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THE 3DP PHARMACEUTICAL COMPANY

Emerging Technologies in 3D Printing of Pharmaceuticals:

Manufacturing unique dosage forms, accelerating drug development, and enabling personalized medicine

NABP-AACP District IV Meeting
October 18, 2019

Kimberly Bone, PharmD
VP Medical and Clinical Affairs

Overview

- Introduction to Aprecia Pharmaceuticals
- Features of 3DP Technologies
- Select Methods for 3DP Pharmaceuticals
- Applying 3DP in the pharmaceutical industry
- Benefits and Example applications
- Looking ahead

Aprecia Facts

- Privately held technology company
- Founded in 2004
- Headquartered in Blue Ash, Ohio
- 60+ employees
- Innovative and patent-protected 3DP technology platform

Aprecia Milestones

KEY MILESTONES

2004	Operations initiated
2007	ZipDose® Technology development begins
2008	Proprietary 3DP forming system built
2011	Registration and launch facility opens in East Windsor, NJ
2014	Filing of first NDA with the FDA
2015	First product approved: SPRITAM® (levetiracetam)
2016	Next generation 3DP forming system built
2017	Commercial manufacturing facility in Blue Ash, OH approved by FDA
2018	East Windsor facility focused on R&D; new development machines built

*SPRITAM is the **first** and **only** FDA approved 3DP pharmaceutical product*

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Key Advantages of 3DP Over Conventional Pharmaceutical Processes

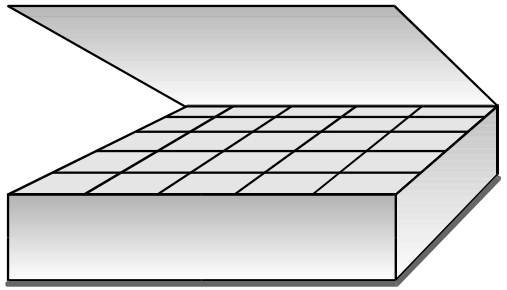
Features of 3DP Technologies

- Control of internal and external geometry
- Spatial control of composition
- Simpler, compact process
- Rapid prototyping

Benefits for Pharmaceutical Industry

- Dosage forms with unique properties
  - Instant dispersion
  - Ultra low dose
  - Complex release profiles
  - Combination therapy
  - Anti-counterfeit features
- Agile, simplified supply chain
- Accelerate development cycle

Example Device Demonstrating Various Features



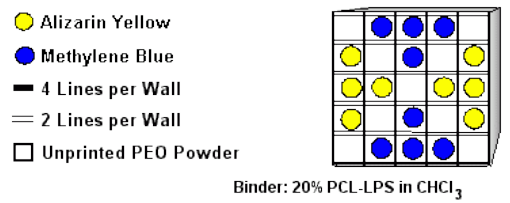
PCL (Top Layer)

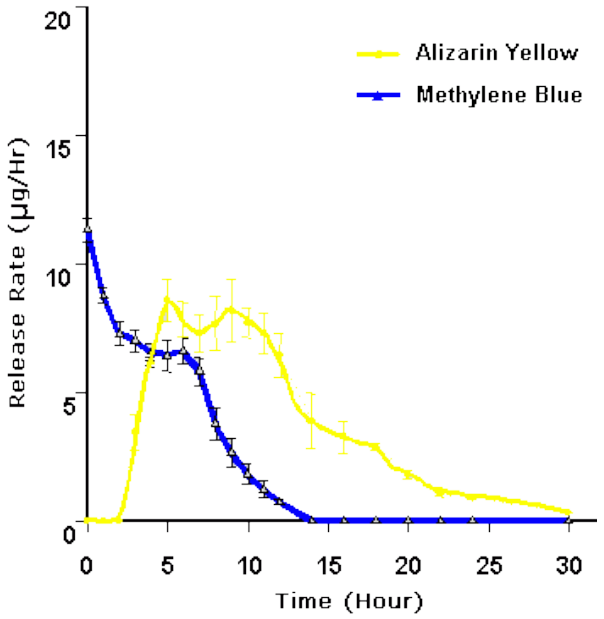
PEO (Middle Layer)

PCL (Bottom Layer)

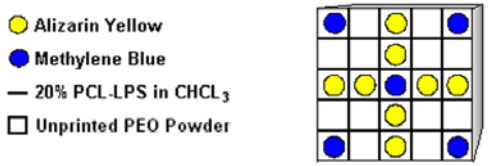
Wu et al J. of Controlled Release 40 (1996) 77-87

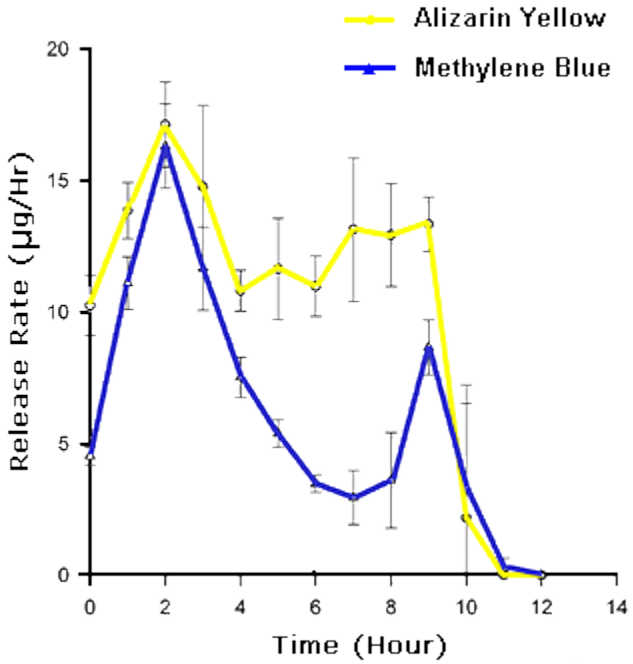
Microstructural Control - Symmetric Spatial Distribution
Varying Wall Microstructure





Positional Control - Asymmetric Spatial Distribution
Identical Walls





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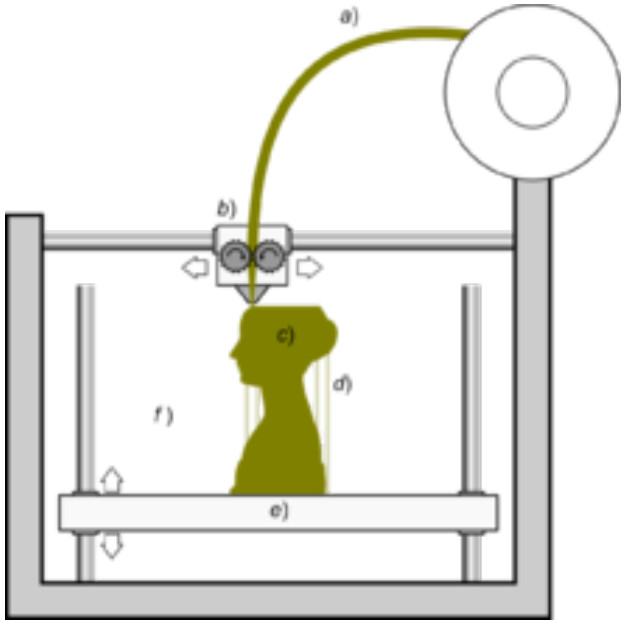
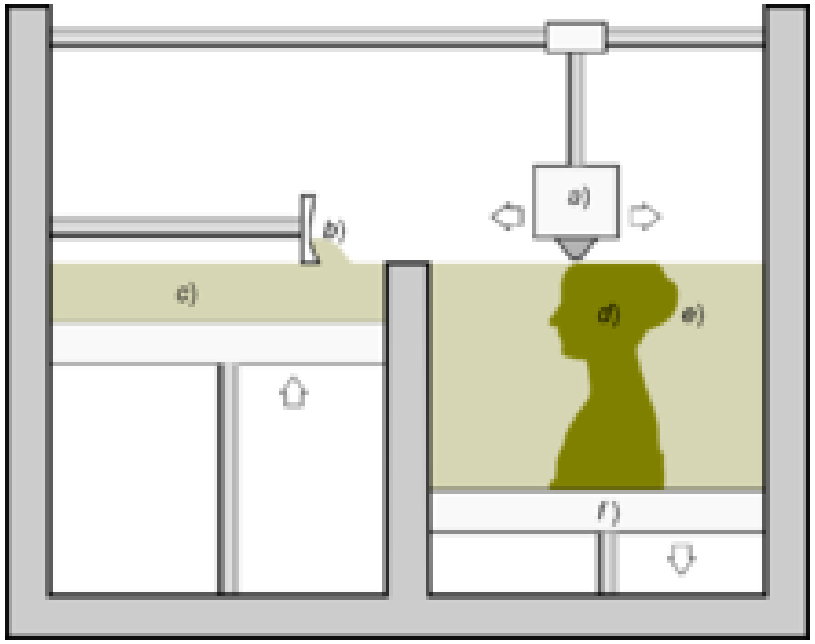
Selected Methods for 3D Printing Pharmaceuticals

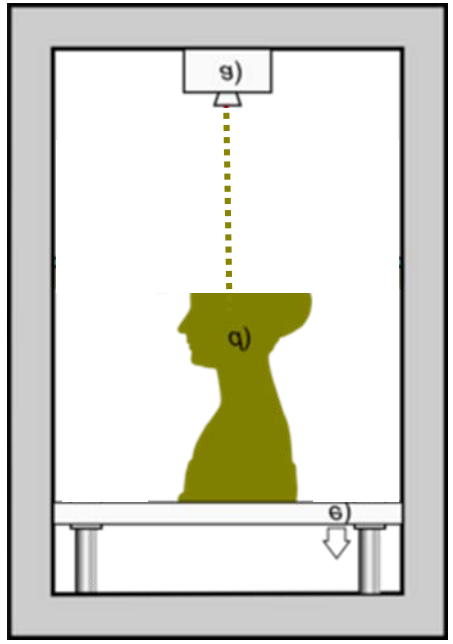
3D Printing: The action or process of making a physical object from a three-dimensional digital model, typically by laying down many thin layers of a material in succession.



Fused Deposition Modeling (Material Extrusion)



Powder-Liquid Deposition (Binder Jetting)



Polyjet (Material Jetting)

Scopigno R., Cignoni P., Pietroni N., Callieri M., Dellepiane M. (2017). "Digital Fabrication Techniques for Cultural Heritage: A Survey". *Computer Graphics Forum* **36** (1): 6–21. DOI:10.1111/cgf.12781.

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Aprecia's 3DP Technology Platform

- Utilizes powder-liquid or binder jetting 3DP TECHNOLOGY
  - Platform validated through FDA approval of first and only 3DP pharmaceutical product (Spritam®)
- Pharmaceutical products are assembled layer-by-layer, without the use of compression forces or molds
  - Eliminates potential for disrupting particles of drug or particle coatings (e.g., modified release)
- Spreading of thin layers of powder and depositing ("printing") pre-programmed patterns of liquid droplets onto selected regions of each layer are carried out repeatedly until tablet is formed
  - Allows for controlling regional tablet hardness, dispersibility characteristics and overall form/shape
- Interaction between powder and liquid during the 3DP process bonds the layered materials together
  - Dose forms can be designed to disperse on contact with liquid or to be swallowed whole

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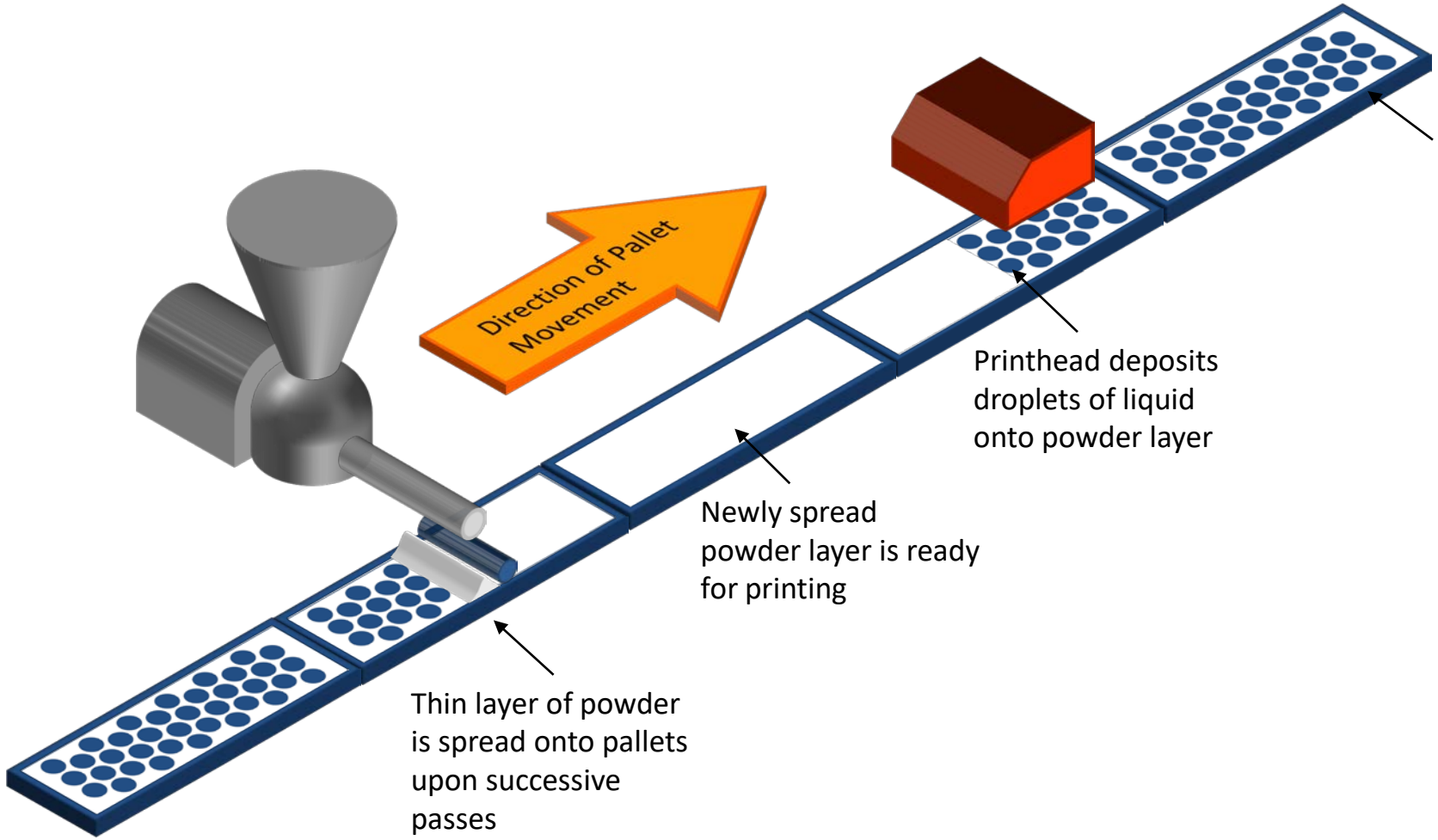
3DP Binder Jet Printing of Pharmaceuticals



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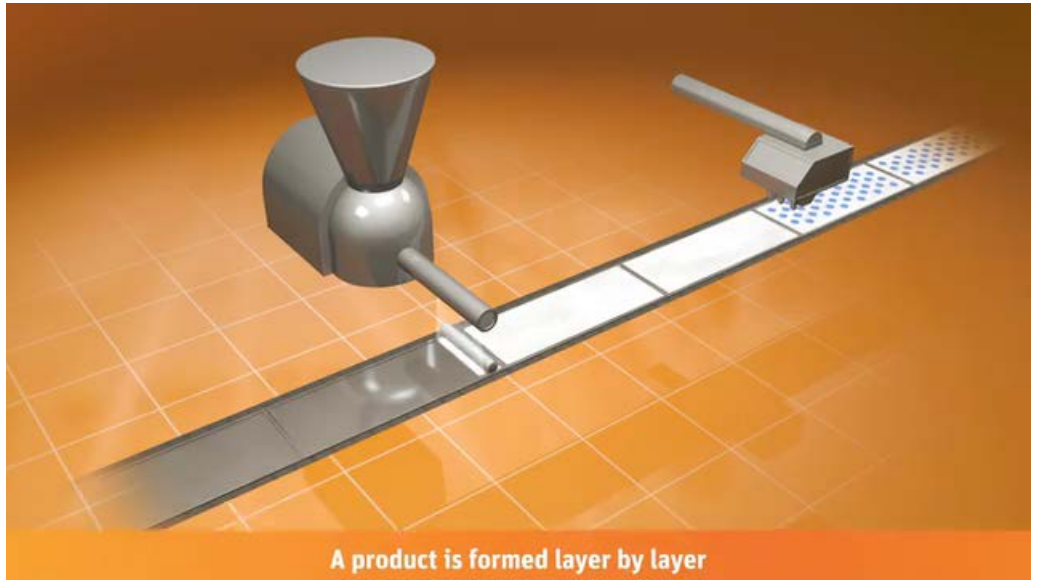
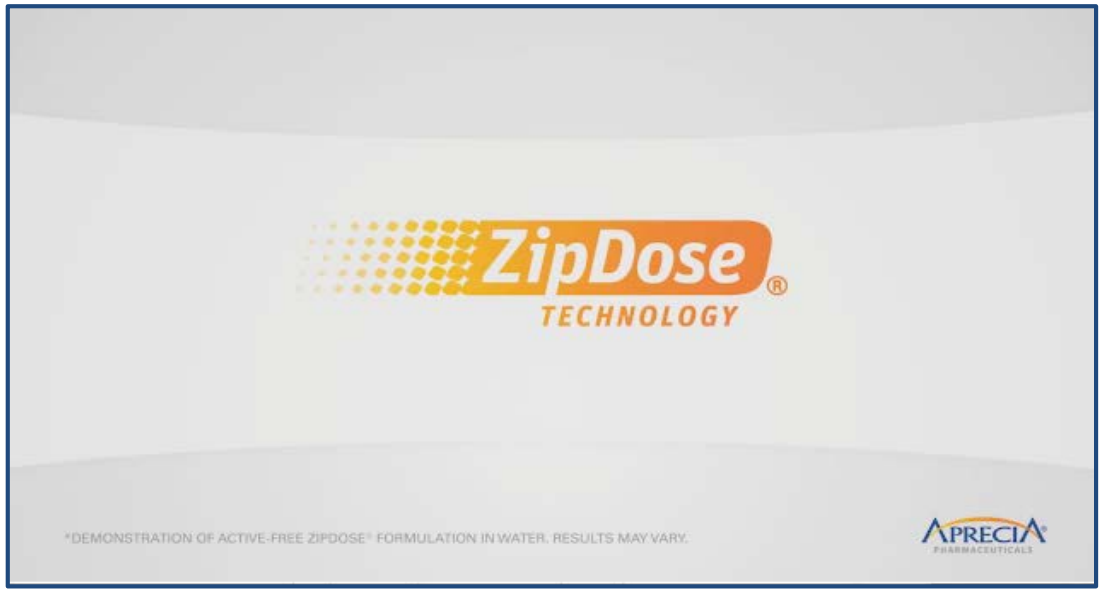
Introducing ZipDose® Technology



The powder-liquid additive manufacturing process produces a porous formulation of high drug load and rapid dispersion with a sip of liquid.



ZipDose® disperses with a sip of water in less than 10 seconds, a previously unachievable rate for high-dose formulations.

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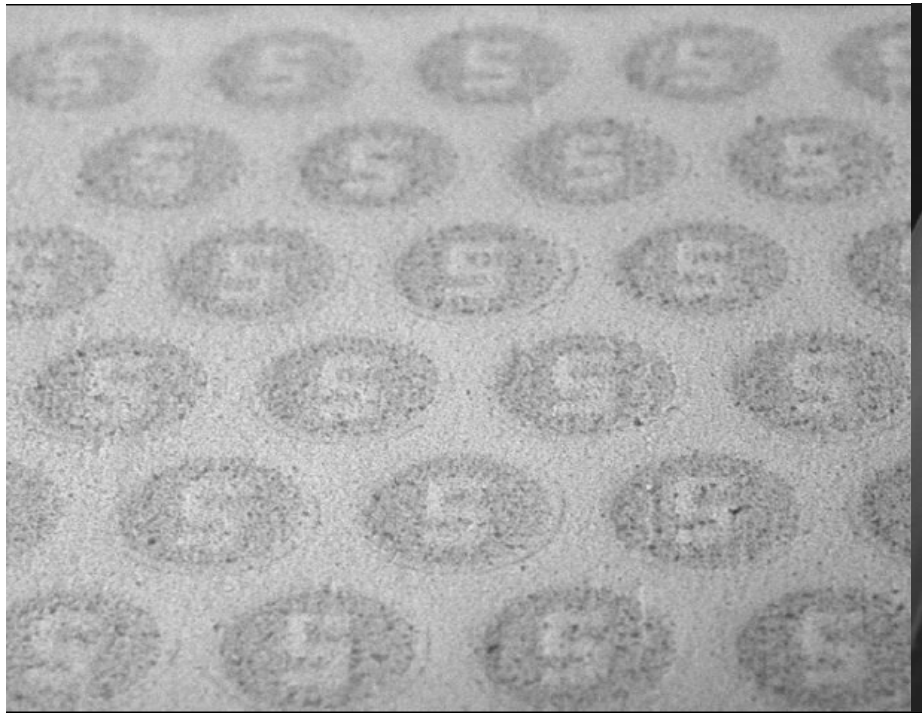
Harvesting the Dosage Forms

Printed ZDFs are dried and then harvested to remove unused powder



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Components Necessary for 3DP Pharmaceutical Manufacturing

Printing Fluid

- Aqueous Solution
- Deposition controls physical properties of dosage form
- Formulation depends on product
- Could incorporate API

+

Powder Blend

- API along with functional fillers
- Controls performance properties of ZDF
- Particle size, shape, packing create the matrix

Defined printing design

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Critical Elements

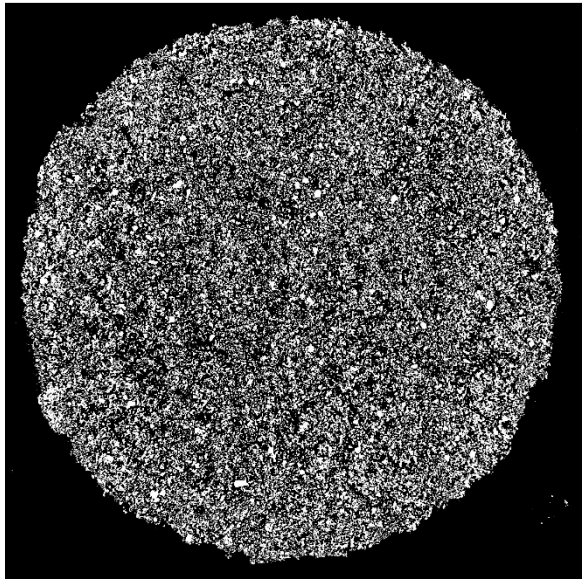
- Powder composition and compatibility
- Powder flowability
- Control of powder layer thickness and uniformity
- Print fluid composition and compatibility
- Deposition of printing fluid
- Speed

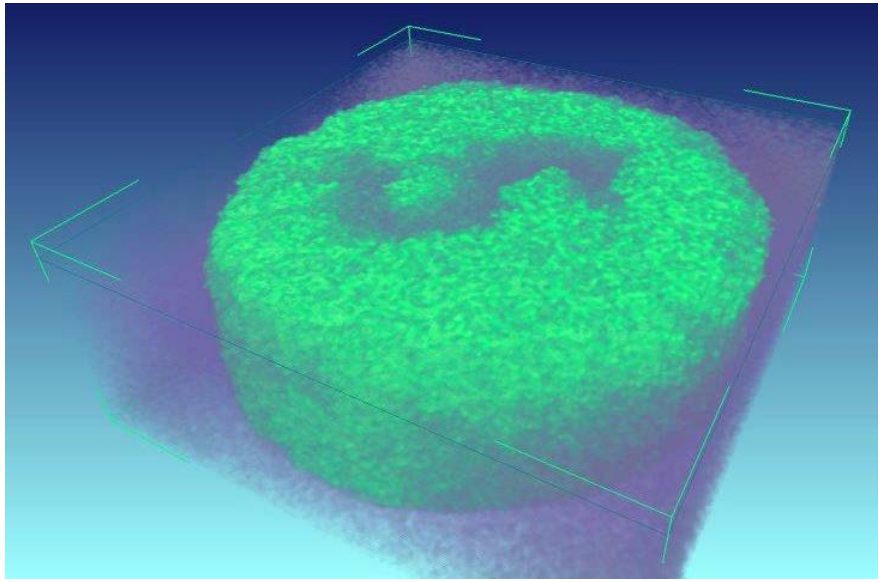
Key Considerations for Applying 3DP to Pharmaceuticals

- Achieving the speed and scale
- Complying with regulatory requirements
- Making economic sense
- Identifying and meeting the unmet needs

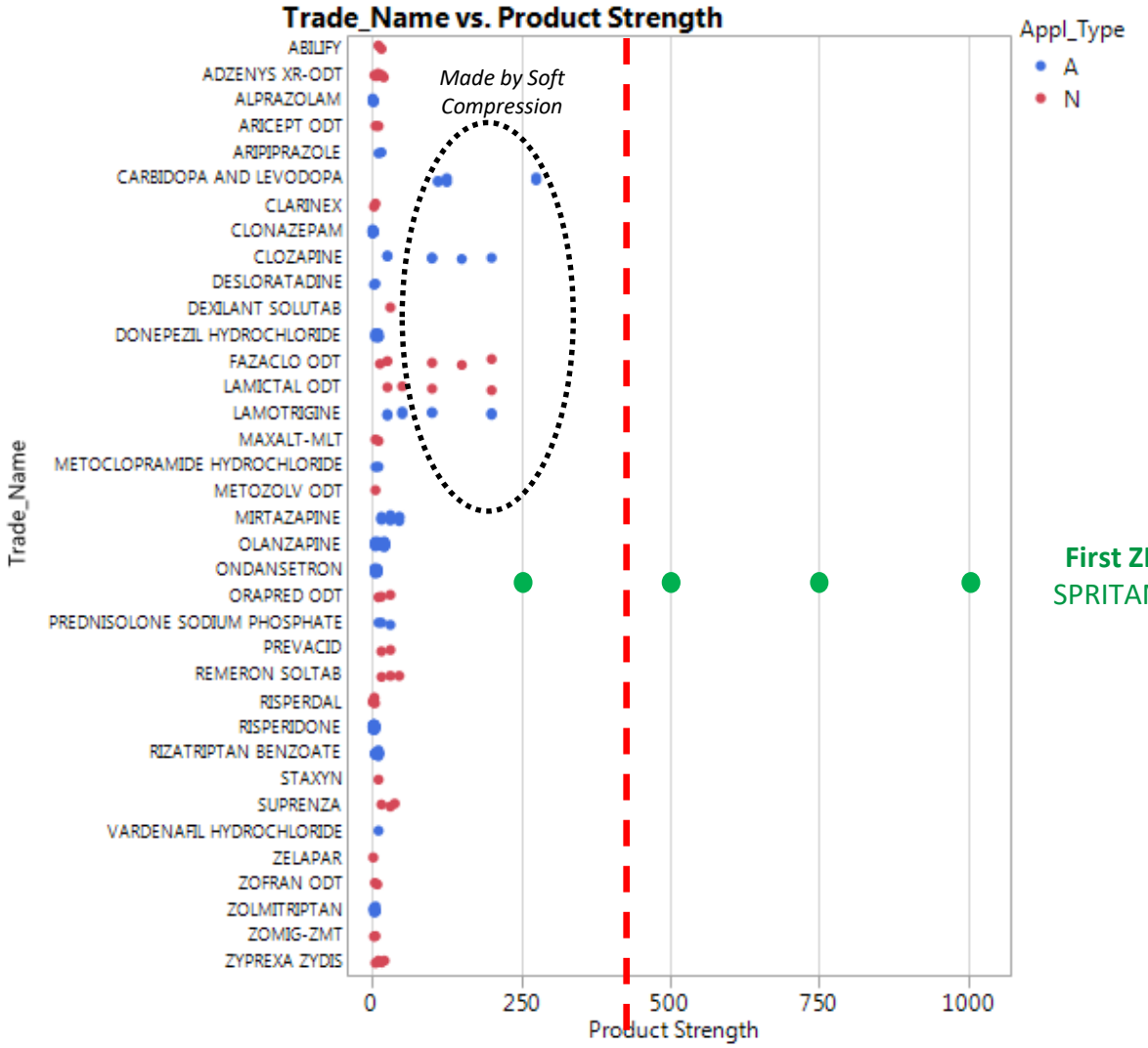
Application Example: Rapidly Dispersing Dosage Forms

- Controlled binding of powder allows instant dispersion upon contact with water
- Conventional pharma techniques were limited to low dose compounds





Application Example: Rapidly Dispersing Dosage Forms, ZipDose® Technology



"Over/Under" for Freeze-Drying claims: **400 mg**

- Conventional pharma techniques were limited to low dose compounds

First ZIPDOSE product:
SPRITAM (levetiracetam)

Source: U.S. Orange Book data
All Rx ODTs, 258 total records
May 9, 2016

(No new ODTs over 50 mg in OB in the interim as of Sept 2017)

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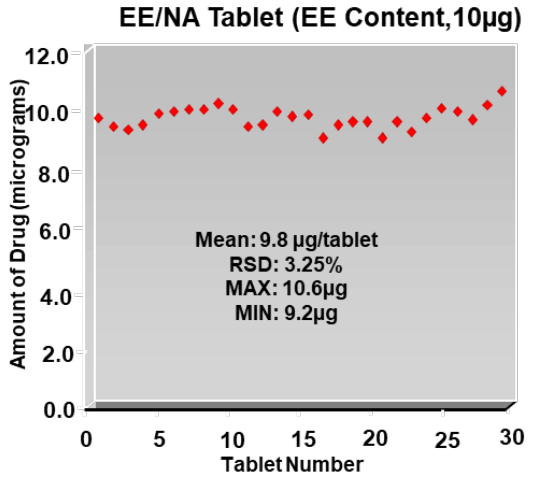
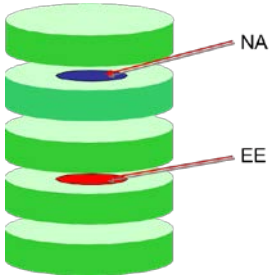
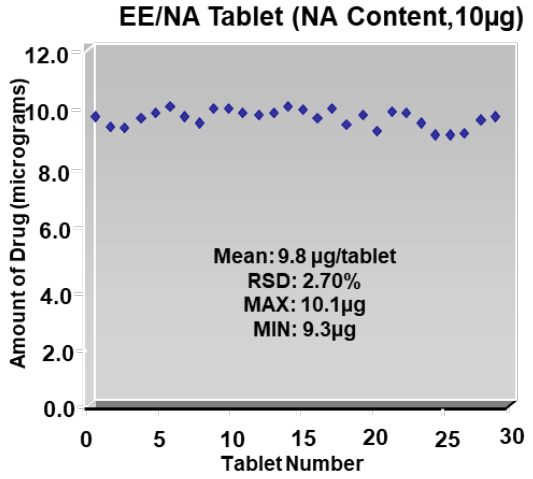
Application Example: Highly Accurate Low Dose Products

- Deposit metered amount of actives in each tablet
- No blending of actives
- Complete encapsulation of actives
- Physical separation of multiple actives
- Safer process and product







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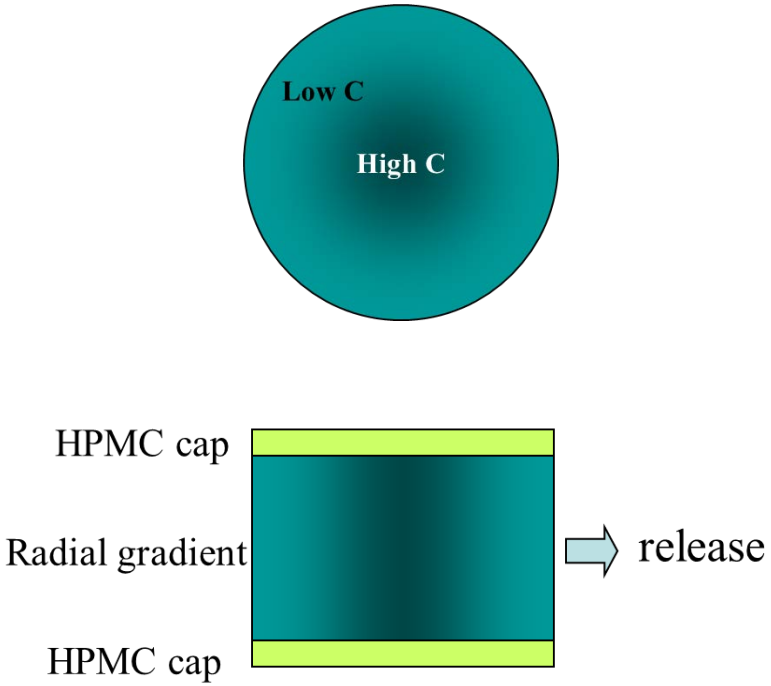
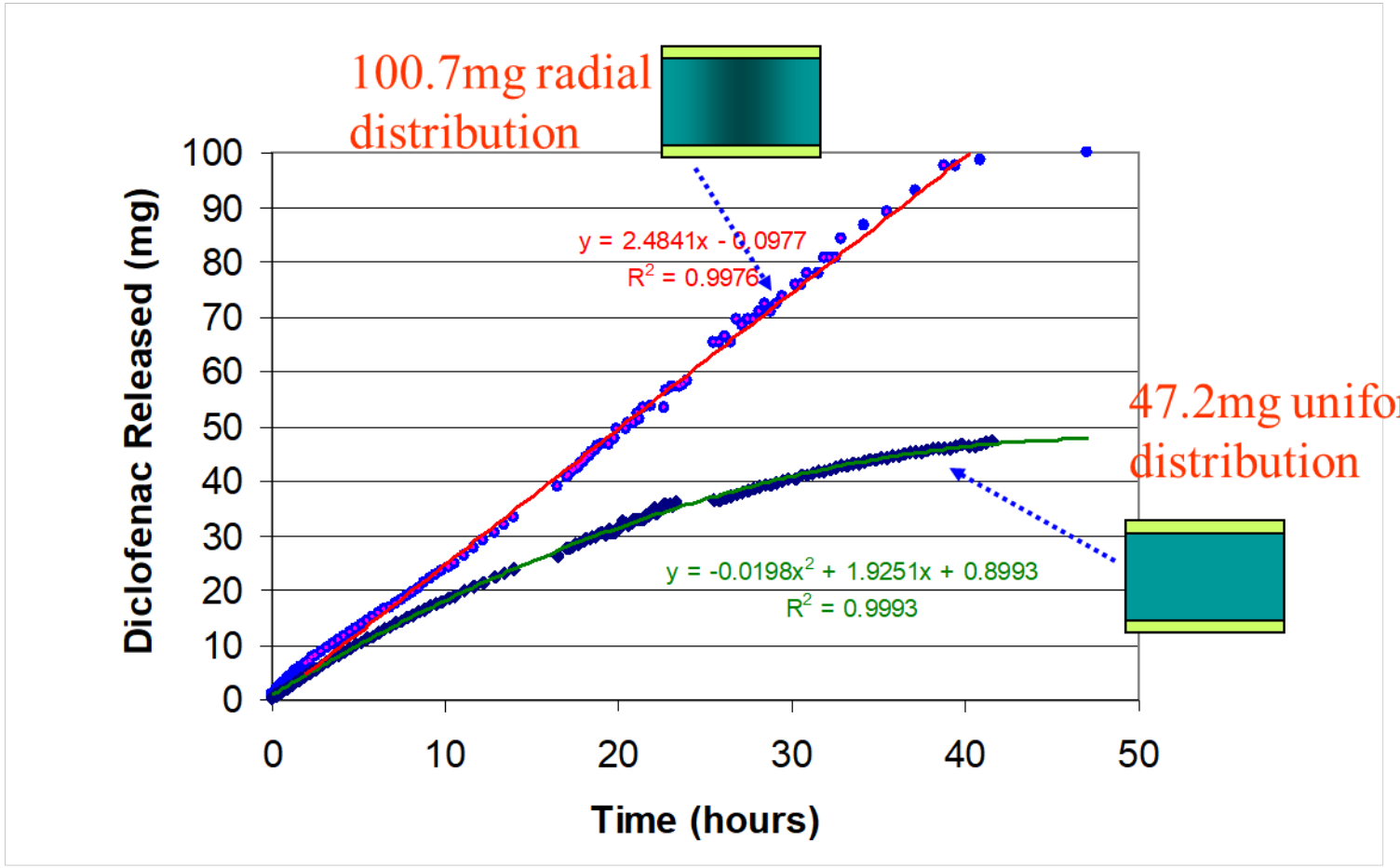
Application Example: Zero-Order Release Profile

- Introduce concentration gradient to achieve constant release





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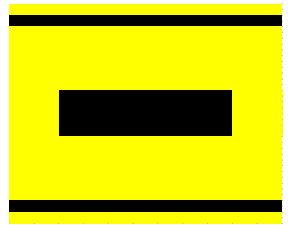
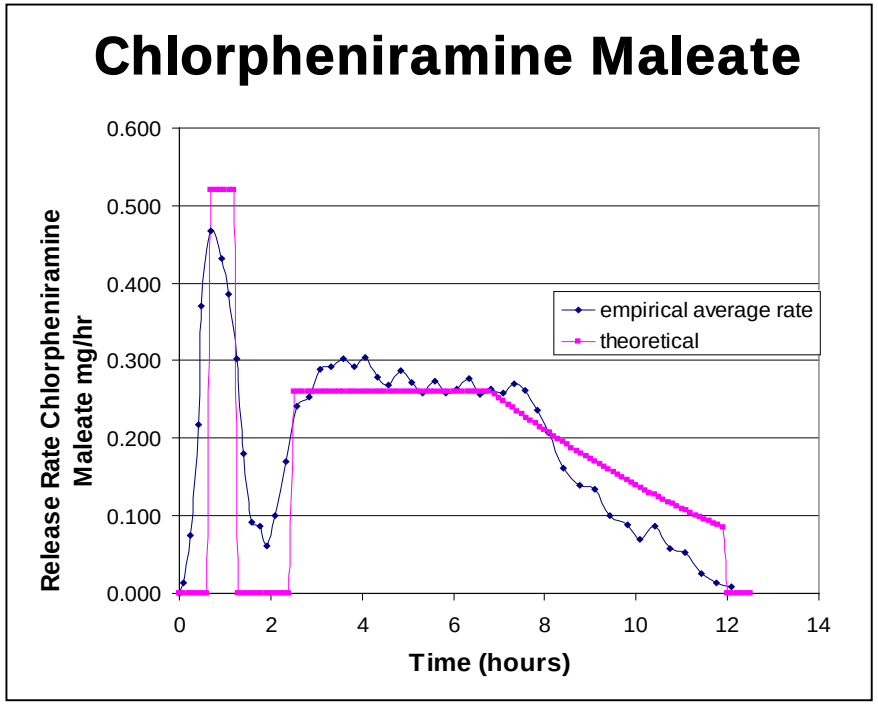
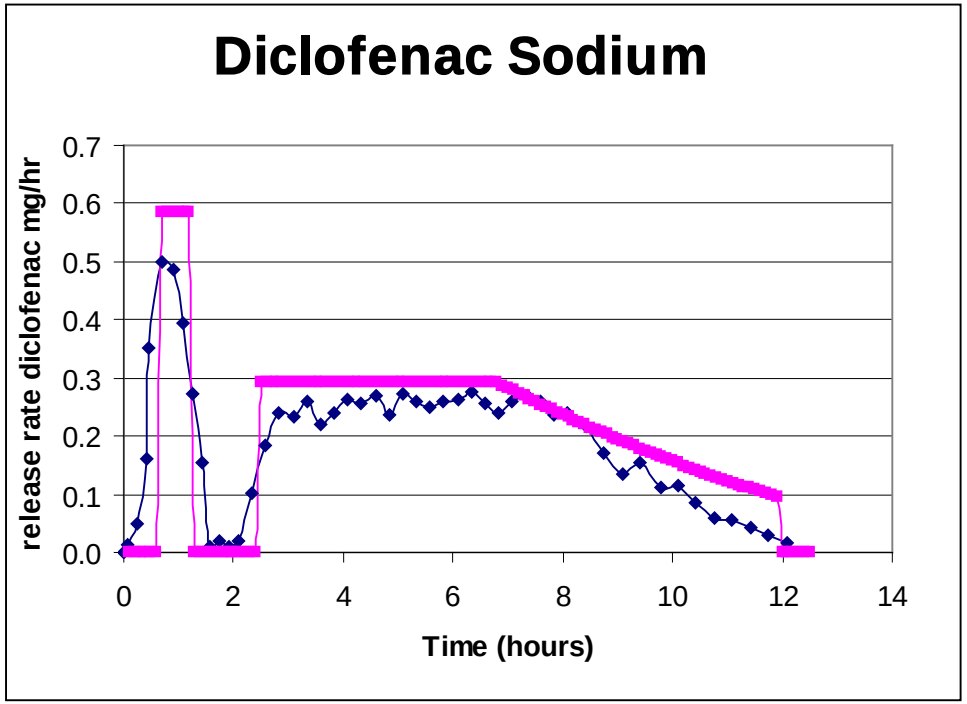
Application Example: Complex Release Profile

- Spatial control of composition to achieve pulsed release







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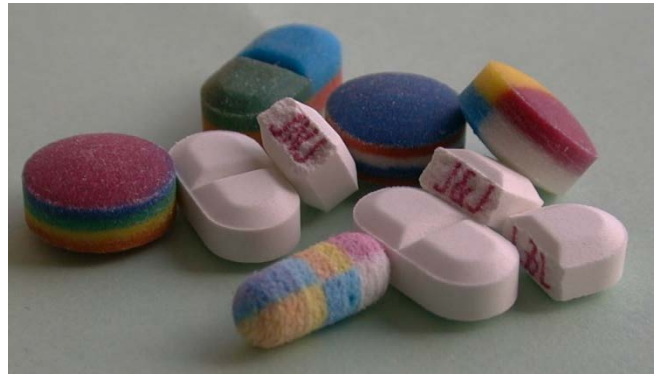
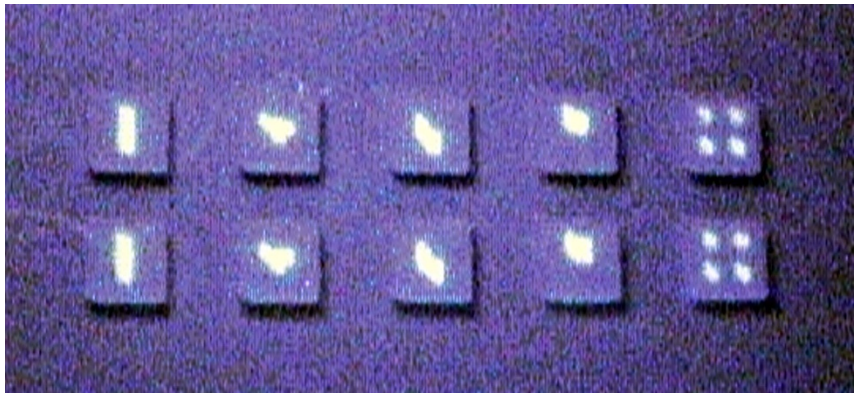
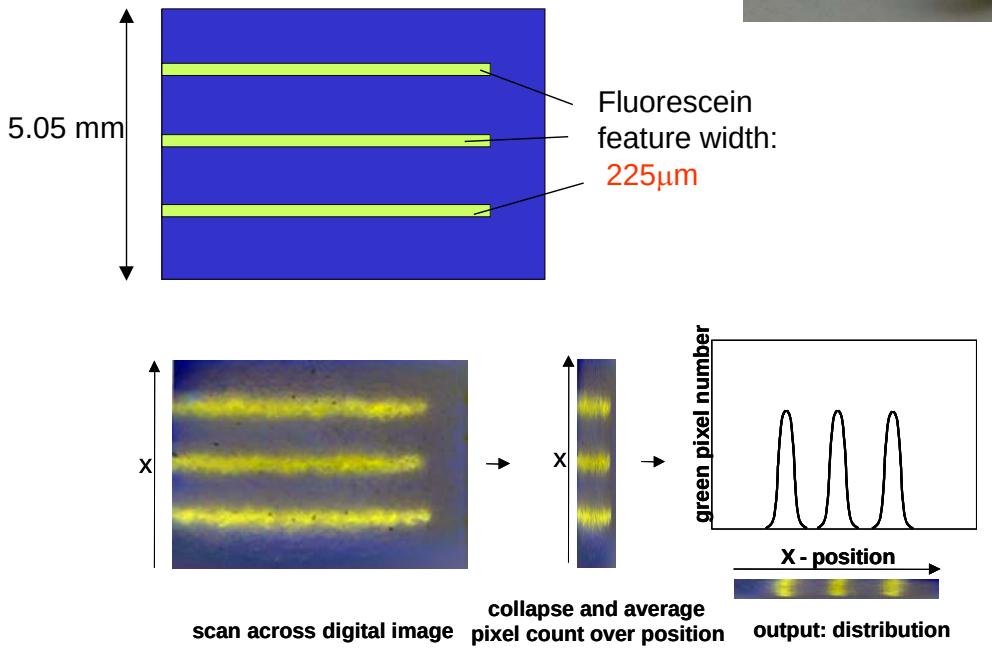
Application Example: Anti-Counterfeit Features

- Place designed markers within dosage forms
- Control location, amount, and shape of the marker
- Use invisible markers increase the level of difficulty for counterfeiting







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Pharmaceutical Solutions Provided by 3DP Technology

Solution Provided by 3DP	Problem Being Addressed
Rapidly dispersing tablets containing dose loads up to 1000mg (ZipDose®) address patient swallowing difficulties	Dose ceiling is a major limitation of commercially available fast melt manufacturing technologies

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Rapid dispersion of high drug loads and the ability to print drug-loaded solutions means more room to deliver multiple actives in the same dosage form	Large tablets that do not disintegrate rapidly in the mouth are difficult to swallow and pose design space limitations when using

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Rapid adjustment of formulated dose through layered production technique	Difficulty in rapidly changing doses in adaptive trials

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Delivering the Next Generation of Medicine Today

3D printing is another approach to advanced manufacturing. These methods are capable of manufacturing pre-determined 3D geometric structures of solid drug products in various shapes, strengths and distributions of active and inactive ingredients. *This approach provides a unique opportunity to produce medicines that are tailored for individual needs of patients.* - **Scott Gottlieb, FDA Commissioner (blog of July 13, 2018)**

PharmTech.com
ADVANCING DEVELOPMENT AND MANUFACTURING

Emerging technologies such as 3D printing can be an enabler of personalized medicine by promoting agile manufacturing, an approach to production that is focused on meeting the needs of a specific patient while controlling manufacturing efficiency. *3D printing technologies have the potential for producing final dosage forms that allow patients to be given a personalized regime, which could include multiple active ingredients, either as a single blend or potentially as layers in a multi-layer printed tablet, based on their treatment needs.* **- Kristofer Baumgartner, CDER Spokesperson in PharmaTech.com (August 2, 2016)**

SPOTLIGHT on CDER SCIENCE

3D printing of drug products could offer several advantages for pharmaceutical applications. For example, it has the potential to produce unique dosage forms with characteristics that cannot be achieved in conventional dosage forms, such as instantaneous disintegration of an active ingredient, and other complex drug release profiles. *To date, one FDA-approved drug—Spritam®--is manufactured using 3D printing technology. Spritam® tablets, for the treatment of epilepsy, are designed so that a large dose of active ingredient (1000 mg of levetiracetam) disintegrates within seconds after taking a sip of water.* - **Ahmed Zidan, FDA Spotlight on Science**

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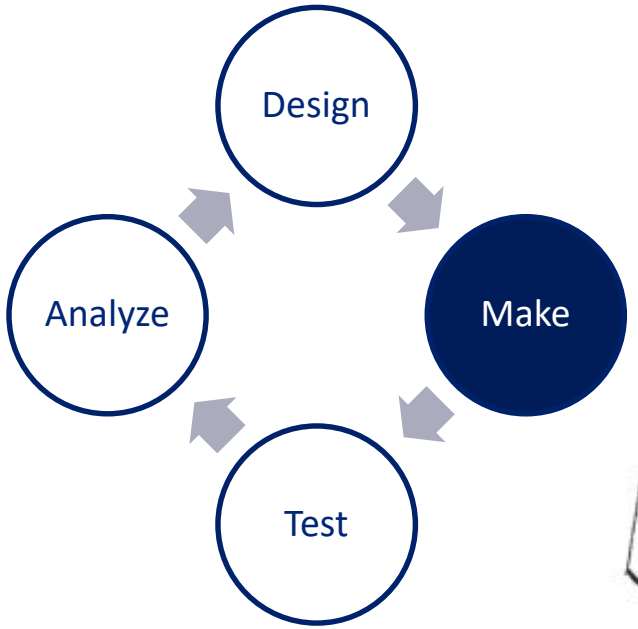
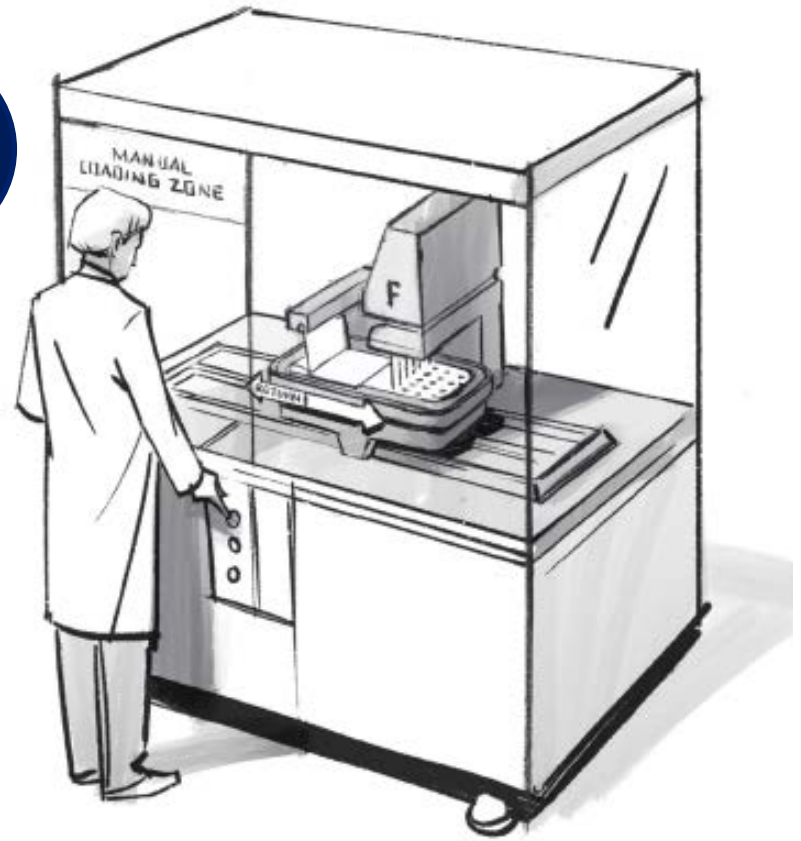
Examples of Unmet Needs

- Accelerating drug development cycle (e.g. adaptive clinical trials)
- Solving the “last mile” issue
- Optimized dose and release profiles
- Personalized medicine and reducing pill burden





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Adaptive Clinical Trials

- **Definition:** "A study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of date (usually interim data) from subjects in the study" – FDA
- **Example:** First in Human (FIH) Dose Ranging Study (estimate dose 0.5 to 100mg)
- **Traditional design:** Dose ten subjects at each dosing level in a progressive manner. May be planned for 5-10 or more dose levels
- **Adaptive Design:**
  - Two to five subjects receive 0.5mg dose and blood samples taken. Drug concentrations measured overnight.
  - Based on results of these five, next dose is determined and process is repeated until desired concentrations achieved.

How Could 3DP of Pharmaceuticals Aid an Adaptive Clinical Trial?

Benefits:

- Dosage strength could be printed on-site, as needed.
- No need for large scale, manufacturing of all possible doses.
- Just enough tablets for each step of trial could be produced.
- Less worry about tablet stability.
- Reduced cost and time.

What if Pharmaceuticals Could be “Printed” at the Point of Sale?

- Would obviate the need for large production facilities

- Could use clinical data from individual patients
  - Electronic monitoring of patient parameters
    - E.g., blood pressure, heart rate, glucose, weight, compliance, etc.
    - Patient privacy issues?

- Would allow for personalized doses for each individual patient

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Potential Role of 3DP in Precision Medicine

- Dosage forms containing patient-specific amounts of active ingredient manufactured either from a regional location or at the point of care.
  - Theoretically could adjust dose as often as every dose
  - Could allow for “near real-time” dosage adjustments
  - Could simplify dosage titration
- Creation of combo medications with patient-specific doses of each drug.
  - Expands possibilities beyond traditional fixed dose combinations
  - Potential for release of different active ingredients at different times or in different parts of GI tract

The "Multi-Pill"

JAMA | Original Investigation

Fixed Low-Dose Triple Combination Antihypertensive Medication vs Usual Care for Blood Pressure Control in Patients With Mild to Moderate Hypertension in Sri Lanka A Randomized Clinical Trial

Ruth Webster, PhD; Abdul Salam, PhD; H. Asita de Silva, DPhil; Vanessa Selak, PhD; Sandrine Stepien, MStat; Senaka Rajapakse, MD; Stanley Amarasekara, MD; Naomali Amarasena, MD; Laurent Billot, MRes; Arjuna P. de Silva, MD; Mervyn Fernando, MD; Rama Guggilla, MMed; Stephen Jan, PhD; Jayanthimala Jayawardena, MD; Pallab K. Maulik, PhD; Sepalika Mendis, MD; Suresh Mendis, MD; Janake Munasinghe, MD; Nitish Naik, MD; Dorairaj Prabhakaran, MD; Gotabaya Ranasinghe, MD; Simon Thom, MD; Nirmali Tisserra, MD; Vajira Senaratne, MD; Sanjeewa Wijekoon, MD; Santharaj Wijeyasingam, MD; Anthony Rodgers, PhD; Anushka Patel, PhD; for the TRIUMPH Study Group

JAMA 2018;320:566-579.

Could this be a precursor to a customized "one-tablet" regimen?

Summary

- Powder liquid 3DP offers unique advantages and opportunities for the pharmaceutical industry, as recognized by FDA and other industry leaders.
- 3DP for pharma offers formulation advantages over traditional methods, opening doors for oral drug delivery in ways otherwise unachievable.
- 3DP offers flexibility and efficiency in early stage development work from animal studies to clinical trials
- 3DP can help address unmet patient needs and transform how medicines are delivered
- Because of the customization possible with 3D printing of pharmaceuticals, it may provide a platform for precision medicine

Questions

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Thank You!