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## **Harmonizing Medication Delivery with the Body's Natural Rhythms**

*An Important Consideration for Patient-Centric Care*



**Srini Shanmugam, Ph.D.,**  
*Executive Director,  
Pharmaceutical Sciences, Business Support, & New Technologies*  
**JULY 2023**

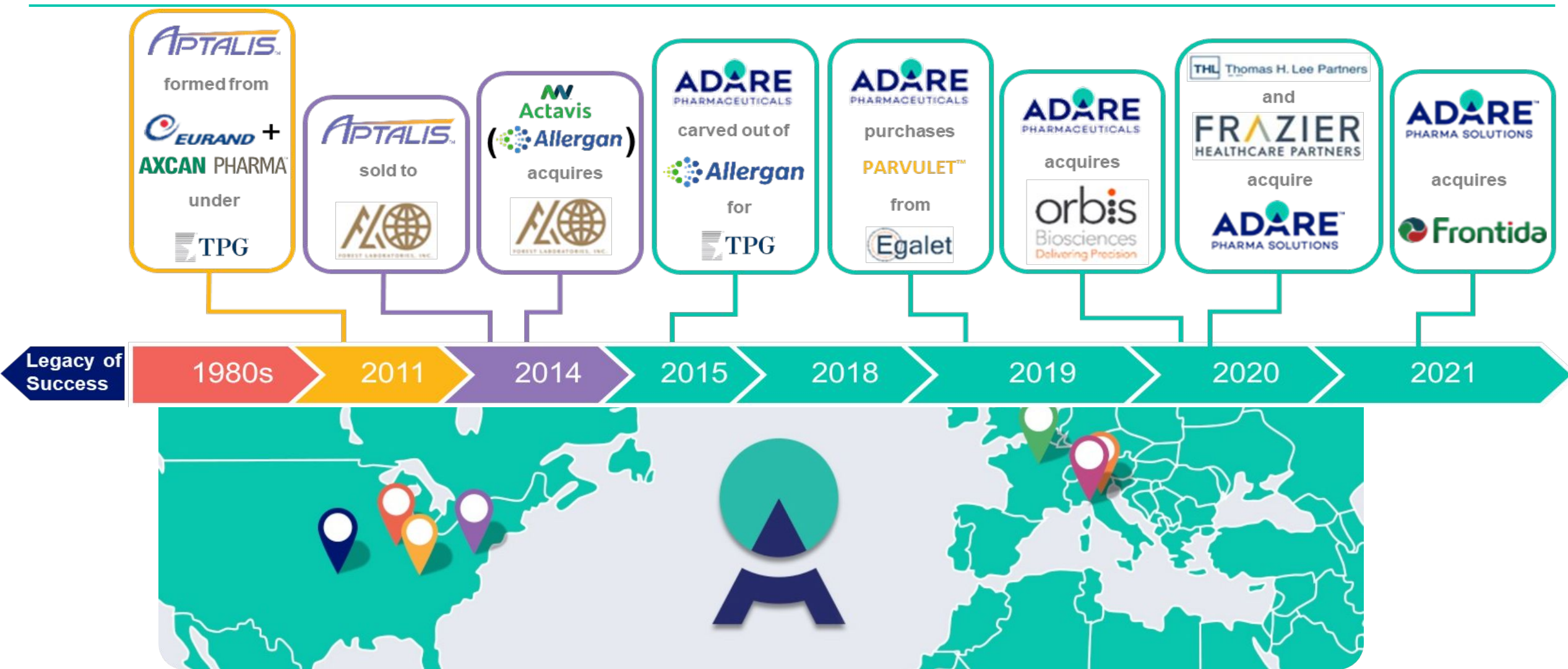


# Agenda

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- Adare – An Intro
- Patient Centric Care
- Chronotherapy & Pulsatile Delivery
- Multiparticulates for Pulsatile Delivery
- Diffucaps® - A Pulsatile System for Chronotherapy
- Case Studies
- Concluding Remarks

# Adare Pharma Solutions: Long Legacy of Success





# Impeccable Quality Record:

## REGULATORY AGENCIES INSPECTION HISTORY

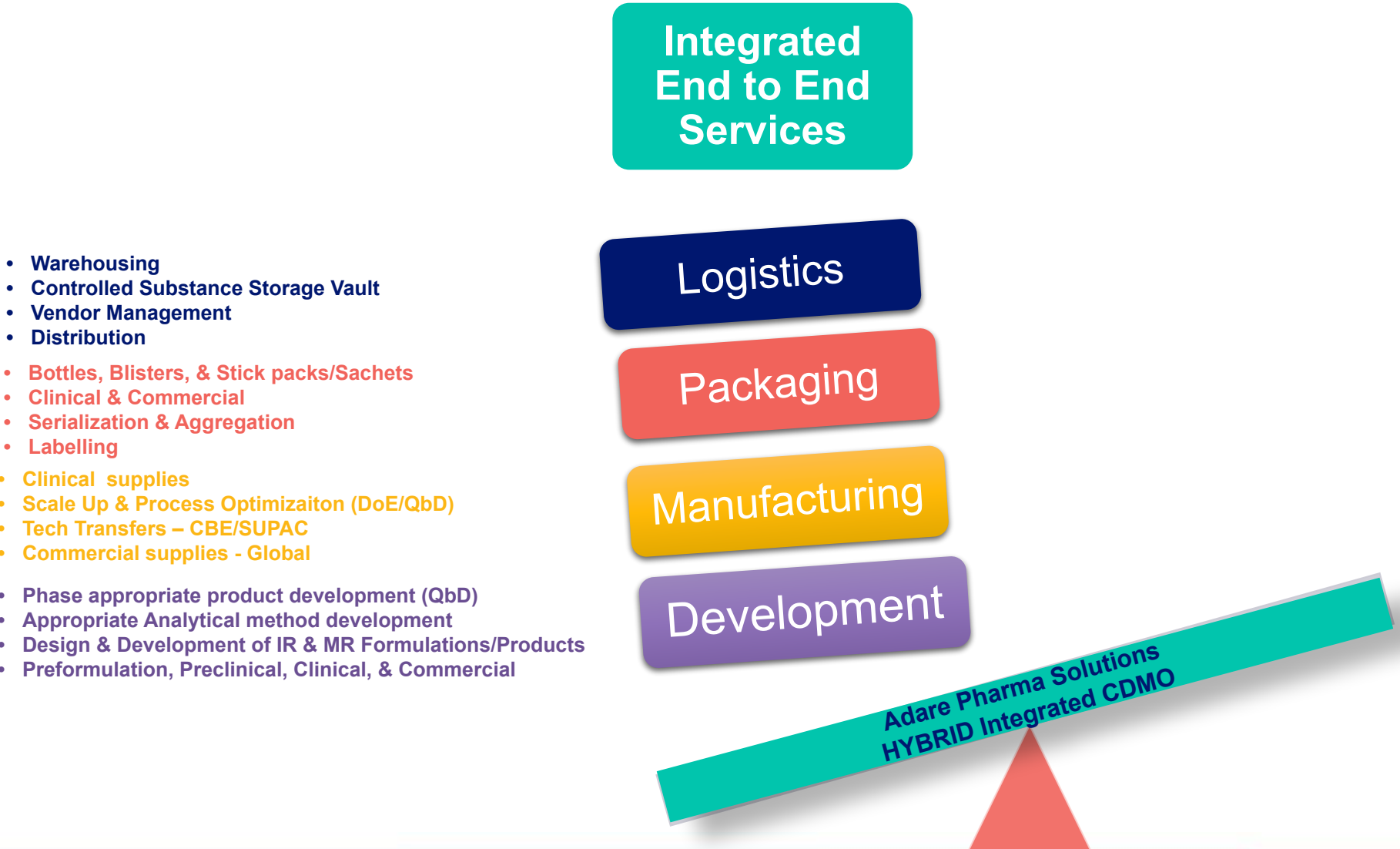
Inspection Date	Site	Authority	Inspection Type	Status
Feb-17	Pessano	FDA	General	Corrective actions accepted
Mar-17	Orthodox	FDA	General	Corrective actions accepted
Apr-17	Vandalia	FDA	General	No observations
Apr-17	San Giuliano	Italian Drug Agency (AIFA)	General	Corrective actions accepted
Jul-17	Orthodox	FDA	PAI for client product	No observations, product approved
Jul-17	Dungan	FDA	General	No observations
Apr-18	Pessano	Italian Drug Agency (AIFA)	General	Corrective actions accepted
Jul-18	Pessano	FDA	PADE	No observations
Nov-18	Pessano	Ministry of Industry and Trade of the Russian Federation	General	Corrective actions accepted
Jan-19	Vandalia	FDA	General	No observations
Jul-19	Orthodox	FDA	General	Corrective actions accepted
Nov-19	Pessano	Italian Ministry of Health	Veterinary	Corrective actions accepted
Feb-21	Aurora	FDA	General	No observations
Feb-21	Philadelphia	FDA	Virtual PAI	No observations, product approved
Nov-21	Pessano	Ministry of Industry & Trade of the Russian Federation representing the EAEU	General	Corrective actions accepted
Oct-22	Pessano	Italian Drug Agency (AIFA)	General	Corrective actions accepted

## DEA INSPECTION HISTORY

Inspection Date	Site	Authority	Status
Nov-16	Dungan & Orthodox	DEA	No Observations
Dec-16	Dungan	DEA	Corrective actions accepted
Dec-17	Orthodox	DEA	No Observations
May-18	Orthodox	DEA	No Observations
Dec-19	Orthodox	DEA	No Observations
Mar-20	Orthodox	DEA	No Observations
Jul-20	Orthodox	DEA	Inspection for Export License (Issued)
Jun-21	Vandalia	DEA	No Observations



# Customer-Centric Integrated CDMO Services & Patient-Centric Solutions



# Customer-Centric Integrated CDMO Services & Patient-Centric Solutions



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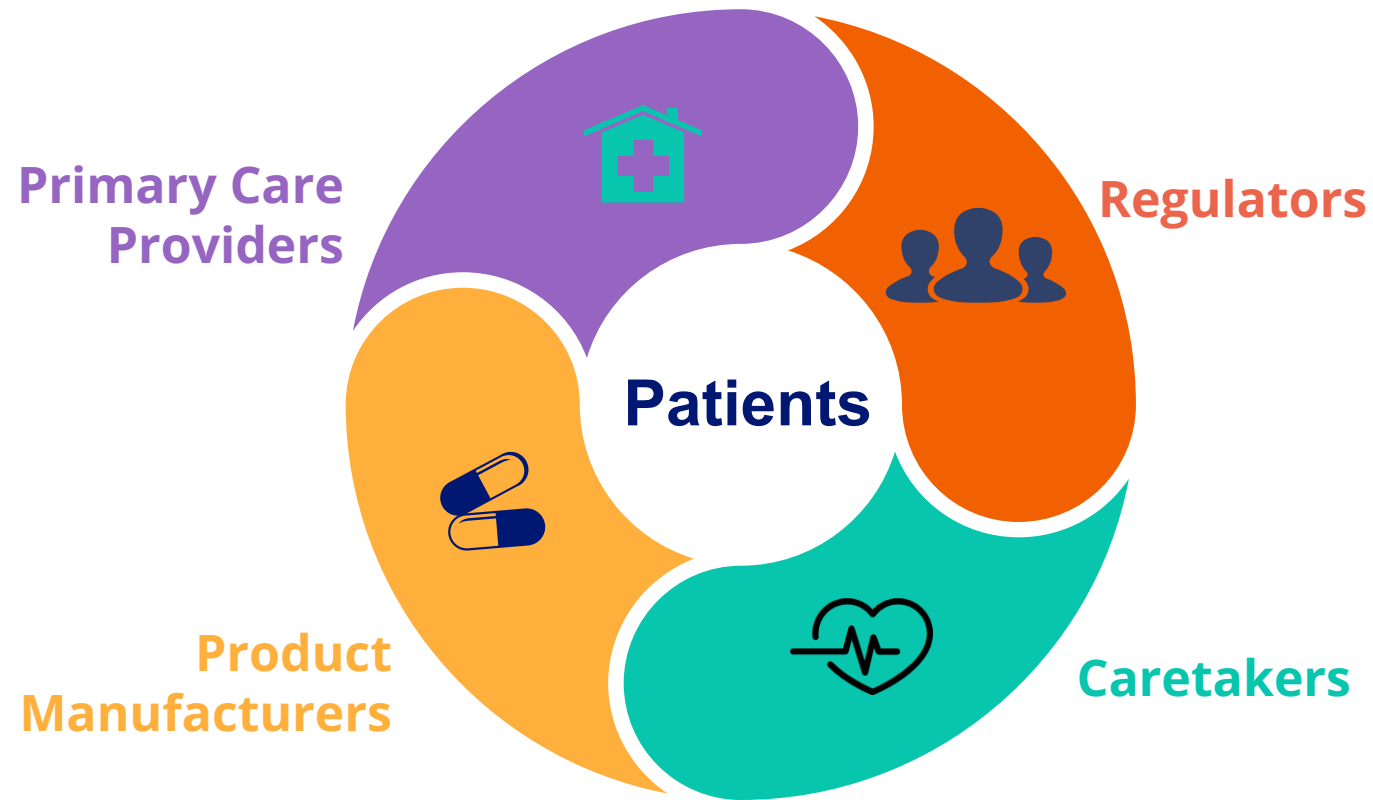
**PATIENT-CENTRIC CARE**



**ADARE<sup>TM</sup>**  
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# Patient Centric Care: Patient Centricity

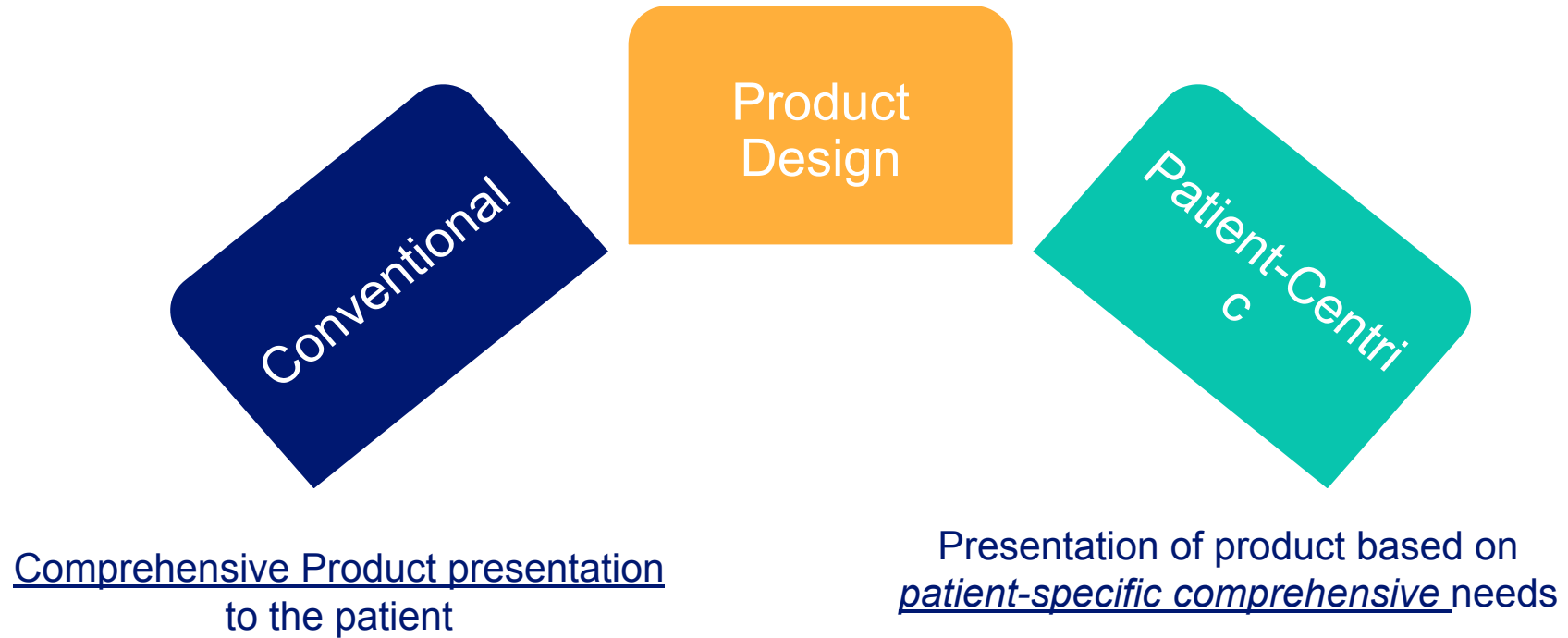
The recognition of the needs of an individual patient or distinct patient populations and their specific needs as the focal point in the overall design of a medicine including the targeted patients' physiological, physical, psychological, and social characteristics



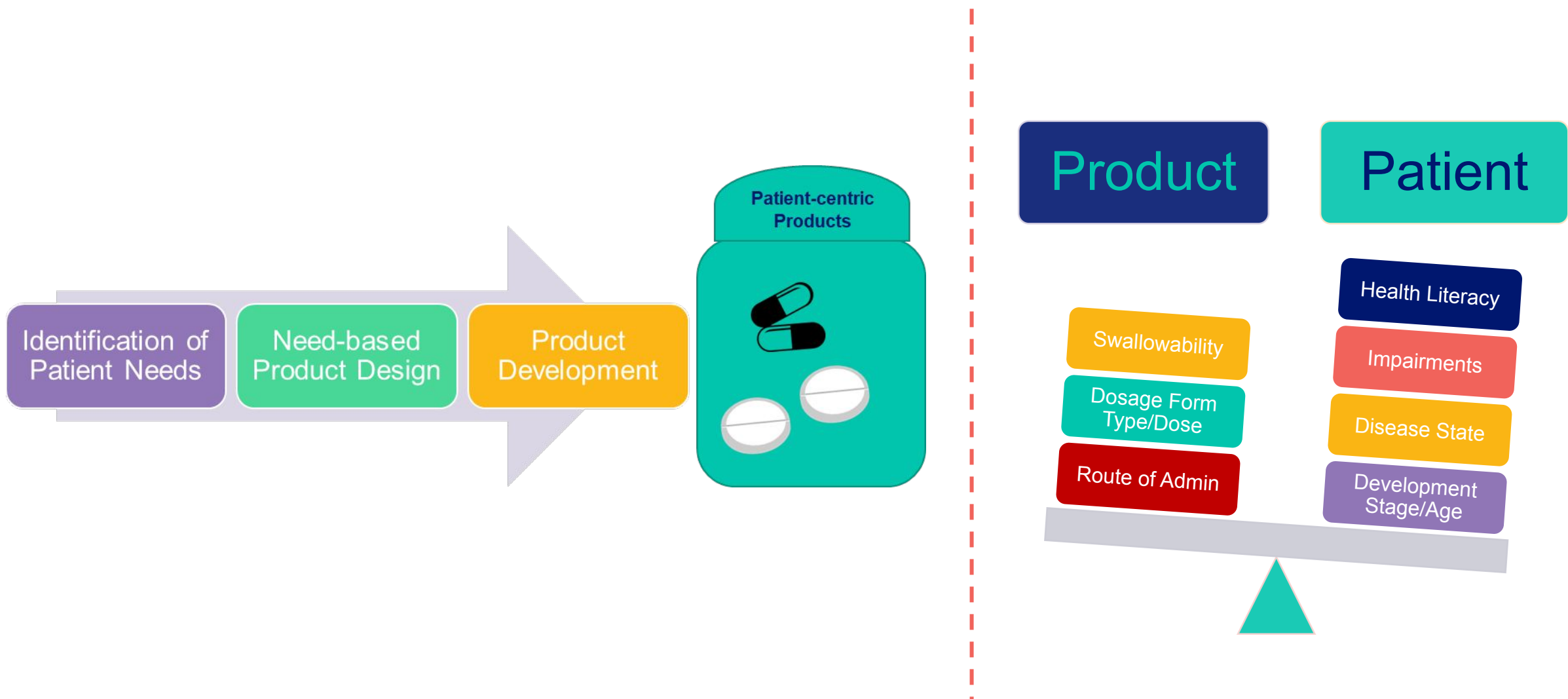


# Patient Centric Product Design:

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# Patient Centric Product Design:



# Patient Need: Harmonizing the Medication Release

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- All bodily functions follow a pattern or rhythm – organized and synchronized in time
- Similarly, many diseases exhibit exacerbations (high incidence of symptoms/events) at a particular time of day – follows a pattern or rhythm
- The need is to achieve maximum efficacy with reduced side effects and most importantly WHEN IT IS NEEDED
- Right site (WHERE NEEDED), right time (WHEN NEEDED), and right amount of drug
- Coordination or synchronization or harmonization of drug or medication release with body rhythms – **Chronotherapy**

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Body's Natural Rhythms

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# Body's Natural Rhythms

- Appetite
- Sleep Phases
- Pulse/Heart rate
- Hormonal secretions

Ultradian

>1 cycle  
per 24  
hr

- Sleep/Wake Cycle
- Acid secretion
- Blood pressure

Circadian

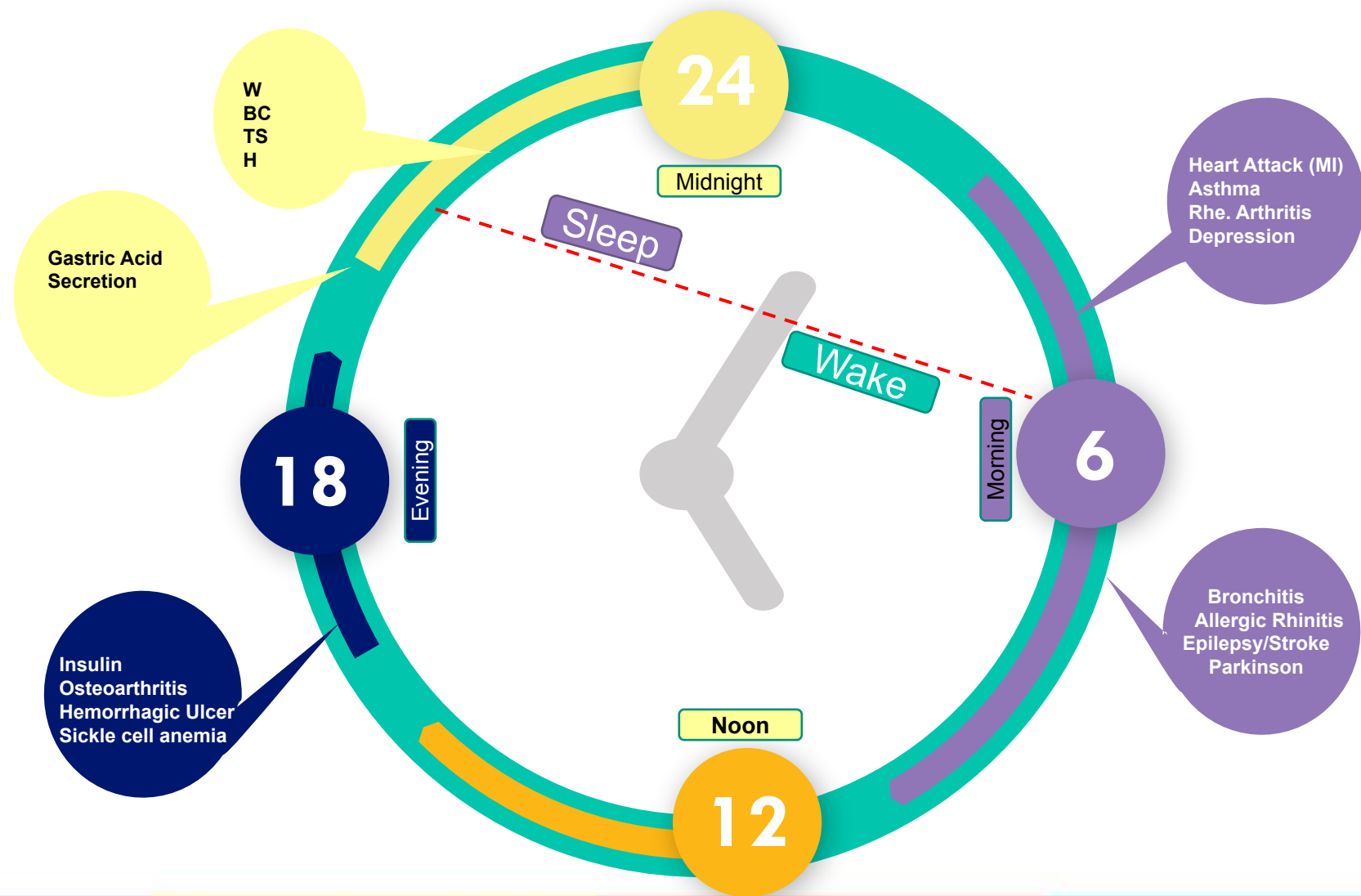
1 cycle  
per 24  
hr

- ❖ Monthly cycles
- ❖ Annual cycles
- Menstruation
- Breeding
- Hibernation

Infradian

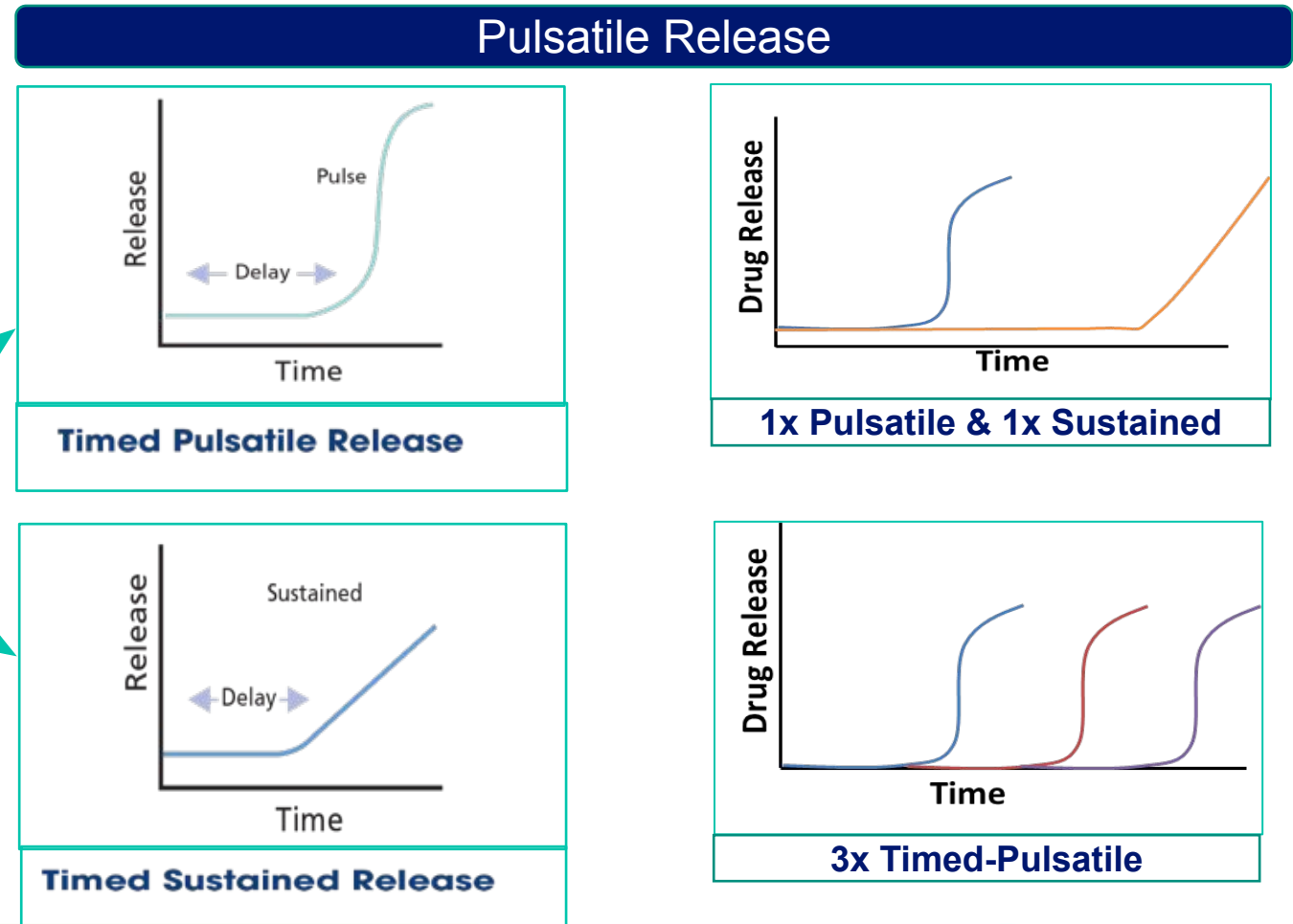
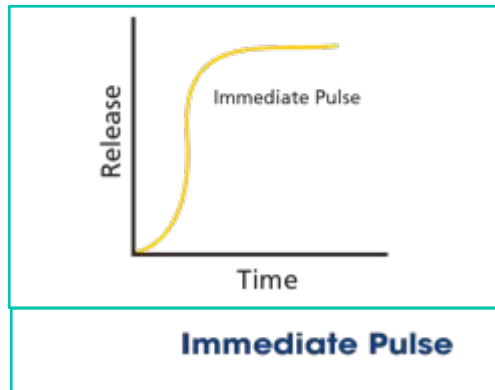
Cycle  
>24 hr

# Circadian Rhythm:

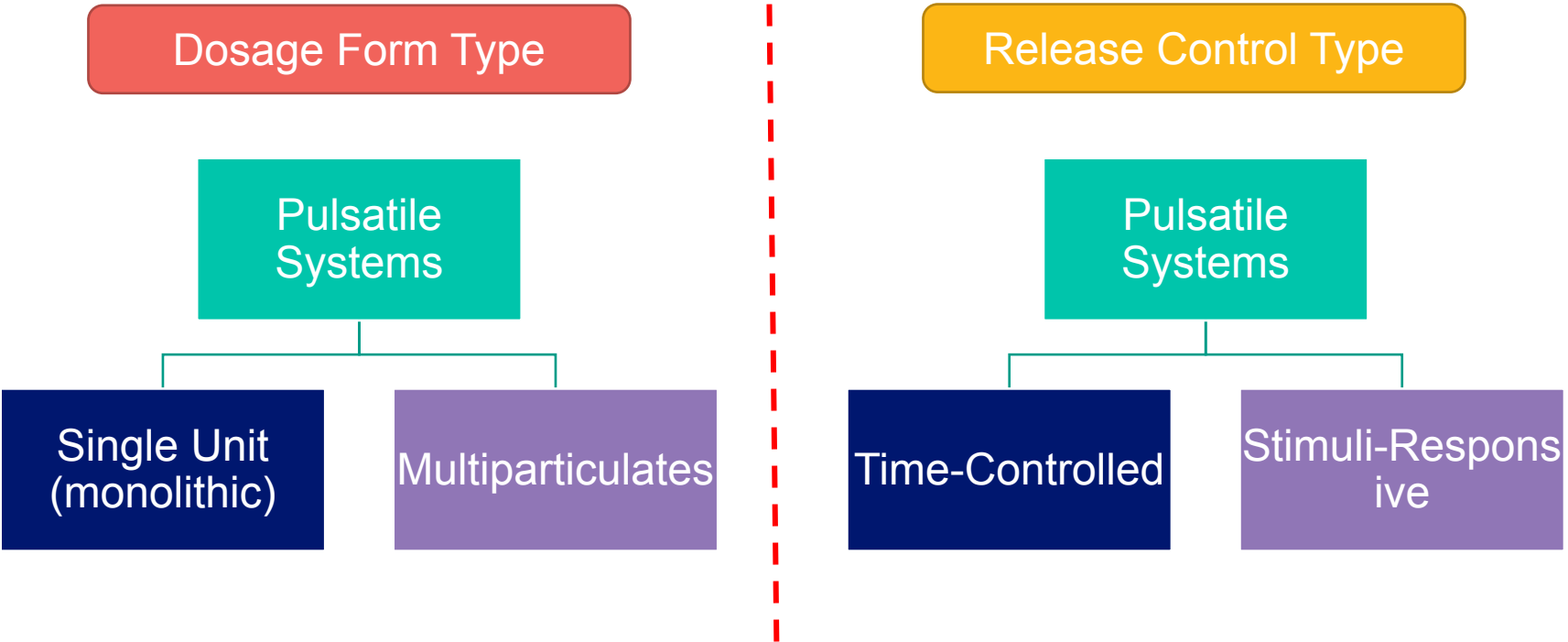


# Pulsatile Release:

- Pulse Release = Pulsatile Release = Release of a drug after a well-defined Lag time
  - Spatial (site) & Temporal (time) Release
  - **Time and Rate-controlled**
  - *Timed Pulsatile = Immediate Pulse*
  - *Timed Sustained = Sustained Pulse*



# Pulsatile Release Systems:





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## Multiparticulates

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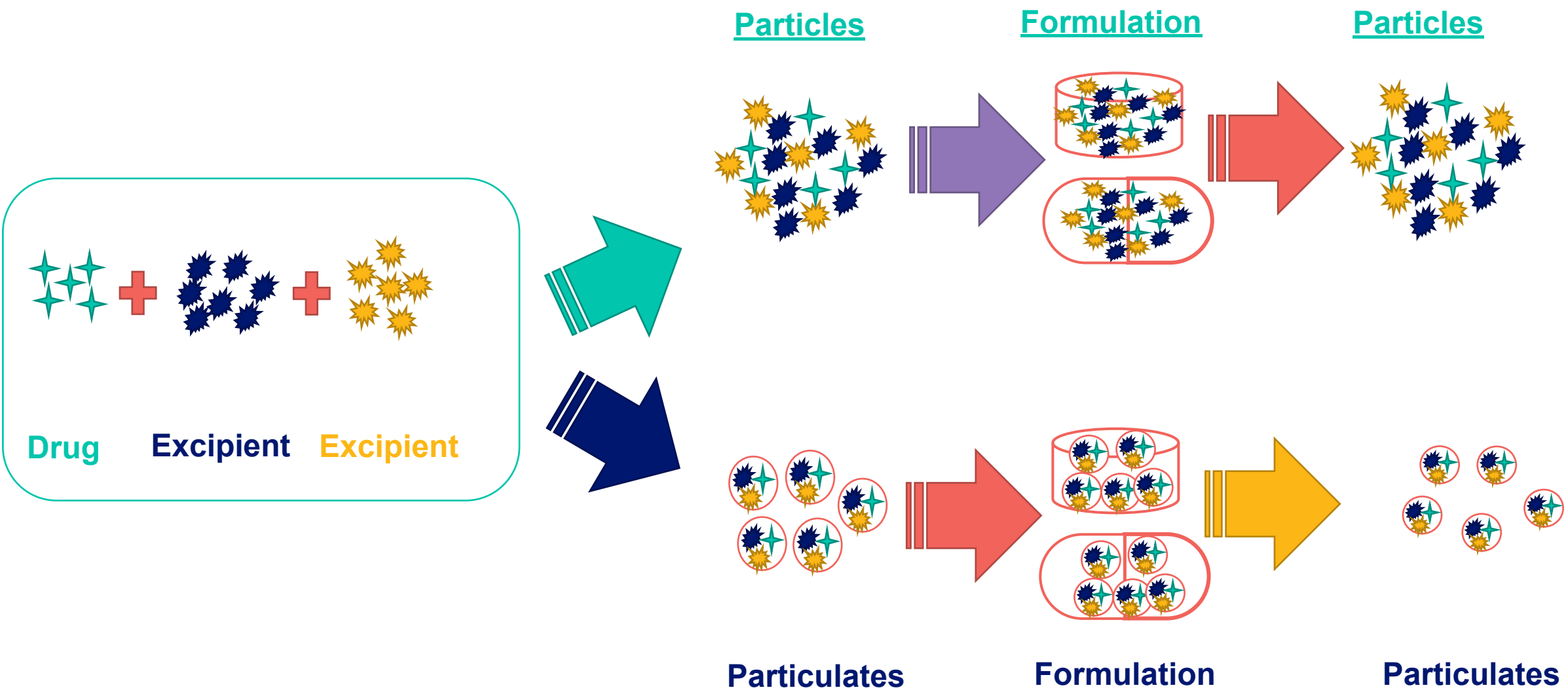
**Taste Masking Solutions** | Modified or Custom Release Solutions | Patient Centric Dosage Forms

# Multiparticulates:

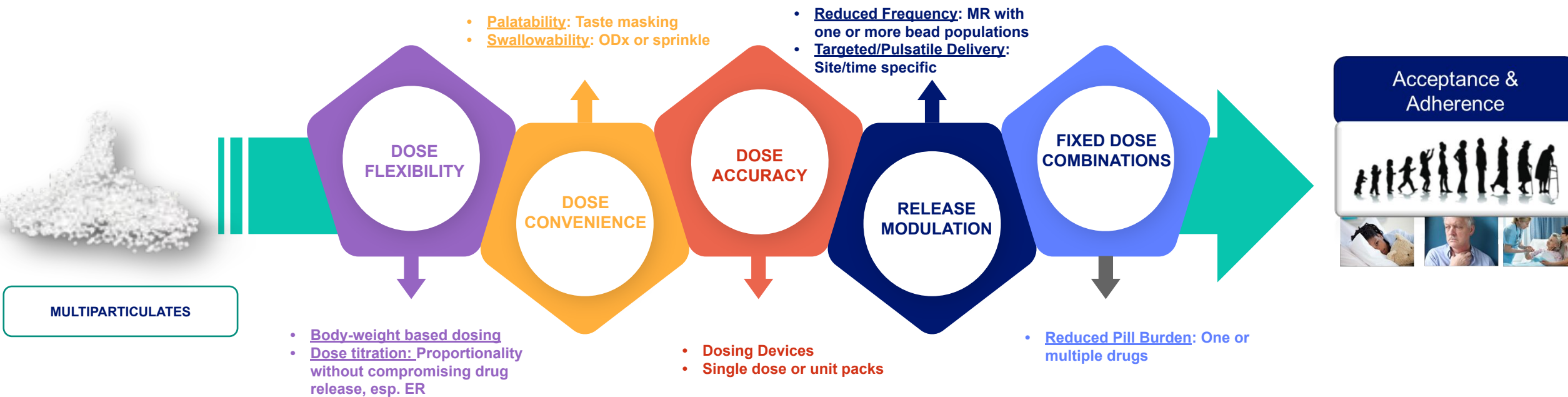
- Multiple particles - Multiple ***small discrete units***
- Size < **3 mm** (Range: 100  $\mu\text{m}$  to 4 mm)
- Each unit functionality or **performance is independent** of other units – same or different release profile
- Improved PK profile, reduced side effects, etc.
- Improved stability, and reduced weight/bulkiness over liquid formulations



# Particle(s) vs. Particulate(s):



# Multiparticulates: A Flexible Dosing System





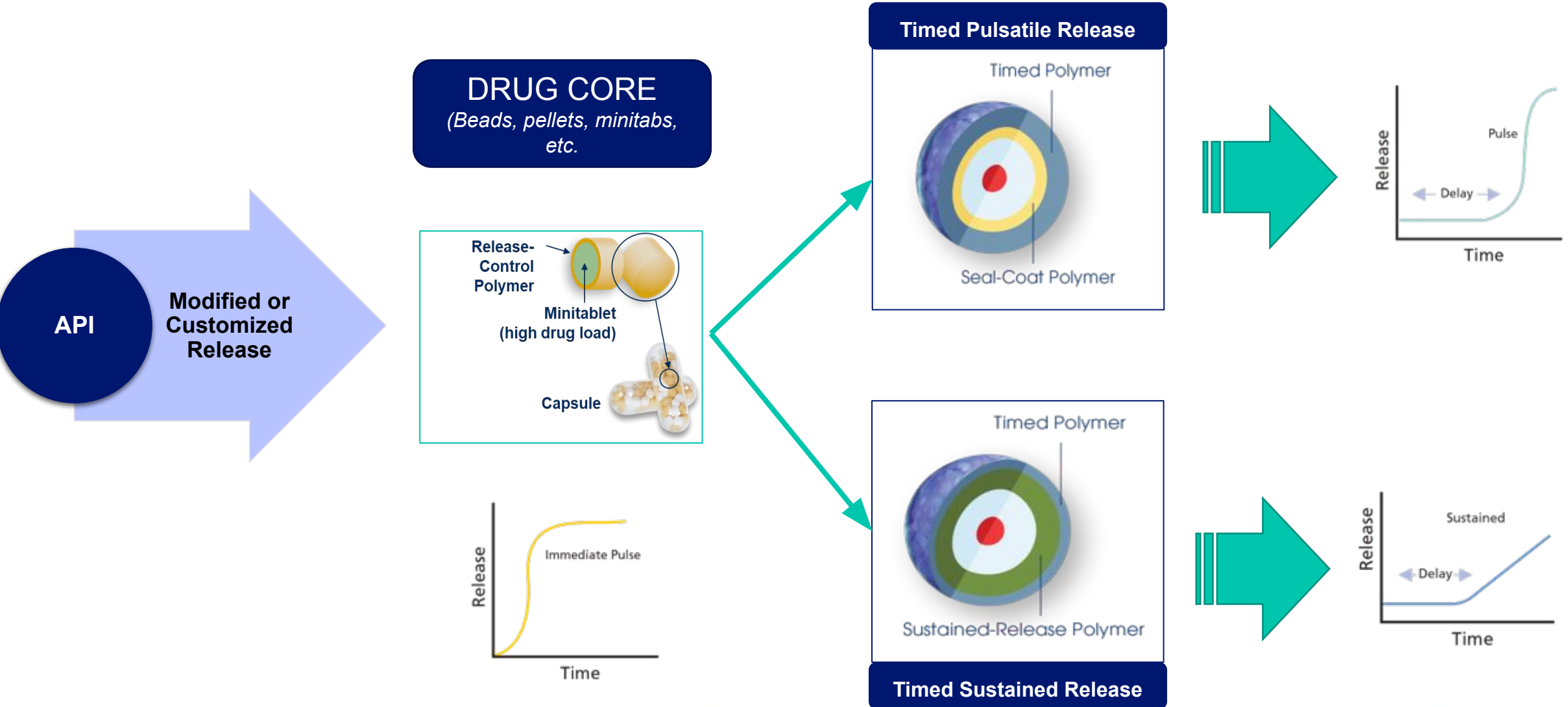
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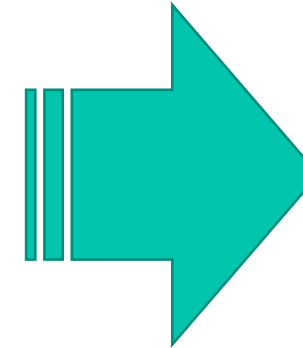
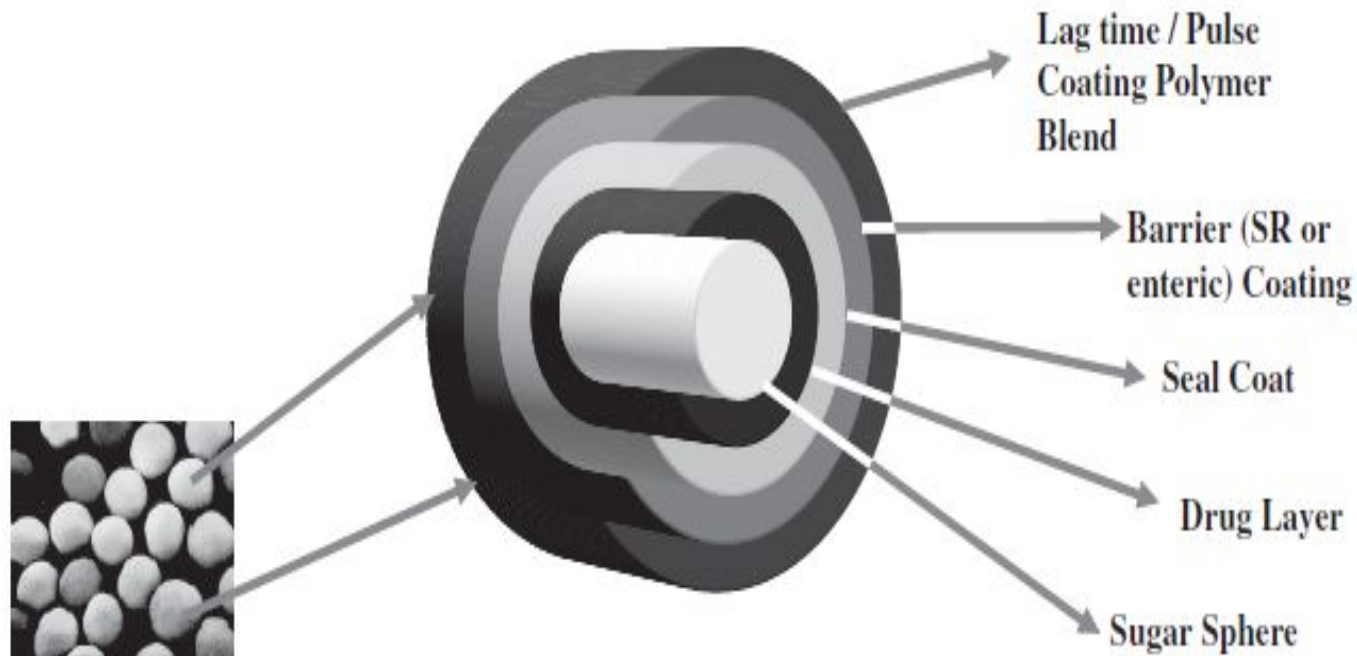
**Diffucaps®: Adare's Multiparticulate-Based Pulsatile  
Release Systems**

**ADARE®**  
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# Diffucaps®: Design Customized Release Systems



# Diffucaps®: Design Customized Release Systems



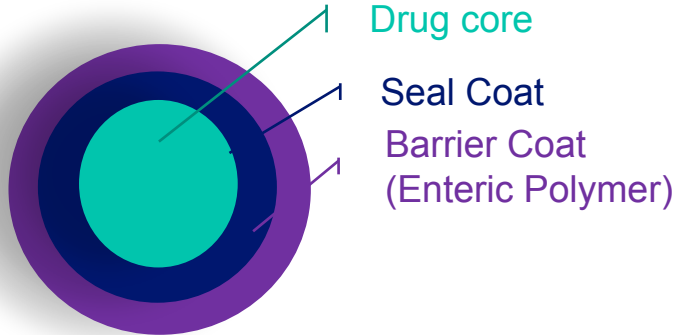
## Final Dosage Form:

- Tablets
- Capsules
- ODTs/Advatab
- Novel formats

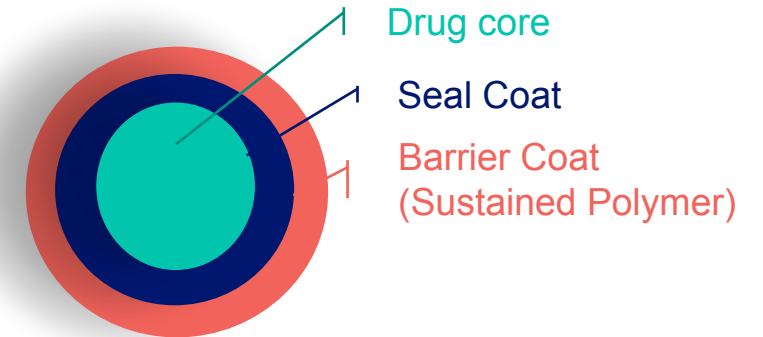
# Diffucaps®: Design Customized Release Systems



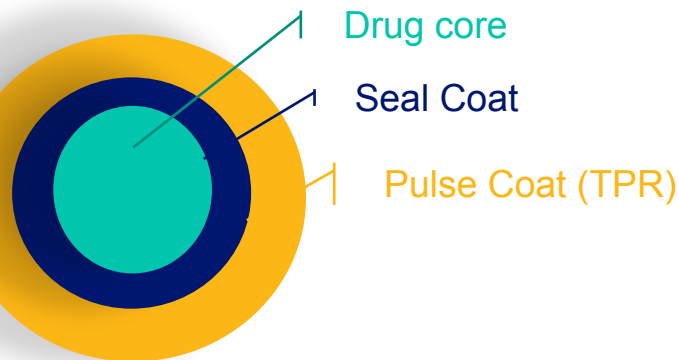
## Delayed Release



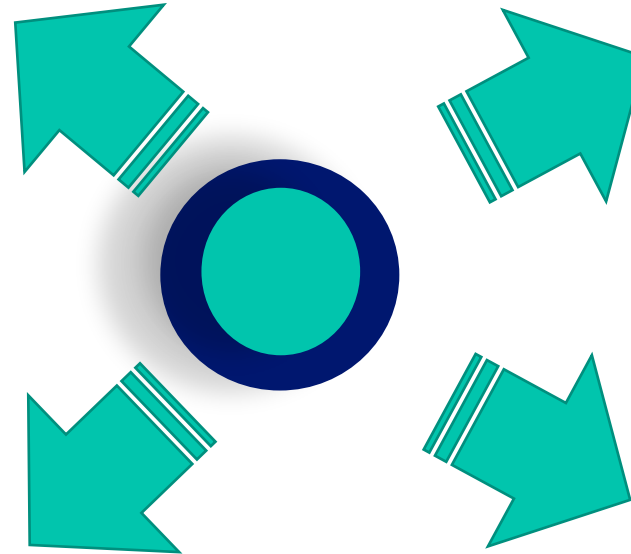
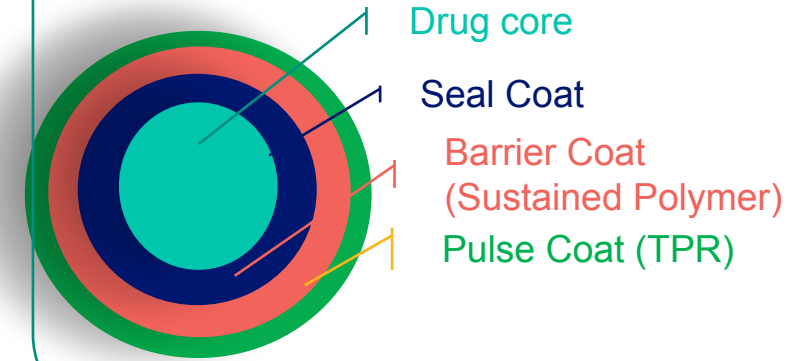
## Sustained Release



## Immediate Pulse (Timed)



## Sustained Pulse (Timed)

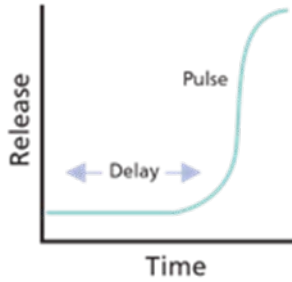
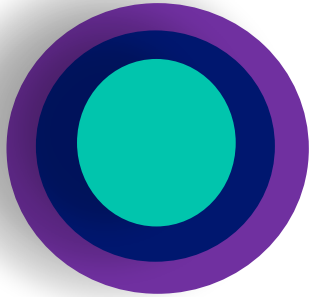




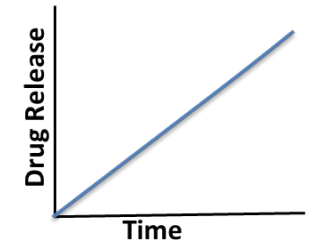
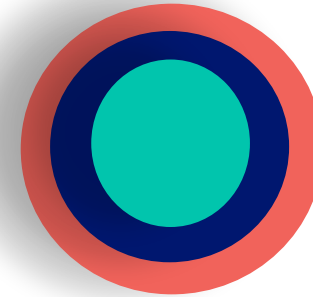
# Diffucaps®: Design Customized Release Systems



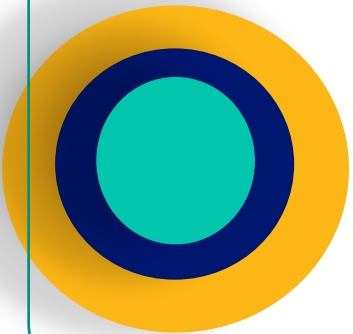
## Delayed Release (pH Sensitive)



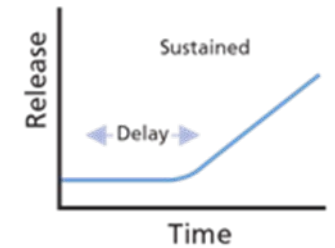
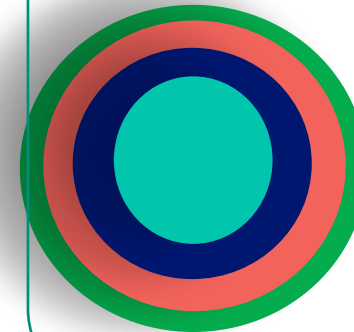
## Sustained Release



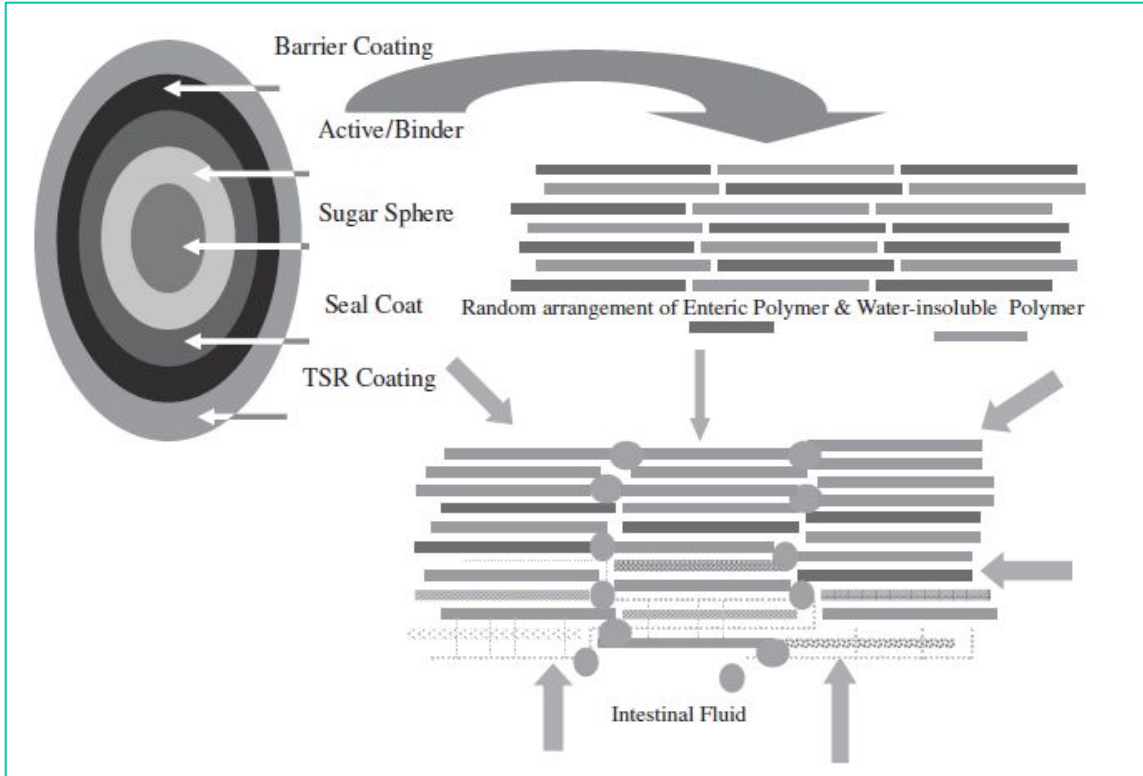
## Immediate Pulse (Timed)



## Sustained Pulse (Timed)



# Diffucaps®: Mechanism of Drug Release



- Lag period of up to ~10 hours
  - SR period of up to 20 hours after lag period
- 
- **Release duration depends on**
    - Drug physicochemical properties
    - Composition and thickness of barrier coat
    - Composition and thickness of TPR coat
    - Ratio of water insoluble polymer to enteric polymer

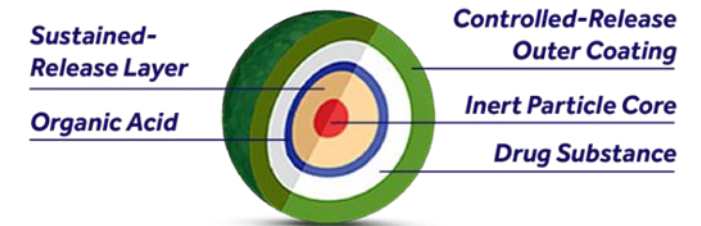


## Control of drug release via solubility modulation

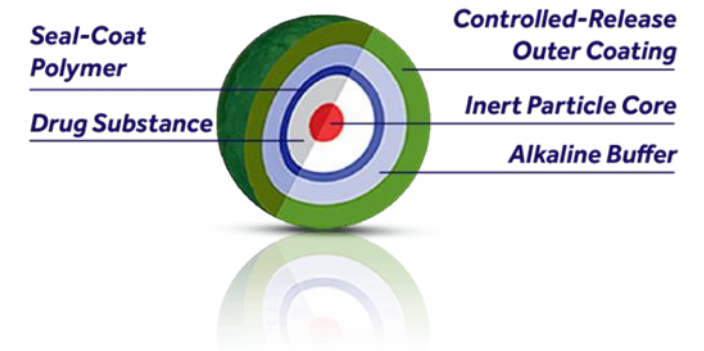
- **Weakly Acidic or Basic Drugs:** Enhancing solubility by creating acidic or basic microenvironment using organic acid or alkaline buffer
- **Highly Soluble Drugs:** Limiting solubility using alkaline buffer (>7 pH) to limit solubility for SR formulations
- **Amorphous Solid Dispersion:** Enhancing solubility and bioavailability by amorphization, and modified release by polymer coating

## Multiparticulate Bead System

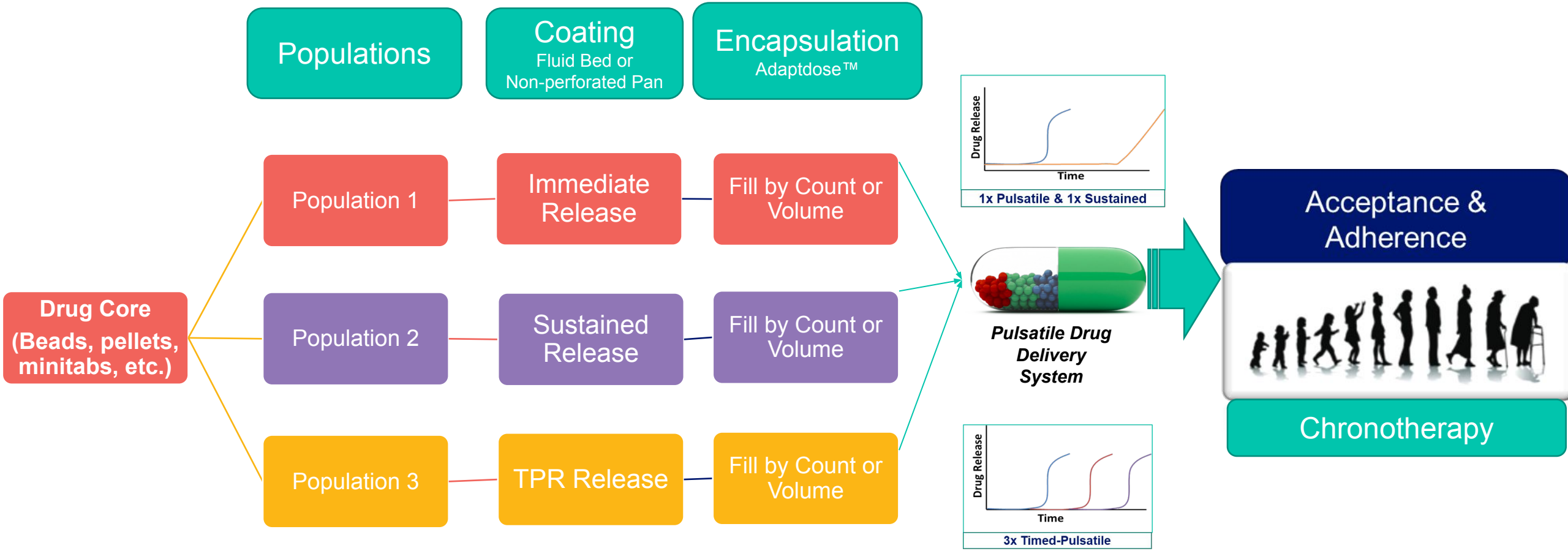
### Organic Acid Diffucaps® Bead



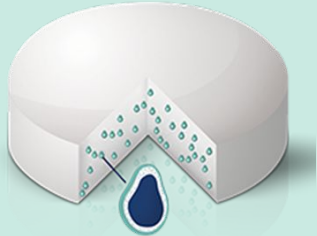



### Alkaline Buffer Diffucaps® Bead



# Diffucaps as Pulsatile Drug Delivery System



# Adare's Patient-Centric Dosage Forms: Easy to Swallow Formats

Advatab	Parvulet®	Adaptdose™	Liquitard
<b>ODT Platform</b>  <i>Superior ODTs with higher hardness and cost-effective packaging</i>	<b>Swellable/Dispersible Platform</b>  <i>Tablets or Granules that converts into <u>semi-solid mass with water without agitation</u></i>	<b>Sprinkle and FDC Platform</b>  <i><u>Sprinkle on soft food</u> in capsules</i>	<b>Powder for Reconstitution Platform</b>  <i><u>Temporary suspension with water</u>, Direct-to-mouth, or sprinkle on soft foods – sachet, stick packs, or bottles</i>
			
<ul style="list-style-type: none"> <li>External lubrication technology – <u>Matsui Exlub System</u></li> <li><u>Higher hardness</u> with low compression force to maintain multiparticulates integrity with <u>fast disintegration (&lt;30s)</u></li> <li>Cost-effective packaging options – bottles, push through blisters, etc.</li> </ul>	<ul style="list-style-type: none"> <li>Patented &amp; trademark protected in US and Europe</li> <li>Solid powder/tablet converts to soft food like texture in 30 seconds</li> <li>Ideal for patients with difficulty swallowing and for high dose medications</li> </ul>	<ul style="list-style-type: none"> <li>Powder, pellets, beads, granules, minitabs can be combined or filled as single population into capsules</li> <li>Max. of 3 populations can be filled -<u>FDC of 3 drugs or multiple release profiles</u> possible</li> <li>Ideal for patients with <u>difficulty swallowing (dysphagia)</u> and for high dose range medications requiring <u>dose flexibility</u></li> </ul>	<ul style="list-style-type: none"> <li>Hydrophilic powder-based suspension platform</li> <li>Direct-to-mouth, temporary suspension or even sprinkle on soft foods</li> <li>Dosing accuracy, portability/convenience, and dose flexibility</li> </ul>

**All platforms are compatible with Diffucaps®**



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## CASE STUDIES

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## Case Study #1: Chronotherapy for Coronary Artery Disease/Hypertension

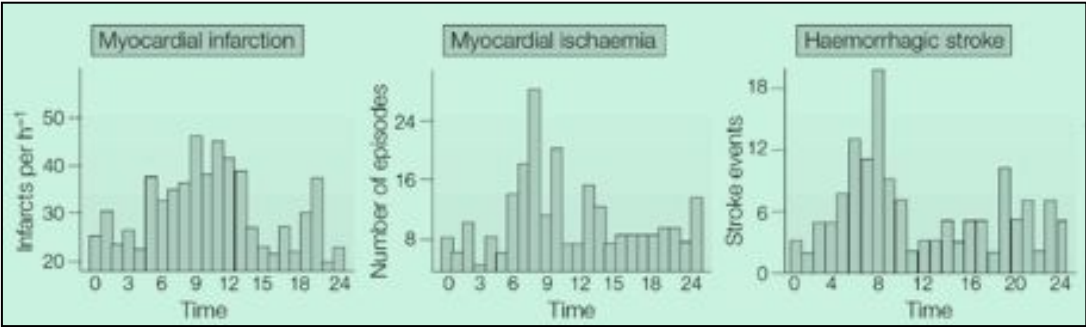


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# Case Study #1: Chronotherapy for Coronary Artery Disease/Hypertension

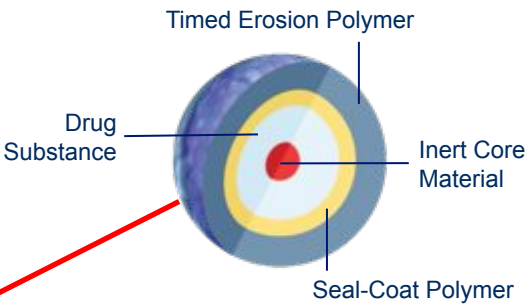
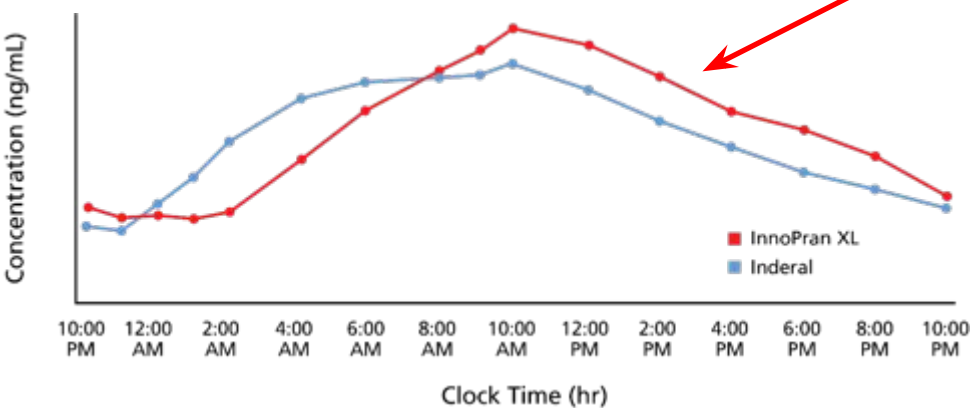
DRUG	<ul style="list-style-type: none"><li>• Propranolol HCl</li><li>• Anti-hypertensive drug – nonselective beta-adrenergic receptor blocker</li><li>• Drug is rapidly and completely absorbed from GIT</li><li>• Half life - 4 hours</li></ul>
NEED	<ul style="list-style-type: none"><li>• Pulsatile release – release at specified time with pre-determined lag (<b>chronotherapy</b>)</li><li>• Maximum release during early morning to prevent cardiac events</li></ul>
SOLUTION	<ul style="list-style-type: none"><li>• Capsules containing ER beads prepared via Diffucaps® technology with timed-release (CRR Circadian Rhythm Release)</li></ul>



- Cardiac events happen in the morning
- Lowest BP 8PM-2AM
- BP peaks in late morning and falls during afternoon and evening
- 40% higher risk of heart attack, 30% of cardiac death, 50% of stroke
- Marketed SR products – 25% decrease in cardiac events – Tmax of ~6h - NOT CHRONOTHERAPY

# Case Study: Chronotherapy for Coronary Artery Disease/Hypertension

Plasma Profiles of InnoPran XL versus Inderal LA



- Delay or Lag Time:** 4 hrs
- Populations:** Two – Mix of IR TPR & SR TPR
- Dose:** 80, 120, 160, and 640 mg
- RLD:** Inderal LA
- Launch:** Year 2003

InnoPran XL is a registered mark of ANI Pharmaceuticals, Inc.  
Inderal is a registered mark of ANI Pharmaceuticals, Inc.

Hastings MH, Reddy AB, Maywood ES. *Nature Reviews Neuroscience*. 4(8):649-61, 2003 Aug.

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## Case Study #2: Chronotherapy for ADHD



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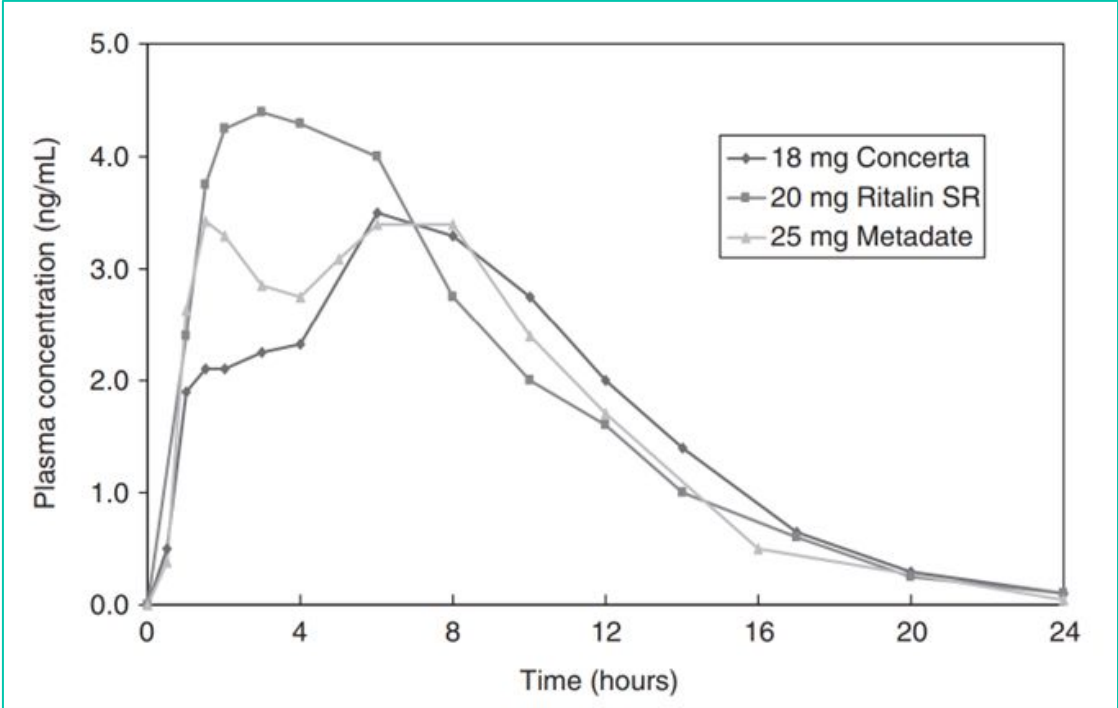
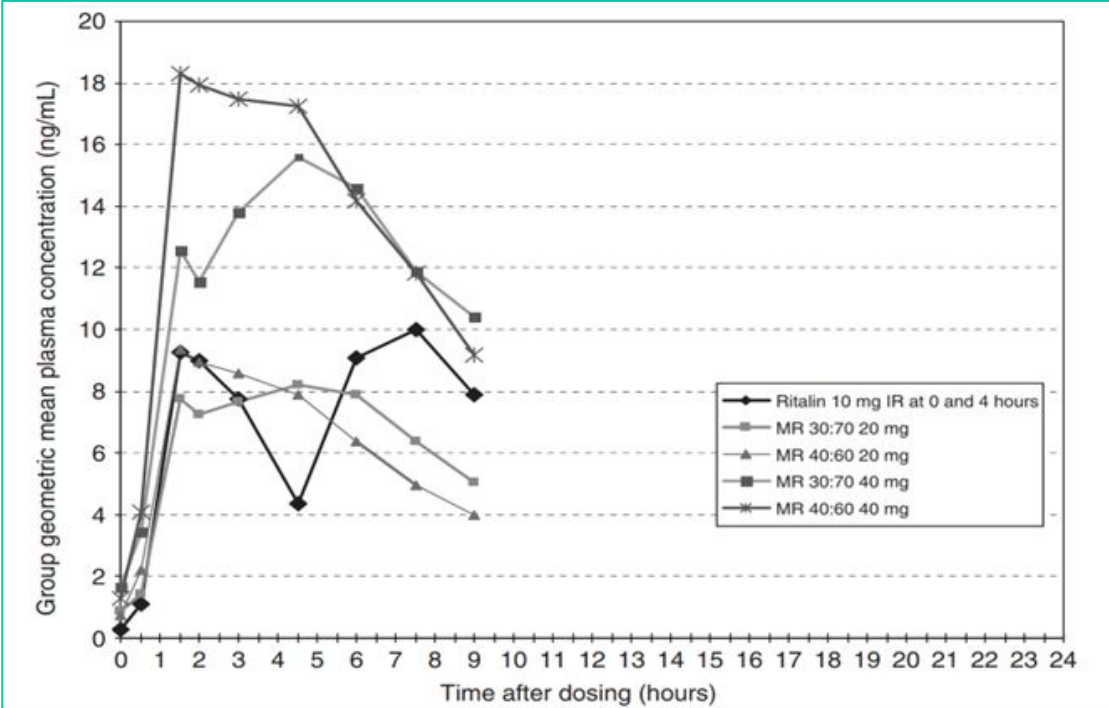


# Case Study #2: Chronotherapy for ADHD

DRUG	<ul style="list-style-type: none"><li>• Methylphenidate HCl</li><li>• A CNS stimulant for treatment of ADHD</li><li>• Half life - ~2-3 hrs</li><li>• Controlled/scheduled drug</li></ul>
NEED	<ul style="list-style-type: none"><li>• Pediatric patients, adolescents, and adults with ADHD</li><li>• Dose proportional - Six dose strengths (10 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg)</li><li>• Extended Release (ER) product (half life is about 2-3 hrs with max. effect of 1.5-2 hr)</li></ul>
SOLUTION	<ul style="list-style-type: none"><li>• <b>Capsules Containing Diffucaps® Metadate CD:</b> Capsules containing ER Diffucaps® can be opened, and the contents can be sprinkled on a small amount applesauce,</li><li>• Drink some fluids like water. No chewing or crushing of capsule content</li></ul>

- Requires frequent dosing given short half life
- Need to maintain plasma levels during day and avoid midday dosing for school going children
- Reduced plasma levels in the evening to avoid side effects such as appetite suppression and insomnia
- Marketed SR formulations – Eg. Ritalin SR – Not well accepted and NOT CHRONOTHERAPY
- Combination of 30% IR & 70% ER Beads for rapid onset and maintenance for 12 hrs

# Case Study #2: Chronotherapy for ADHD



**Launch: 2001**  
Currently discontinued



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## Case Study #3: Chronotherapy for GERD



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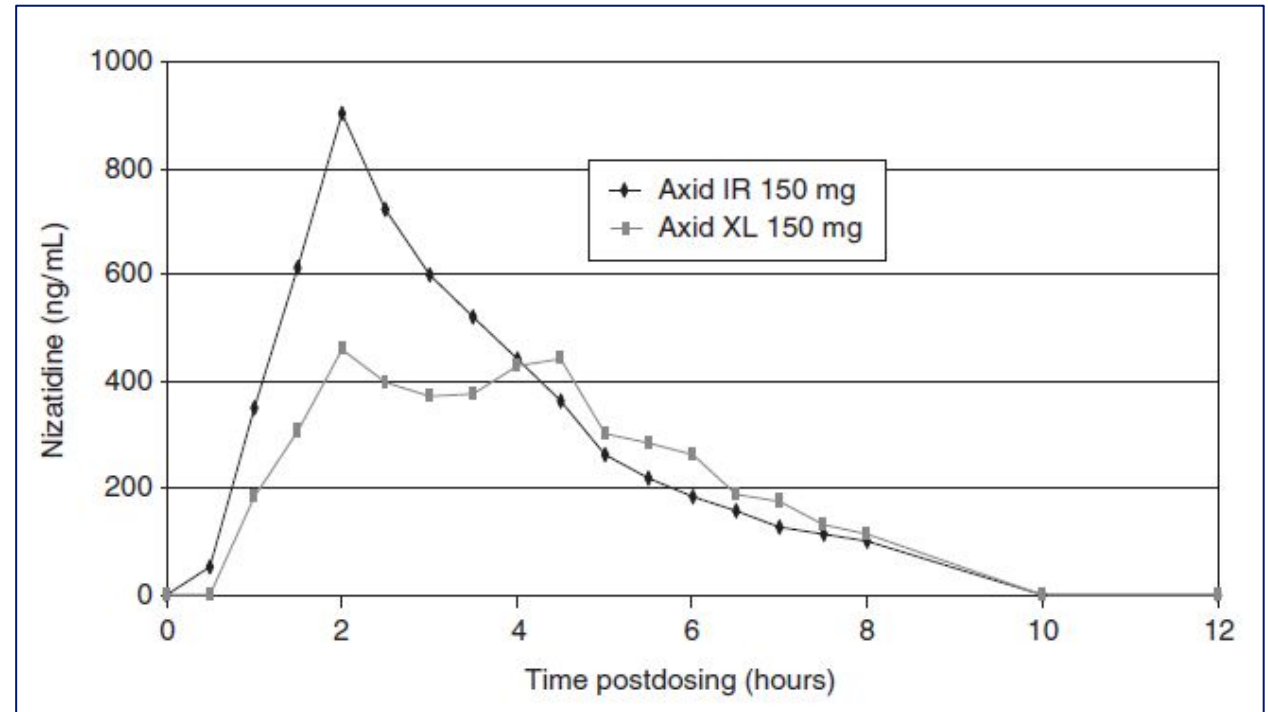
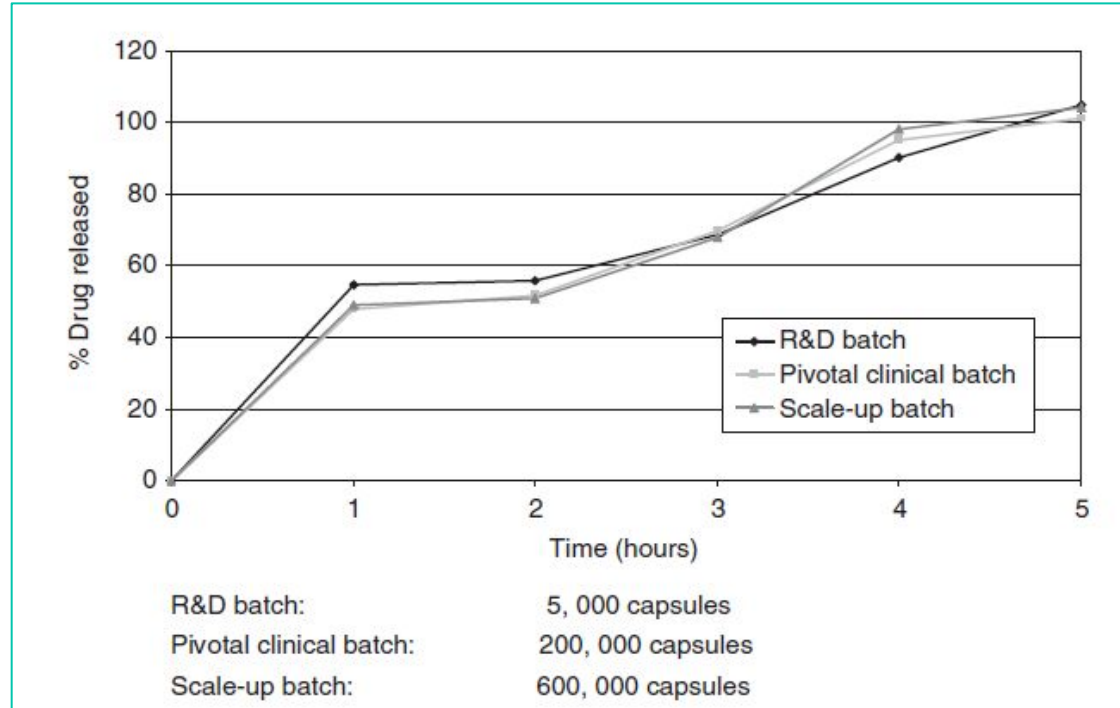
# Case Study #3: Chronotherapy for GERD



DRUG	<ul style="list-style-type: none"><li>• Nizatidine</li><li>• GERD (Gastroesophageal reflux disease) - H2-receptor antagonist</li><li>• Half life - ~1-2 hrs</li></ul>
NEED	<ul style="list-style-type: none"><li>• Adults</li><li>• Sustained release</li></ul>
SOLUTION	<ul style="list-style-type: none"><li>• <b>Capsules Containing Diffucaps® - Axid XL:</b></li></ul>

- Requires frequent dosing given short half life
- Typically requires BID/twice a day dosing regimen
- Four peaks of gastric acid secretion – 3 x each meal and nocturnal/overnight peak after bedtime
- Chronotherapy – drug delivery before meals and before midnight
- IR+TPR Blend with 2-3h delay for AM dose: morning and afternoon heartburn, and PM dose: evening and nocturnal heart burn
- Bid/twice daily and qd/once daily dosing were developed

# Case Study #3: Chronotherapy for GERD



- Axid XL BA was 92% of Axid IR – good acid suppression
- Good healing of GERD for bid and qd Axid XL

## Concluding Remarks:

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- Patient centric formulations offer enhanced acceptance and adherence to therapeutic regimen
- Harmonizing medications with bodily rhythm or circadian rhythm offers great benefit in terms of efficacy and reduce side effects and so improved acceptance and adherence.
- Chronotherapeutic medications can be designed and developed using pulsatile drug delivery systems with multiparticulates
- Adare's Diffucaps® technology is multiparticulates-based pulsatile drug delivery system that offers chronotherapeutic medications
- Diffucaps® offer patient-centric solutions with dose convenience, dose flexibility and dose accuracy for all patient populations – **Right drug, Right Place, & Right Amount when it is NEEDED (Right Time!)**



**Thank you!**

**For Any Questions or interested in knowing more about Adare's technologies?**

**Please contact us at [busdev@adareps.com](mailto:busdev@adareps.com)**



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