How-to Use Oral Drug Delivery Technology Innovatively

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Agenda

01 Company Highlights

02 Technology Platform

03 Pulsatile Release and Multiparticulates

04 Possible Applications

05 Developing Patient Centric Medicines

06 Case Studies

07 Summary & Remarks
One of only a handful of global, turnkey, high-quality specialty CDMOs

- Global focus and reach
- Quality track record
- Manufacturing capabilities
- Pharmaceutical development
  - Clinical
  - Regulatory affairs
- Global R&D
- Marketed product experience
- Intellectual property
  - >300 patents
Proven track record
Over 40 products with blue-chip partners in more than 100 countries

Human / Veterinary – Prescription / Over-the-Counter – Adult / Pediatric

Abbott  
adcock ingram  
Bayer  
Allergan  
Bristol-Myers Squibb  
GSK  
GlaxoSmithKline  
Johnson & Johnson  
Pfizer  
Takeda  
Teva  
Sanofi

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Proven innovative technology platforms

Pharmaceutical Technologies

Right drug
Right patient
Right form

Microbiome

Our bacteria influencing our state of being
Pharmaceutical technologies
Right drug, right patient, right form

**Taste Masking and ODTs**

*To improve taste and provide alternative dosage forms*

- High dose, immediate release, and/or customized release
- Orally disintegrating tablets (ODTs), rapidly disintegrating tablets (RDTs), powder for extemporaneous suspensions, and sprinkles for ease of administration and convenience
- Effective taste masking
- Patient-friendly, ideal for those who experience difficulty swallowing regular capsules and tablets

**Customized Drug Release**

*To optimize therapeutic performance*

- Customized drug release profiles to optimize efficacy, safety, and dosing frequency
- Drug formulations exhibiting unique release profiles can be combined in a single dosage form

**Bioavailability Enhancement**

*To improve solubility*

- Enables the development of viable formulations of drugs with limited solubility
- Solid solutions, hot-melt extrusion (HME), and spray-drying capabilities also available
Pulsatile Release

Pulsatile release dosage form\(^1\)

A pulsatile release dosage form is a modified-release dosage form showing a **sequential release of the active substance(s)**. Sequential release is **achieved by a special formulation design and/or manufacturing method.**

\(^1\) European pharmacopoeia. 9th ed. Strasbourg Council of Europe; 2016.

Multiparticulate - Flexibility and Improved Safety

• Dose is divided in multiple units ensuring better distribution on the mucosa with lower risk of local irritation

• Reproducible pharmacokinetic, being GI transit time less dependent on gastric emptying

• Minimizes the risk of “dose dumping” for modified release systems,

• Easier titration of a broader range of dosages,

• Possibility to develop multiple strength products using the same formulation

• Opportunity to facilitate development programs based on dose proportionality
Multiparticulate - Precise Dosing and Improved Compliance

- Different APIs or same APIs with different dissolution profiles can be combined in the final dosage form.

- Can be combined with a measuring/dispensing device to facilitate administration and/or adjust the dose based on dosage directions (weight/age).

- Can be formulated as a direct dose sachet or ODT to further improve patient compliance, make it easier to swallow, and support oral administration without need for liquid.

- Multiparticulates can be used as a "sprinkle" formulation.
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Possible Applications

Pulsatile Drug Delivery

Colonic Absorption  Challenge Generics  Fast Onset and Termination  Address Tolerance  BID and TID Mimicking  Site Specific Delivery  Chronotherapy  Timed Deliver Multiple Actives
Real Case Applications

![Simulated plasma profiles and Impact on SKAMP SKAMP Deportment Index graphs]


Source: [https://hznp.azureedge.net/](https://hznp.azureedge.net/), Vimovo Full Prescribing Information PDF, Page 28; accessed 03/05/2018.
Adare’s experience: Cyclobenzaprine

- Once daily delivery of Cyclobenzaprine ER shows optimal PK profile

**Single-day PK study:**
Mean Cyclobenzaprine Concentration Over Time (N=36)

- Cyclobenzaprine ER 30mg once daily
- Cyclobenzaprine IR 10mg 3 x daily
Adare’s experience: Chronotherapy

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Traditional approach

- Trial & Error
- Use of dissolution methods developed for quality control testing
- Extensive use of in vivo testing
- Conservative quality criteria based on history more than linked to clinical performance
Quality Target Product Profile (QTPP)

Prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality

Understand PK/PD, develop predictive in vitro tools to tailor, optimize and target the in vivo performance

QTPP is the guide to establish the product design strategy and focus the development effort to the therapeutic efficacy

QTPPP - Quality Target Patient Product Profile
QTTPPP and De-risking Development... can be complex

1IVIVC: Current Perspectives on Models and Practices April 5, 2018 - AAPS Webinar Series
2Pharmaceutical Science and Clinical Pharmacology Advisory Committee, March 15, 2017
3Adapted from Suarez, S – Strategies for developing dissolution tests methods fitted for purpose – AAPS Annual Meeting 2015
Learning Exercise

- Understanding of Clinical Pharmacology and identification of best candidate
- Listen at the Patient. Care, not only cure.
- One size does not fit all.
- Expert use of powerful, but complex, simulation and descriptive tools
- Drug is a Physico-Chemical entity, not only biologically active
- Understand and use the right Formulation Approach
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Case 1

CNS - behavioral disorder

Need Identification

- Current long acting medications only last up to 8 hours and patients need control symptoms in the early evening.
- Currently patients need to supplement their long acting medication with a short acting medication (IR supplement).
- Side-effects of insomnia and appetite suppression are impacting the quality of life of the patient.

Possible Solution

- Product that lasts up to 14 hours.
- Optimized PK profile can limit the side-effects of insomnia and appetite suppression without meaningfully reducing efficacy.
Modelling & Simulation

Case 1

Target Plasma Profiles for XXX 20 mg

Target Dissolution Profiles

Simulation of Ideal PK (target plasma profiles)

Target dissolution profiles
Formulation Approach

- Bead combinations each with a distinct release profile
- Optimize peak-to-trough ratios
- Single and combination products
- Ease of dose adjustment

Examples of Customized Release Particles/ Mini-tablets

**Case 1**

- Immediate Pulse
- Timed Sustained Release
- Timed Pulsatile Release

Images are not shown actual size.
Feasibility Prototypes and Expected Outcome

Actual Dissolution Data

- **Prototype 1 (ACT)**
- **Prototype 2 (ACT)**
- **Prototype 3 (ACT)**

Calculated Plasma Profile

- **Prototype 1 (CALC)**
- **Prototype 2 (CALC)**
- **Prototype 3 (CALC)**

Case 1

Actual dissolution profiles

Calculated plasma profiles
CNS - Sleep Disorder

Case 2

Need Identification
Medication for insomnia that provides rapid sleep induction, improved sleep maintenance and limited residual (next day) effects

Possible Solution
- Rapid sleep induction → an initial pulse to help you get to sleep (IR)
- Improved sleep maintenance through the entire night → an additional pulse/s to prevent middle-of-the night awakening (DR)
- Limited, generally tolerable residual (next day) effects → rapid elimination preserves superior side effect profile from next day sedation
A model is as good as the parameter that are fed to it
- As more data is collected the modelling will become more powerful
Conceptual Target Profile

- **Sleep Onset**
- **Sleep Maintenance**
- **No Residual Effect**

![Graph showing sleep profile with dosing and plasma levels](image)
Modelling utilized to establish target profiles meeting objectives

Potential profiles of interest identified:

- **Prototype A**: Capsule containing X mg IR + X mg DR with a 3hr lag
- **Prototype B**: Capsule containing X mg IR + X mg DR with a 2 hr lag + X mg DR with a 4 hr Lag
• Combining the different components (IR and DR) into a capsule for administration results in a prototype with a unique release profile that can be added to the PK Model to simulate the expected plasma level
Summary and Remarks

Patient Centric Medicines at Adare

01 Need Identification
Capabilities and processes for Need Scouting and identification of Product Opportunities

02 Clinical Pharmacology
Deep understanding of Clinical Pharmacology, Efficacy, Safety

03 Enabling Technologies
Access to specialized and enabling formulation technologies

04 Modelling and Simulation
Dedicated expertise and tools for M&S

05 BioPharmaceutics
Deep knowledge in Material Sciences and BioPharmaceutics

06 ClinDev - ClinOps
Integrated capabilities for Clinical Development and Operations

07 IP and Regulatory
IP and Regulatory functions fully integrated in QTPPP definition and development

08 Development Chain
Control and understanding of the entire Development Chain
THANK YOU!

Interested in knowing more about Adare’s technologies? Please visit us at Boot #15