

TRANSFORMING DRUG DELIVERY.
TRANSFORMING LIVES.



Harmonizing Medication Delivery with the Body's Natural Rhythms

An Important Consideration for Patient-Centric Care

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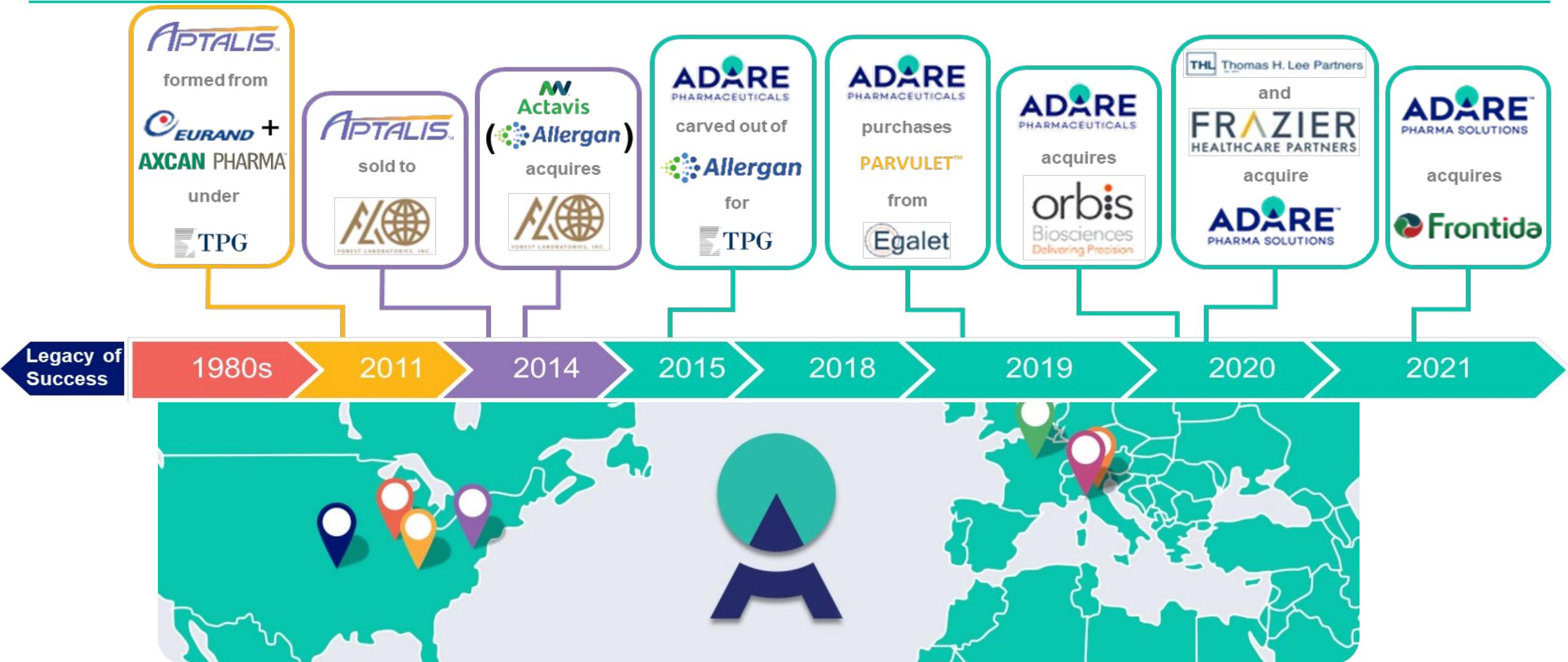
Srini Shanmugam, Ph.D.,
Executive Director,
Pharmaceutical Sciences, Business Support, & New Technologies
JULY 2023



Agenda

- 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

Integrated End to End Services

- Warehousing
- Controlled Substance Storage Vault
- Vendor Management
- Distribution
- Bottles, Blisters, & Stick packs/Sachets
- Clinical & Commercial
- Serialization & Aggregation
- Labelling
- Clinical supplies
- Scale Up & Process Optimizaiton (DoE/QbD)
- Tech Transfers – CBE/SUPAC
- Commercial supplies - Global
- Phase appropriate product development (QbD)
- Appropriate Analytical method development
- Design & Development of IR & MR Formulations/Products
- Preformulation, Preclinical, Clinical, & Commercial

Logistics

Packaging

Manufacturing

Development

Adare Pharma Solutions
HYBRID Integrated CDMO

Customer-Centric Integrated CDMO Services & Patient-Centric Solutions

Integrated End to End Services

Best of Breed (BoB) Technologies

Logistics

Packaging

Manufacturing

Development

Easy to Swallow

Fixed Dose Combo

Modified Release

Taste Masking



Adare Pharma Solutions
HYBRID Integrated CDMO

- Warehousing
- Controlled Substance Storage Vault
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- Bottles, Blisters, & Stick packs/Sachets
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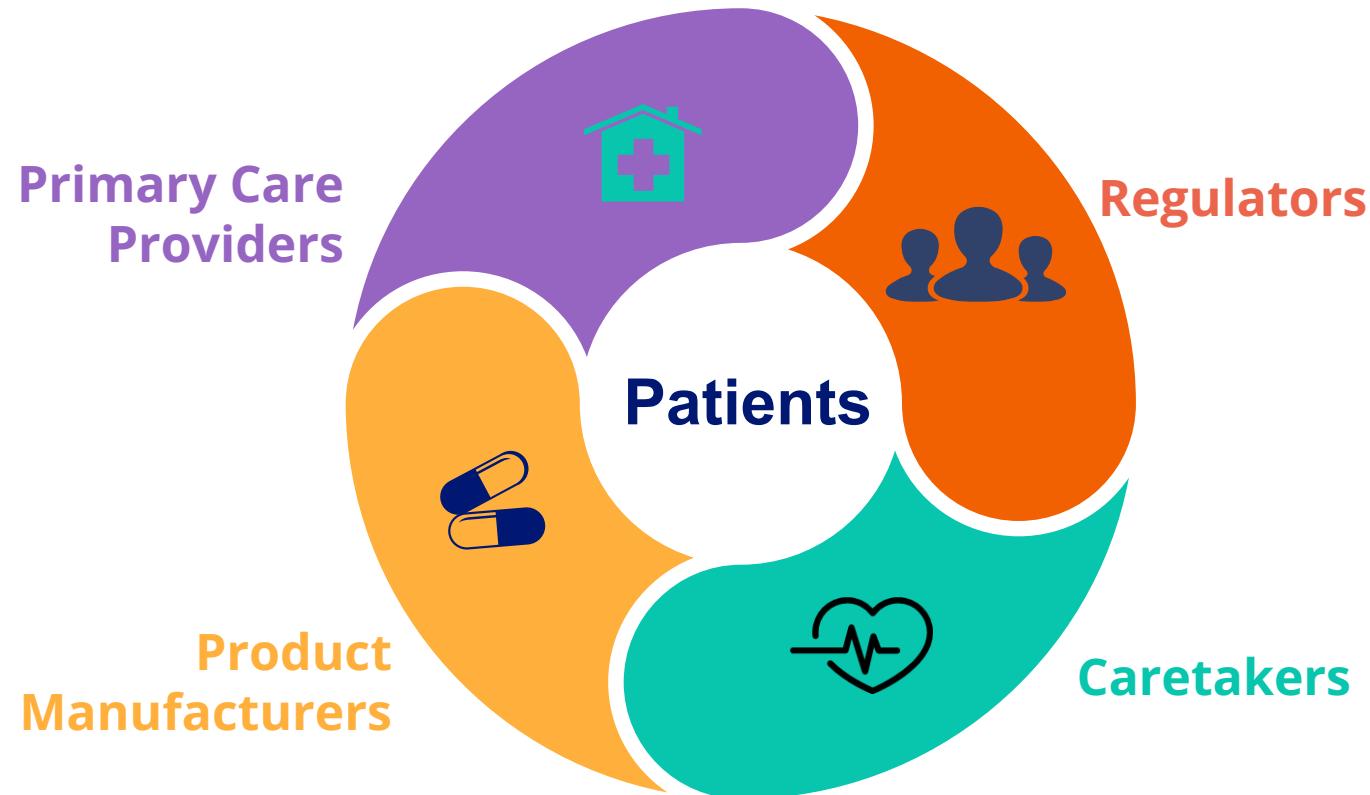


PATIENT-CENTRIC CARE

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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



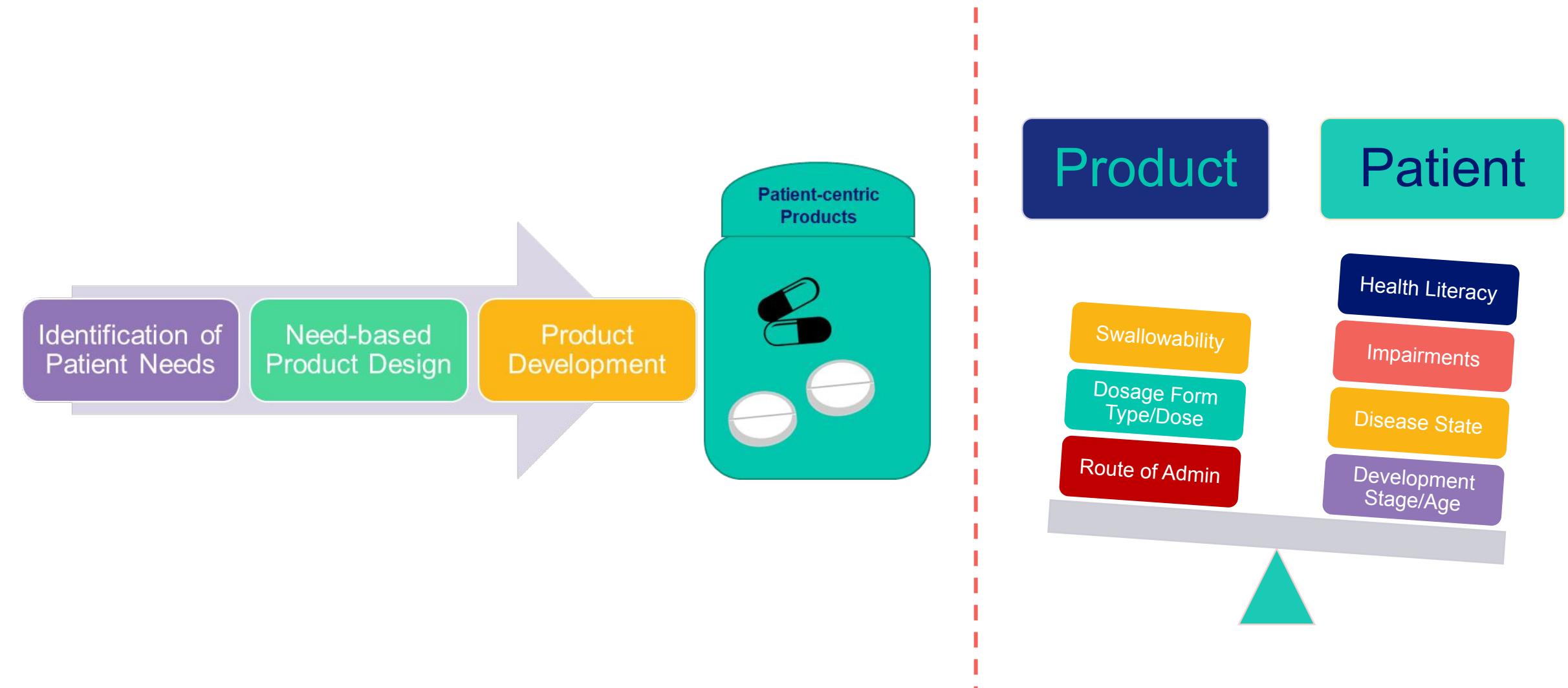
Patient Centric Product Design:



Comprehensive Product presentation
to the patient

Presentation of product based on
patient-specific comprehensive needs

Patient Centric Product Design:



Patient Need: Harmonizing the Medication Release

- 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

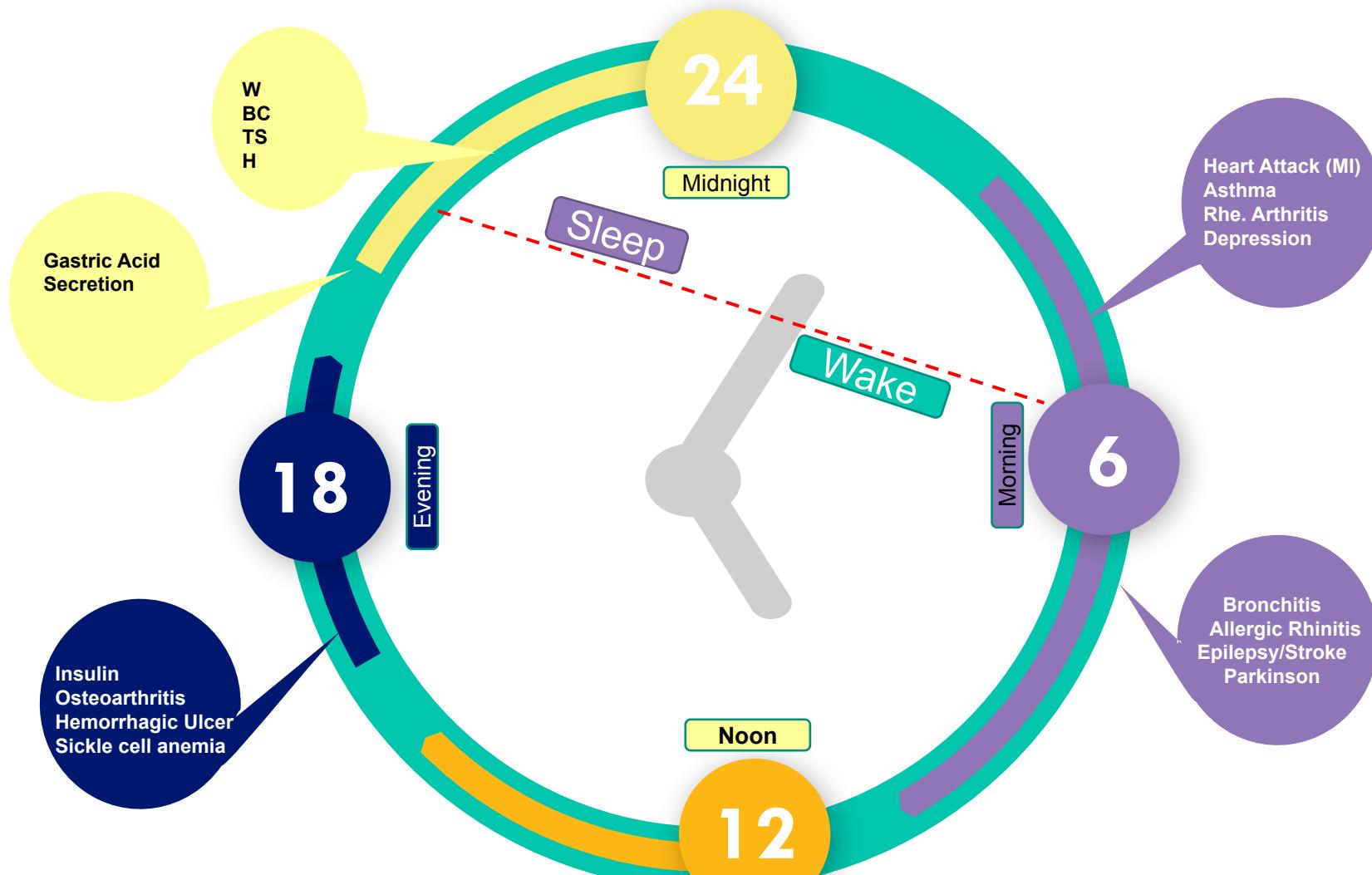
1 cycle
per 24
hr

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

Infradian

Cycle
>24 hr

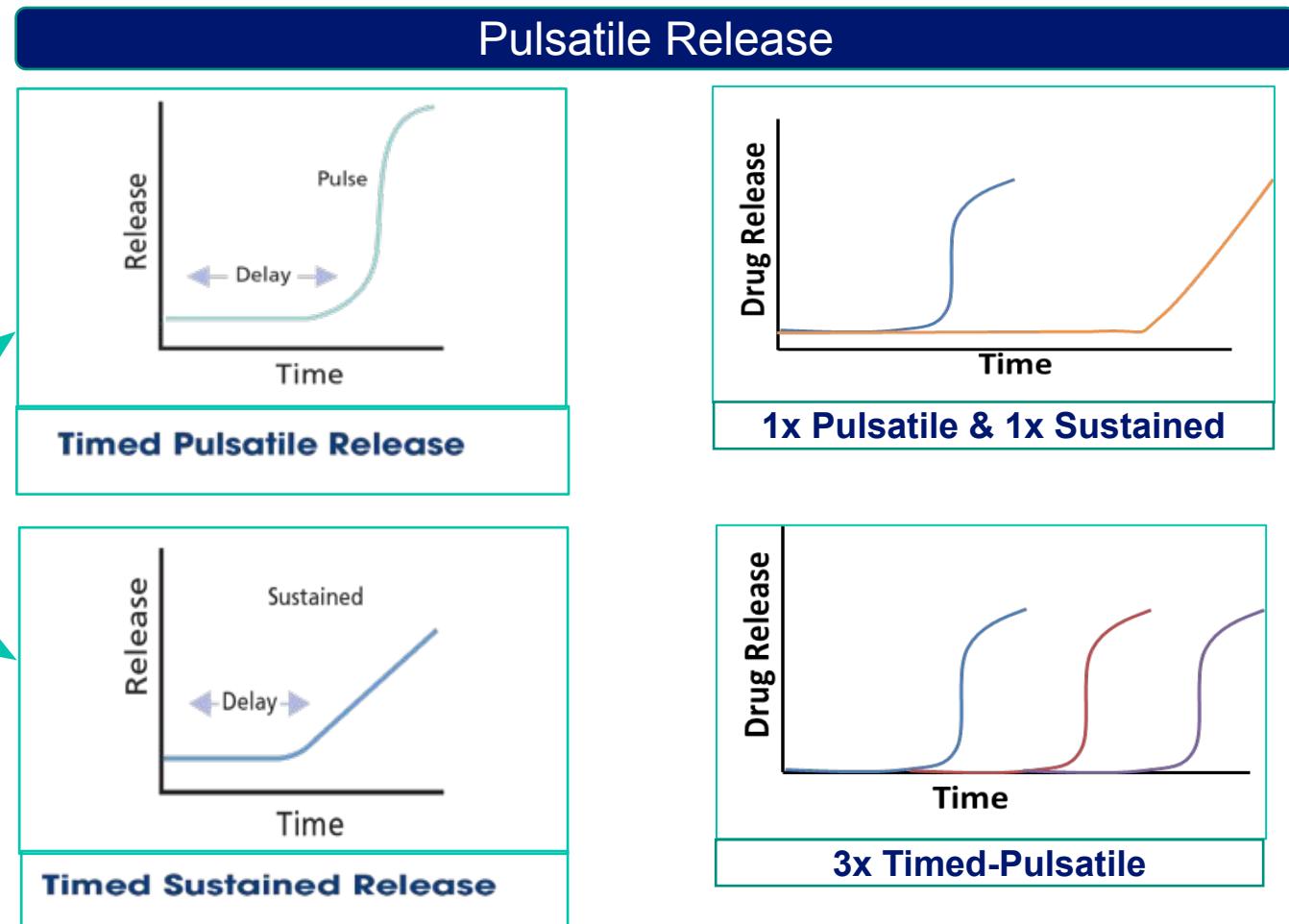
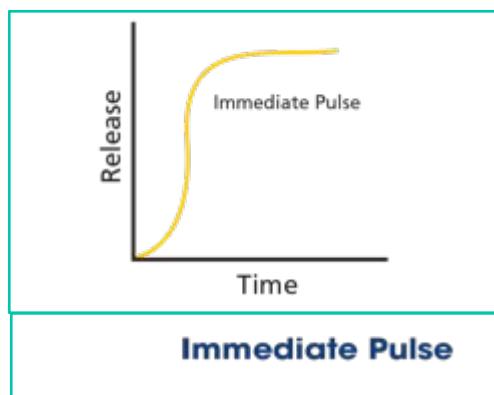
Circadian Rhythm:



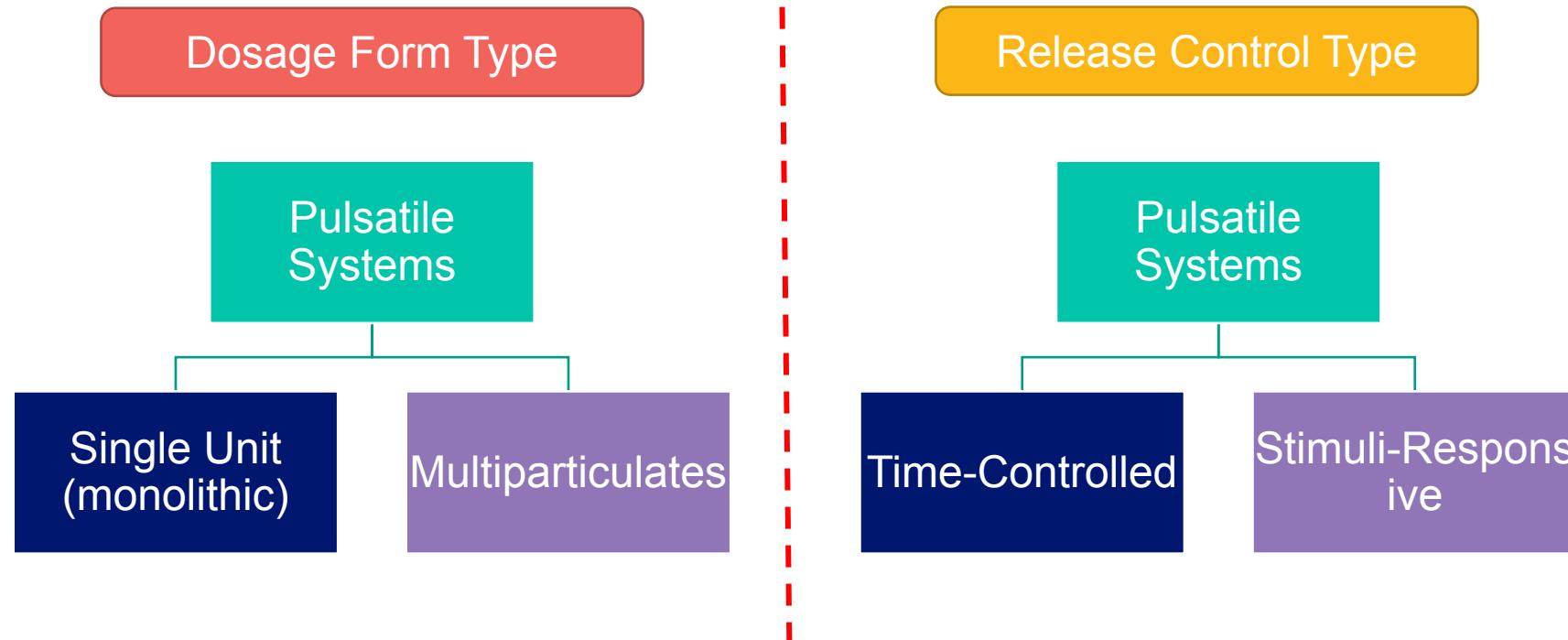
Pulsatile Release:

- 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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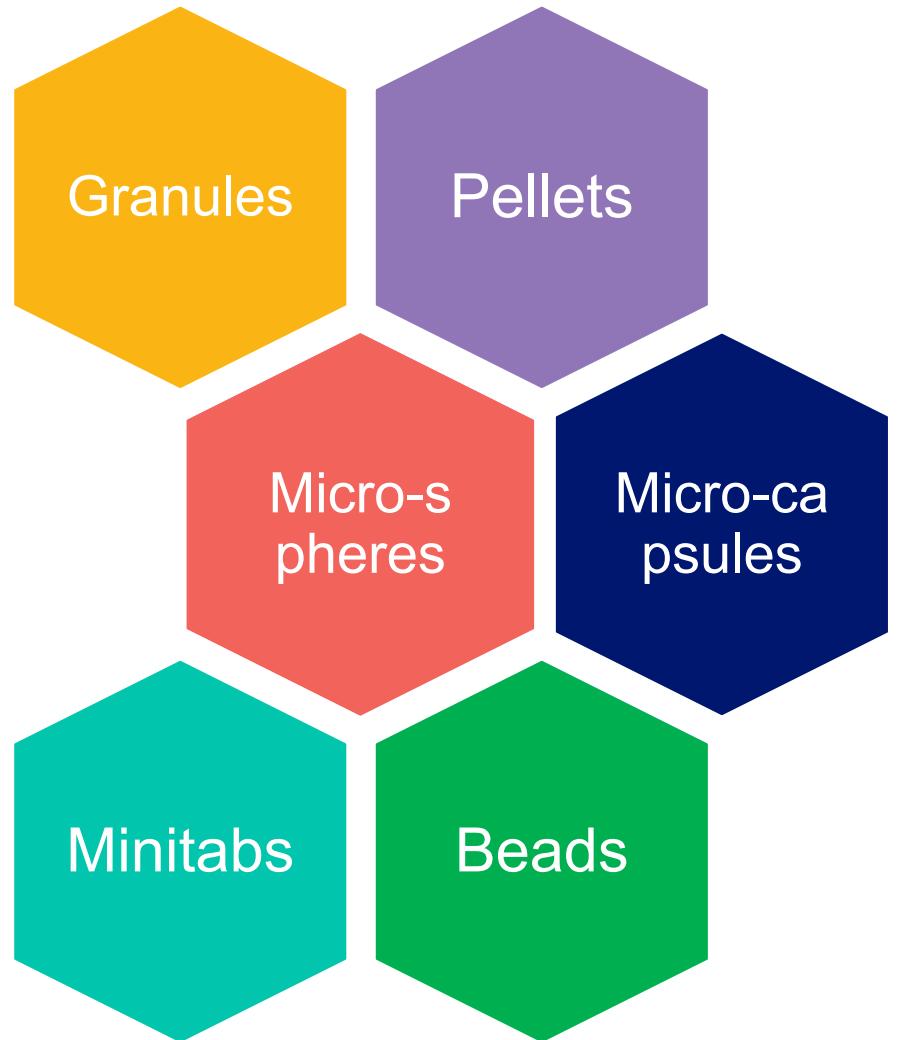
Multiparticulates

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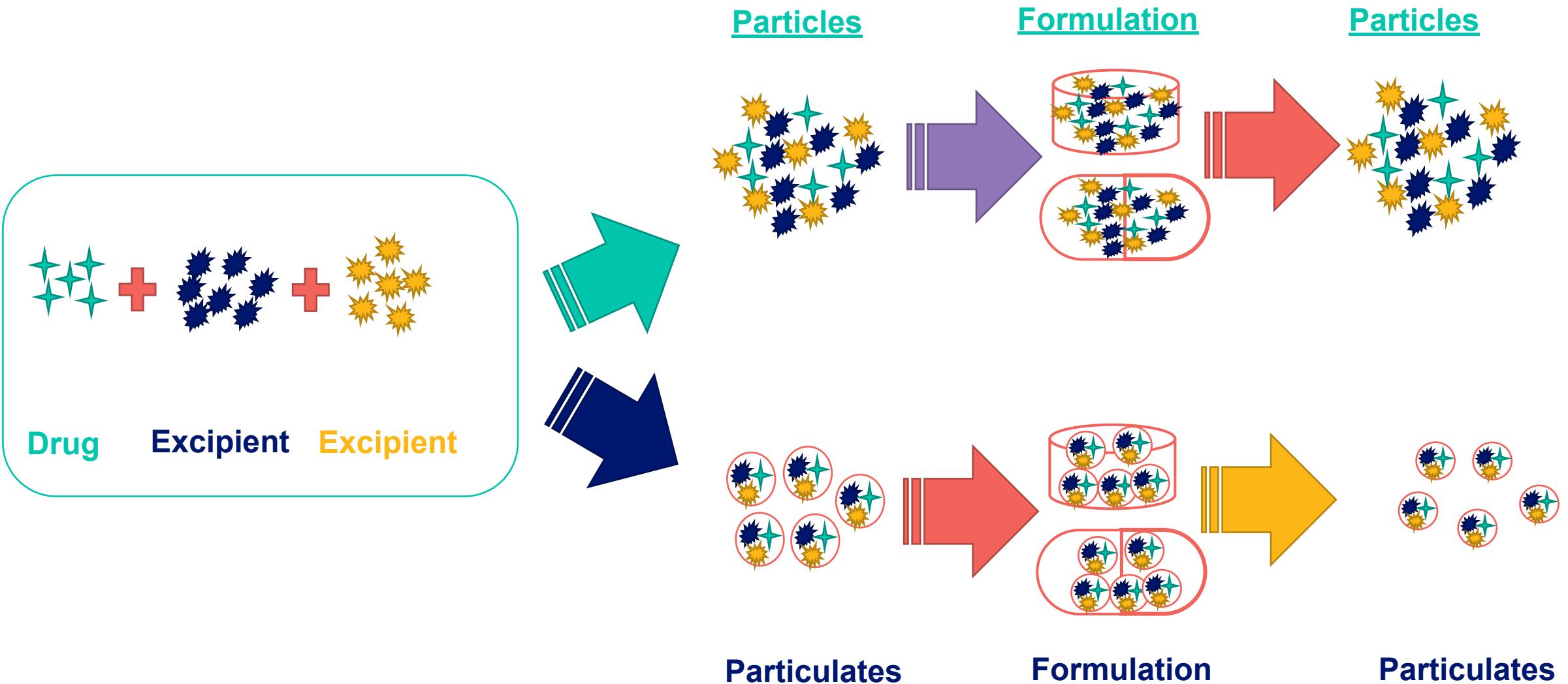
Taste Masking Solutions | Modified or Custom Release Solutions | Patient Centric Dosage Forms

Multiparticulates:

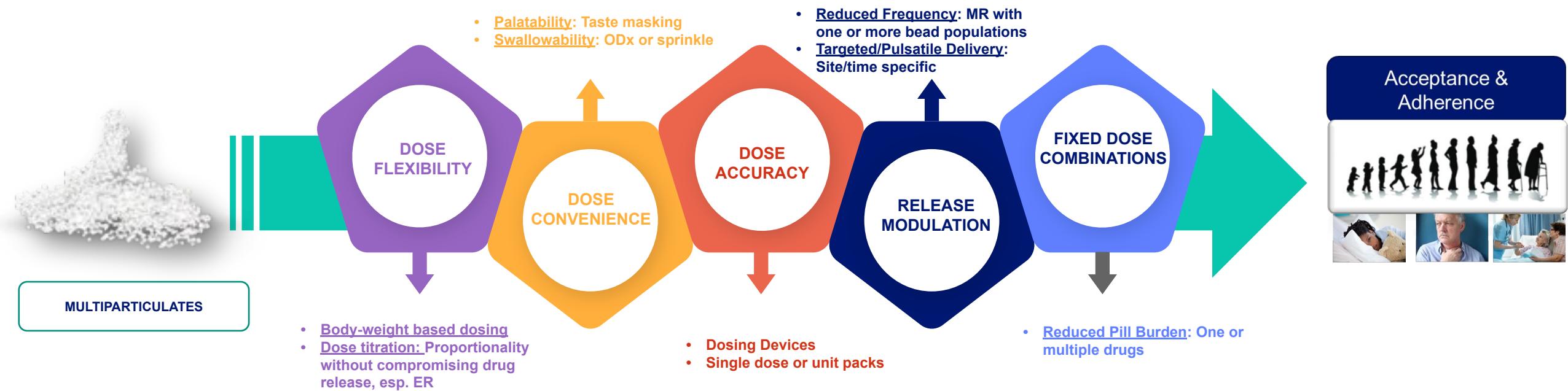
- Multiple particles - Multiple ***small discrete units***
- Size < 3 mm (Range: 100 μ m to 4 mm)
- Each unit functionality or **performance is independent** of other units – same or different release profile
- Improved PK profile, reduced side effects, etc.
- Improved stability, and reduced weight/bulkiness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



Particle(s) vs. Particulate(s):



Multiparticulates: A Flexible Dosing System



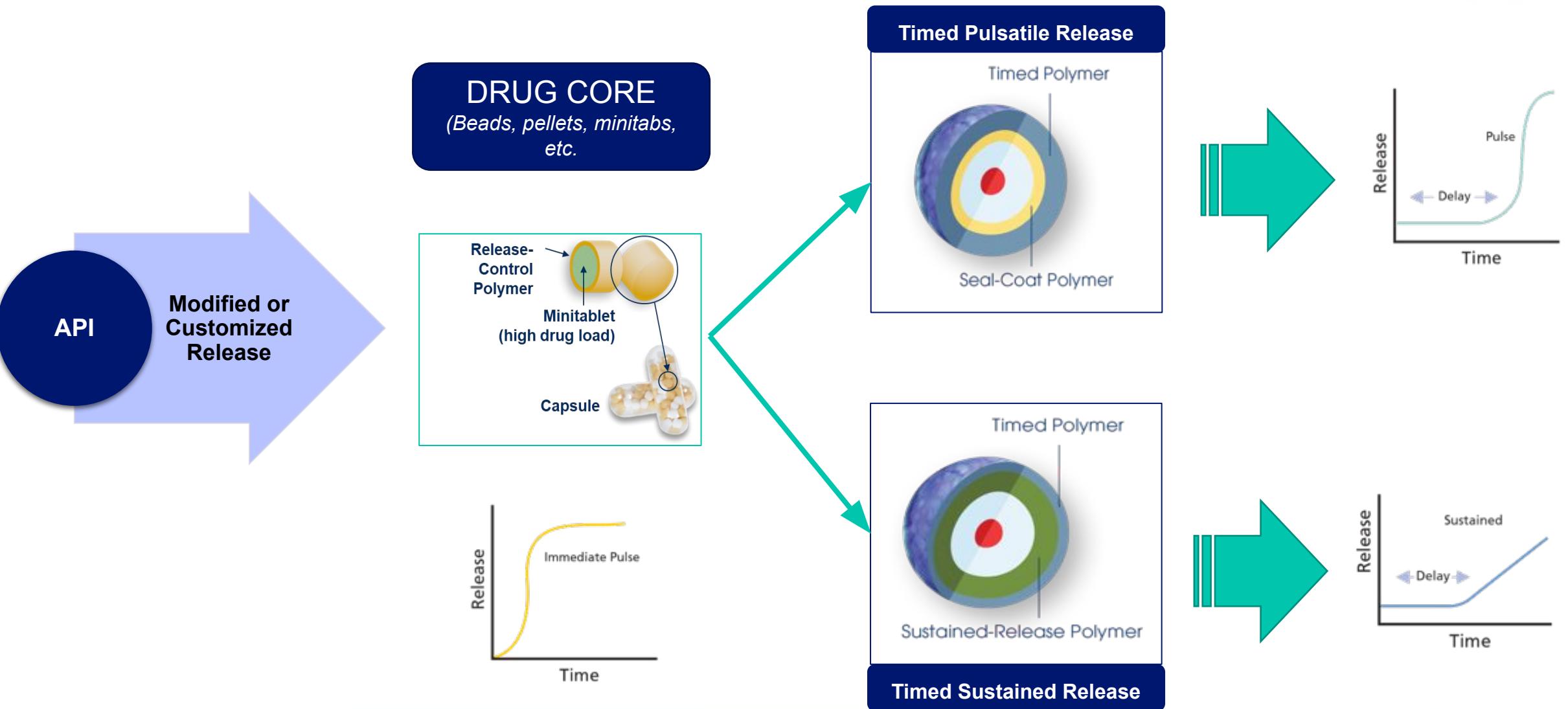
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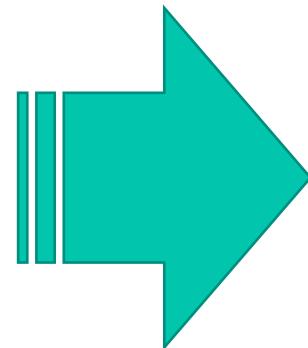
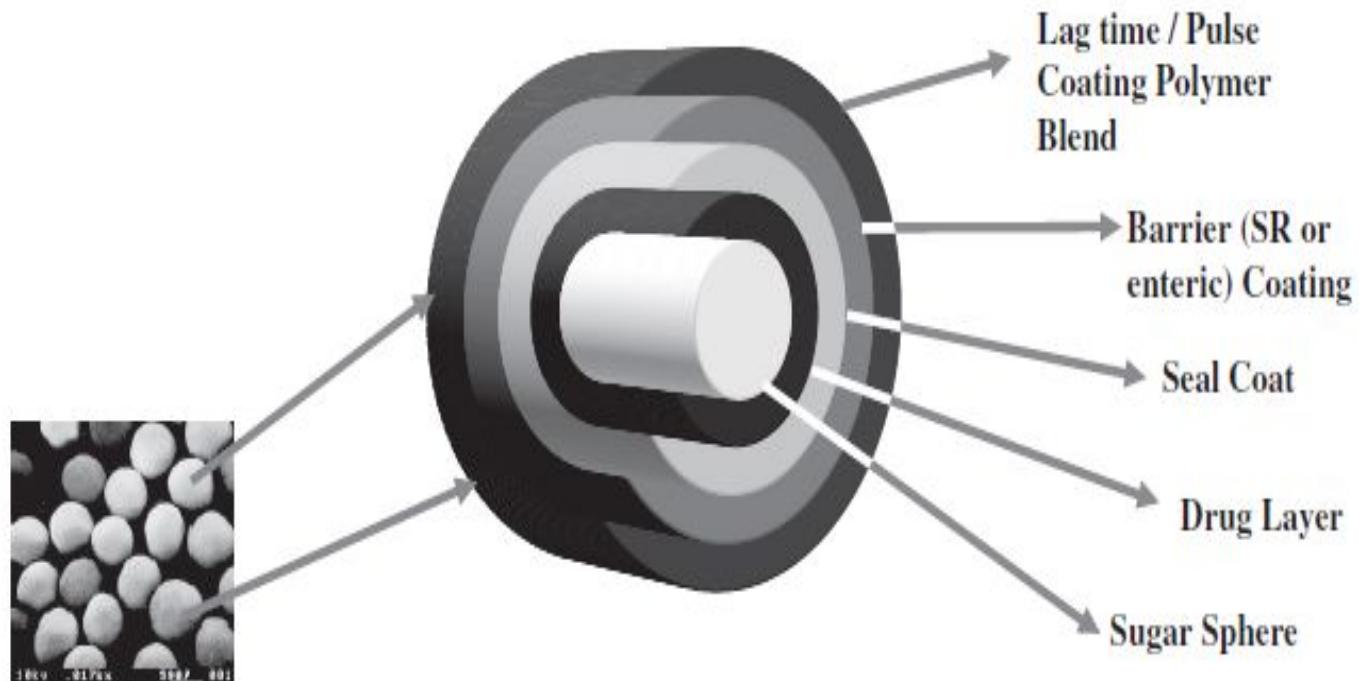


**Diffucaps®: Adare's Multiparticulate-Based Pulsatile
Release Systems**

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Diffucaps®: Design Customized Release Systems





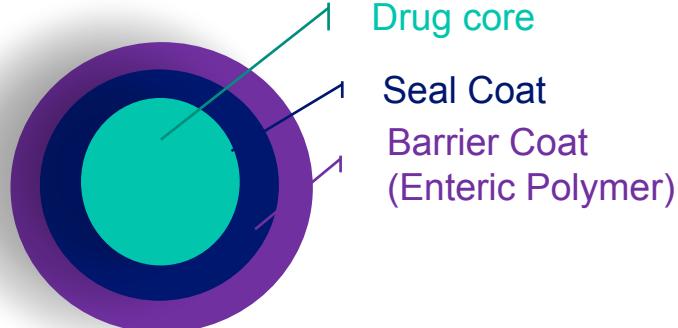
Final Dosage Form:

- Tablets
- Capsules
- ODTs/Advatab
- Novel formats

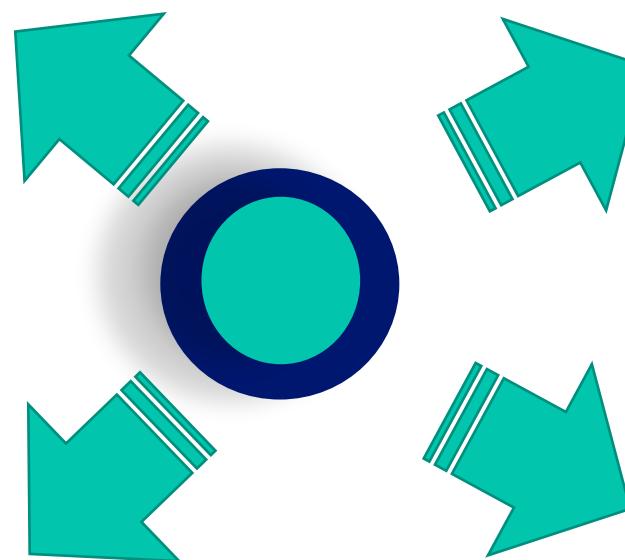
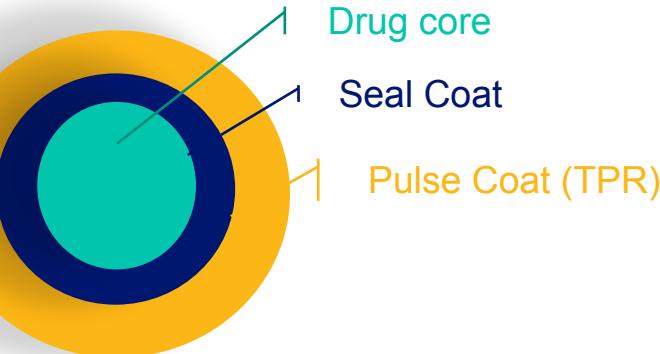
Diffucaps®: Design Customized Release Systems



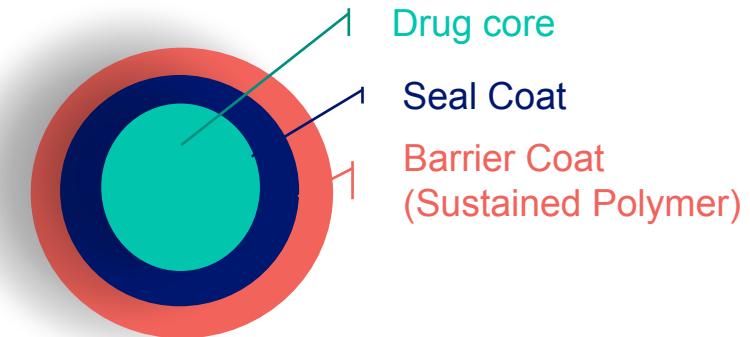
Delayed Release



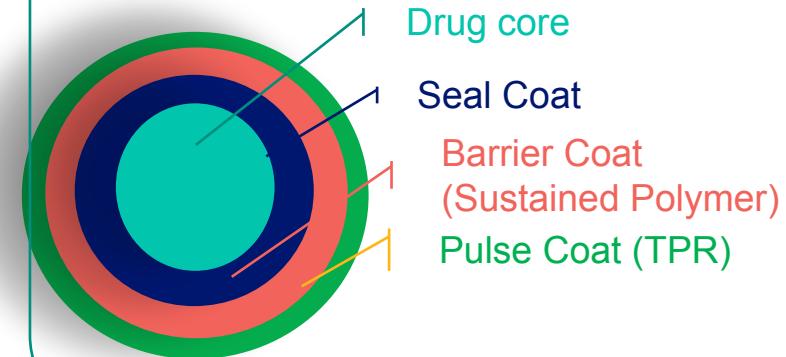
Immediate Pulse (Timed)



Sustained Release



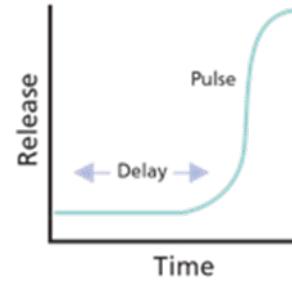
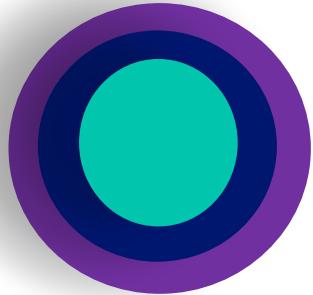
Sustained Pulse (Timed)



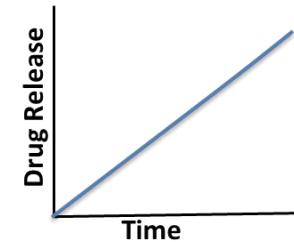
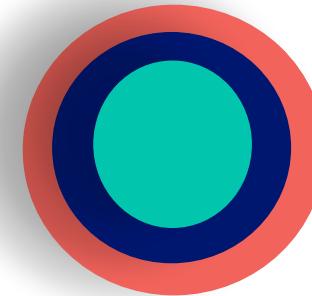
Diffucaps®: Design Customized Release Systems



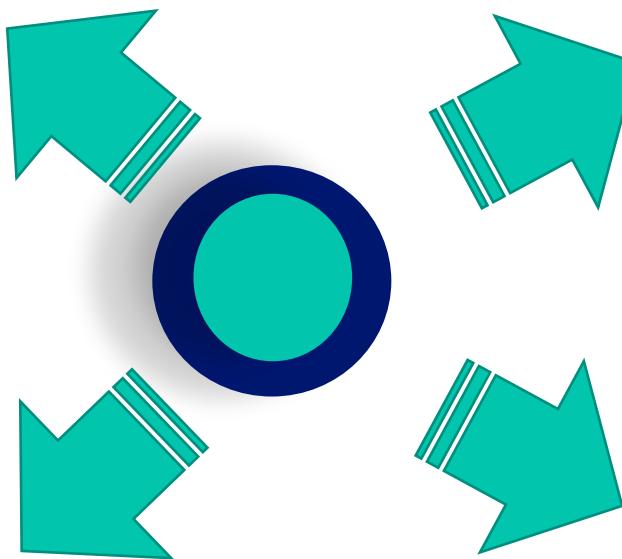
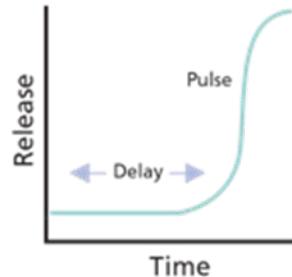
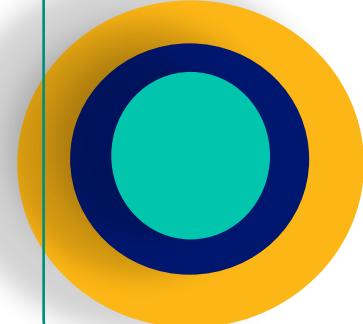
Delayed Release (pH Sensitive)



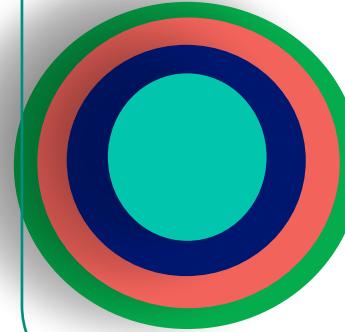
Sustained Release



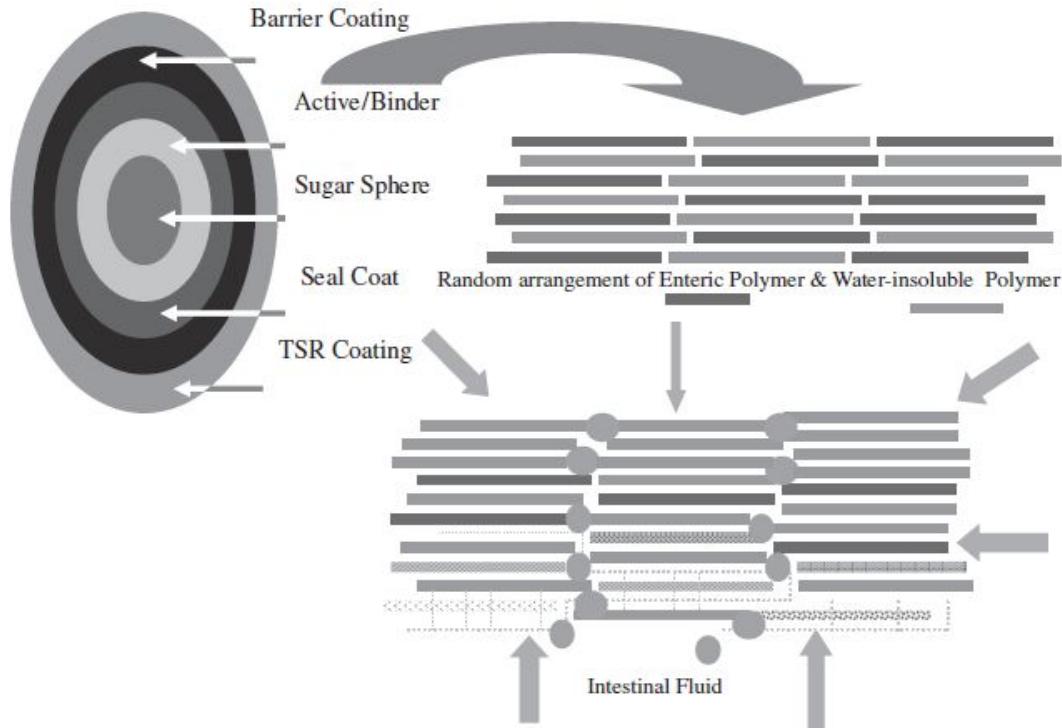
Immediate Pulse (Timed)



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

Diffucaps®: Solubility Modulation

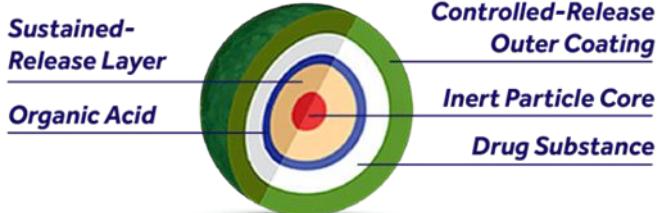


Control of drug release via solubility modulation

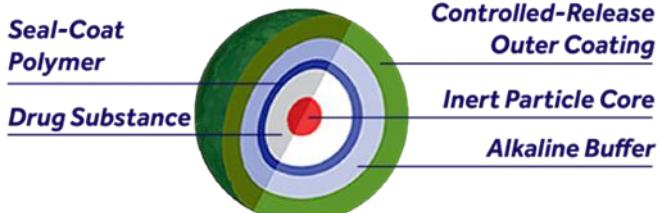
- **Weakly Acidic or Basic Drugs:** Enhancing solubility by creating acidic or basic microenvironment using organic acid or alkaline buffer
- **Highly Soluble Drugs:** Limiting solubility using alkaline buffer (>7 pH) to limit solubility for SR formulations
- **Amorphous Solid Dispersion:** Enhancing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

Multiparticulate Bead System

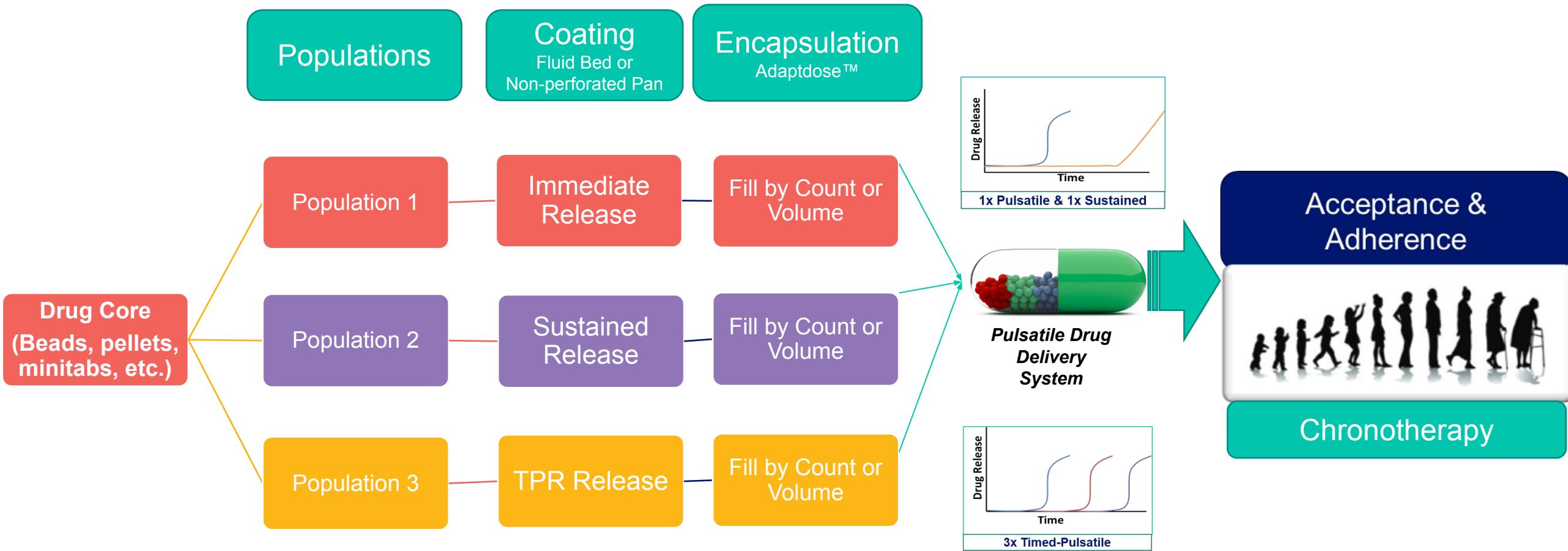
Organic Acid Diffucaps® Bead



Alkaline Buffer Diffucaps® Bead



Diffucaps as Pulsatile Drug Delivery System



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

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

All platforms are compatible with Diffucaps®



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CASE STUDIES

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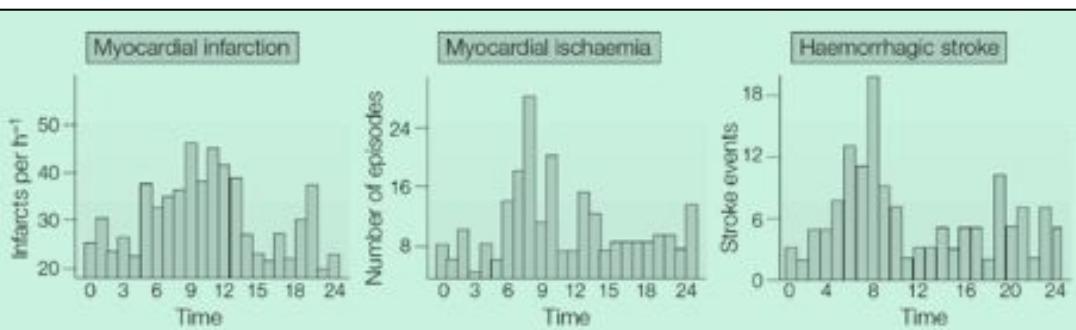


Case Study #1: Chronotherapy for Coronary Artery Disease/Hypertension



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

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

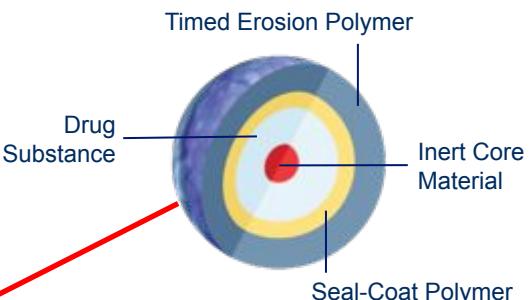
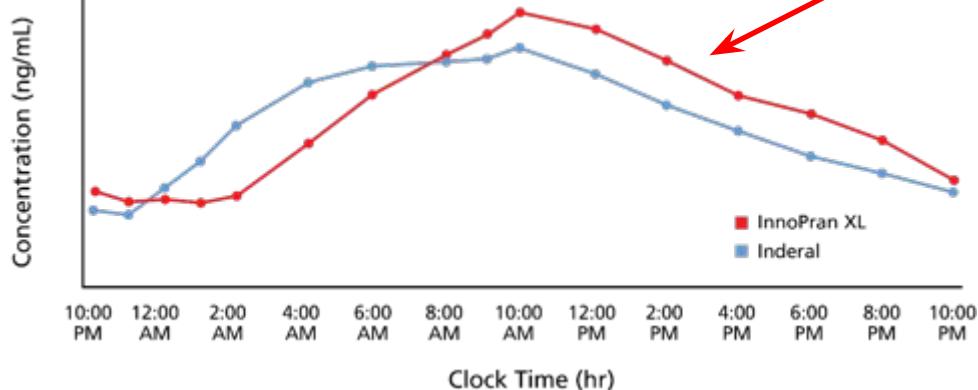


- Cardiac events happen in the morning
- Lowest BP 8PM-2AM
- BP peaks in late morning and falls during afternoon and evening
- 40% higher risk of heart attack, 30% of cardiac death, 50% of stroke
- Marketed SR products – 25% decrease in cardiac events – Tmax of ~6h - NOT CHRONOTHERAPY

Case Study: Chronotherapy for Coronary Artery Disease/Hypertension

Chronotherapy

Plasma Profiles of InnoPran XL versus Inderal LA



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.

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

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Case Study #2: Chronotherapy for ADHD



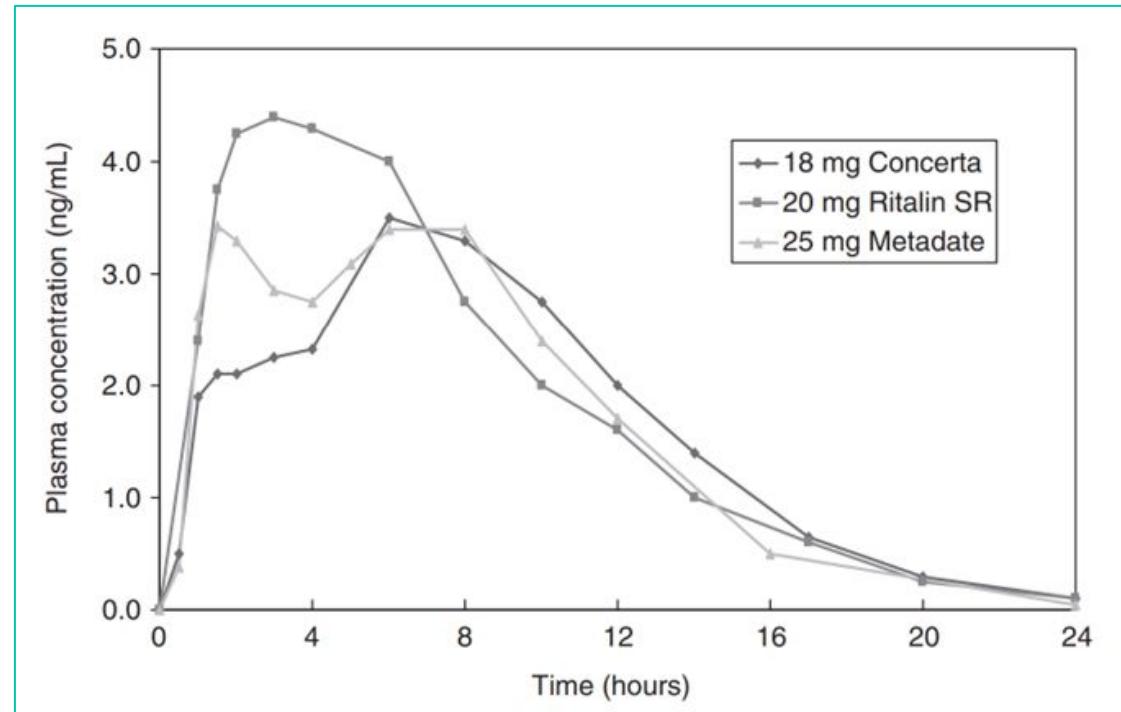
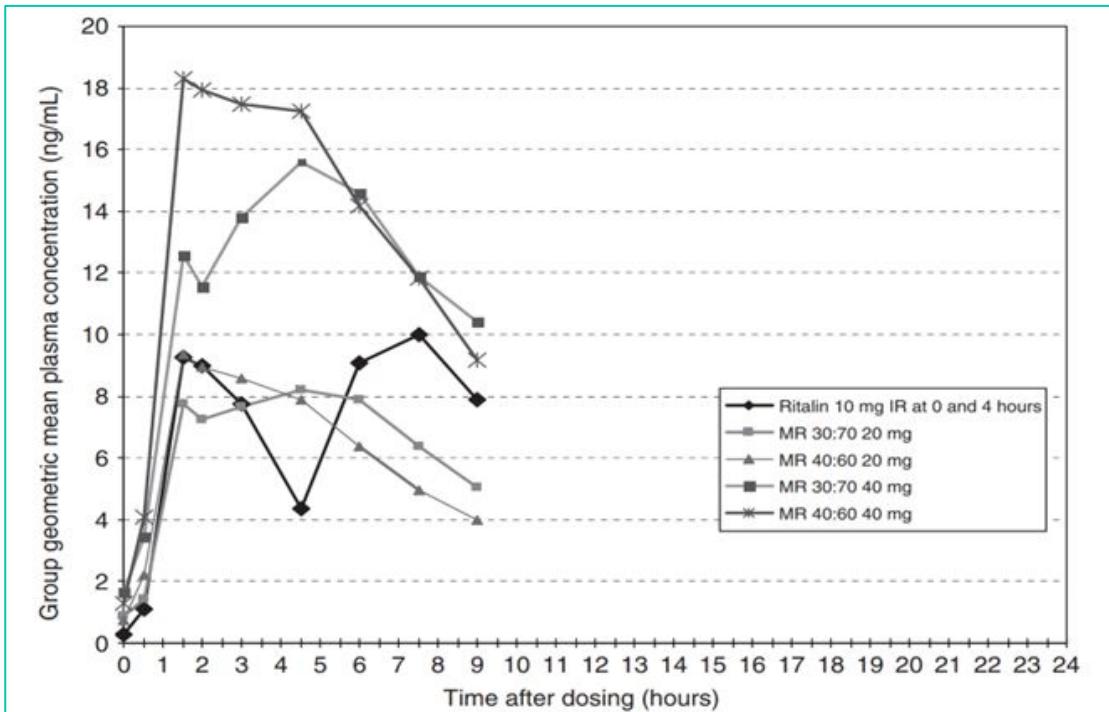
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Case Study #2: Chronotherapy for ADHD

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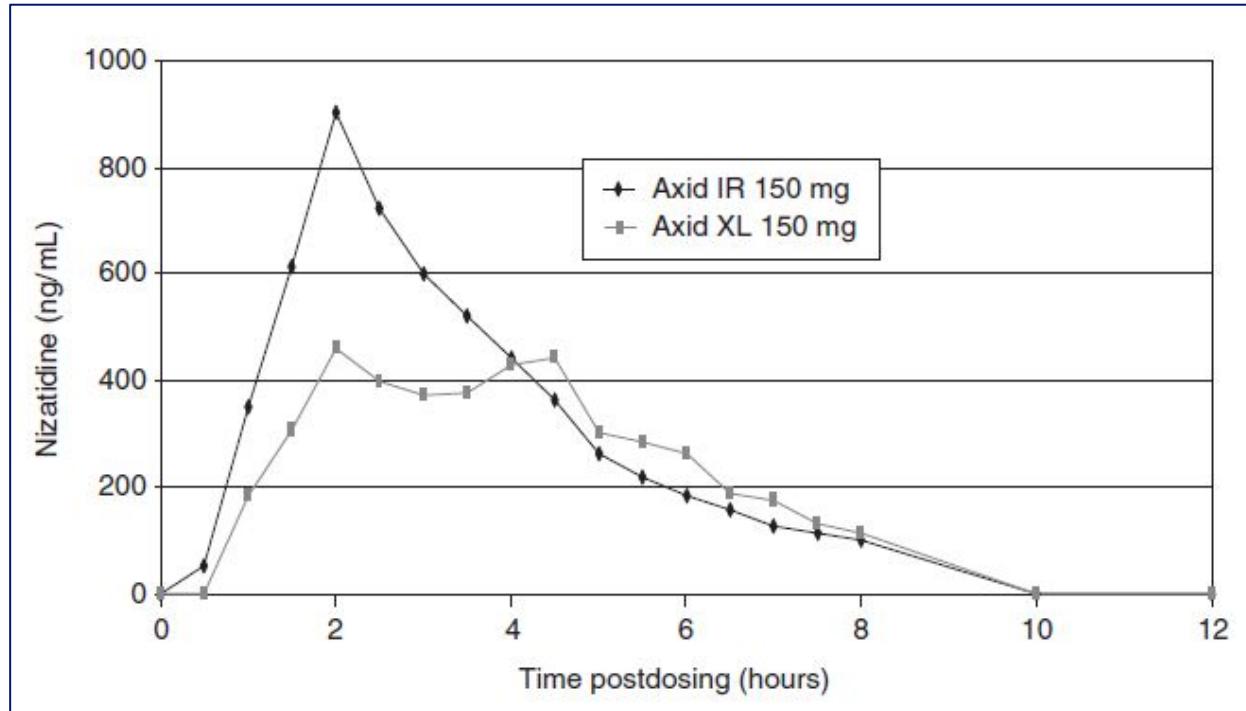
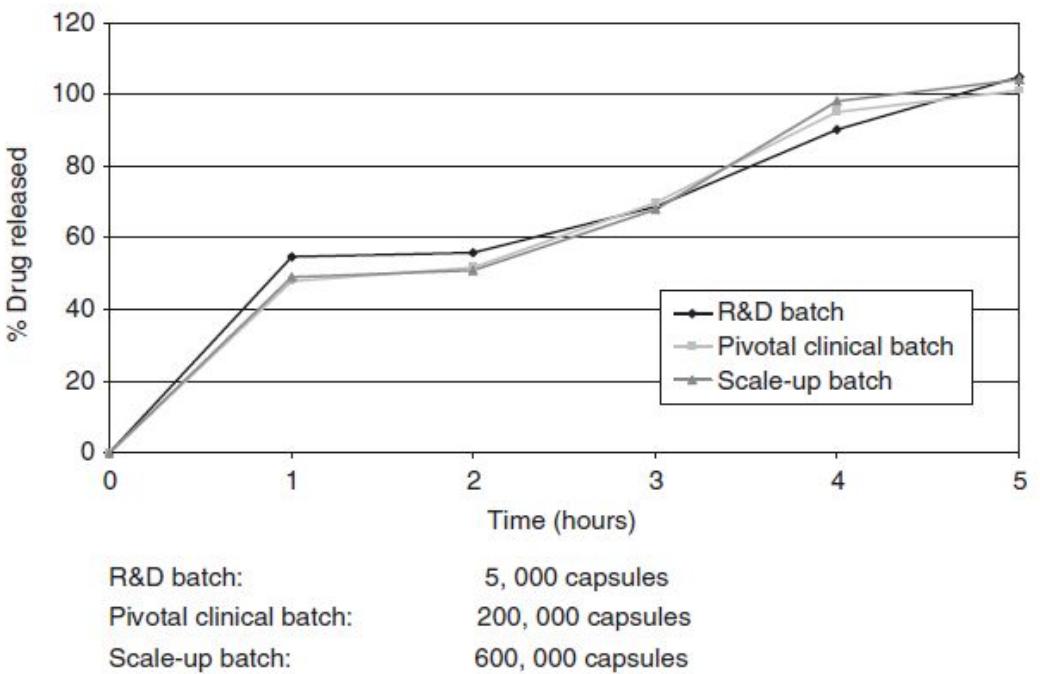
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Case Study #3: Chronotherapy for GERD



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



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

Concluding Remarks:

- 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



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