ORALOGIK™

A NEW APPROACH TO COMPLEX ORAL DRUG DELIVERY PROFILES

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Chairman, BDD Pharma

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DRUG DELIVERY PROFILES
WHAT IS COMPLEX?

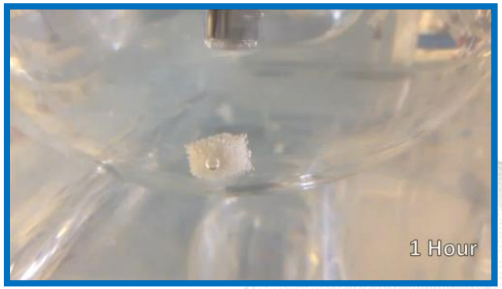
WAYS TO ACHIEVE COMPLEX RELEASE

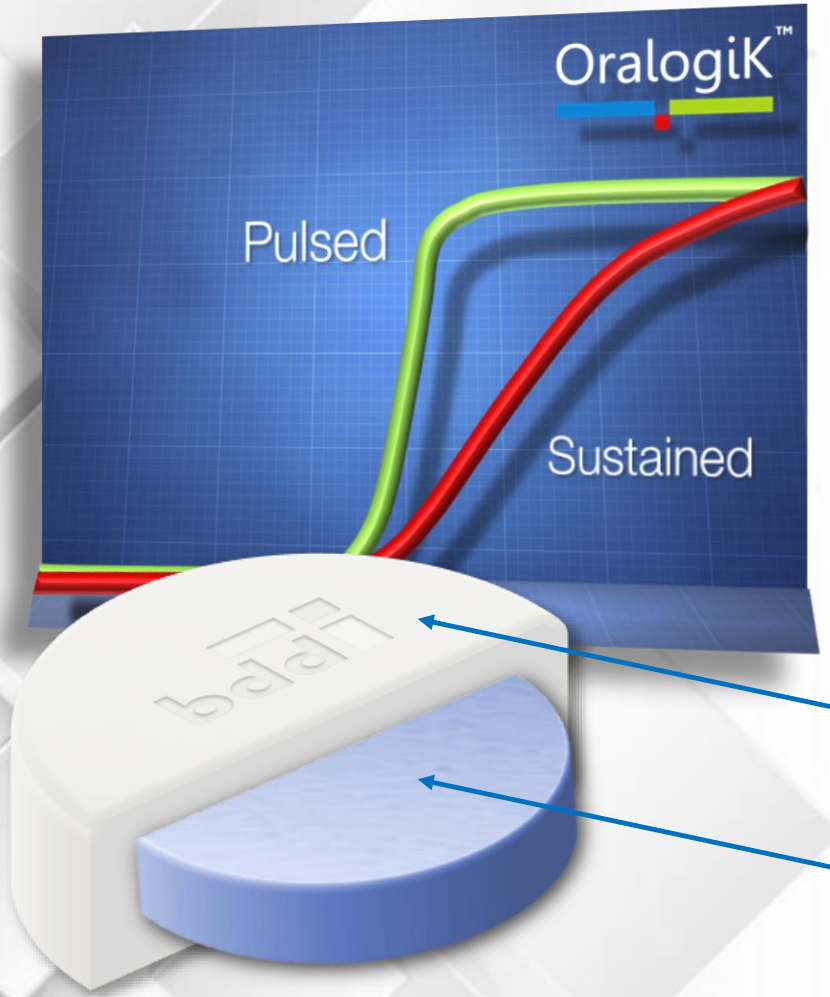
MULTIPARTICULATES

TABLETS

Rupture

Erosion





COMPLEX RELEASE WITH EROSION

Delivery of a drug at pre-determined times after dosing

Erodible compression coating that erodes independently of pH, agitation and foodstuffs (fat)

Core tablet containing drug substance

CONTROL OF EROSION

- The erosion layer is composed of a combination of wax and disintegration agent, selected to achieve refined control of erosion rate.

- Erosion is controlled by

  - nature of the wax and disintegrant
  - ratio of the wax to disintegrant
  - processing of wax and disintegrant
  - thickness of the erodible layer

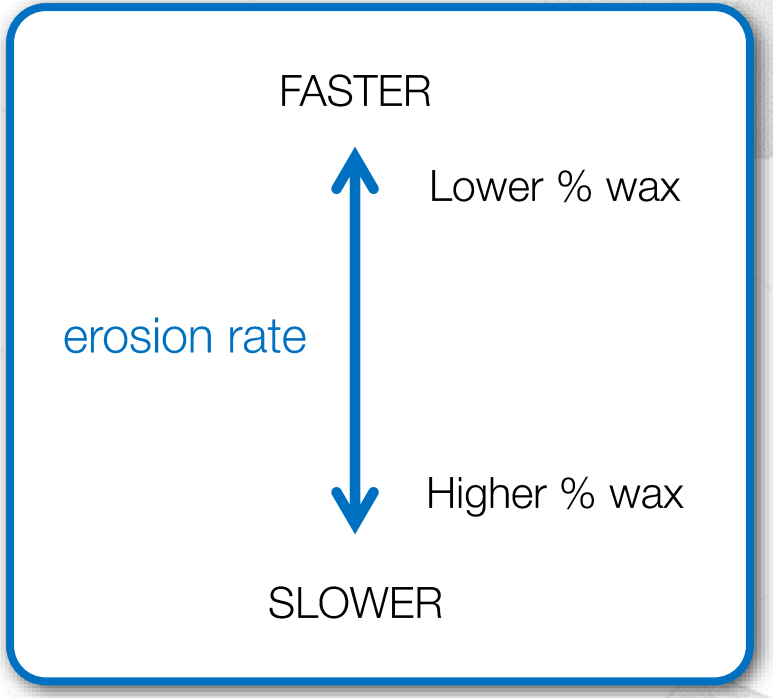
EROSION RATE

eg.

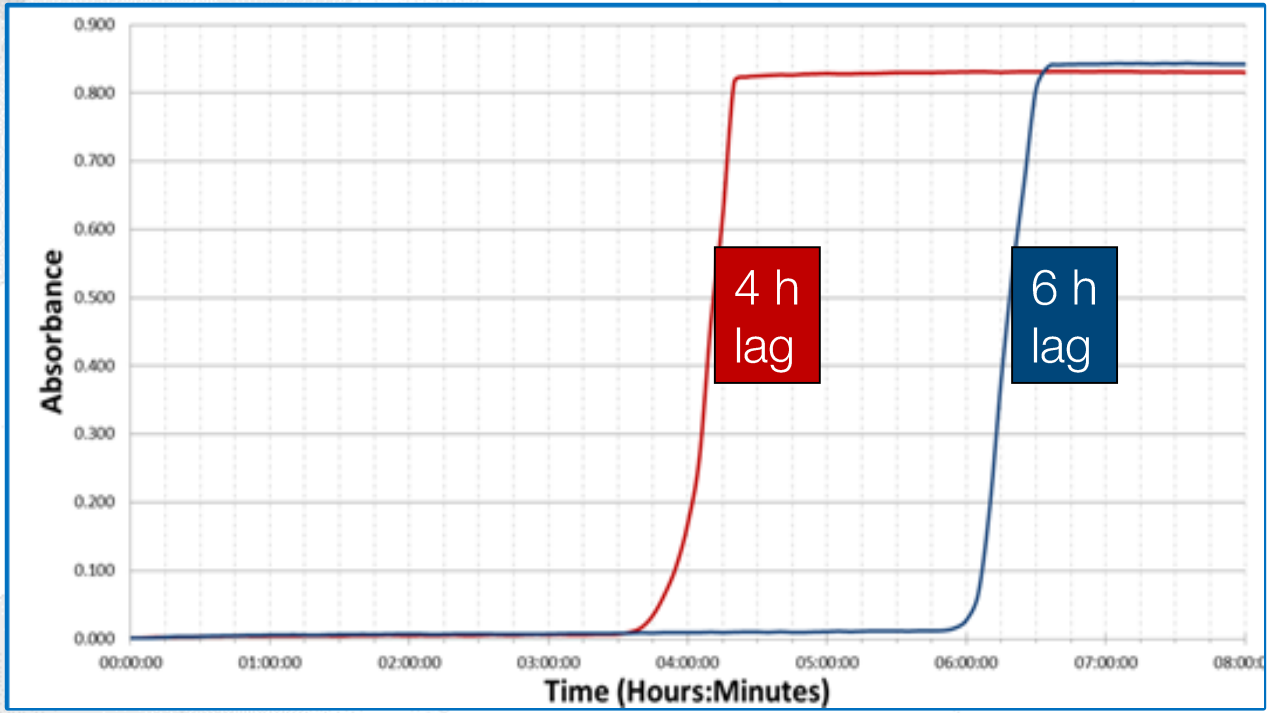
Wax

+

Disintegrant



IN-VITRO DISSOLUTION



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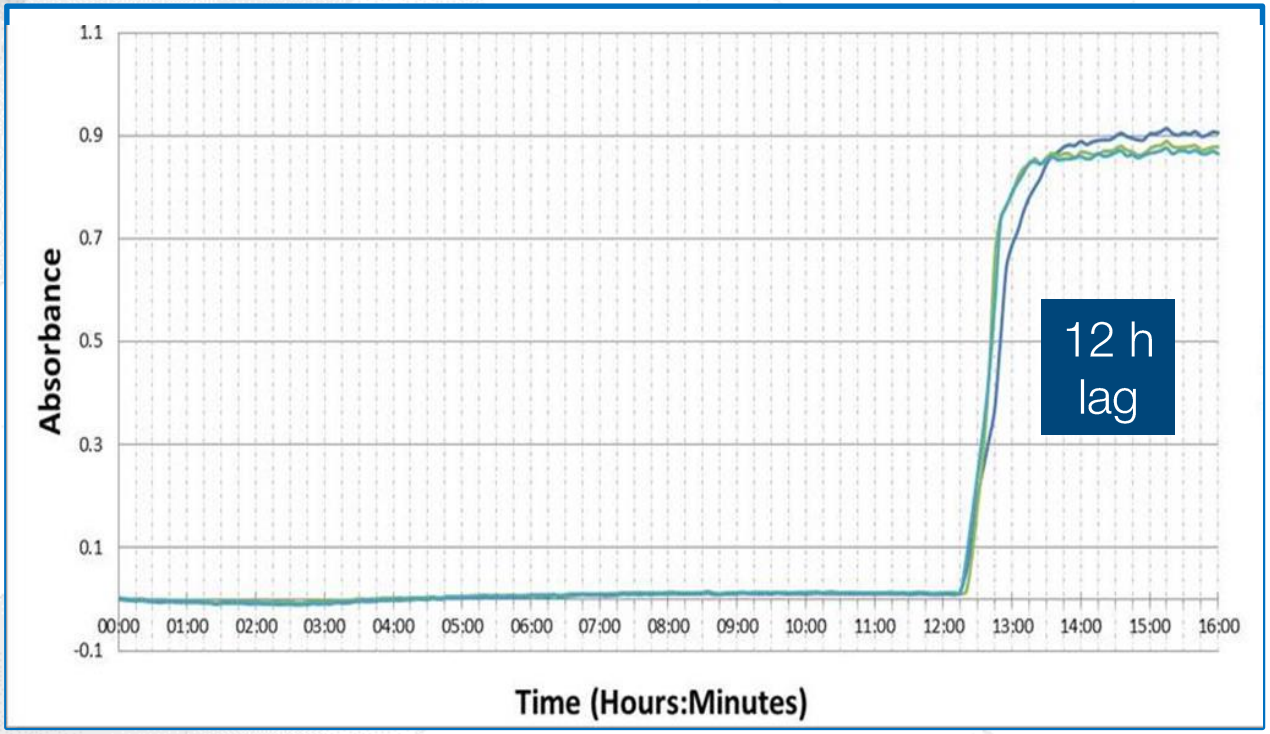
EFFECT OF BARRIER LAYER THICKNESS

LAYER THICKNESS →

IN-VITRO DISSOLUTION



4 h lag → (wax content) → 12 h lag

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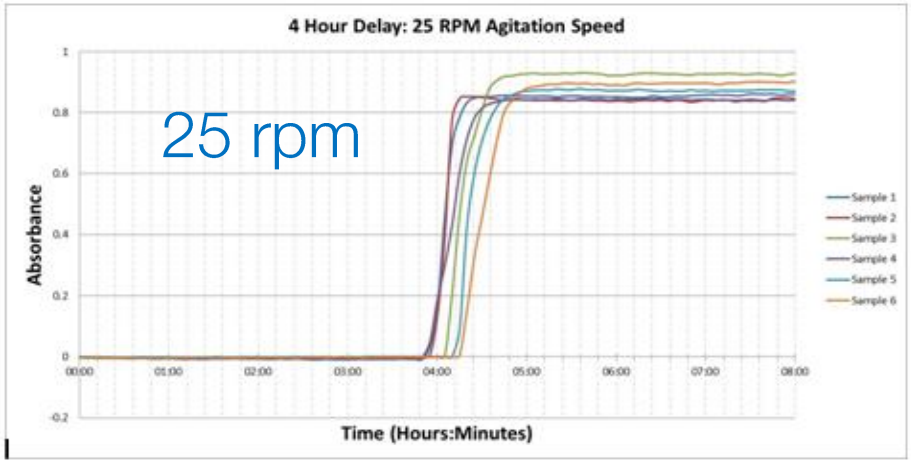
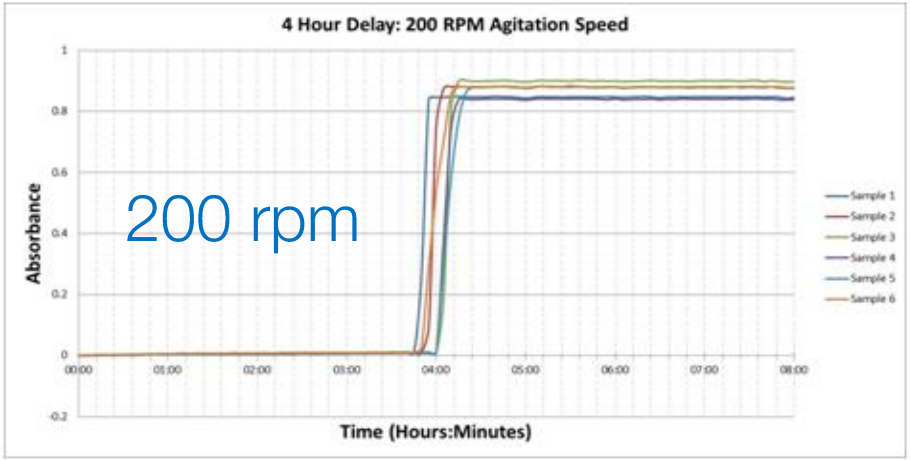
EFFECT OF INCREASING WAX CONTENT





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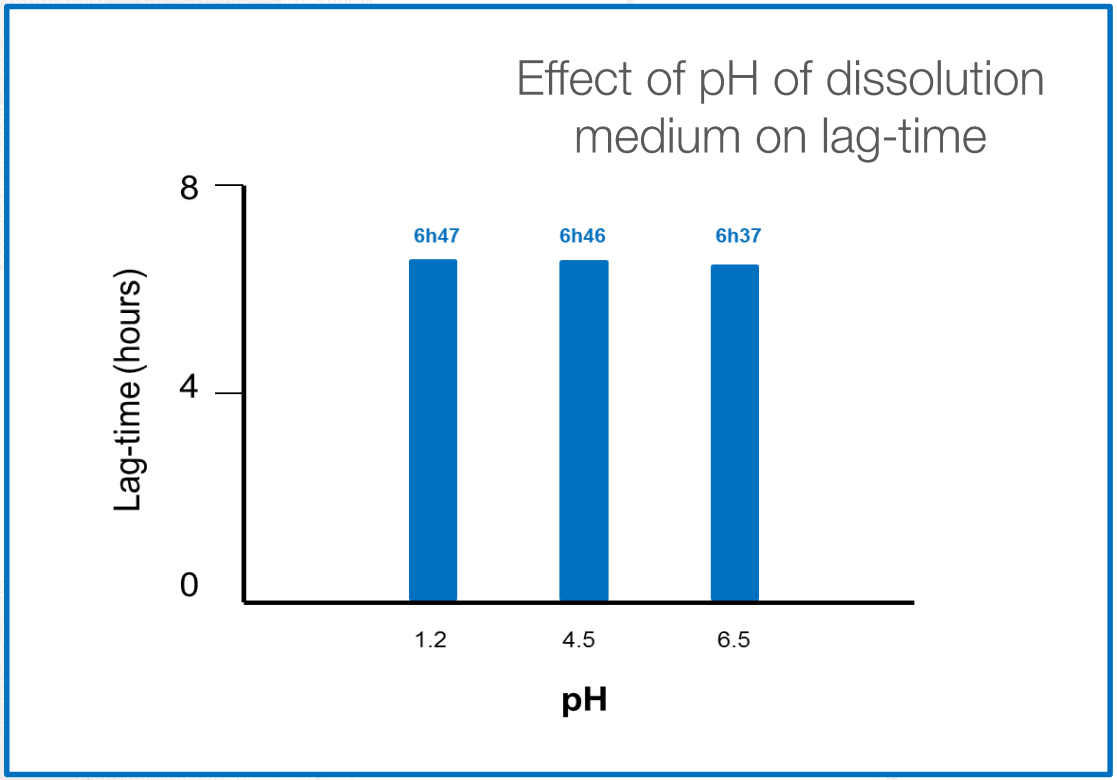
NO EFFECT OF VARYING PADDLE SPEED



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UNAFFECTED BY pH

COMPARISON OF CONTROLLED TABLET EROSION AND MICROPARTICULATES

MULTI-PARTICULATE SYSTEMS

- Low Drug Loading
- pH Dependant
- Diffusion - Agitation Dependent
- Solvent used in production

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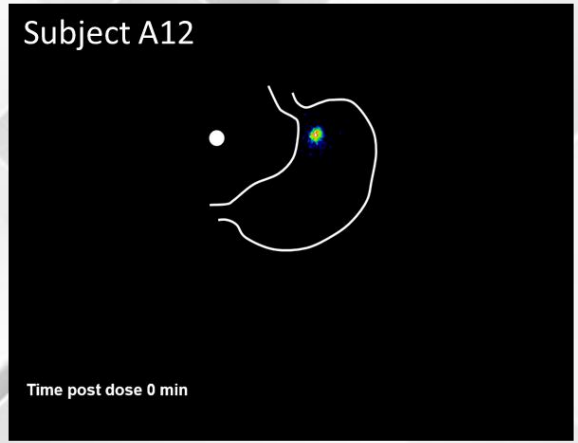
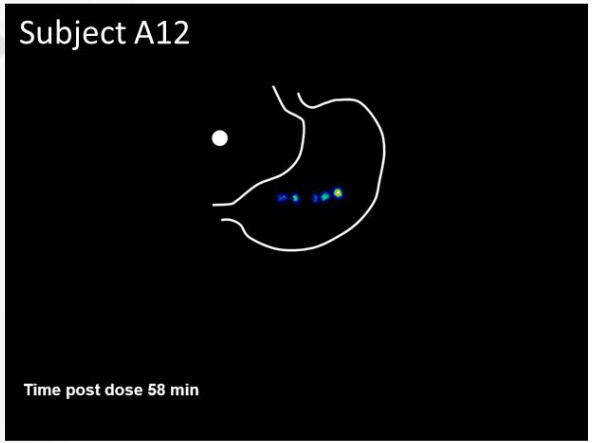
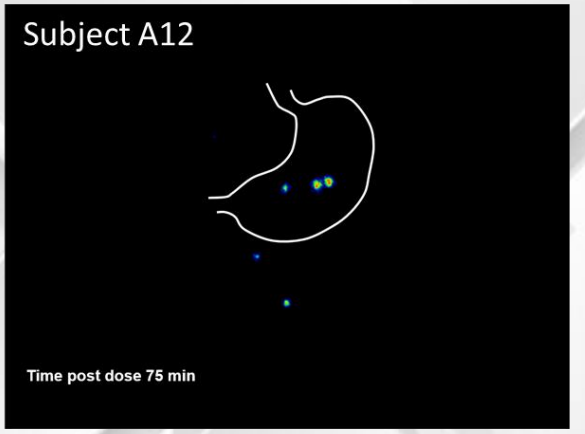
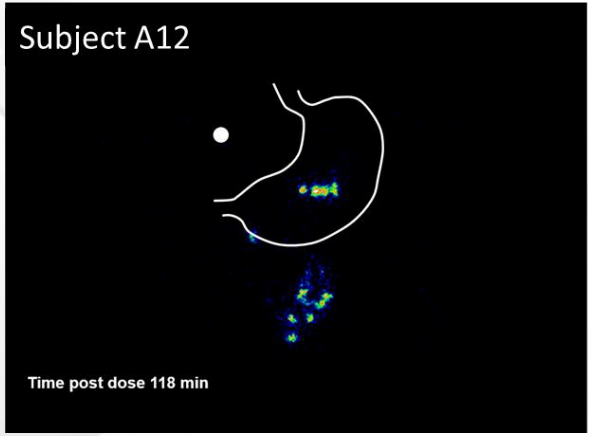
- Higher Drug Loading
- pH Independent
- Erosion - Agitation Independent
- Solvent Free









GASTRIC EMPTYING OF MULTIPARTICULATES

Capsule containing microtablets of which 10 were radiolabelled

- Gastric emptying of pellets is phased
- Potential pharmacokinetic consequences

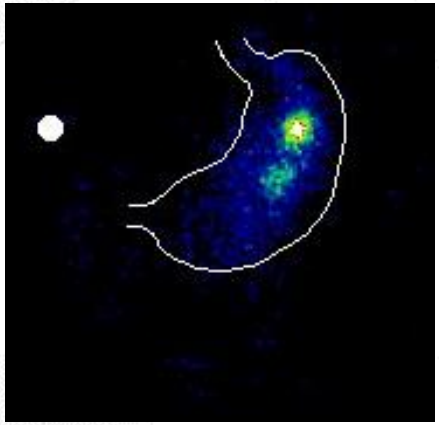
C_{max} ↓

BDD Scintigraphy

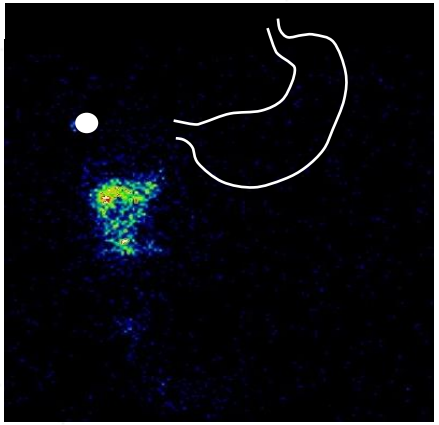
VISUALISING COMPLEX RELEASE IN VIVO

WHAT IS GAMMA SCINTIGRAPHIC IMAGING

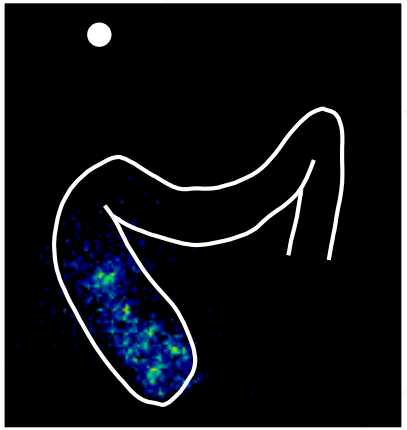
Adding ^{99m}Tc radiolabel enables gamma scintigraphy to follow the *in-vivo* fate of a formulation



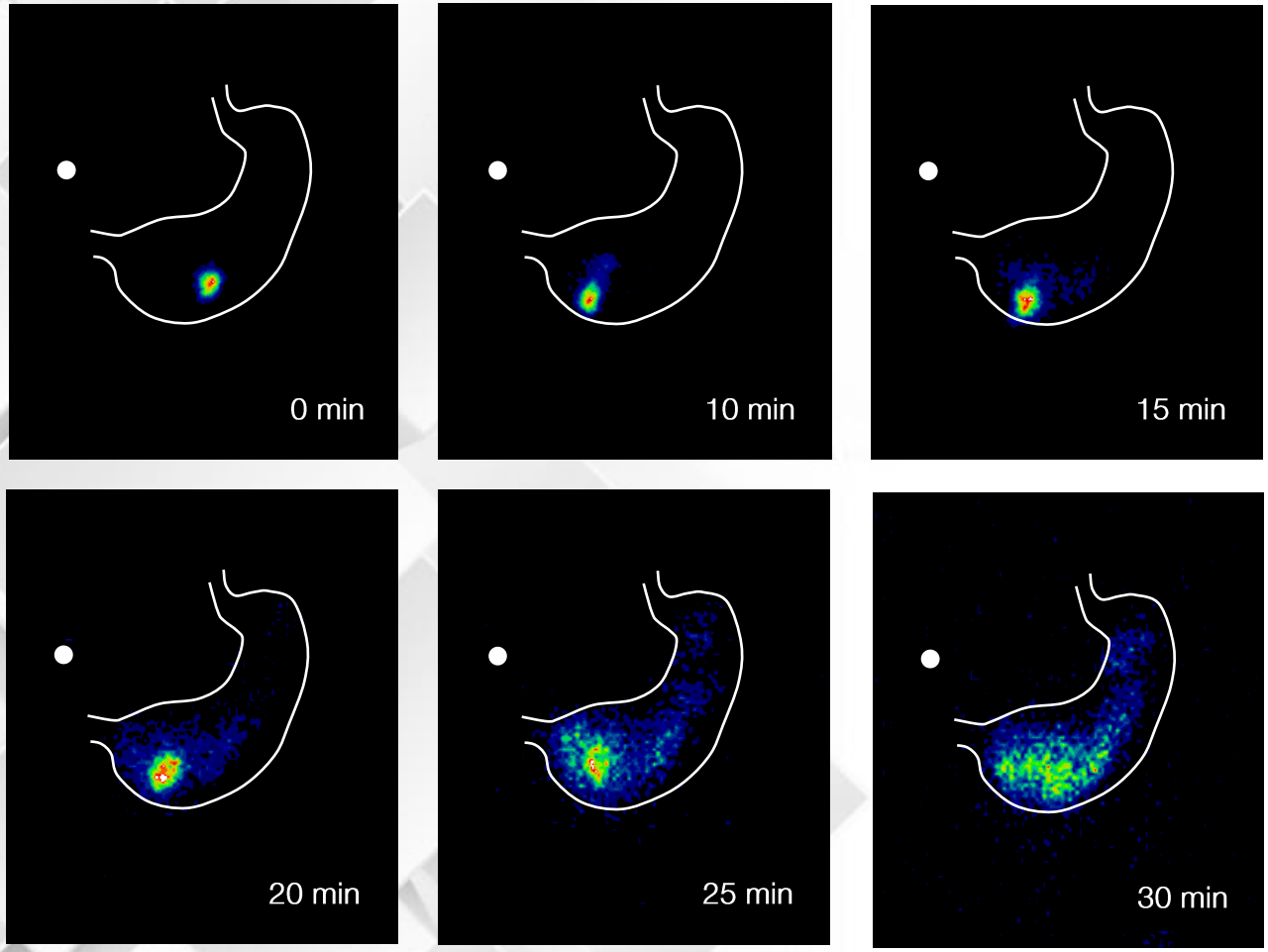
Disintegration in stomach



Disintegration in small intestine



Disintegration in colon

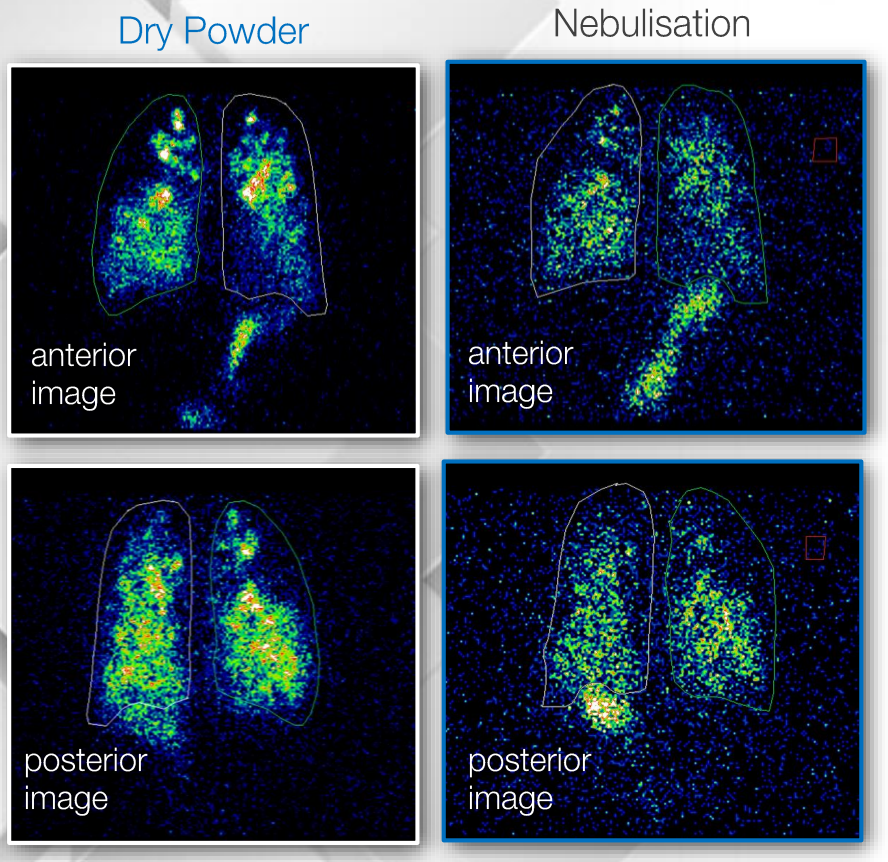


VISUALISATION OF EROSION IN-VIVO

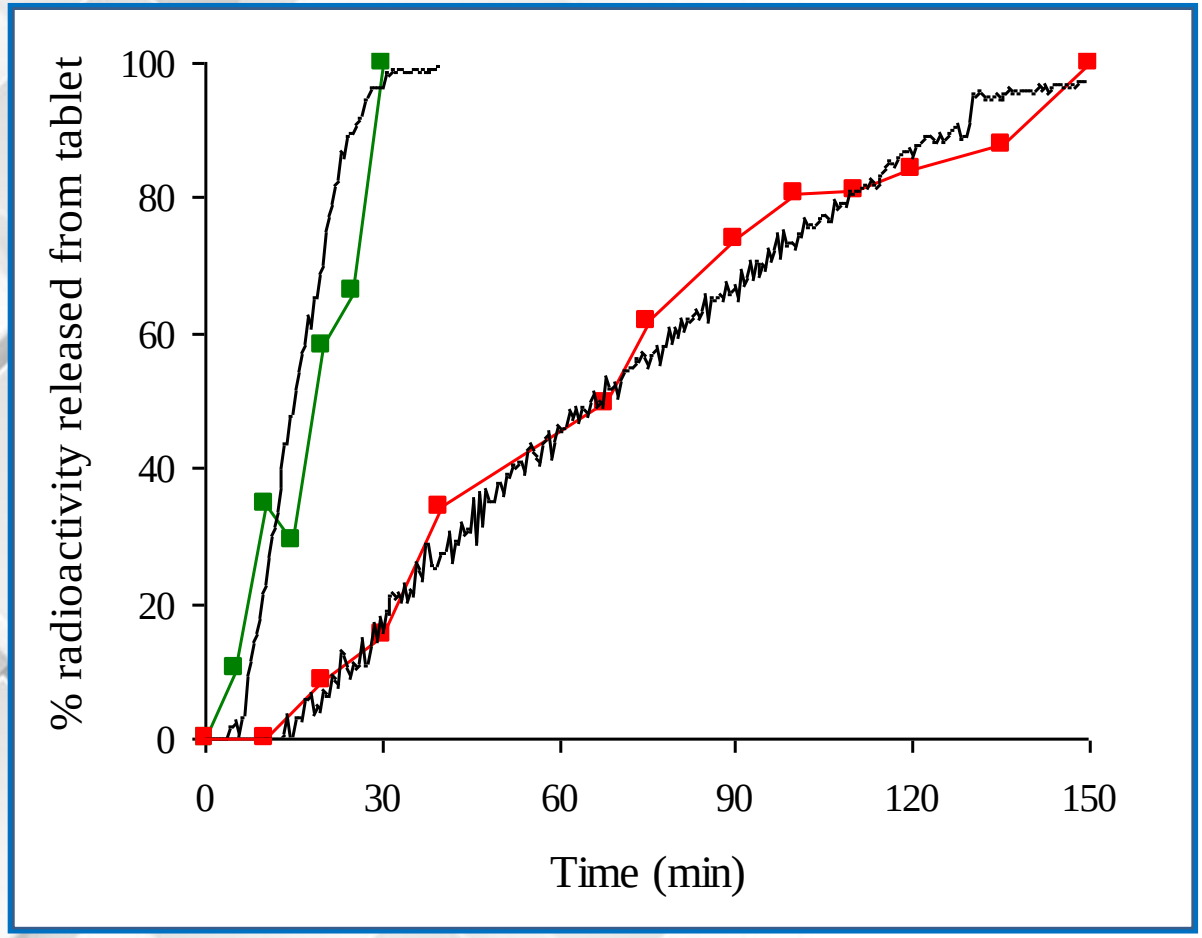
In-vivo erosion kinetics determined using gamma-scintigraphy

IMAGING THE LUNG

Showing



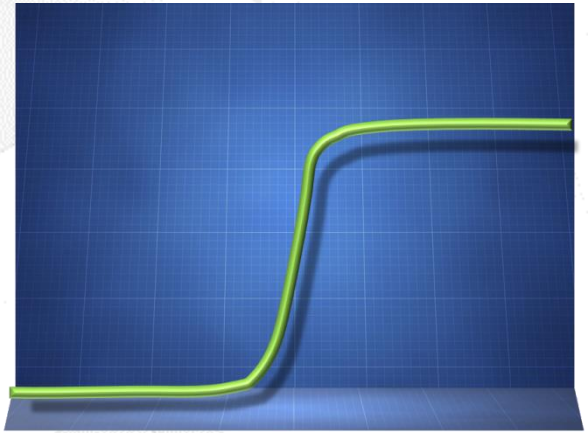
- The performance of devices
- Residence time in the lung
- Lung deposition patterns



QUANTIFICATION OF EROSION BEHAVIOUR IN MAN

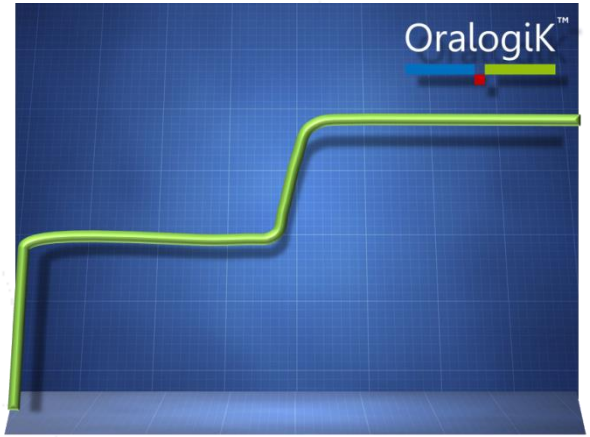
In-vitro / in-vivo correlation

EARLY PROOF OF CONCEPT STUDIES



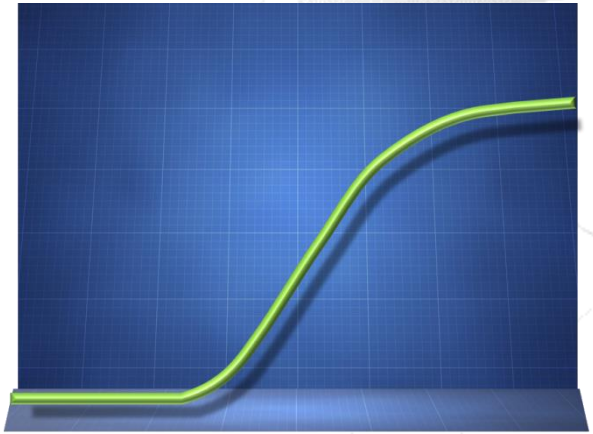
DELAY + PULSE

e.g. Timed delivery of zolpidem for sleep maintenance



IR + DELAY + PULSE

e.g. Conversion of 2x to once-a-day diclofenac treatments



DELAY + SR

e.g. Night-time verapamil for circadian cardiovascular event

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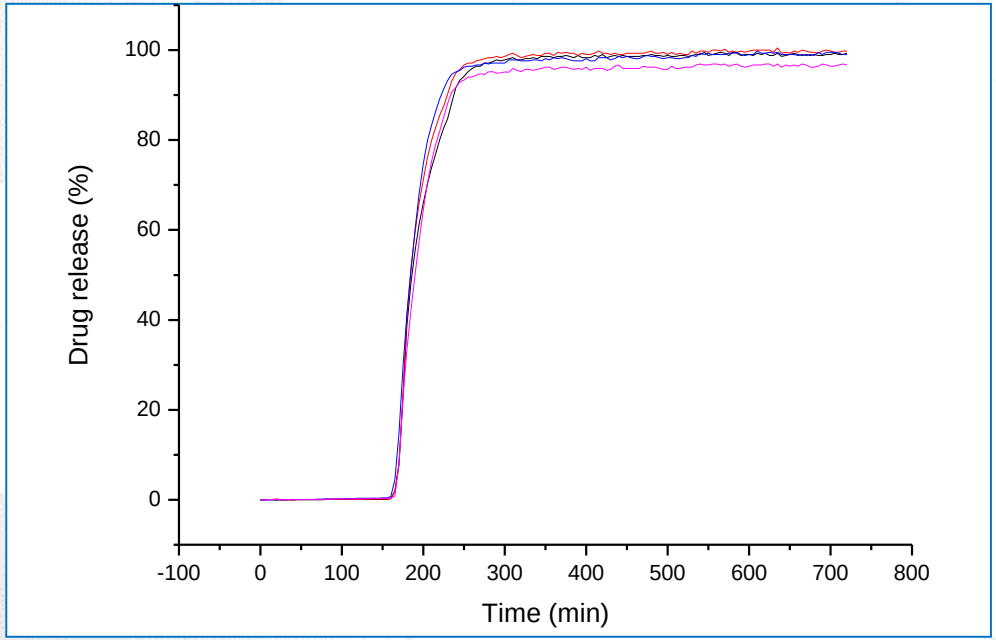
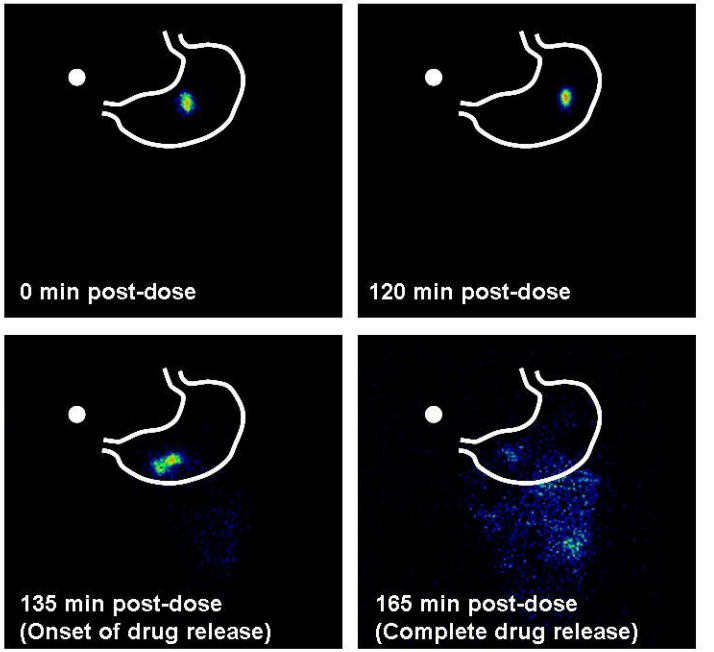
2 HR DELAYED RELEASE OF ZOLPIDEM FOR SLEEP MAINTENANCE



In-vitro dissolution



In-vivo release

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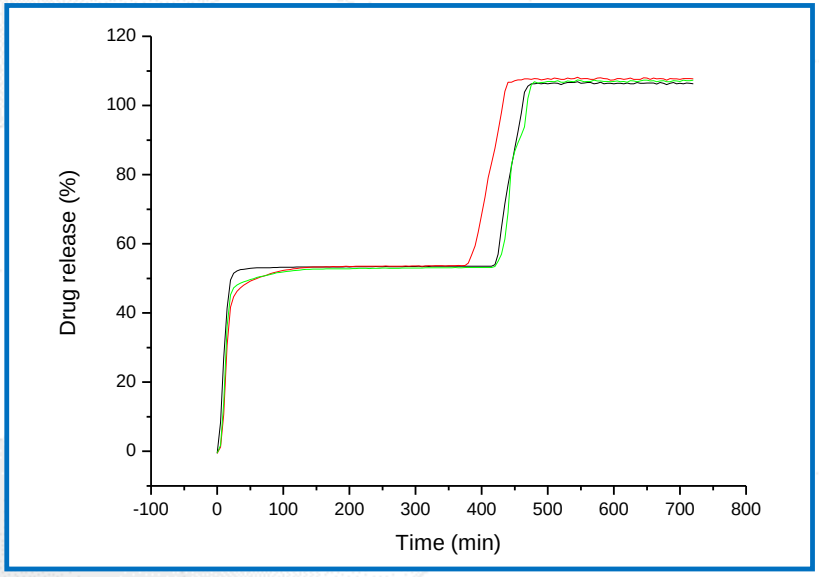
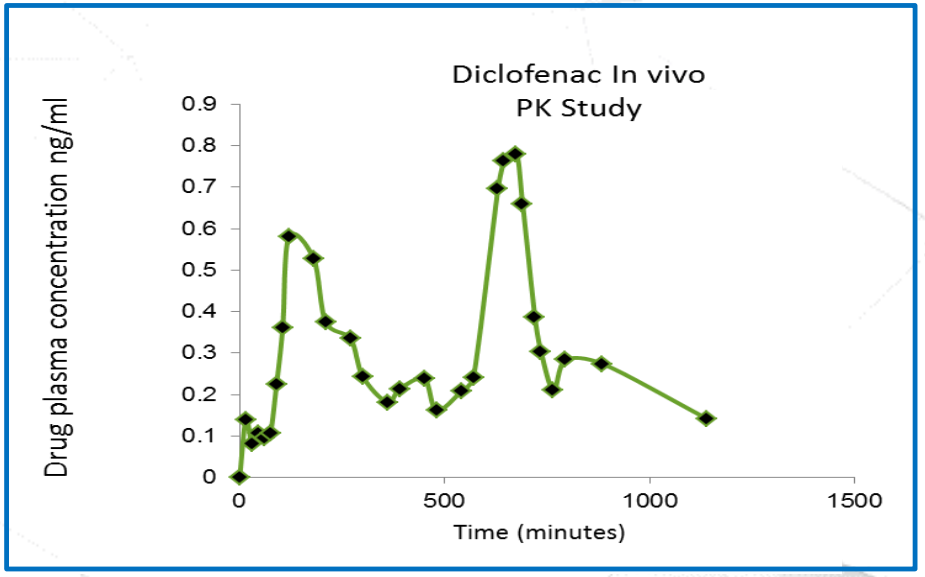
IMMEDIATE AND DELAYED RELEASE OF DICLOFENAC



In-vitro dissolution



Drug plasma profiles in man

OralogiK™ PATENTS

- 3 patents filed 2010
  (granted in USA, EU and in Japan)
- 3 additional patents filed 2014
  (in examination)
- Further filings planned for 2018

Elizabeth

bdd

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INDUSTRIAL PROCESS DEVELOPMENT

Core Tablet

- Conventional tablet compression technology

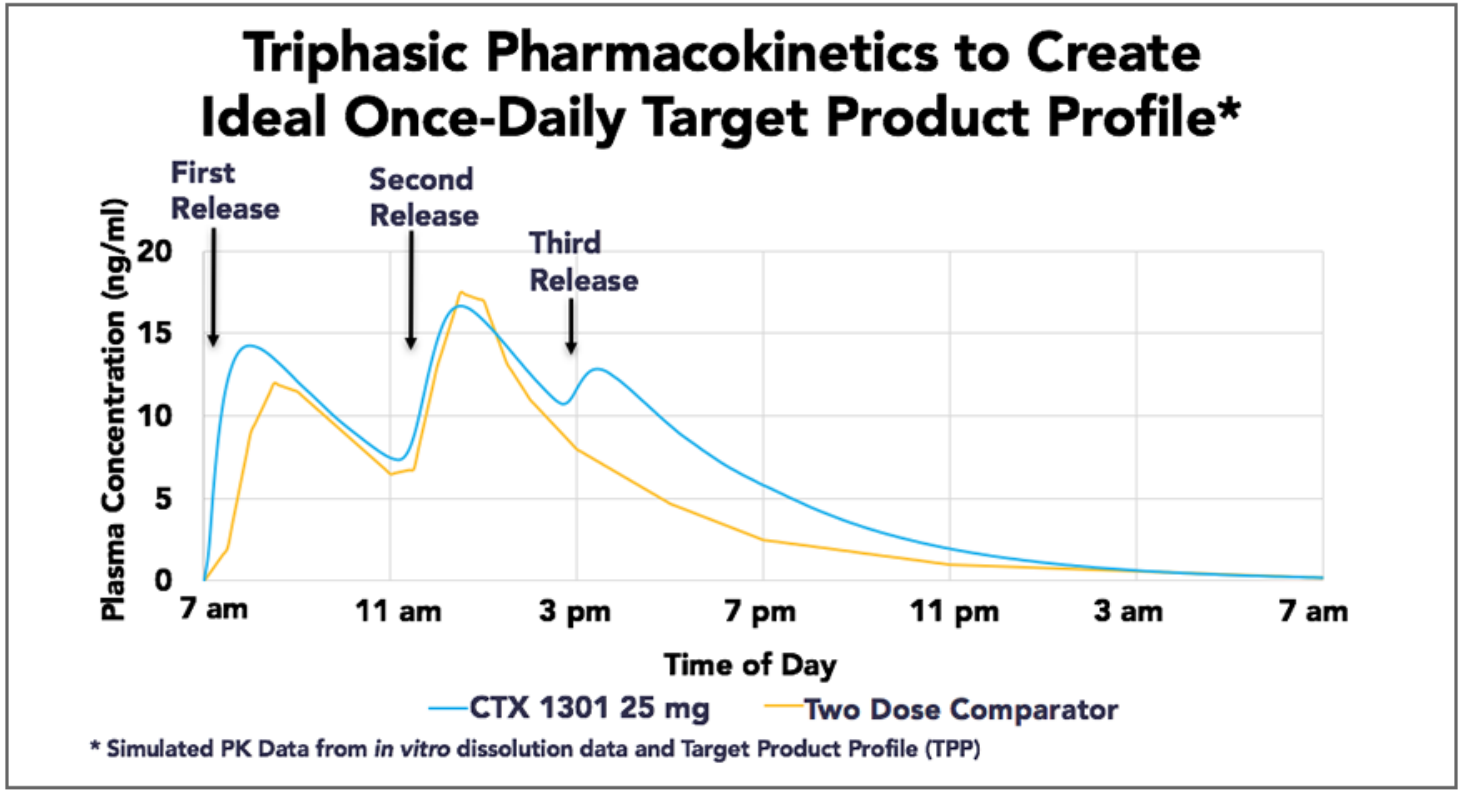
Barrier Layer

- HME to prepare mix of wax + disintegrant

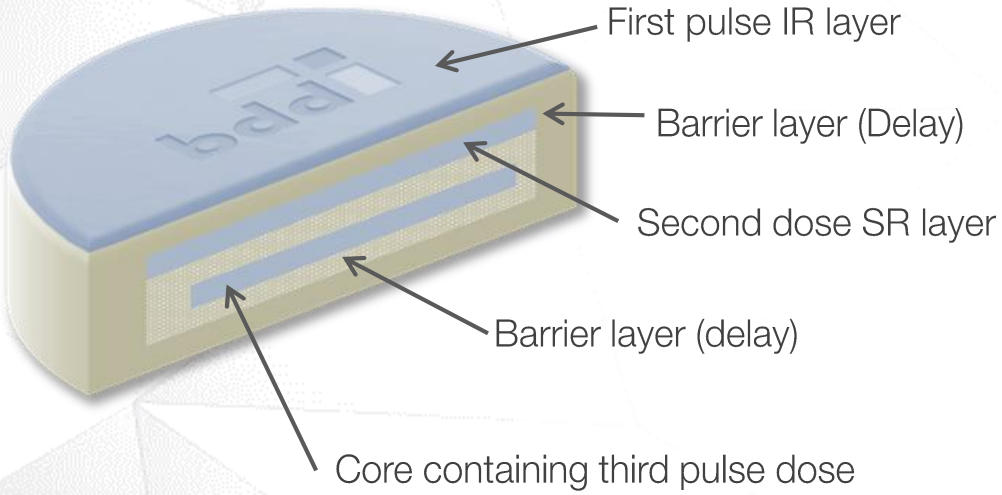
Tablet-in-Tablet

- Conventional Tab-in-Tab compression technology

- Barrier Layer has been successfully scaled up to 60Kg -

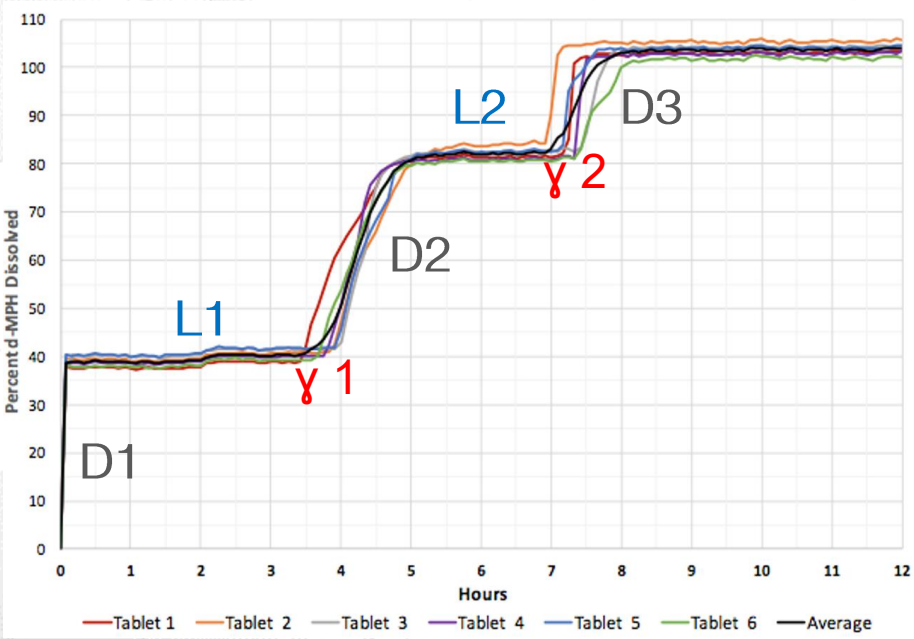

Triphasic Pharmacokinetics to Create
Ideal Once-Daily Target Product Profile*
First Release
Second Release
Third Release
Plasma Concentration (ng/ml)
20
15
10
5
0
7 am
11 am
3 pm
7 pm
11 pm
3 am
7 am
Time of Day
CTX 1301 25 mg
Two Dose Comparator
* Simulated PK Data from in vitro dissolution data and Target Product Profile (TPP)

OralogiK™ TRI-PHASIC RELEASE



Combined immediate, sustained and delayed release

OralogiK™ TRI-PHASIC RELEASE



3 drug doses D1 D2 D3

2 lag periods L1 L2

2 sites with scintigraphic radiolabel ɣ 1 ɣ 2

15 subject, 3-way crossover clinical study

- Arm 1 Focalin XR (reference multiparticulate)
- Arm 2 ɣ 1 OralogiK™ tablet
- Arm 3 ɣ 2 OralogiK™ tablet

CINGULATE™ THERAPEUTICS CTx-1301 triple-pulse dexmethylphenidate

OralogiK™ TRI-PHASIC RELEASE

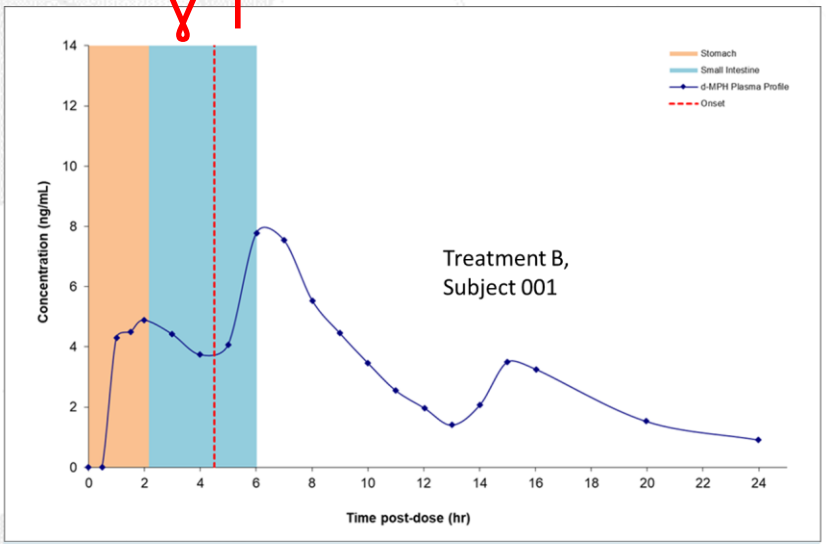


Figure 1. **Composite of Treatment B, Subject 001 12.5-mg CTx-1301 d-MPH drug plasma profile with identification of the time/point of radiolabel release from the Second Release Layer**

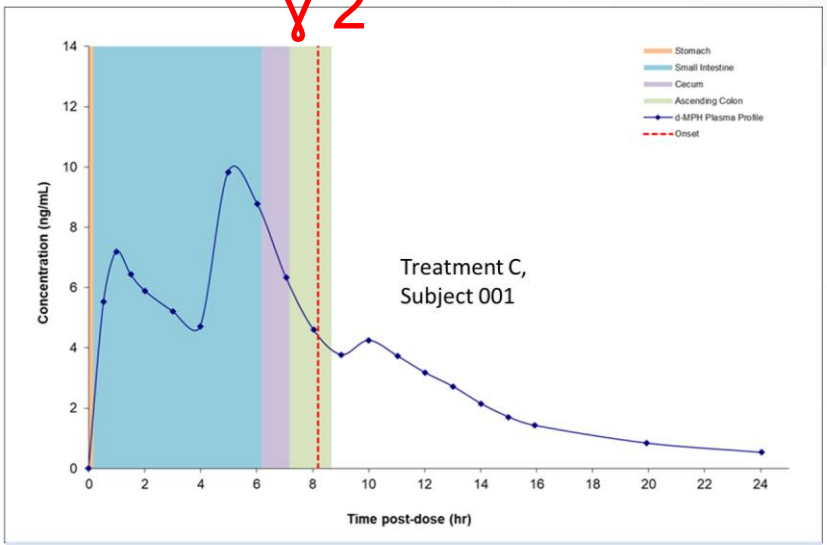
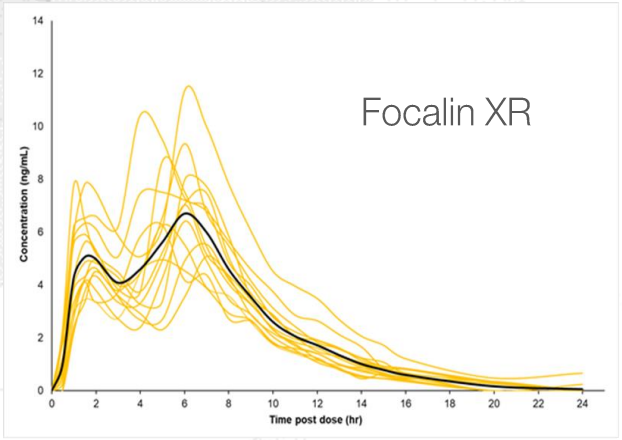
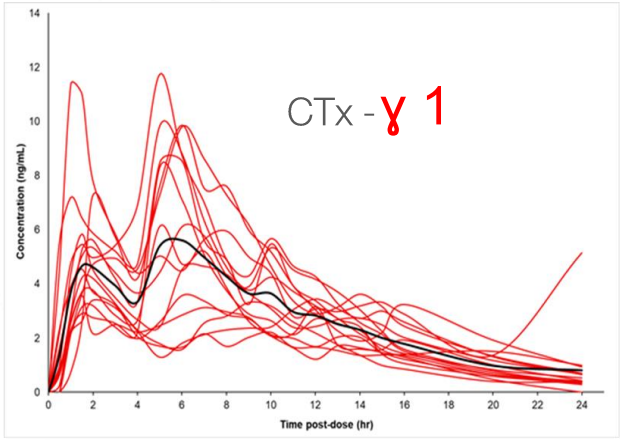
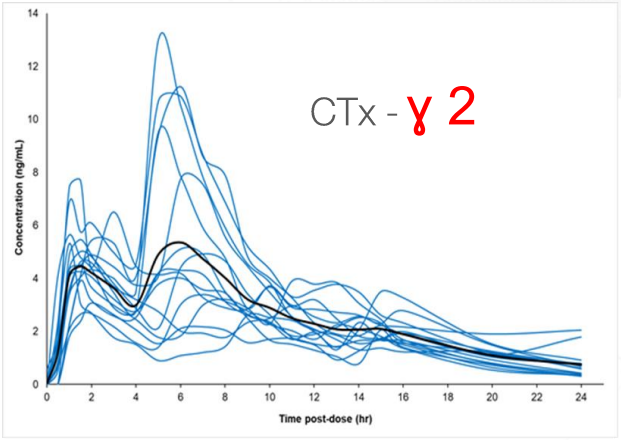


Figure 2. **Composite of Treatment C, Subject 001 12.5-mg CTx-1301 d-MPH drug plasma profile with identification of the time/point of radiolabel release from the DR2 layer**

OralogiK™ TRI-PHASIC RELEASE







OralogiK™ technology successfully delivered a triple dose of dMPH. Release from the 2nd and 3rd peaks resulted in prolonged therapeutic drug levels between 8-24 hours post-dose compared to Focalin XR, confirming that the OralogiK™ based CTx-1301 tablet offers a clinically relevant new treatment option for ADHD patients.

CONCLUSIONS

- Understanding erosion mechanisms in the GI tract enables the design of novel complex oral drug delivery profiles.
- Incorporating delay periods into drug release provides opportunities for design of complex bi- and tri-phasic release profiles from a single tablet.
- Such profiles permit opportunities for unique combinations of drugs released at different time points

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