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In Vivo Applications of 3D Printed Pharmaceuticals: Solutions for Challenging Molecules

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NEXT-GENERATION DELIVERY INNOVATIONS

Overview

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Precision Delivery

3D printing can be utilized to control the rate, duration, amount and location of drug release to maximize therapeutic efficacy

Bioavailability Enhancement

Solubility and bioavailability of poorly soluble drugs can be enhanced with novel 3D printed tablets

Dose Adherence

Gastro-retentive tablets can be created through 3D printing that can increase adherence through daily, weekly or even monthly dosing

Oral Biologics Delivery

3D printed tablets show promise in delivering peptides and large molecules orally

Lego Building Block Approach to Achieving Both Immediate and Extended Release

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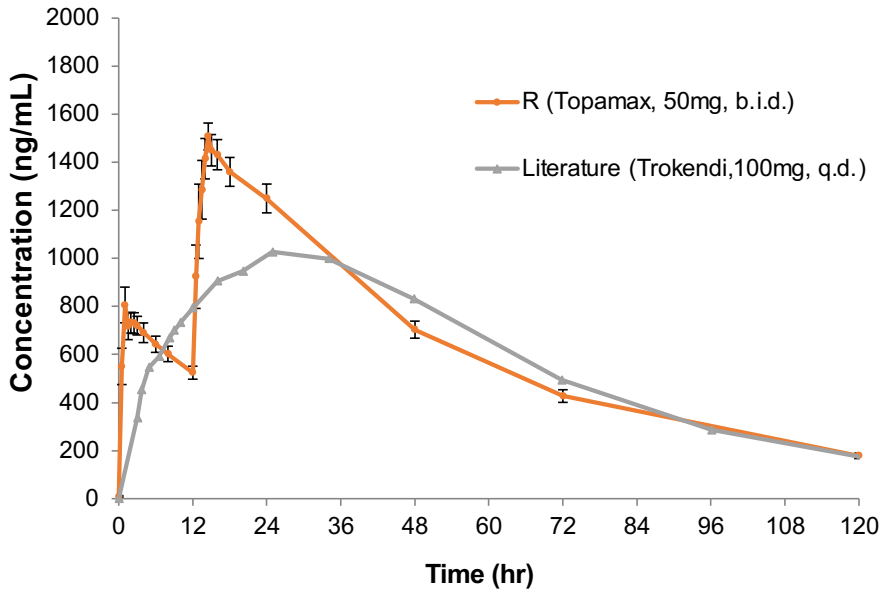
Drugs that require immediate release to achieve therapeutic concentrations quickly can pose a challenge to convert them from multiple-times-a-day dosing to once daily dosing, while maintaining C_{max} and total AUC.

Can the use of unique internal tablet geometry be used to achieve both target C_{max} and AUC?



IR/ER Tablets: Topiramate

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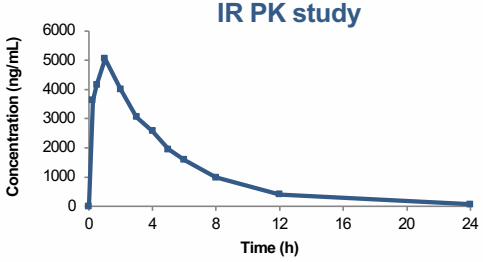
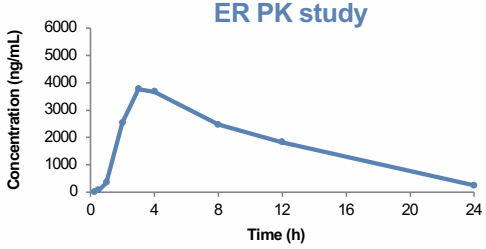
Step 1:
"LEGO"module PK study

IR PK study



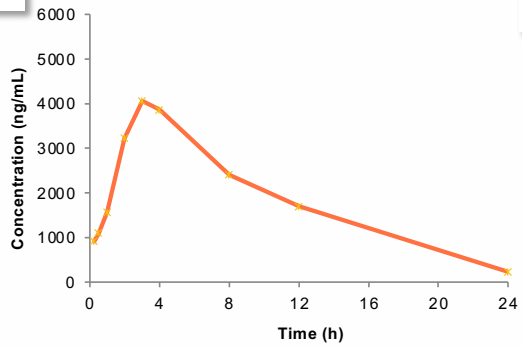
ER PK study



PK Simulation

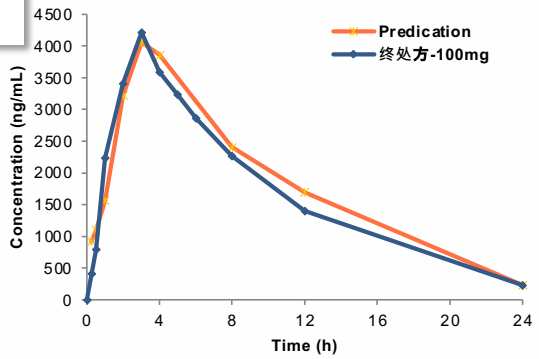
Step 2:
LEGO combination theory calculation

Combine IR and ER according to a designed dose (IR:ER=1:7)



3D Printed Tablet by Design

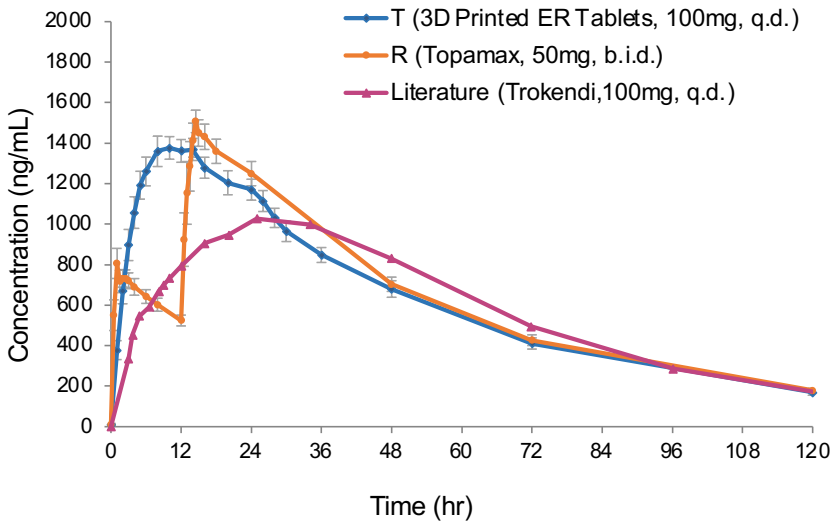
Step 3:
3D printed tablet PK verification



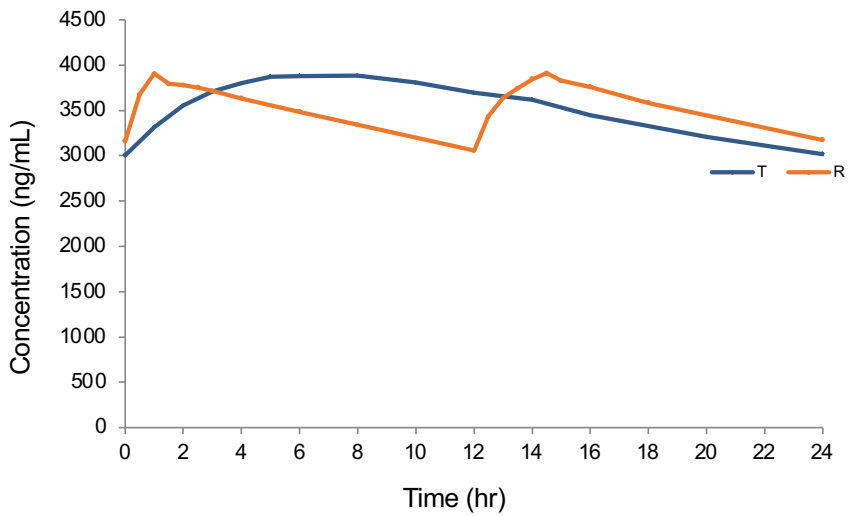
IR/ER Tablets: Topiramate

Lego approach to IR/ER formulations allows maintenance of Cmax of BID dosing, while maintaining exposure (AUC) over 24 hours

Single Dose Topiramate PK(n=12)



Day 9 Steady State PK



Assuring Consistent Formulations of Very Low Dose Drugs and Achieving Desired PK

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1

With traditional batch processing (e.g., 150kg), assuring tablet dosage uniformity can be challenging for very potent, low dose drugs (e.g., levothyroxine, clonidine, etc.) where the total amount of API added in the batch is extremely small (e.g., 0.1kg of API in 150kg total batch size).

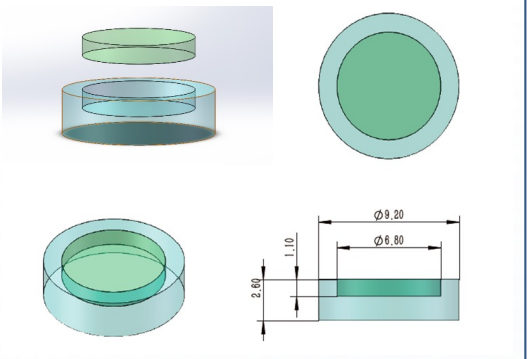
2

Furthermore, creating formulations that deliver extended release with this low API dose can also be challenging.

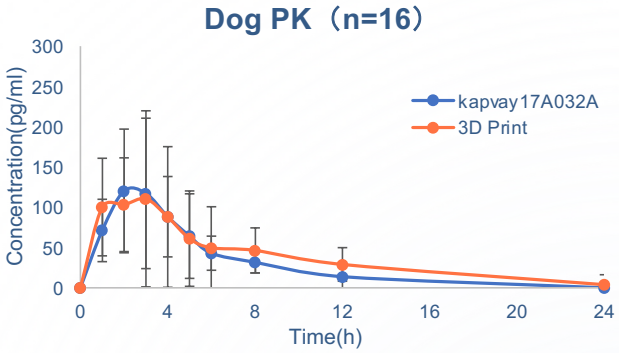
Question

Can 3D printing overcome some of these very low dose drug challenges?

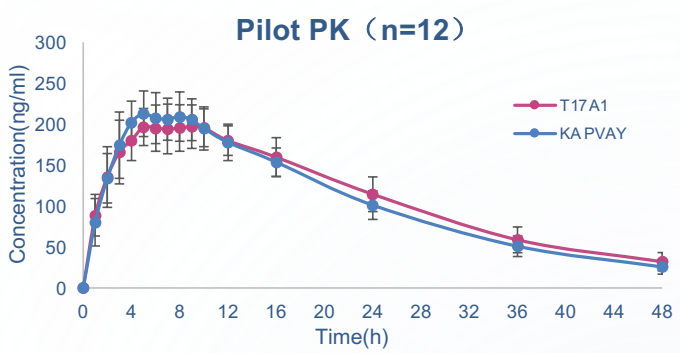
Matching PK of Extended Release Very Low Dose Drug: Clonidine



Kapvay (clonidine) 0.1 mg
extended release for ADHD



Dog（n=16）	AUC_{0-24}	C_{max}	T_{max}
KAPVAY	627±259	139±93.5	2.44±1.15
3D Print	784±525 (122%)	132±102 (110%)	1.69±0.95



PK（n=12）	AUC_{0-48}	C_{max}	T_{max}
KAPVAY	5155±636	222±30.3	6.00±2.13
T17A1	5382±657 (106%)	208±25.1 (94%)	6.83±2.48

Altering Release Rate to Match Pharmacodynamic Requirements – Morning Stiffness with RA

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1

Goal is generally to match drug concentrations with target engagement to maximize therapeutic effect

2

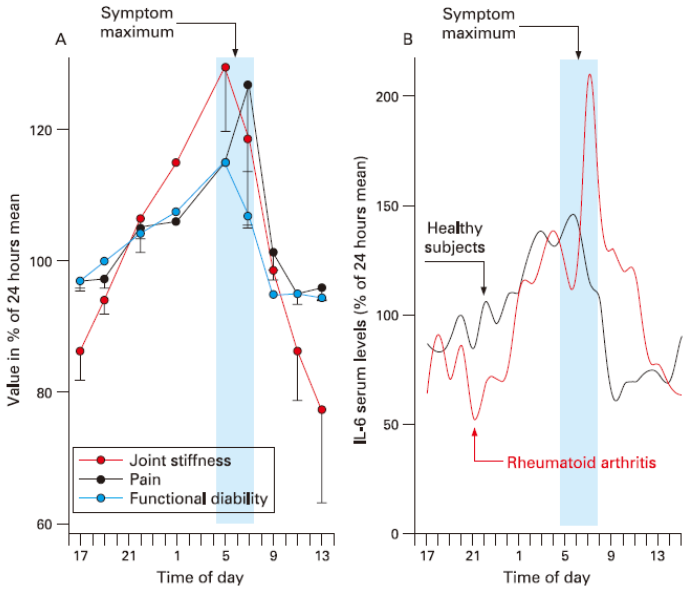
PK-PD relationship can be Cmax-driven, AUC-driven or Cmin-driven

3

What if convenient time of drug administration and subsequent drug release does not result in drug pharmacokinetics that match timeframe of maximum symptoms? E.g., Circadian rhythm situations

Rationale for T19 Product Design

Matching Drug Concentrations with Inflammatory Mediators and Symptoms

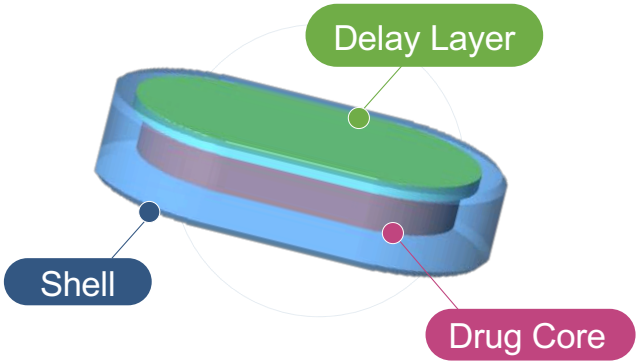


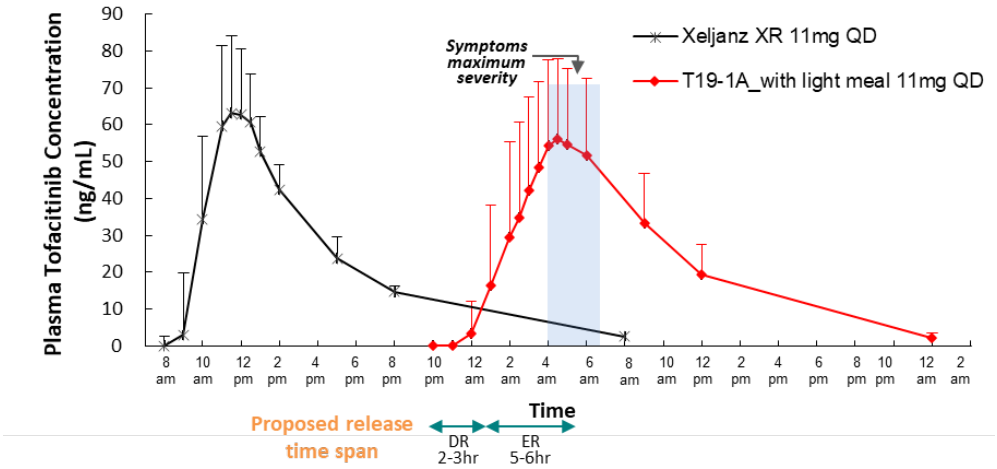
Ann Rheum Dis, 2008; 67: 905-908

T19 was formulated to maximize tofacitinib exposure at the time of greatest symptom severity and IL-6 concentrations, by delivering peak tofacitinib plasma concentrations in the early morning hours while maintaining efficacious concentrations throughout the day.

T19 (Tofacitinib) Design

Flexible Control of Release Rate and Onset Time





Through an innovative internal structure (drug core and delay layer, Drug release onset time and release rate can be precisely controlled.

Primary end point met:

T_{max} between 4-7am with comparable C_{max} (101%) and AUC (108%) compared to RLD

Controlling Drug Release to Maximize Local Exposure and Minimize Systemic Exposure – Ulcerative Colitis

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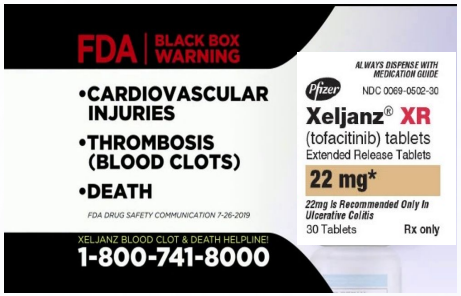
Most commonly drugs are given with intention of maximizing systemic exposure.

Unfortunately, this can lead to adverse events due to exposure at sites other than site of disease

E.g., in ulcerative colitis the primary symptomatology is limited to the colon but oral administration results in systemic exposure and adverse events

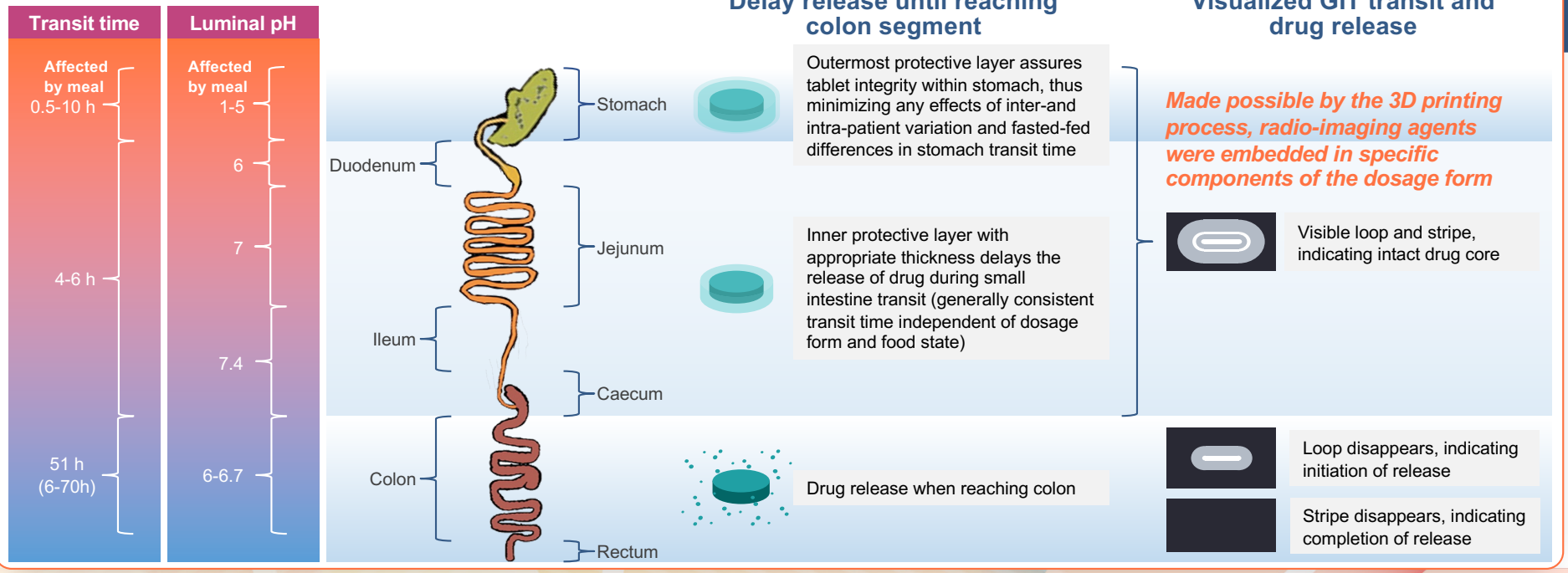


Question

What if we could create a formulation that maximizes exposure in colon but limits systemic exposure?

T21 (Tofacitinb) Product Design Strategy

Delayed-release, Colon-targeted Tofacitinib



3DμS®-CT: 3D Microstructure for Colon Targeting

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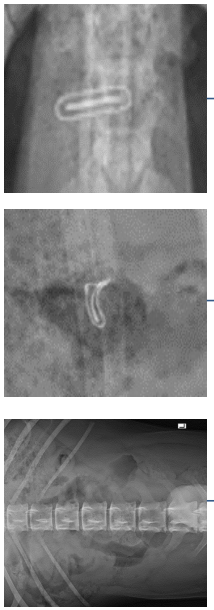
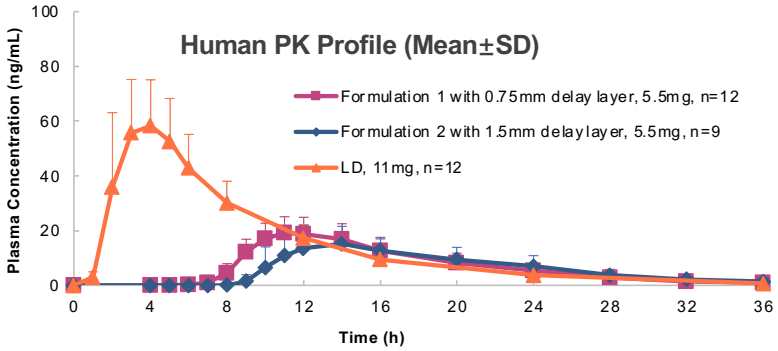
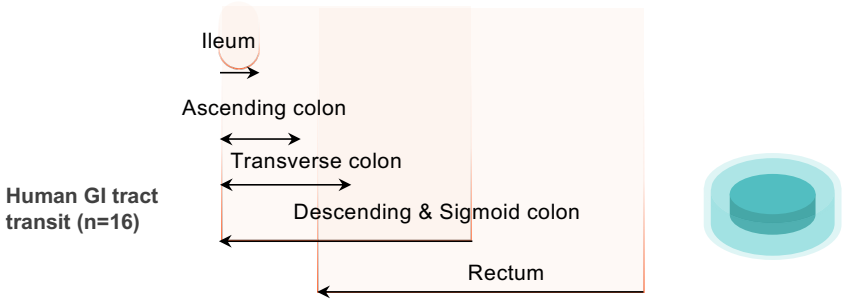
Controlling Release Location

X-ray Images



- 4h: Intact tablet located at ileum, 4h post-dose
- 6h: Start to release drug in ascending colon, 6h post-dose
- 8h: Drug release completion, 8h post-dose





Enhancing Solubility Through Novel Tablet Designs

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1

Many drugs being discovered today are poorly soluble and difficult to formulate (e.g., brick dust, greasy brick dust, etc.

2

Traditional formulation approaches such as spray dry dispersion technology or SEDDS technology can provide some enhancement of solubility but still may be insufficient.

Question

Can novel tablet designs be exploited to complement existing technologies to enhance drug solubility?

3DμS®-SE: 3D Microstructure for Solubility Enhancement

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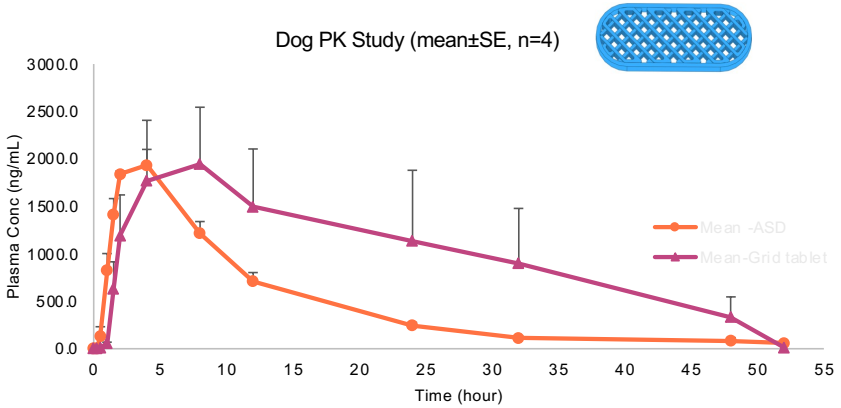
Maintaining Supersaturation to Enhance Solubility

Amorphous spray dry dispersions can be used to enhance solubility of poorly soluble compounds

However, bioavailability can remain low resulting in poor exposure, necessitating higher doses and increasing API costs

Using a “weave” tablet design that markedly increases available surface area, supersaturation can be maintained resulting in enhanced solubility and increased bioavailability

ASD Formulation Combined with Weave Structural Design to Maintain Supersaturation



Formulations	AUC Ratio	C_{max} Ratio
Spray drying ASD	1	1
3D-printed ASD tablet	1.98	1.33

3DμS®-SE: 3D Microstructure for Solubility Enhancement

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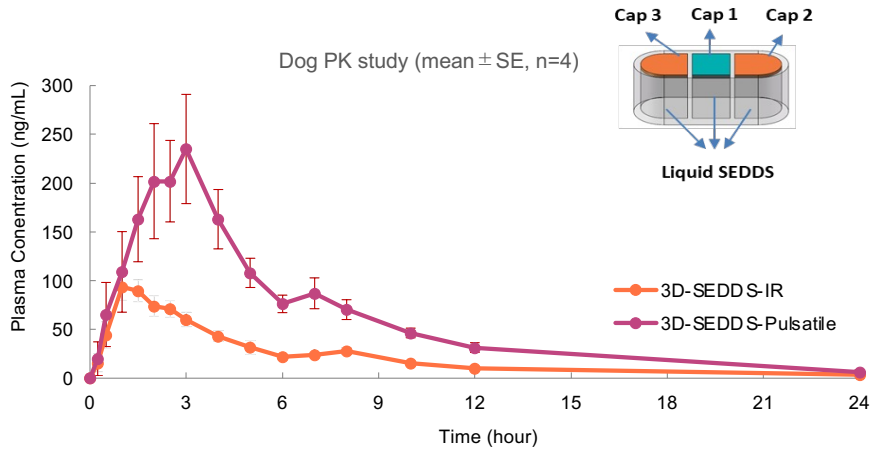
Creating Multiple Supersaturations to Enhance Solubility

- SEDDS formulations can be used to enhance solubility
- However, for some difficult molecules this solublity enhancement may be insufficient
- Molecule on right is double ester, then formulated with SEDDS technology, yet bioavailability remains ~10%
- By using a “multi-compartment” design, a series of low-degree supersaturation states can be created resulting in marked increase in solubility and bioavailability

Pulsatile release from multiple compartments to create a series of low-degree supersaturations



Formulations	AUC Ratio	C_{max} Ratio
3D-SEDDS-IR	1	1
3D-SEDDS-Pulsatile	3.25	3.04

Enhancing Bioavailability and Extending Pharmacokinetics Through Gastric Retention

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- Drugs with a short half-life can require frequent (e.g., TID) dosing leading to adherence issues but for which traditional extended release approaches may be difficult or inadequate
- Dosing orally every week or month may be desired for adherence of patient acceptability reasons (e.g., anti-psychotics, oral contraceptives)
- Drugs that are labile in more basic pH of the intestine may benefit from remaining in the stomach for absorption
- Drugs with increased solubility in acidic pH can have enhanced bioavailability if absorption occurs primarily in stomach

Question

Can a formulation be produced that remains in the stomach throughout the drug release and absorption process?

3DμS®-GR: 3D Microstructure for Gastric Retention

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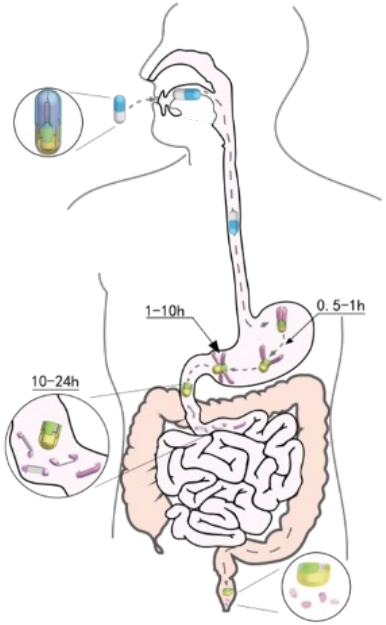
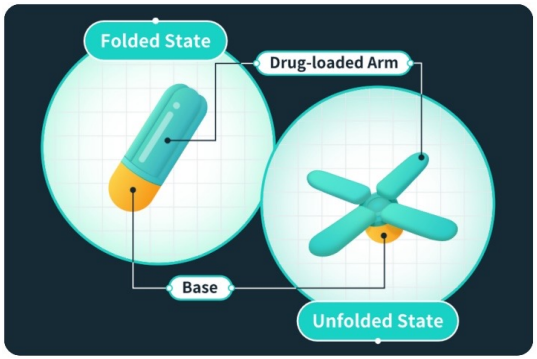
Unfolding Arms Prevent Passage Through Pylorus Until Structure Falls Apart (Time Controlled)

- Similar to a traditional “caplet” design prior to administration
- Upon contact with acidic pH of stomach the “cap” disintegrates quickly allowing ”arms” to unfold
- Arms prevent tablet from passing through the pylorus, thus maintaining location in stomach
- Arm attachments dissolve over time allowing components to pass through pylorus and on through intestinal tract
- Arm detachment time can be tuned to control duration of drug release
- FDA-accepted pharmaceutical excipients





3DμS®-GR: 3D Microstructure for Gastric Retention

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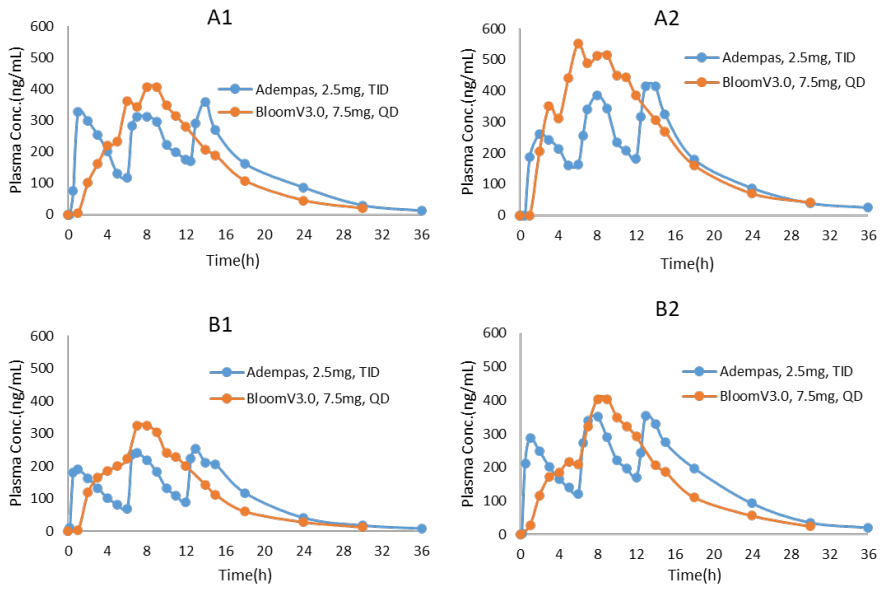
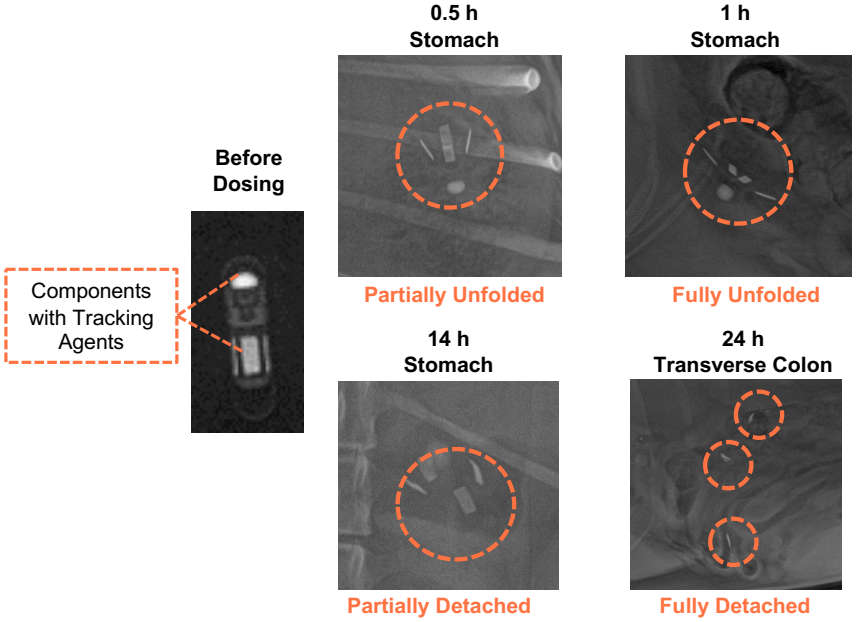
Equivalent Exposure in Dogs Following Either Three Times a Day or Once a Day Dosing of Adempas®



X-ray Imaging Results (Dogs)



Oral Delivery of Peptides and Large Molecules

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1

Oral delivery of peptides and large molecules has proven to be challenging due to rapid degradation in GI tract, poor absorption and general instability

2

Various approaches have been tried to enhance stability and absorption, such as nanoparticles, liposomal formulations, inclusion of permeation enhancers, etc.

Question

Can 3D printed tablets be leveraged to deliver peptides orally?

3DμS® - OP (Oral Peptides) Platform

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Targeted Delivery and Release

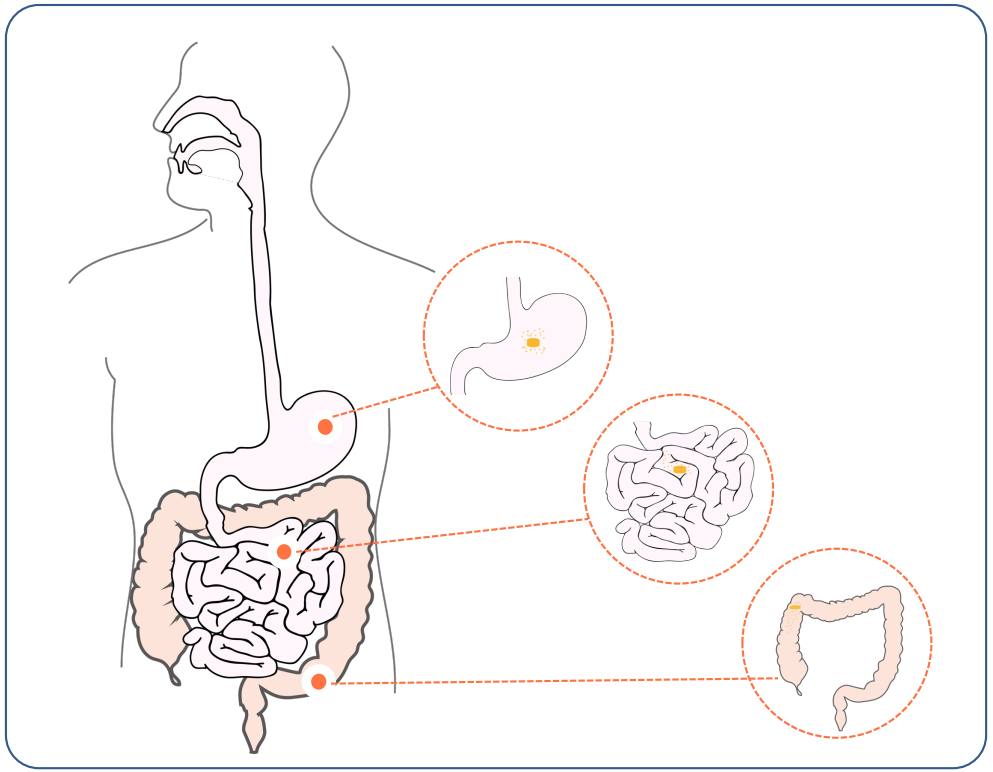
Precise delivery of peptide to targeted area of GI tract with designed release behavior

Targeted delivery

- stomach, small intestine, or colon depending on peptide characteristics.

Designed release behavior

- immediate release, pulsatile release, delayed release, sustained release, etc. to optimize absorption.



3DμS® - OP: Formulation Design Options

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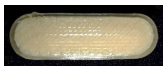
Design	Target Delivery	Compositions	Tablets	Prototype
1	**Stomach IR release**	Fast-dissolving Layer Drug Core		
2	**Stomach pulsatile release**	Fast-dissolving Layer Delay Release Layer Drug Core		
3	**Small intestine release**	Enteric Layer Drug Core		
4	**Colon release**	Enteric Layer Delay Release Layer Drug Core		

Tracking Tablet Delivery and Drug Release

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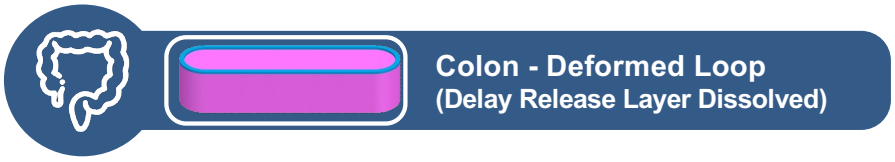

GI Site Preferential In Vivo Absorption In Dogs of a Model Peptide Formulated by 3D Printing

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PK Parameter	Stomach Administration	Jejunal Administration	Colon Administration
T_{max} (h)	1.3 ± 0.5	4.3 ± 2.1	5.3 ± 1.0
C_{max} (ng/mL)	13.5 ± 12.9	2.4 ± 2.2	5.8 ± 3.8
AUC_{0-t} (ng·h/mL)	27.8 ± 22.6	4.7 ± 2.8	8.2 ± 7.0
AUC_{0-inf} (ng·h/mL)	28.3 ± 22.3	5.3 ± 3.7	8.2 ± 6.8

Data presented as mean ± SD

~5X greater absorption in stomach as compared to jejunum or colon

Concept of “by Design” Drives Digital Drug Development and Manufacturing

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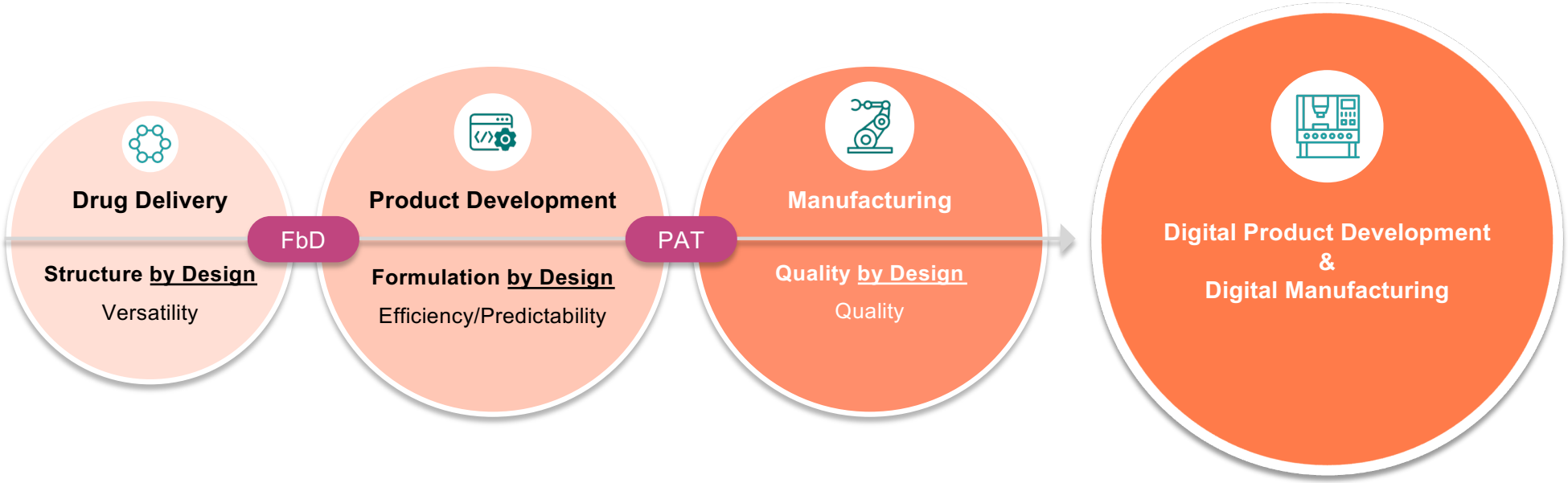

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Revolutionizing Drug Delivery, Development and Manufacturing

Delivery

Simple Process for Precise Release

- Programmed release through 3D structured formulation by design
- Customizable drug release timing, location, and speed
- Versatile delivery techniques using the same process

> **Precisely Controlled Release Mechanism**

Development

Efficient Digital Formulation Development Model

- Digitalized formulation development to accelerate product R&D
- Enhanced success rate with in vivo and in vitro data models

> **Enhanced Efficiency and Success Rate**

Manufacturing

Digital Production Guarantees Drug Quality

- Streamlined continuous manufacturing process and lean equipment
- PATs to achieve end-to-end online QC
- Fully automated digital production allowing for linear scale-up
- Green production: no organic solvents and zero emission

> **Higher Quality and Lower Costs**

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Thanks!

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