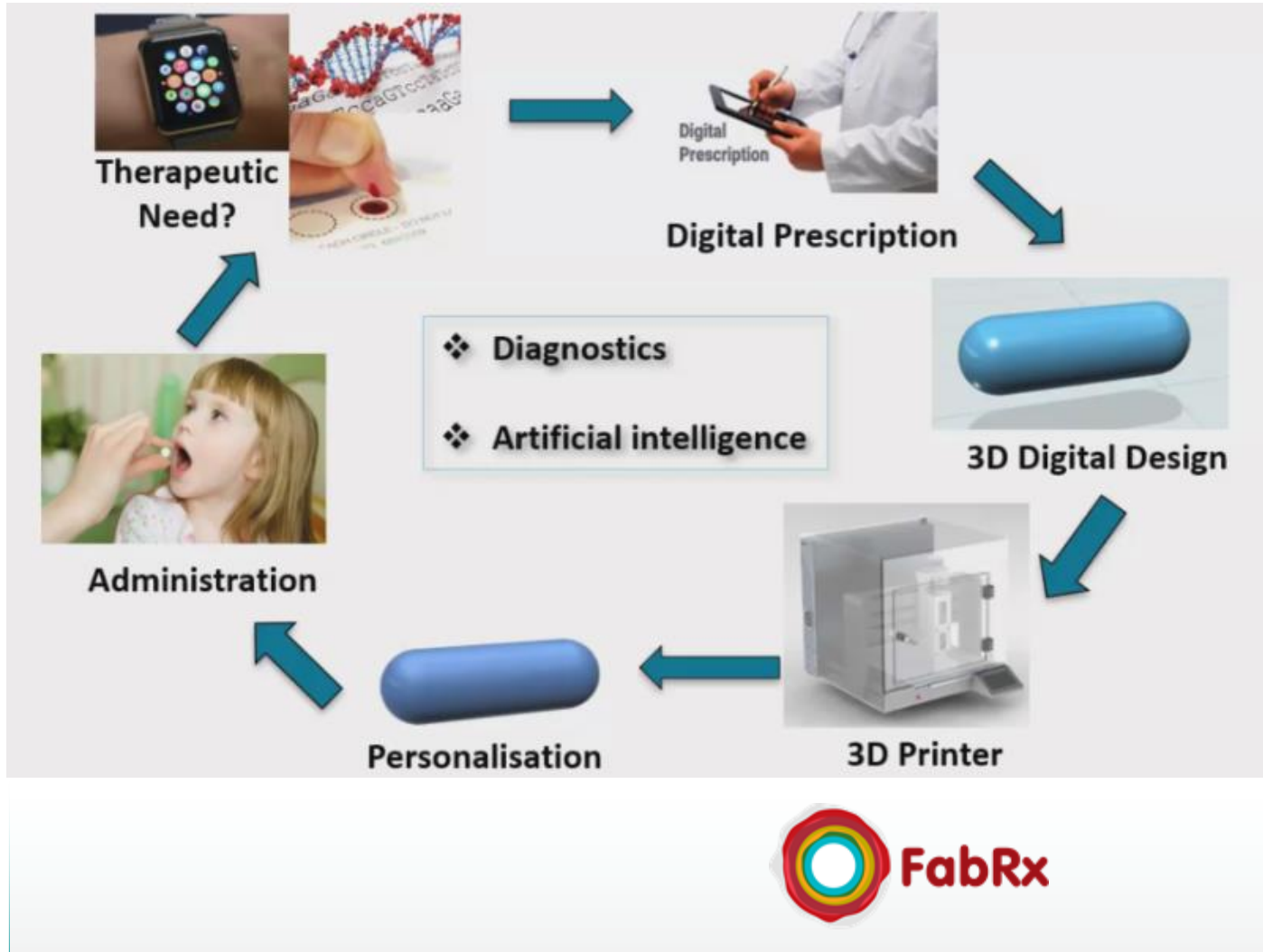
Overcome skin barrier



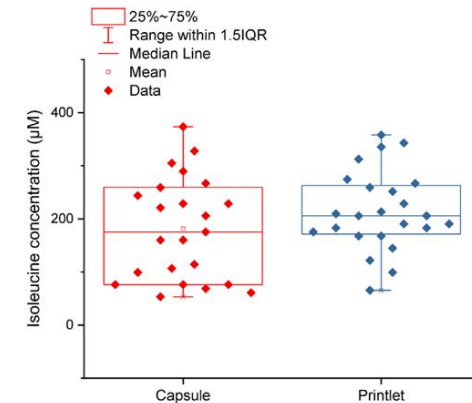
199 needles of arrow-on-waistline printed in 30 sec

Courtesy of Jin-Lab at Shanghai Jiao Tong University

Individualized Dosing



- **Printlet™**
- **Individualized dosing**
- **Drug combinations**
- **Catering to patient population**
 - Size, shape, color, flavor, dosage forms

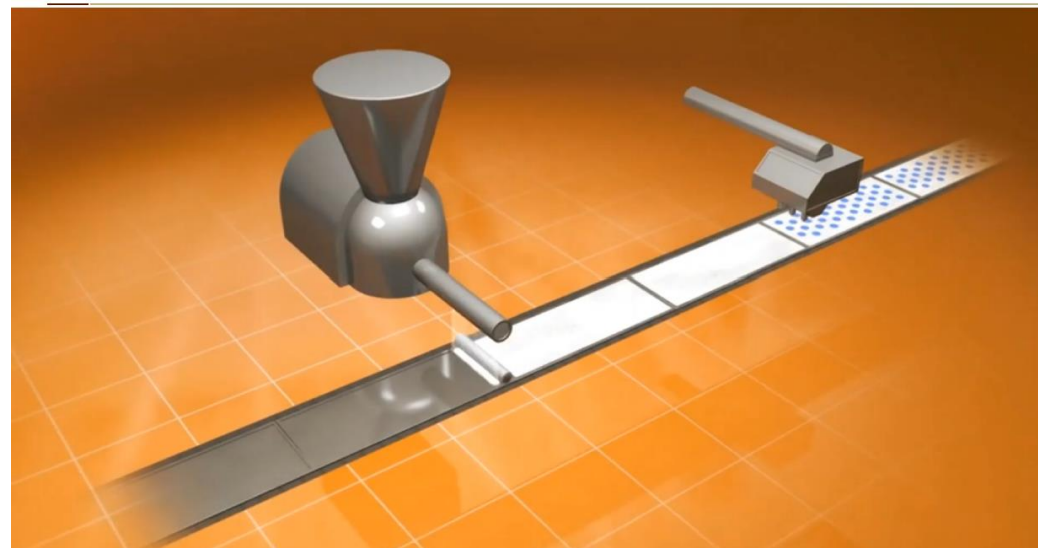


- **Chewable Printlets:** isoleucine for the treatment of maple syrup urine disease
- Investigated patient acceptability of 3D printed formulations with different flavors and colors

Spritam-First FDA Approved 3D Printed Pharmaceutical Product

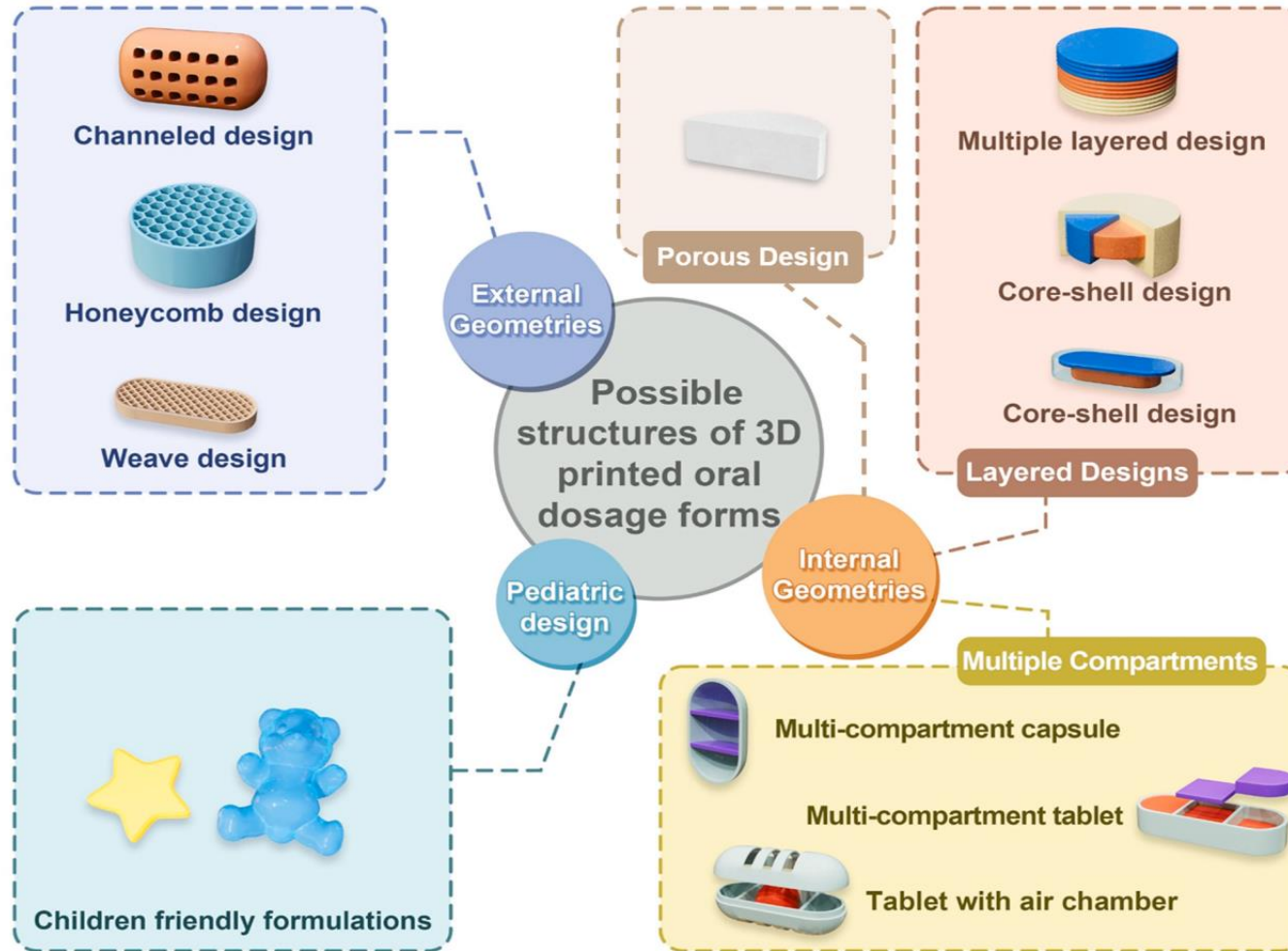


- Active ingredient: levetiracetam
- Indication: epilepsy
- Dose: 250, 500, 750, 1000 mg
- Disintegration time: Average 11 sec (2-27 seconds)
- Manufacturer: Aprelia Pharmaceuticals
- Approval date: Aug 3, 2015



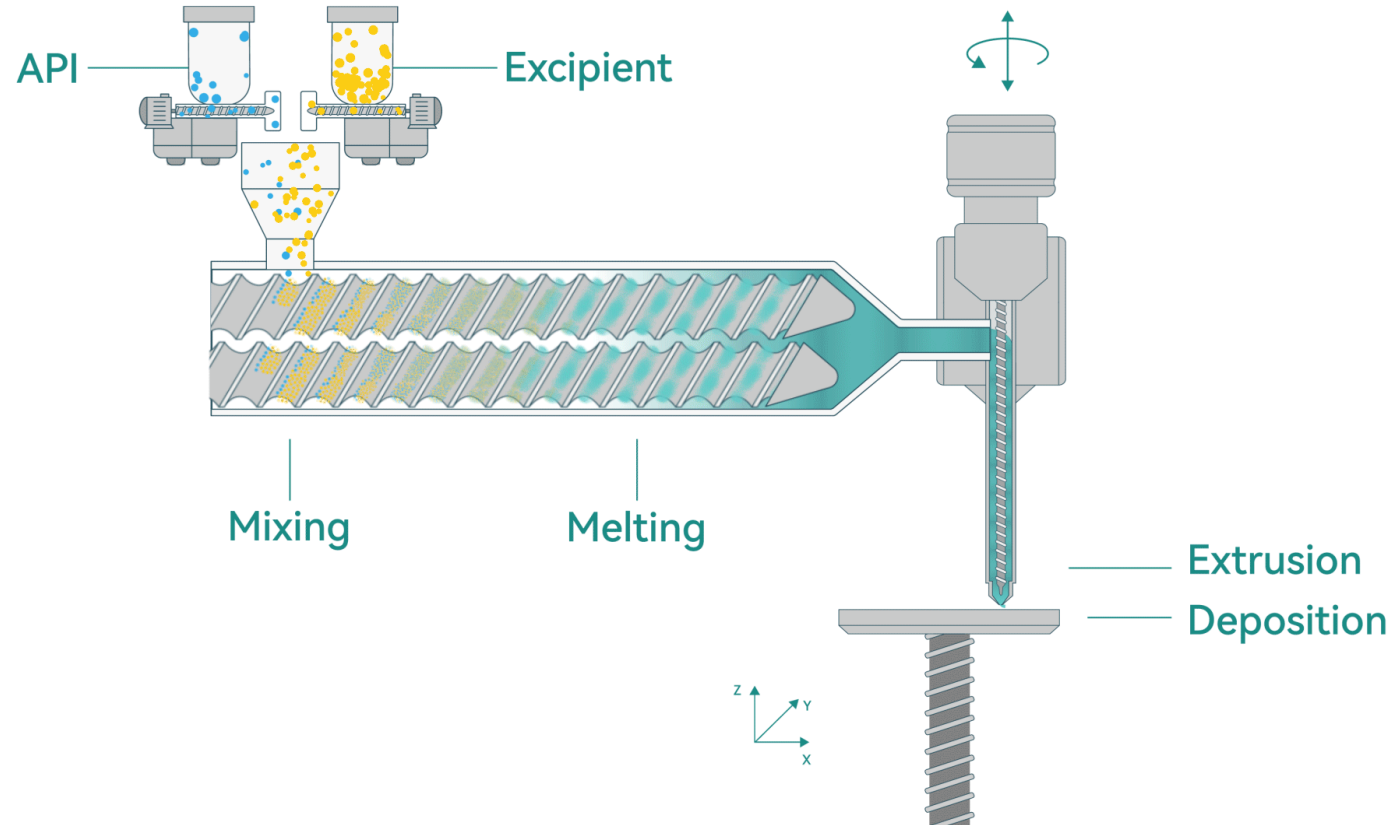
Source: Aprelia

Structures of 3D Printed Oral Dosage Forms



MED[®] 3D Printing

Melt Extrusion Deposition (MED[®]) 3D printing is a technology that continuously converts powder feedstocks into softened/molten states followed by precise layer-by-layer deposition to produce objects with well-designed geometric structures



Continuous process

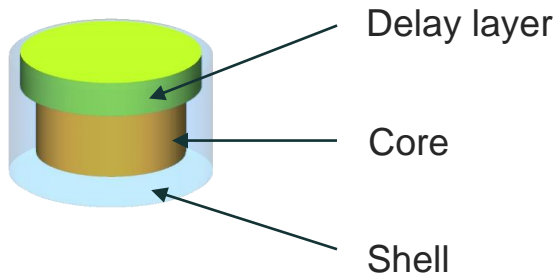
NOT rely on filament

NO post-printing process needed

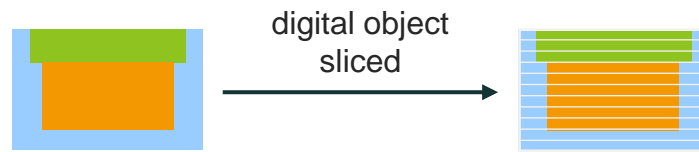
Solvent free process

Coordinate Multiple Materials to Fabricate Tablets with Internal Structures

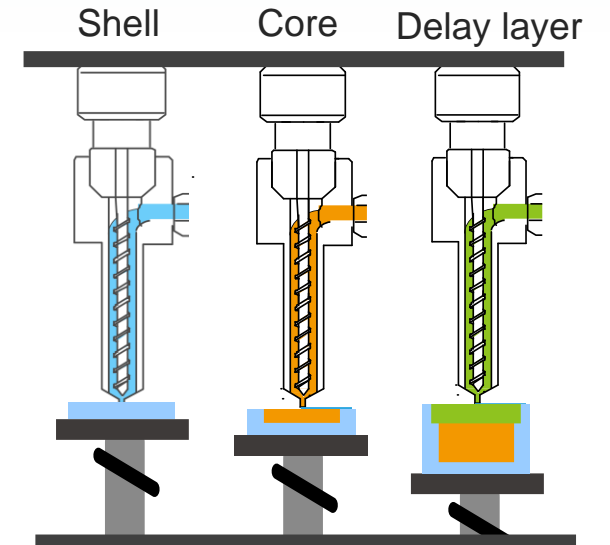
Digital 3D Structure Design



Digital Sliced to G-code



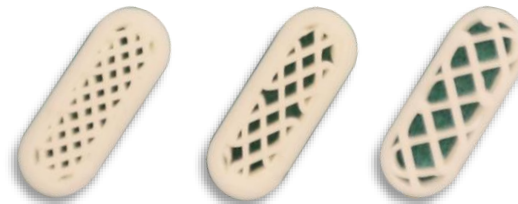
MED 3D Printing



Multi-layered design



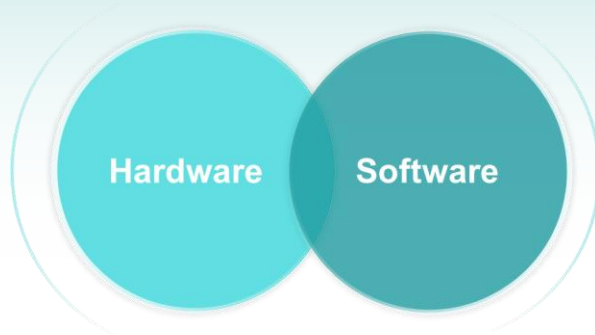
Honeycomb/weave tablet



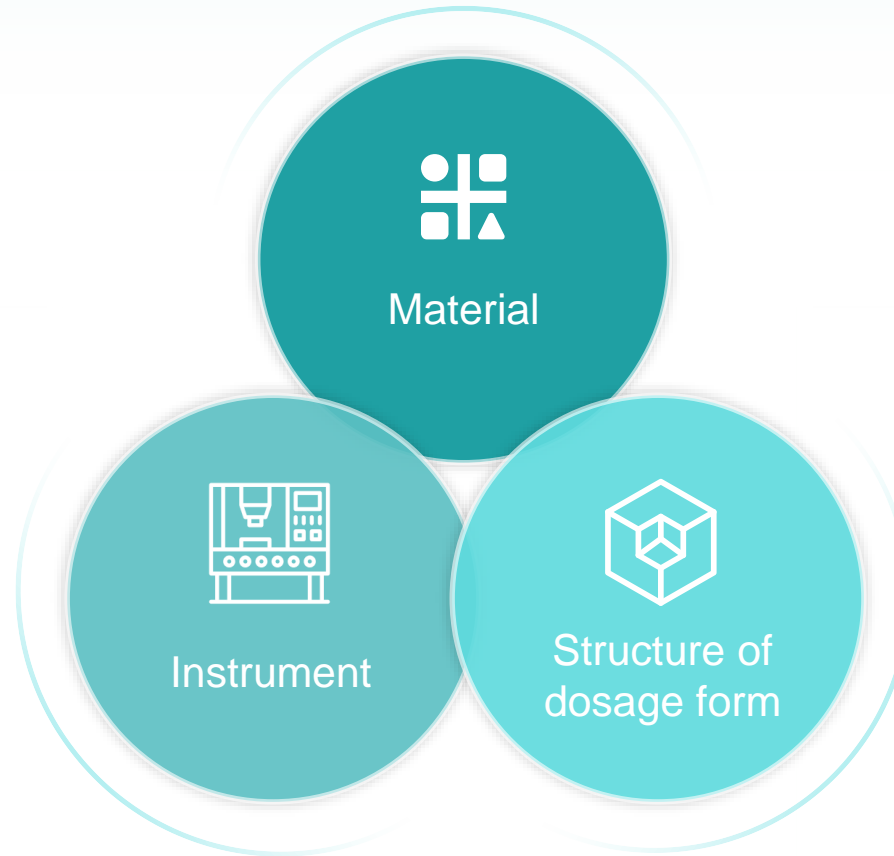
Multi-compartment design



MED[®] Developed Specifically for Pharmaceutical Applications



- Variety of API and pharmaceutical excipients
- Wide range of printing temperature



- Accuracy, precision, and reproducibility
- cGMP
- PAT
- CM
- Scalable, flexible, and fully automated

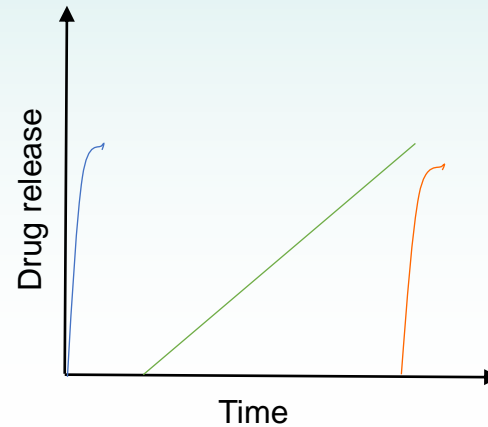
- Programmed drug release rate, mode, duration, and onset time
- Modulated PK profiles

Unique Delivery System Design

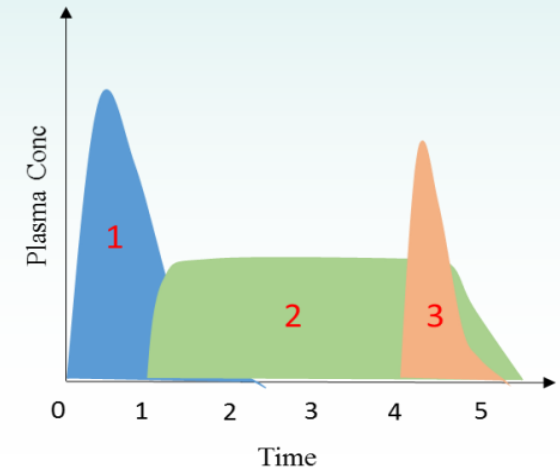
Complex Tablet Architecture



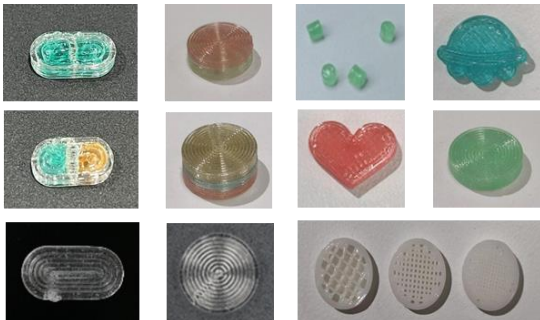
In Vitro Release



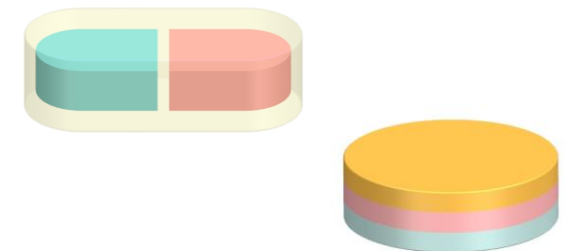
In Vivo PK Profile



- Sophisticated structures such as compartments with various geometric shapes can modulate the release **rate, mode, duration, and onset time**
- Incorporation of multiple APIs with multiple PK profiles can lead to greater outcome of drug therapy



3D printed tablets using sugar-based excipients

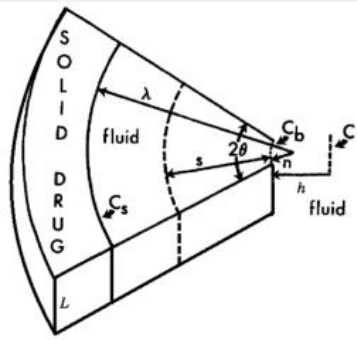


Internal Geometric Structure for Rate and Duration Control

Analysis of Theoretical Behavior of a Proposed Zero-Order Drug Delivery System

R. A. LIPPER and W. I. HIGUCHI*

Journal of Pharmaceutical Sciences
Vol. 66, No. 2, February 1977 / 163



- L Drug filled cavity height (mm)
 - n Opening radius (mm)
 - s Diffusion path length (mm)
 - λ Arcuate radius (mm) at drug dissolving surface
 - 2θ Central angle (radians) of drug filled cavity
 - Cs Drug concentration (mg/mm³) at dissolving surface
 - Cb Drug concentration (mg/mm³) at device opening
 - h Distance (μm) from the opening to the bulk where the drug concentration is zero (sink condition)
 - ρ Drug density (g/cm³)
 - D Drug diffusion coefficient (cm²/s) in fluid
- Device parameter
- Drug Physico-chemical Properties

A sector of a right circular cylinder

Per Fick's law, the rate *J* of transport of drug to the opening at distance *s*, is

$$J = 2\theta LD(s+n) \frac{dc}{ds} \quad (\text{Eq. 1})$$

Integration

$$J = \frac{2\theta LD(C_s - C_b)}{\ln \frac{\lambda}{n}} \quad (\text{Eq. 2})$$

The rate *J* of transport of drug from the opening to bulk is

$$J = \frac{2\theta LDnCb}{h} \quad (\text{Eq. 3})$$

Integration

$$J = \frac{2\theta LDC_s}{\frac{h}{n} + \ln \frac{\lambda}{n}} = \frac{dM}{dt} \quad (\text{Eq. 4})$$

$$M = (\lambda^2 - n^2)L\theta\rho \quad (\text{Eq. 5})$$

Integration

$$t = \frac{(\frac{h}{n} - \frac{1}{2})M + \frac{M+L\theta\rho n^2}{2} \ln(1 + \frac{M}{L\theta\rho n^2})}{2\theta LDC_s} \quad (\text{Eq. 6})$$

Substitution

$$t = \frac{(\frac{h}{n} - \frac{1}{2})(\lambda^2 - n^2)\rho + \rho\lambda^2 \ln(\frac{\lambda}{n})}{2DC_s} \quad (\text{Eq. 11})$$

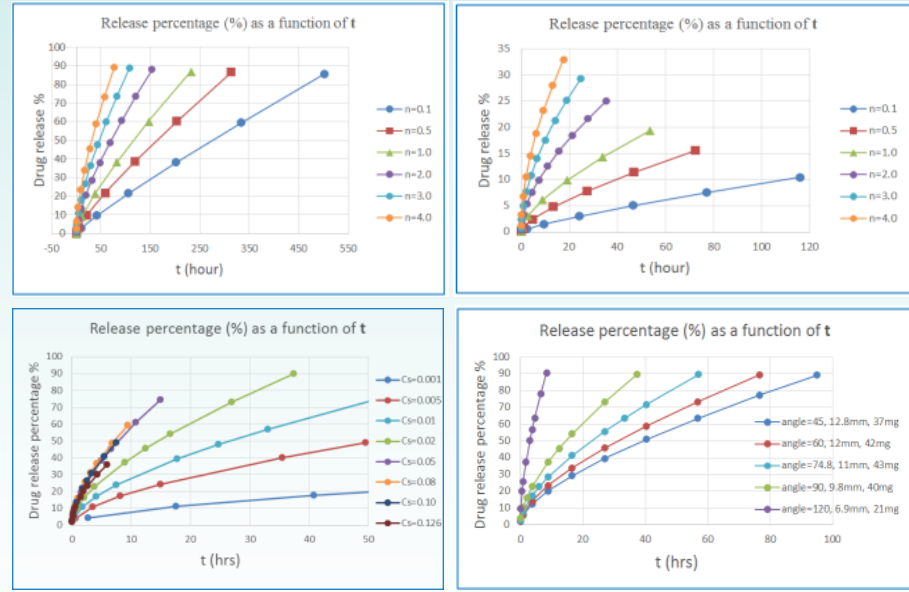
Integration Substitution

$$M_r = (\lambda^2 - n^2) \left[L\theta\rho - L\theta C_s + \frac{L\theta C_s}{2(\frac{h}{n} + \ln \frac{\lambda}{n})} \right] - \frac{L\theta C_s n^2}{\frac{h}{n} + \ln \frac{\lambda}{n}} \quad (\text{Eq. 10})$$

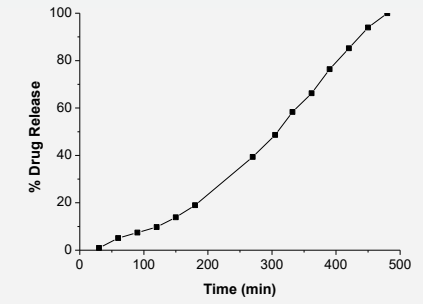
$$M_d = \int_0^{\lambda-n} 2\theta(s+n)LC_s ds \quad (\text{Eq. 8})$$

$$C = \frac{J}{2\theta LD} \ln(\frac{s+n}{\lambda}) + C_s \quad (\text{Eq. 9})$$

$$M_r = M - M_d \quad (\text{Eq. 7})$$



	Device parameters			Drug parameters			
	n↑	θ↑	L↑	ρ↑	D↑	Cs↑ (> ρ)	Cs↑ (≤ ρ)
J	↑	↑	↑	-	↑	-	↑↓c)
M _{total}	- (↓)a)	-	↑	↑	-	-	-
t _{total}	↓	↓	-	↑	↓	-	↓↑d)
Percentage	- (↑)b)	-	-	- (↑)	-	-	↓

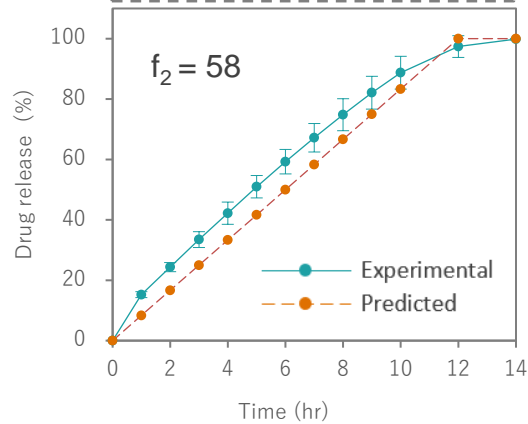
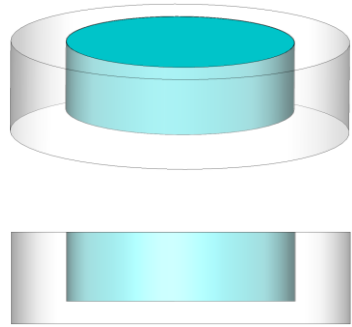


Achieving Challenging Release Profiles with Complex Internal Structures

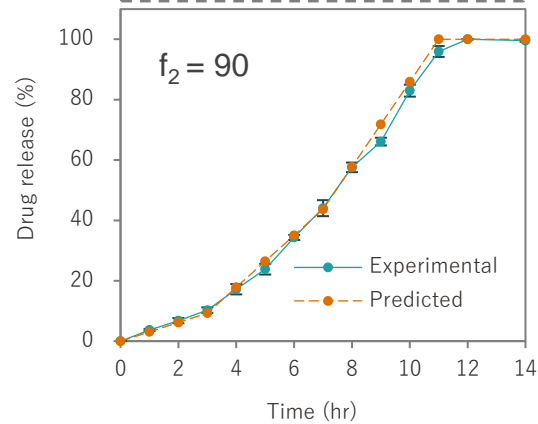
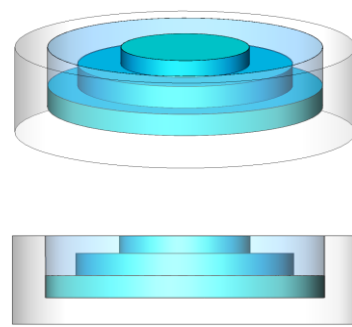
Release rates can be controlled by the varying the area and thickness of each API layer

$$Q(t)\% = \frac{D(t)}{D_{total}} = \frac{R_D \int_0^t S(t) dt}{V} \times 100\%$$

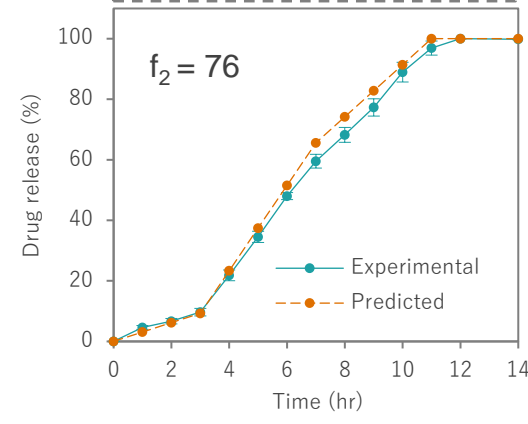
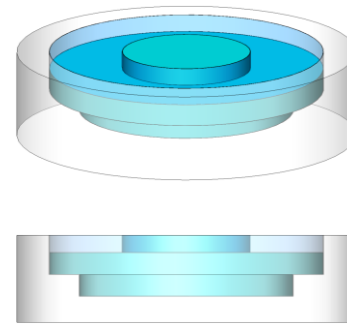
Constant Rate



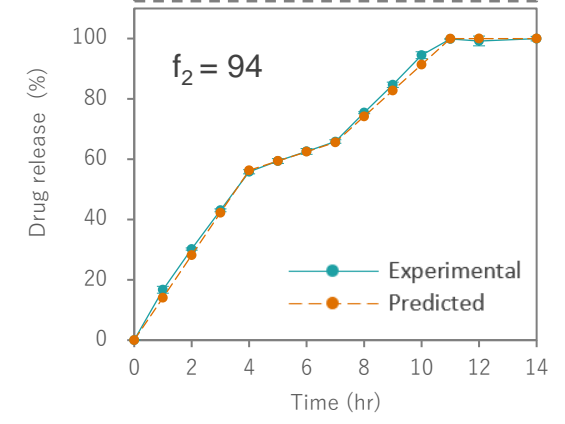
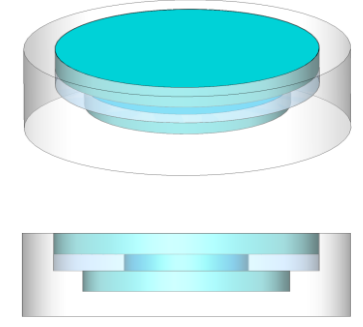
Increasing Rate



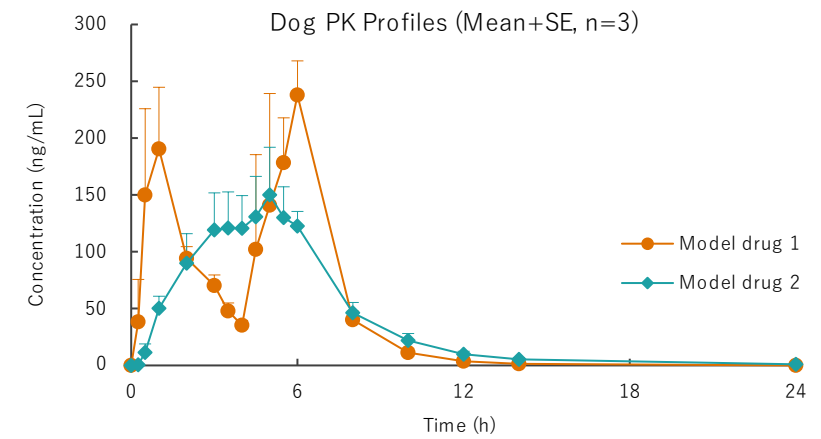
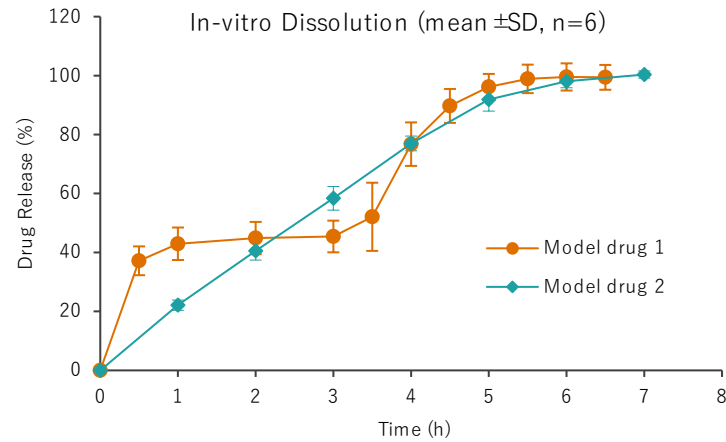
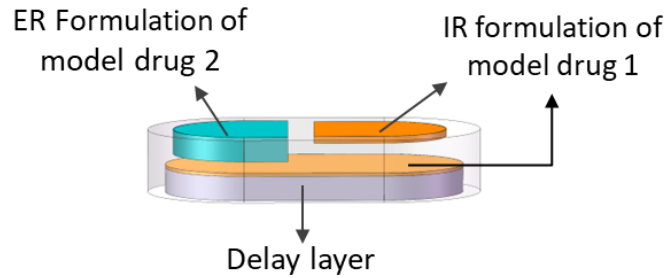
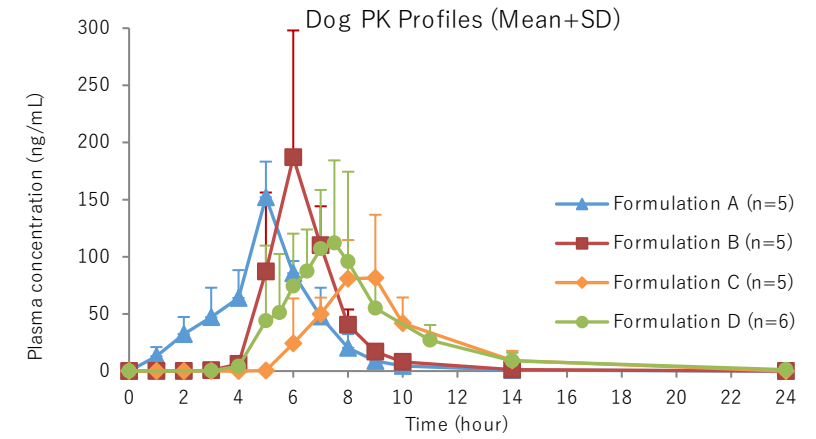
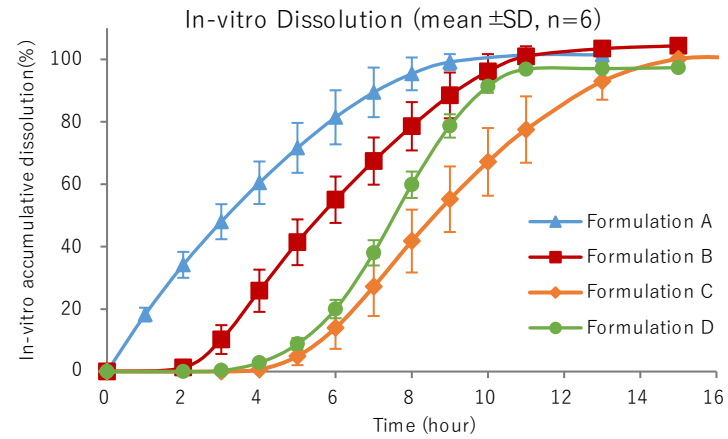
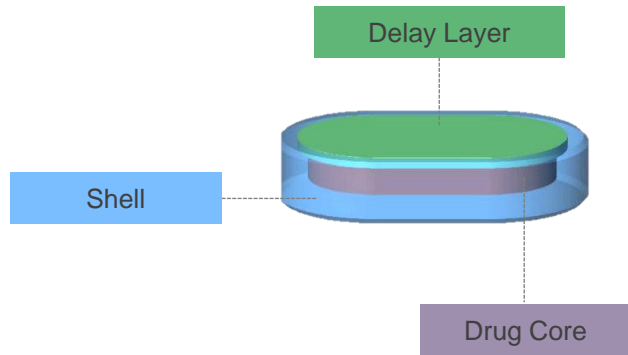
Slow-Fast-Slow



Fast-Slow-Fast



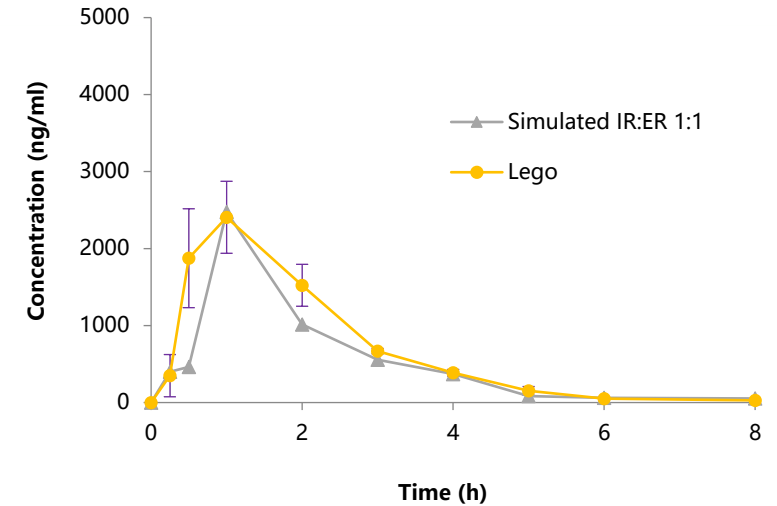
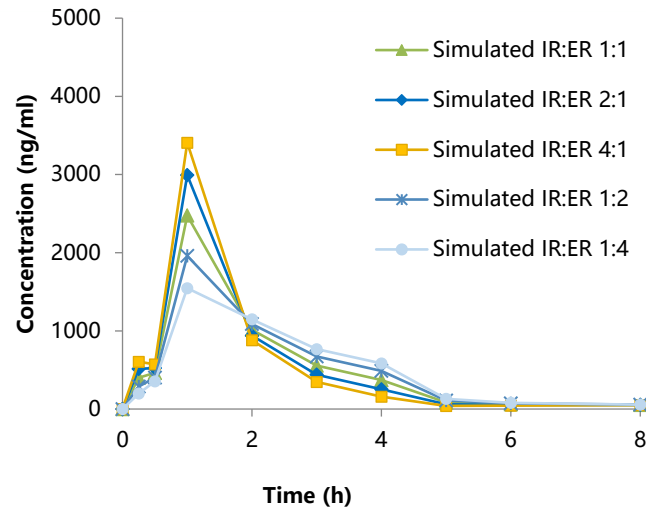
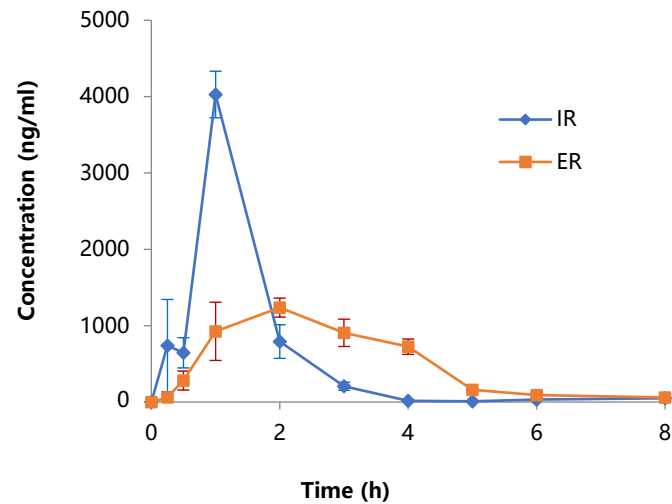
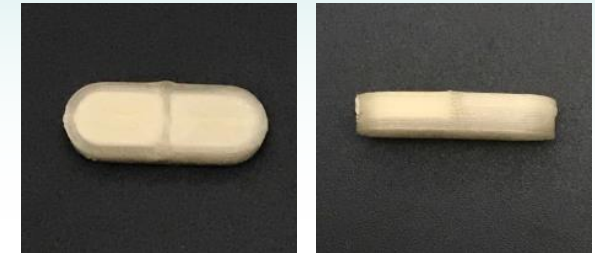
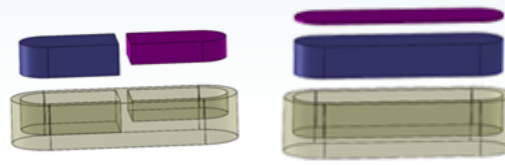
Unique Structure and Programmed Release for Modulated PK Profiles



LEGO Approach for Predictable or Fine-Tuning PK

$$C_i = \frac{F_i k_a D_i}{V(k_a - k)} (e^{-kt} - e^{-k_a t}) \quad C_e = \frac{k_r^0}{kV} \left(1 + \frac{k_a}{k - k_a} e^{-kt} \right) - \frac{k_r^0}{V(k - k_a)} e^{-k_a t}$$

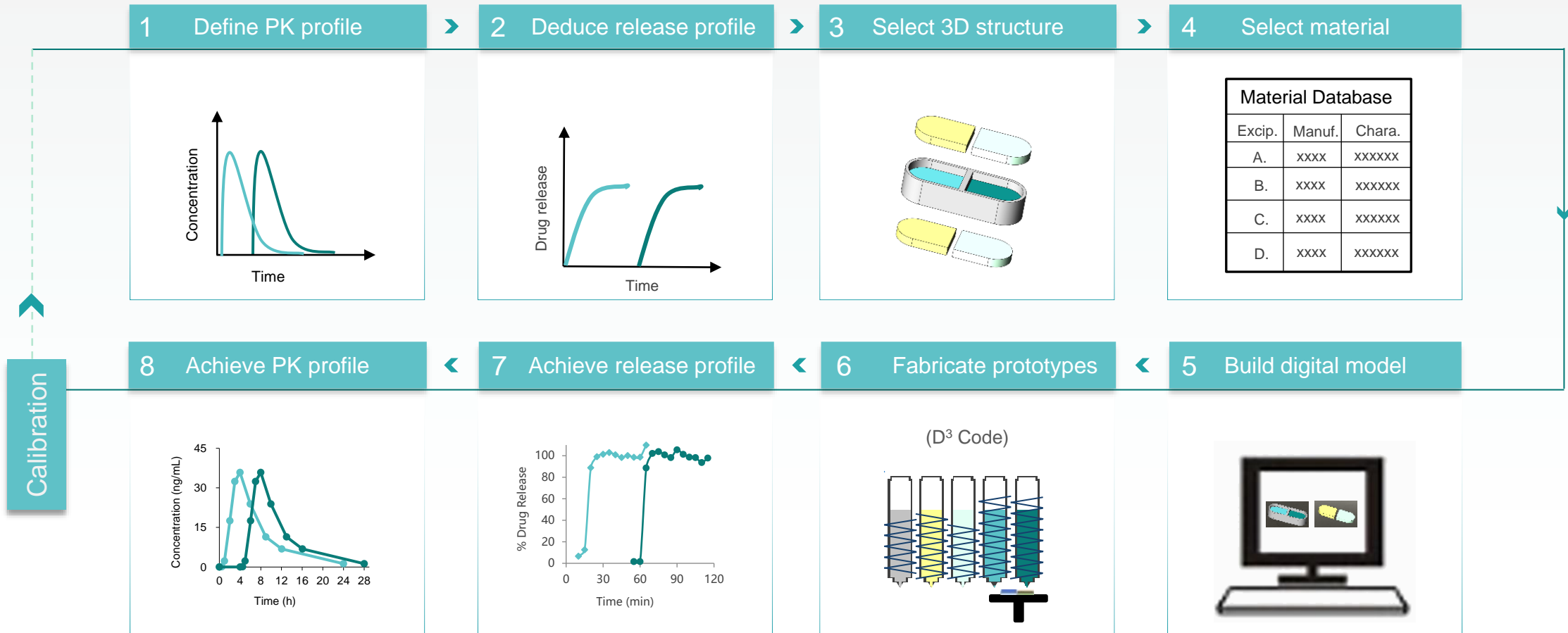
$$C = C_i + C_e$$



Using “Lego Building” approach, theoretical PK profile can be predicted based on PK profiles of individual Lego units.

3D Printing Formulation by Design (3DFbD®)

A Paradigm Shift in Formulation Development



Instrumentations for Early-Phase Development and Commercial Scale Manufacturing

MED 3D Printer

Formulation
Development

IND
Submission

Small-Scale
Clinical Trials



R&D and small-scale clinical supplies

MED 3D Printing System

Pivotal
Clinical Studies

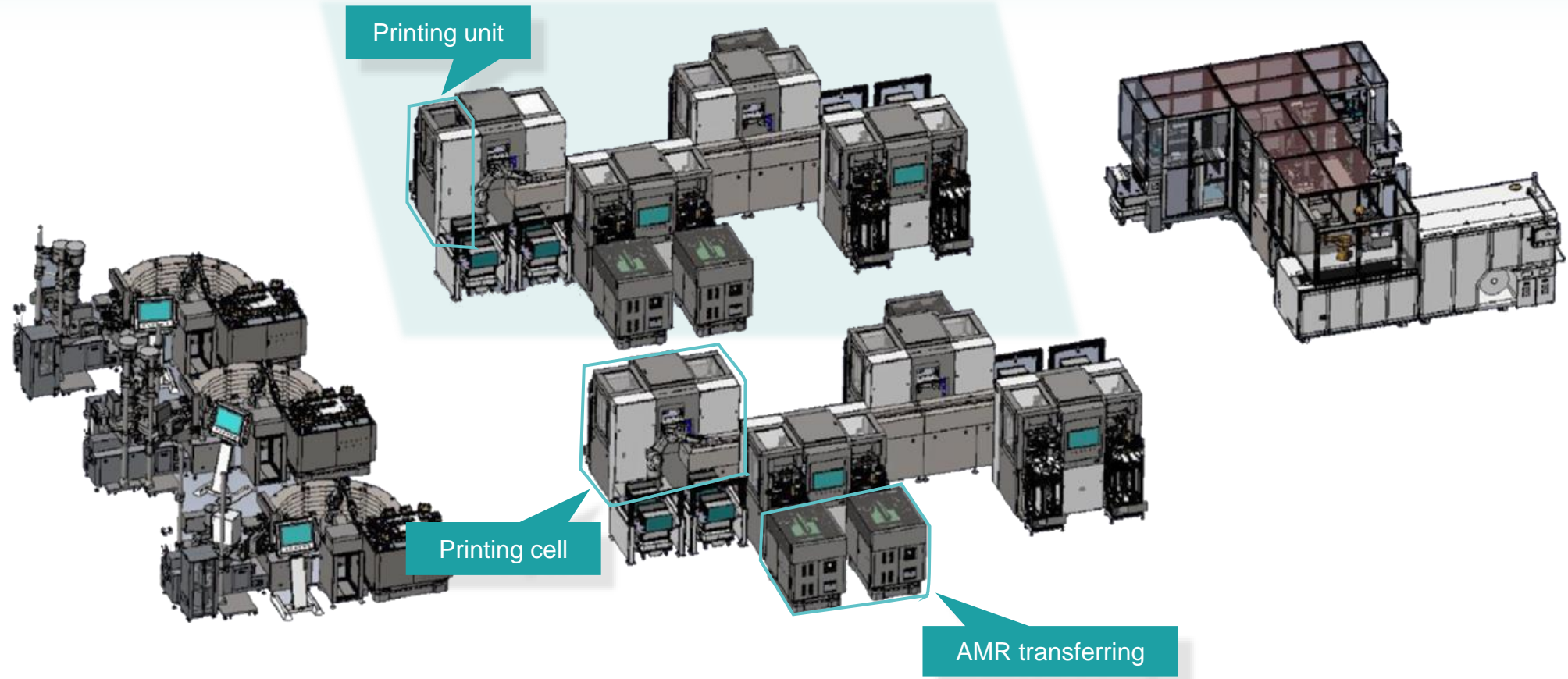
NDA
Submission

Commercial Batch
Manufacturing



Commercial-Scale Production Line

Commercial-Scale Production Line with Modular Design

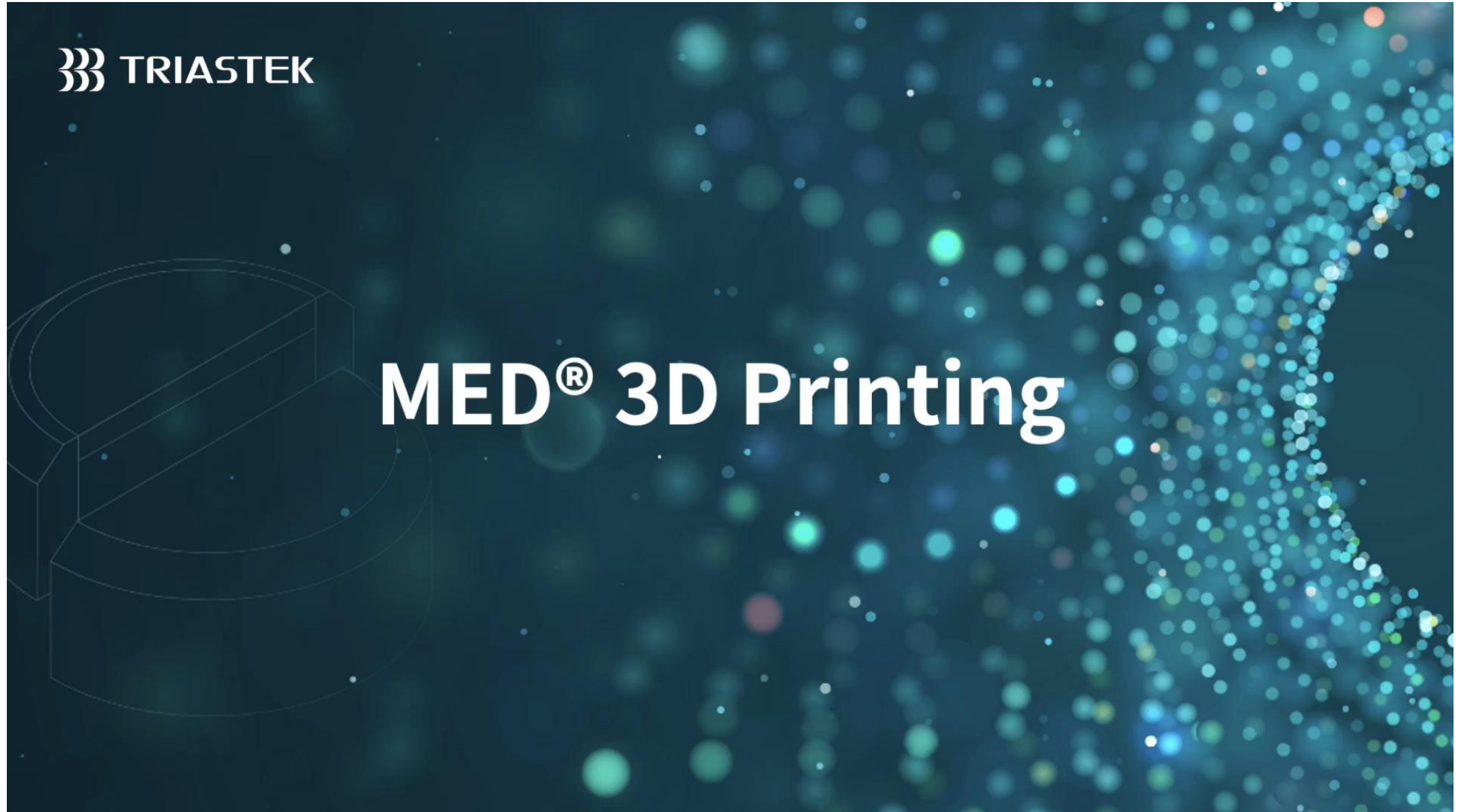


Material preparation zone

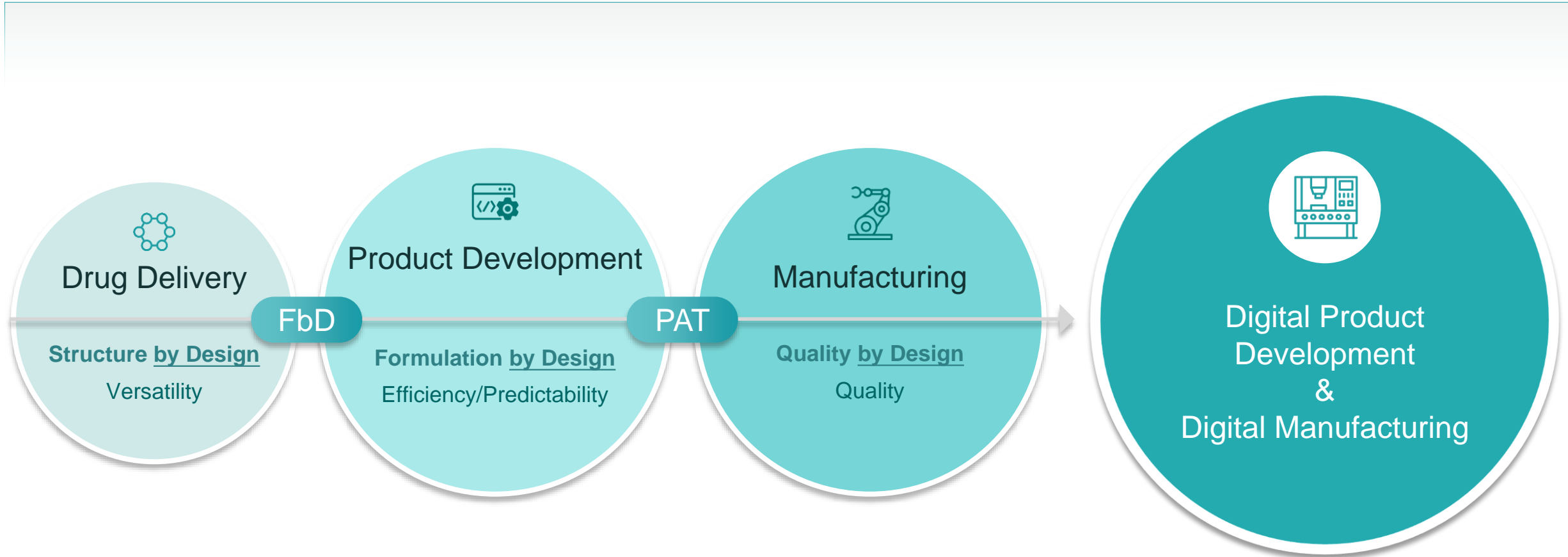
3D Printing zone

Packaging zone

MED 3D Printer and MED 3D Printing System



Concept of “by Design” Drives Drug Development and Manufacturing



3D Printed Pharmaceuticals and Candy-like Drug Products

No clear definition of a candy-like drug product exists.

3D Printing

Structural building

- Internal
- External

Controls

- Rate
- Mode
- Duration
- Onset
- abuse

Personalization/Low volume

Candy-like

Temptation

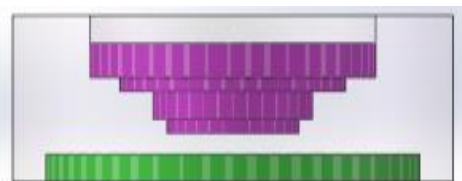
- Taste/odder
- External Appearance

Pleasure

Dependence

User/patient control

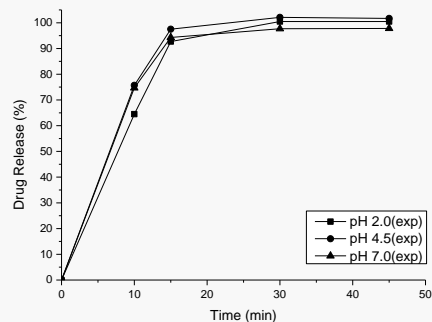
Stimulant/Non-stimulant Combination for ADHD using MED 3DP



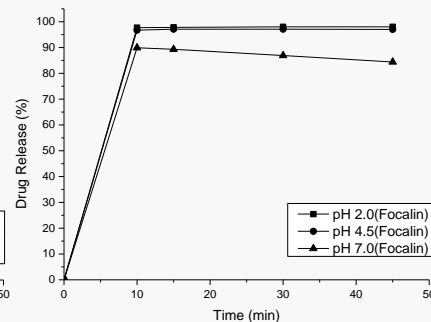
Rapid release of stimulant

>85% dissolved in 15mins

Propranolol 2.5mg (demo drug)



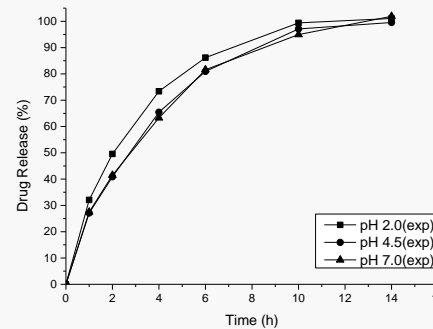
RLD: Focalin 2.5mg



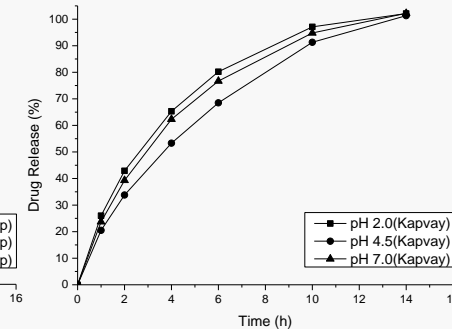
Extend release of non-stimulant

$f_2 = 60.3, 51.6, 75.2$ in pH 2.0, 4.5, 7.0

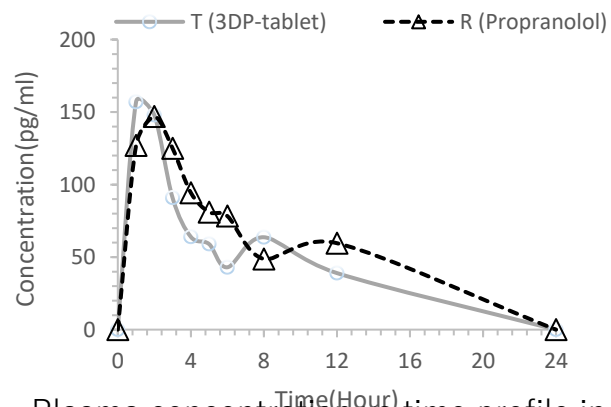
Clonidine 0.1mg



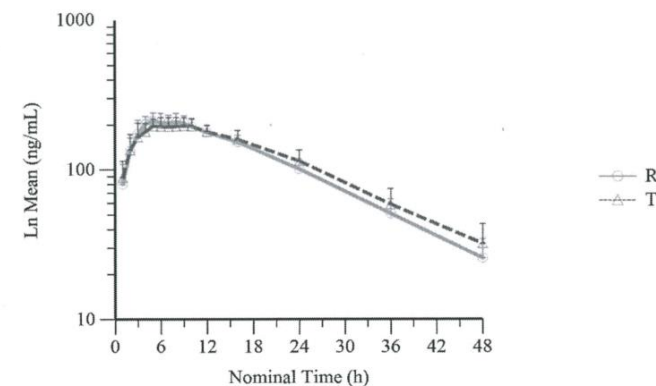
RLD: Kapvay 0.1mg



Advantage:
enhanced long-term effectiveness, higher tolerability and with less adverse effects



Plasma concentration vs time profile in dog



Plasma concentration vs time profile in human

3D Printing Technology for Pharmaceutical Applications

Drug Delivery for Specific In Vivo PK Profile

- Programmed release time
- Designed release rate
- Mixed release kinetics in one tablet
- Gastro retentive tablets
- Fast oral disintegrated tablets
- Combined multiple API with different release parameters

Clinical Testing Material Development

- Short and predictable development time
- Quick dose adjustment
- Flexible batch size

Challenging Formulations

- Poor water solubility
- Enhanced bioavailability
- Nanoparticle embedded tablets
- Overcoming polymorph crystal protection

Continuous manufacturing

On Demand Manufacturing

Personalized dosing

Your imaginations.....

Acknowledgments



Triastek Teams



Engineering



Pharmaceutical Development



Material Sciences



Innovation Center



Intellectual Properties



Investors & Collaborators



TRIASTEK
PHARMACEUTICAL | 3D PRINTING

Creating New Dimensions