

TRANSFORMING DRUG DELIVERY.
TRANSFORMING LIVES.

**Customized Release Systems for Pulsatile
Delivery - A Patient-centric Approach for
Chronotherapy**

ADARE[®]
PHARMA SOLUTIONS

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Agenda

- Adare – Highlights
- Patient-Centricity & Chronotherapy
- Pulsatile Release
- Multiparticulates for Pulsatile Release
- Diffucaps® for Chronotherapy
- Case Studies
- Conclusion

**TRANSFORMING DRUG DELIVERY.
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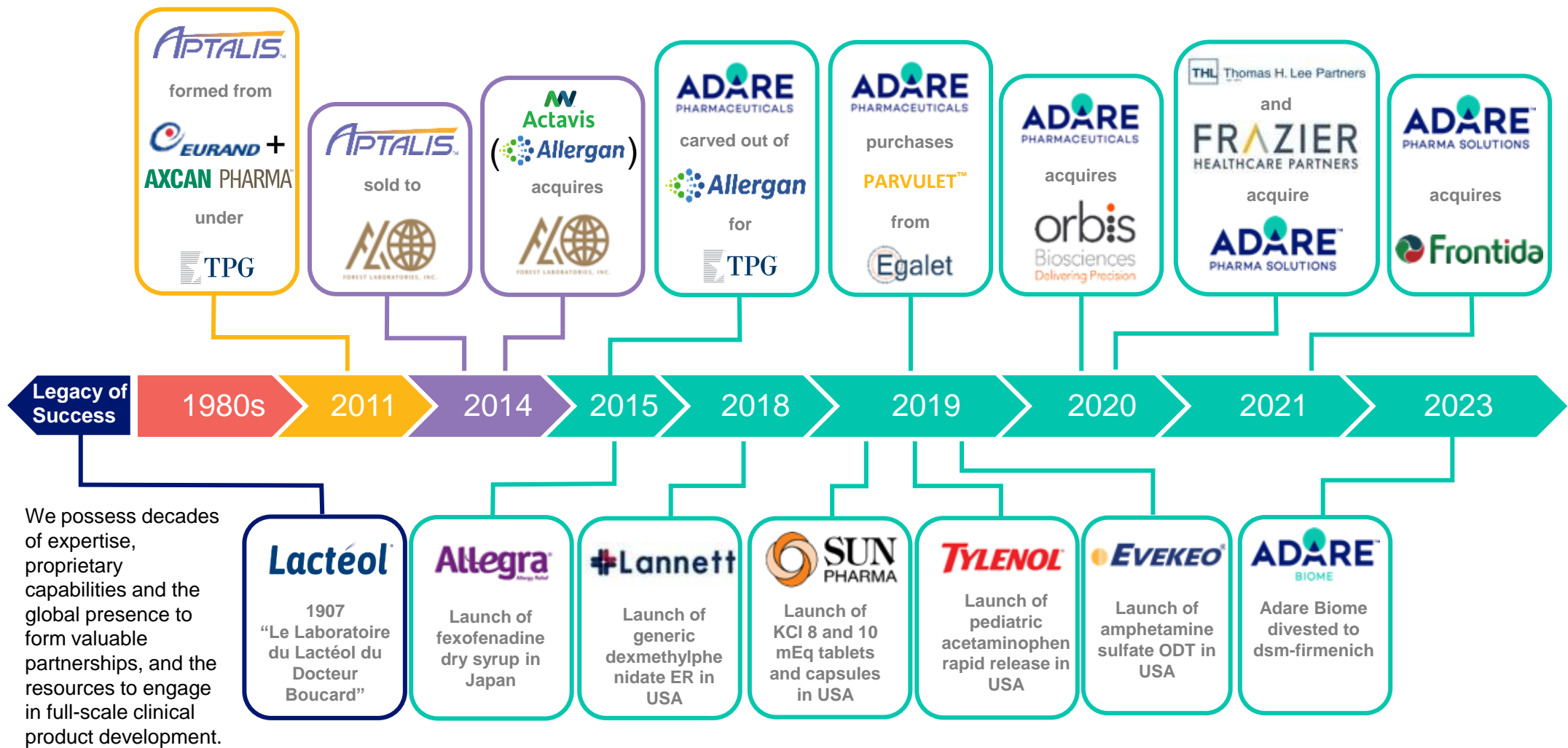


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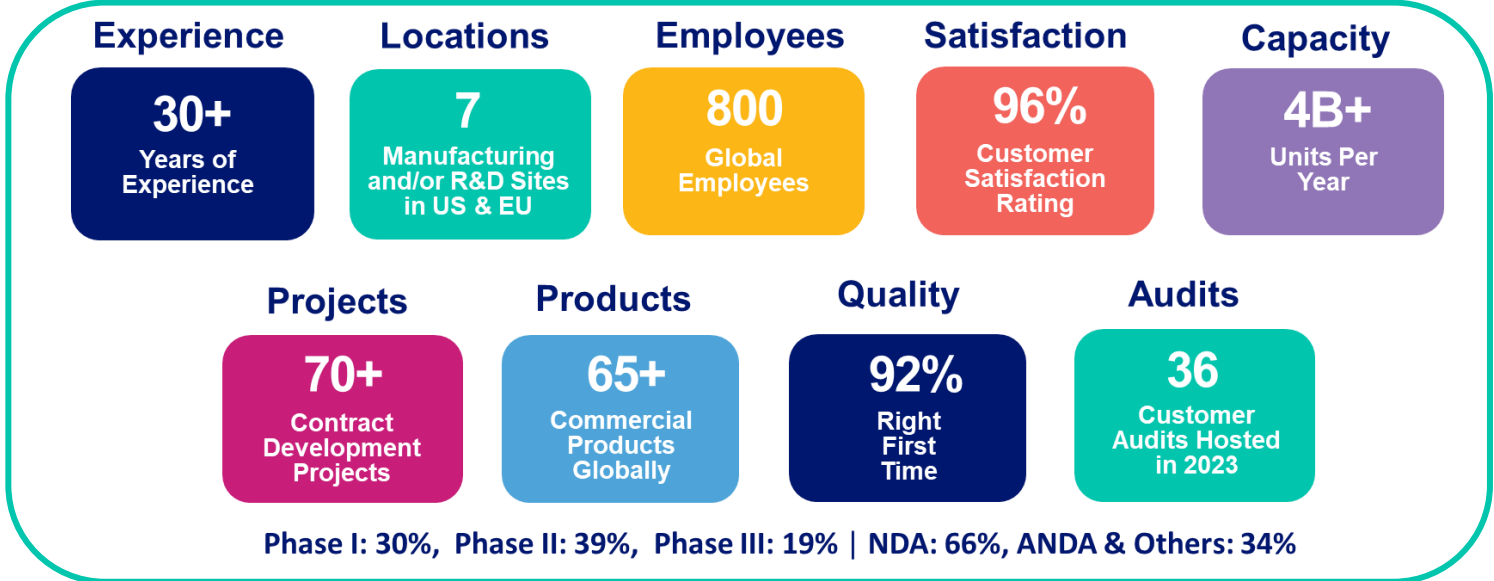
Adare Pharma Solutions: Highlights

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A Long Legacy of Innovation at Adare Pharma Solutions



Adare Pharma Solutions: Long Legacy of Success



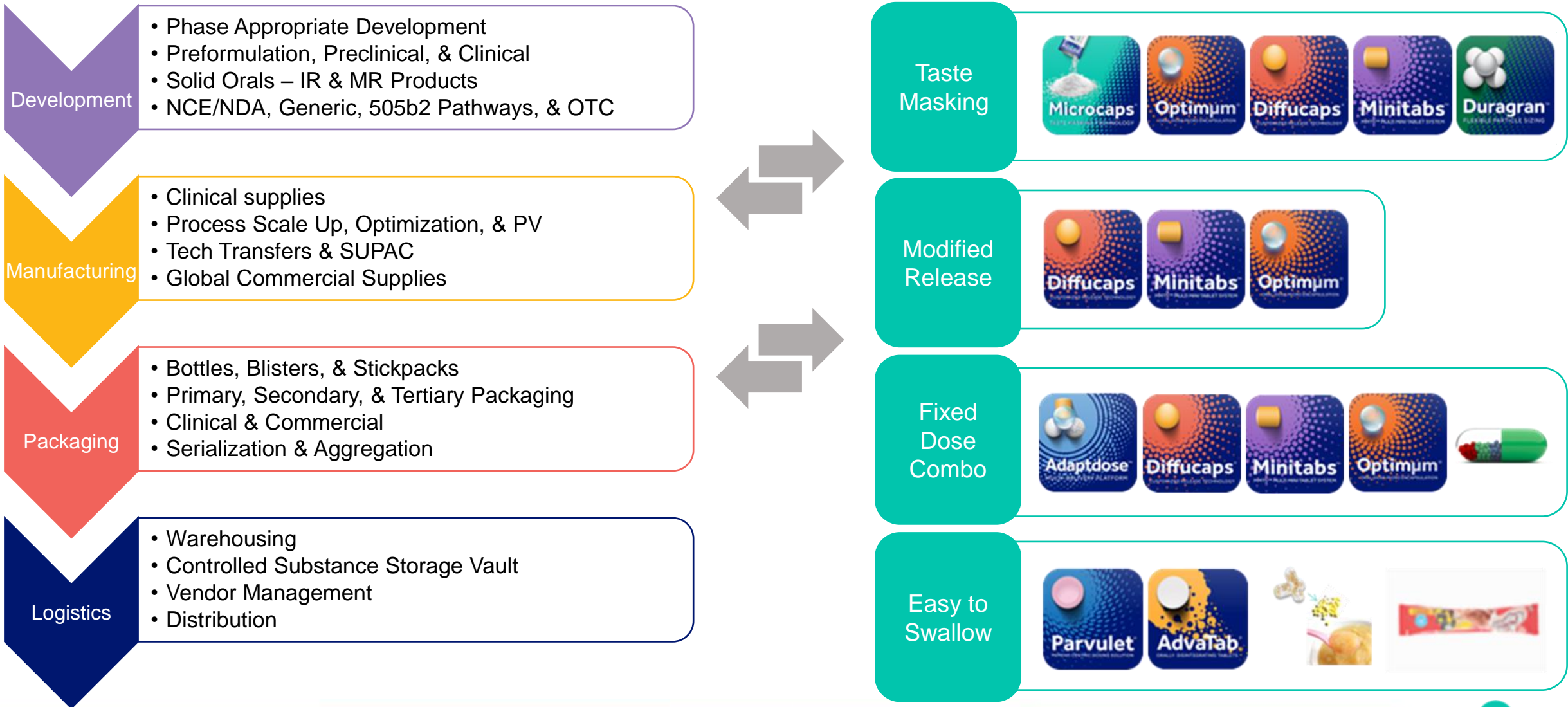
Quality Track Record

Inspection Date	Site	Authority	Inspection Type	Status	Regulatory Authorities
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	Philadelphia	FDA	General, PAI	No observations, product approved	
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) & FDA (through MRA)	General	Corrective actions accepted	
Dec-23	Philadelphia	FDA	General, PAI	Corrective actions accepted	

DEA Inspection History

Inspection Date	Site	Authority	Status	Regulatory Authorities
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	

Adare: Integrated Services & Platform Technologies



Solutions Matrix

		TASTE MASKING	SOLUBILITY ENHANCEMENT	MODIFIED RELEASE	PEDIATRIC FORMULATIONS	COMBINATION PRODUCT	POOR ACCEPTABILITY	SWALLOWING ISSUES	DOSING FLEXIBILITY	CHEMICAL INCOMPATIBILITIES	ORALLY DISINTEGRATING	DOSING CONVENIENCE	CONTROLLED SUBSTANCES	ABUSE DETERRENCE TESTING
ADAPTDOSE™	MULTI-DELIVERY PLATFORM				✓						✓	✓		
ADVATAB®	ORALLY DISINTEGRATING TABLETS				✓		✓	✓			✓	✓	✓	
DIFFUCAPS®	MULTIPARTICULATE CUSTOMIZED RELEASE	✓	✓	✓	✓	✓			✓	✓	✓	✓	✓	
DURAGRAN™	FLEXIBLE PARTICLE SIZING	✓		✓	✓	✓	✓		✓	✓	✓			
MICROCAPS®	TASTE MASKING MICROENCAPSULATION	✓		✓	✓		✓		✓	✓	✓	✓	✓	
MINITABS™	MULTIPARTICULATE DOSE DELIVERY			✓	✓	✓	✓		✓	✓	✓	✓	✓	
OPTIMUM®	ORAL DOSE MICROENCAPSULATION	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	
PARVULET™	PATIENT-CENTRIC DOSING SOLUTION				✓		✓	✓			✓	✓	✓	
STRATUM™	INJECTABLE MICROENCAPSULATION			✓			✓		✓		✓	✓	✓	
UNISUN®	OTIC INJECTABLE TECHNOLOGY			✓			✓		✓		✓			
CAT.ONE™	ABUSE DETERRENCE TESTING													✓
HOT MELT EXTRUSION			✓											
FLUID BED PROCESSING			✓			✓				✓				
SPRAY DRYING			✓											
BI-LAYER TABLETING				✓		✓					✓	✓		

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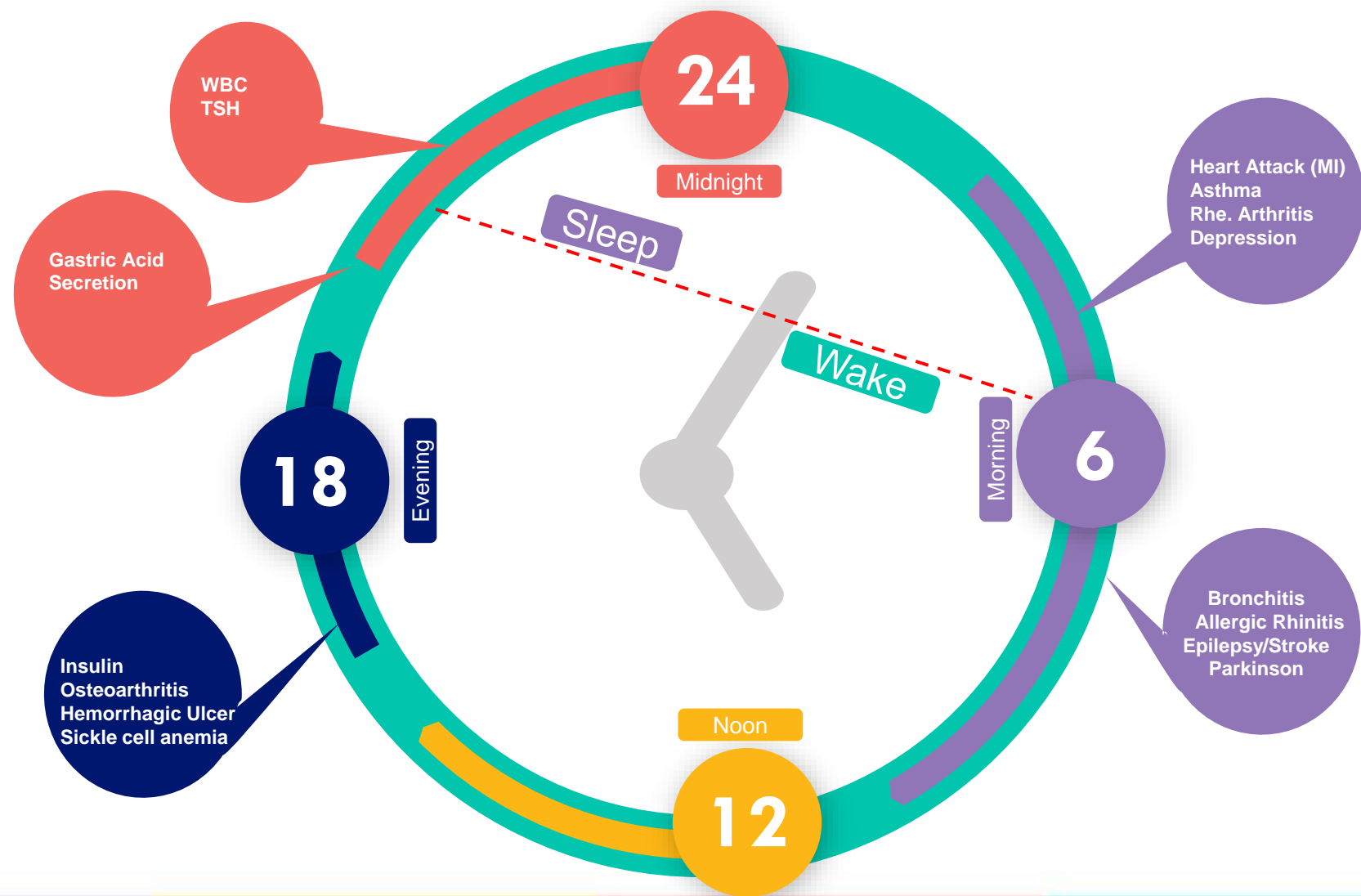
Patient-Centricity & Chronotherapy

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Patient Need: Harmonizing the Medication Release - Chronotherapy

- 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**

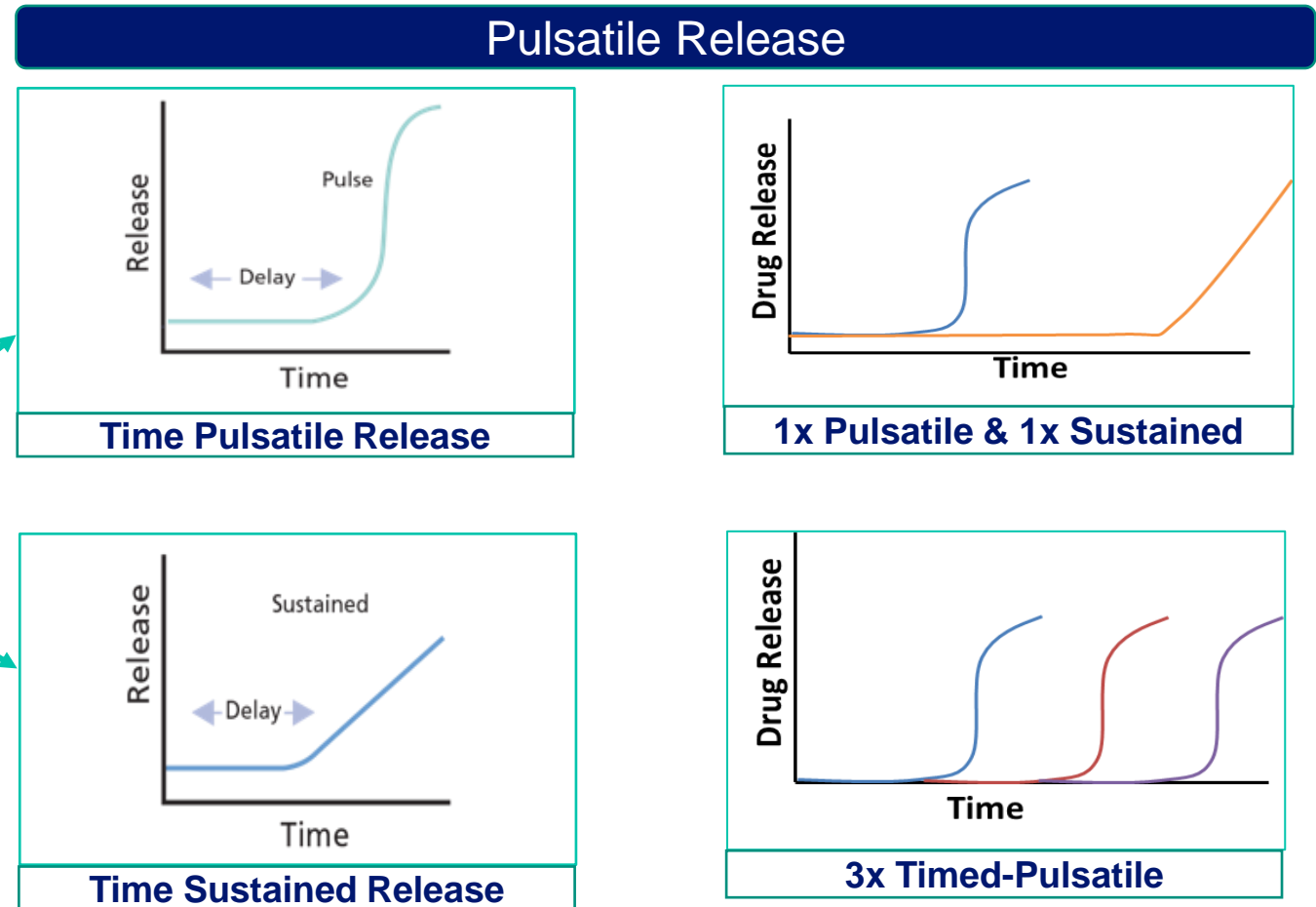
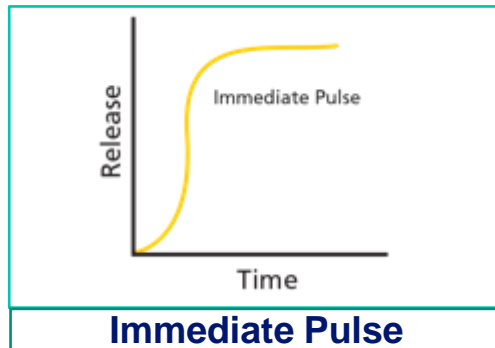
Circadian Rhythm: Body's Natural Rhythm



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



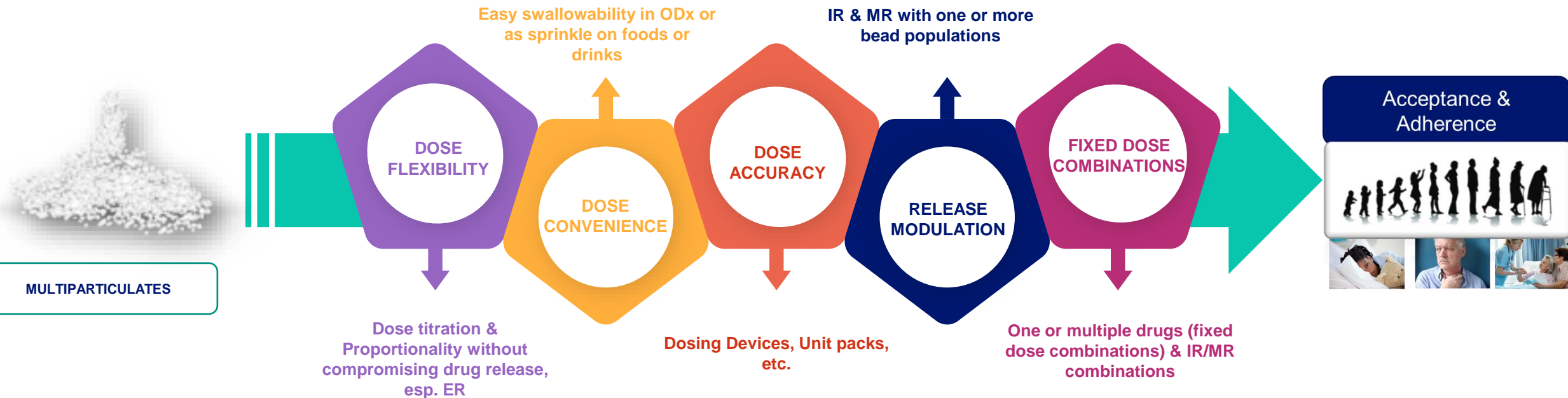
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Multiparticulates-based Technologies for
Pulsatile Delivery

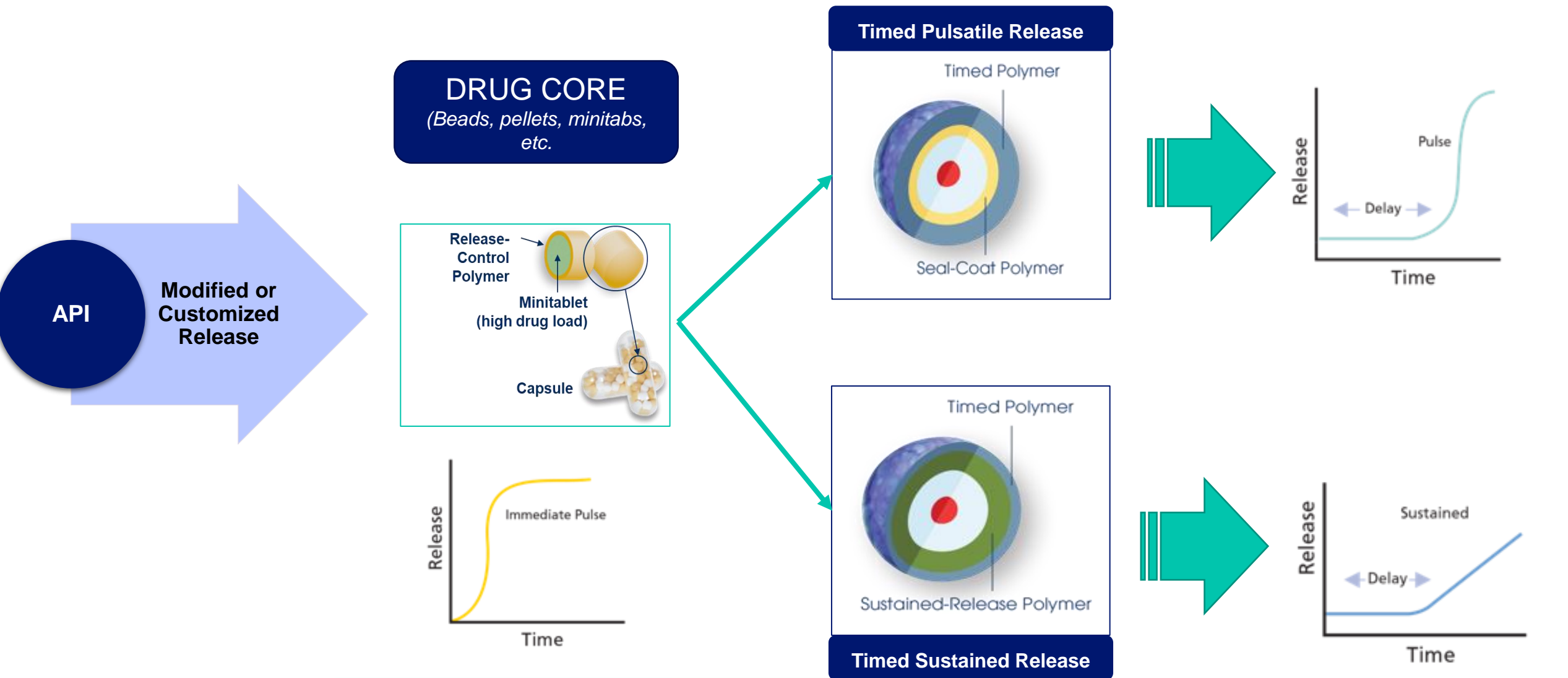
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Multiparticulates for Pulsatile Release Systems

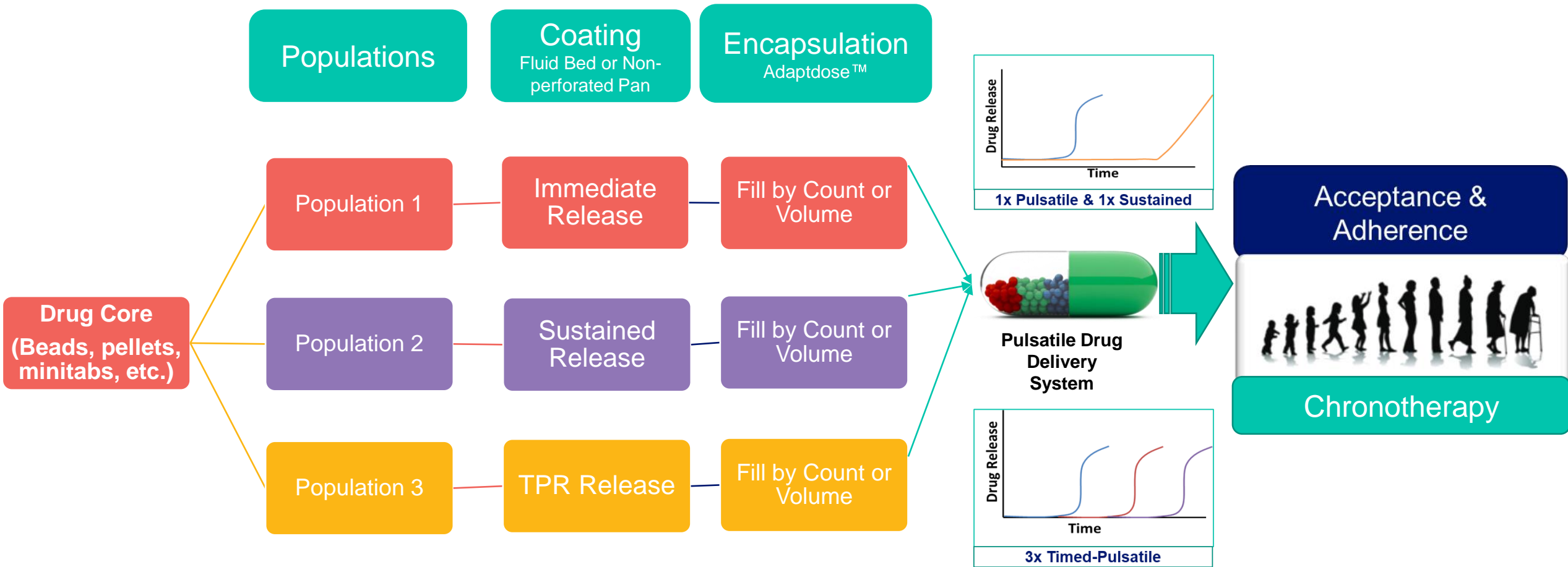
- Multiple particles - multiple small discrete units
- Pellets, granules, spheroids, minitabs, microtabs, etc.
- Size 150 μm to 4 mm
- Ability to achieve various release profiles, IR & MR including DR, ER, CR, PR, etc.
- Improved PK profile, reduced side effects, etc.
- Improved stability, dose accuracy, and reduced weight/bulkiness over liquid formulations



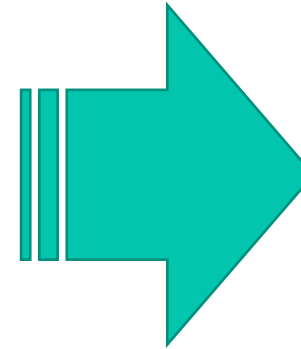
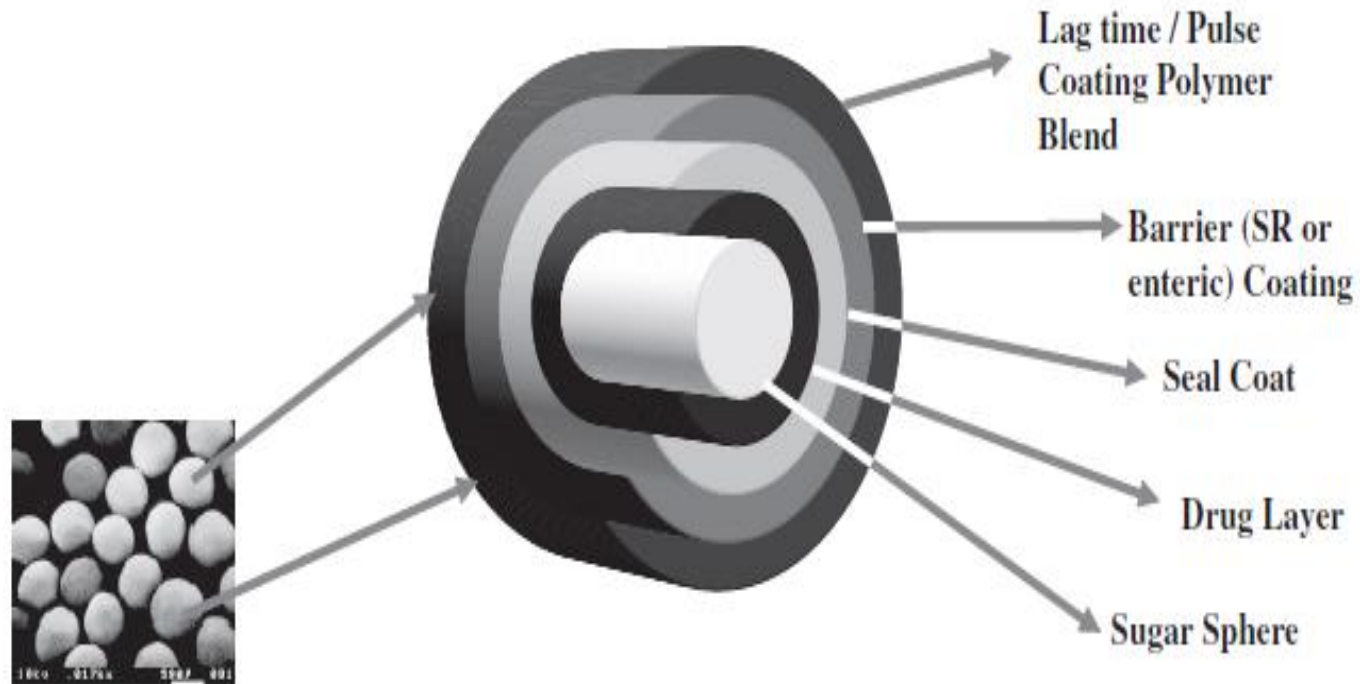
Multiparticulates for Pulsatile Release Systems



Multiparticulates for Pulsatile Release Systems



Diffucaps®: Multiparticulates for Pulsatile Release Systems



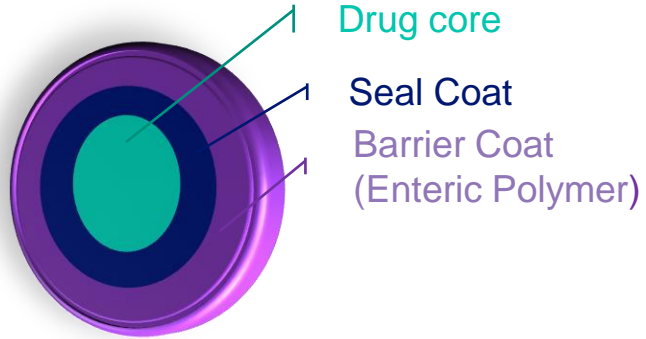
Final Dosage Form:

- Tablets
- Capsules
- ODTs/Advatab
- Novel formats

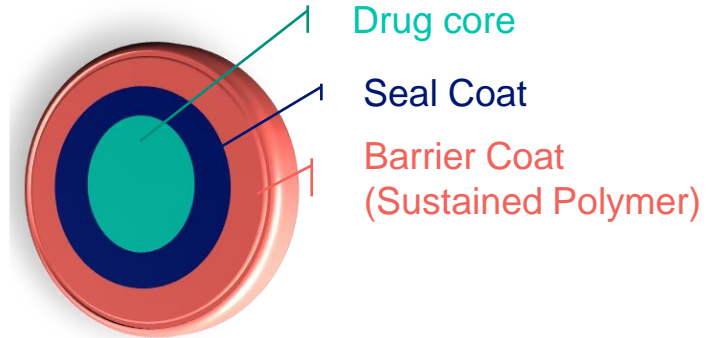
Diffucaps®: Design Customized Release Systems



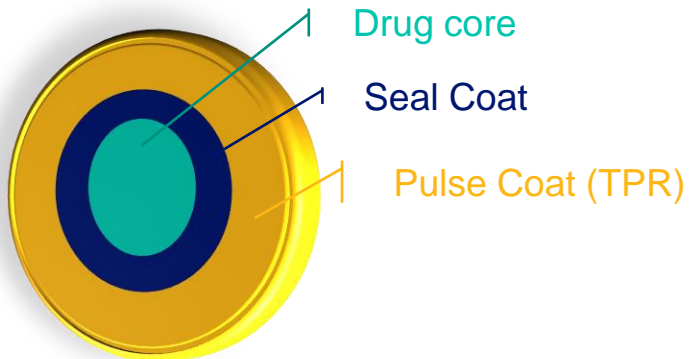
Delayed Release



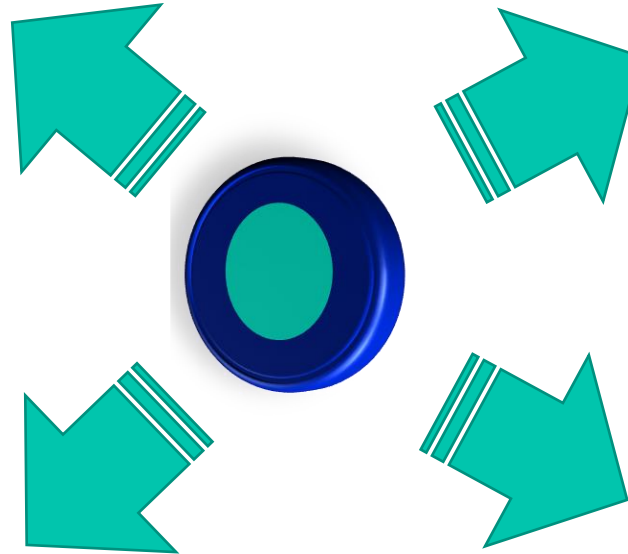
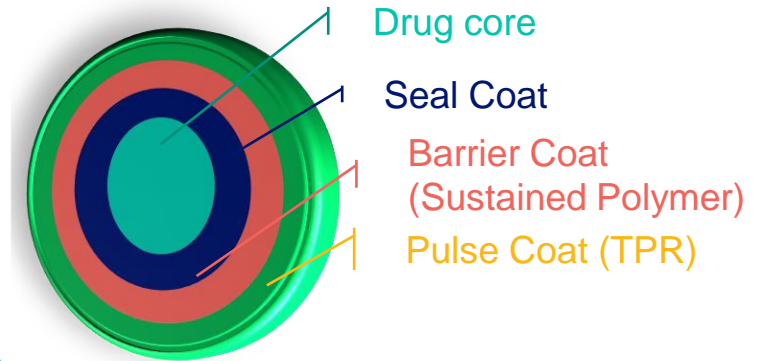
Sustained Release



Immediate Pulse (Timed)



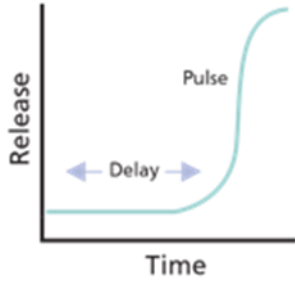
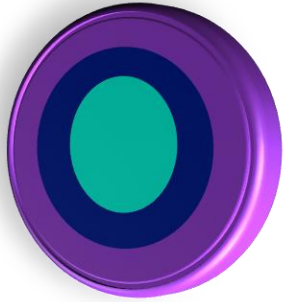
Sustained Pulse (Timed)



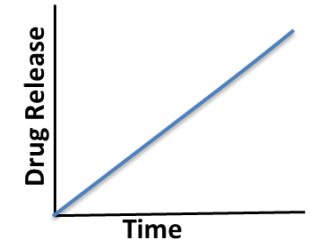
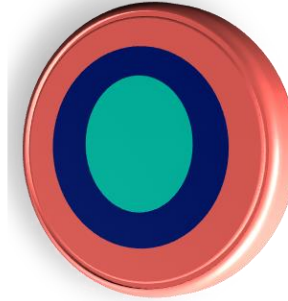
Diffucaps®: Design Customized Release Systems



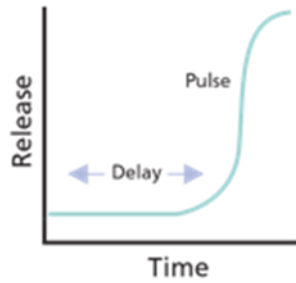
Delayed Release (pH Sensitive)



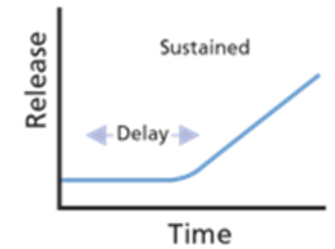
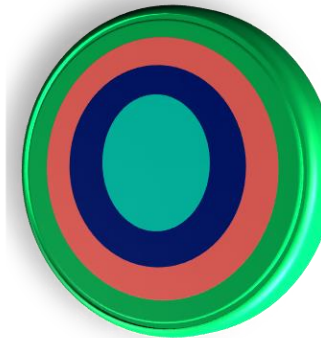
Sustained Release



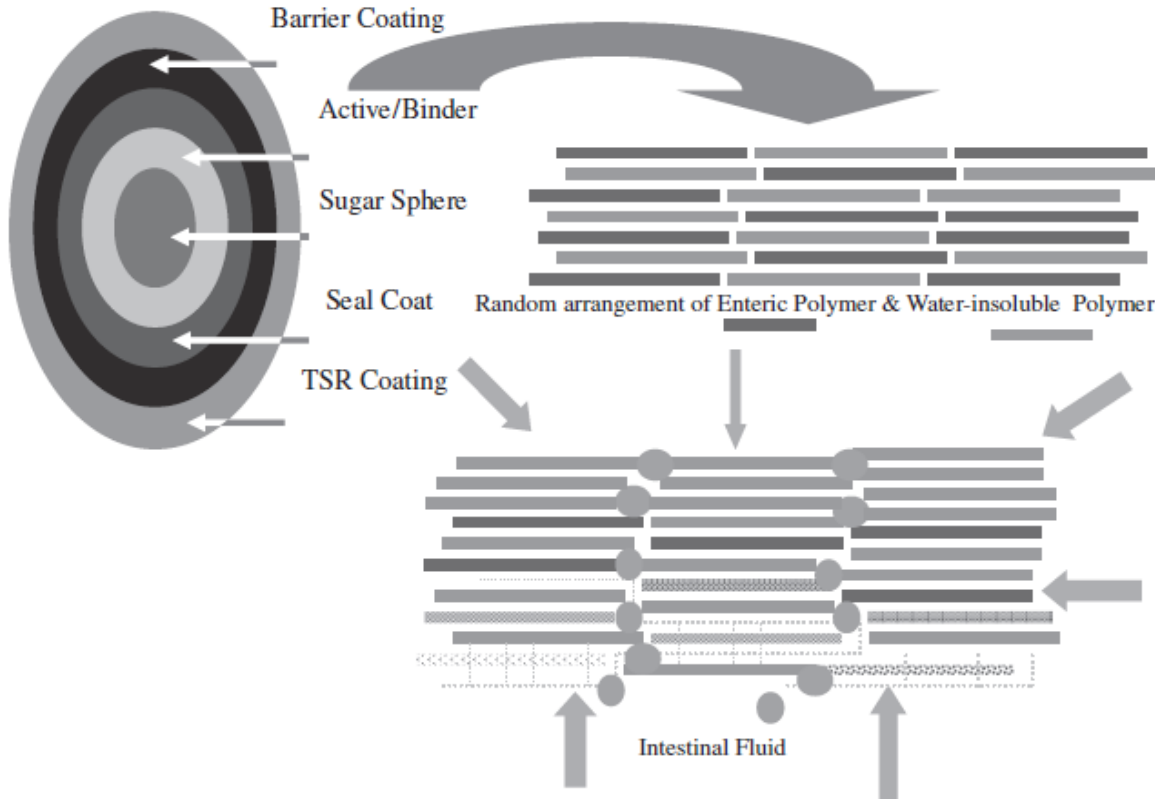
Immediate Pulse (Timed)



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

Diffucaps®: Mechanism of Drug Release

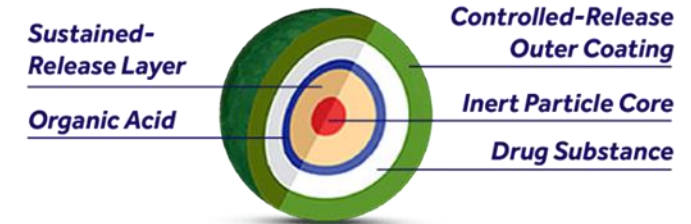


Control of drug release via solubility modulation

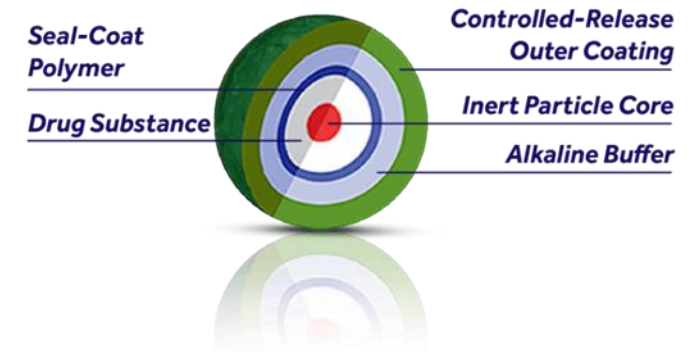
- **Weakly Acidic or Basic Drugs:** Enhancing solubility by creating **acidic or basic microenvironment** using organic acid or alkaline buffer
- **Highly Soluble Drugs:** Limiting solubility using alkaline buffer (>7 pH) to limit solubility for SR formulations
- **Amorphous Solid Dispersion:** Enhancing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

Multiparticulate Bead System

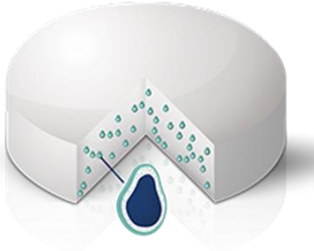



Organic Acid Diffucaps® Bead



Alkaline Buffer Diffucaps® Bead



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 <u>semi-solid mass with water without agitation</u></i></p> 	<p>Sprinkle and FDC Platform</p> <p><i><u>Sprinkle on soft food</u> in capsules</i></p> 	<p>Powder for Reconstitution Platform</p> <p><i><u>Temporary suspension</u> with water, <u>Direct-to-mouth</u>, or <u>sprinkle on soft foods</u> – 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 approximately 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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Diffucaps®: Case Studies

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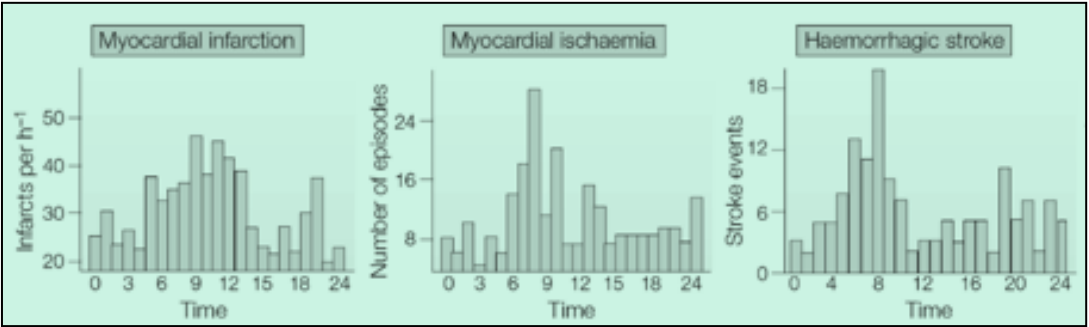


Case Study #1: Chronotherapy for Coronary Artery Disease/Hypertension

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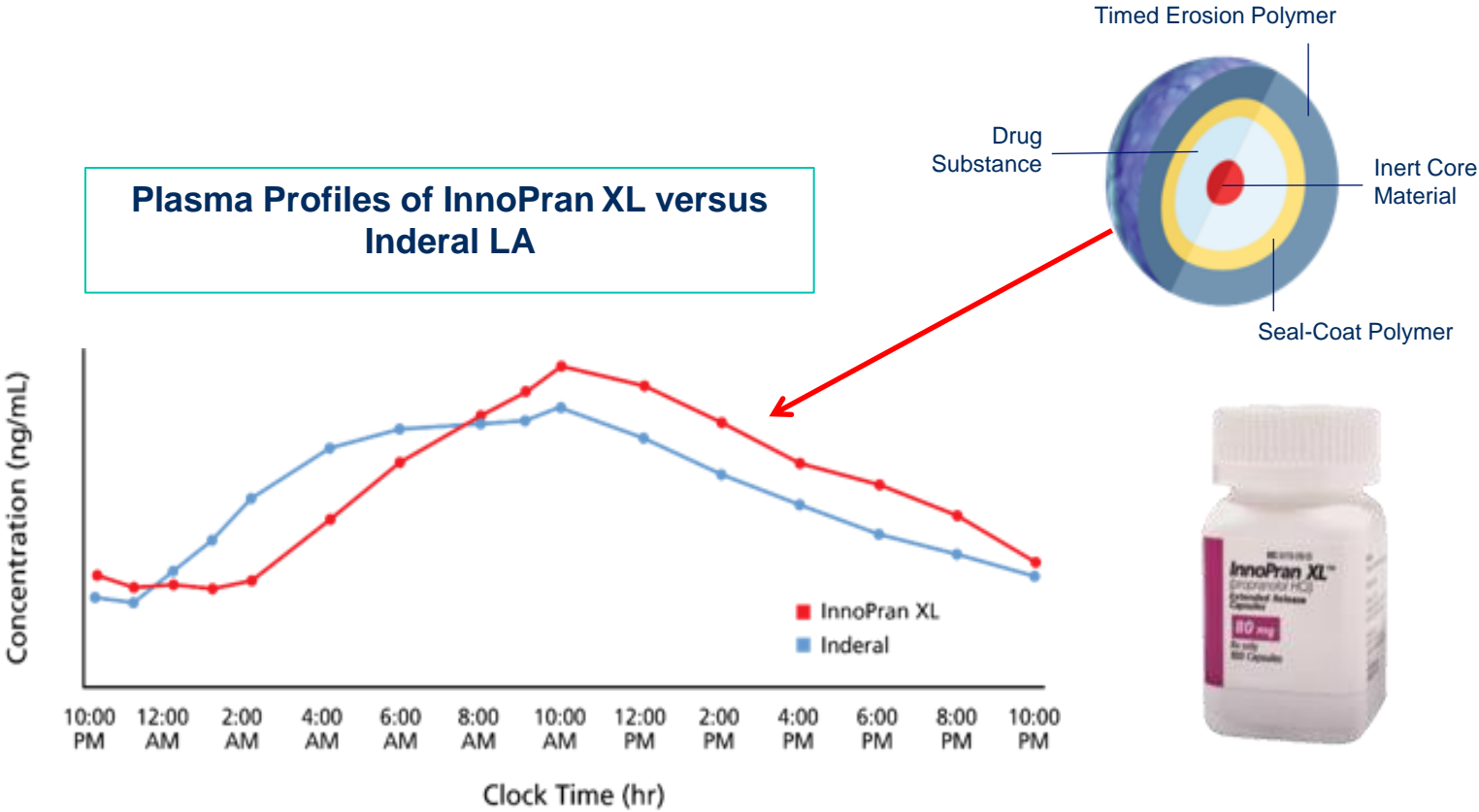
Case Study #1: Chronotherapy for Coronary Artery Disease/Hypertension

DRUG	<ul style="list-style-type: none">• 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

Multiparticulates for Pulsatile Release Systems



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

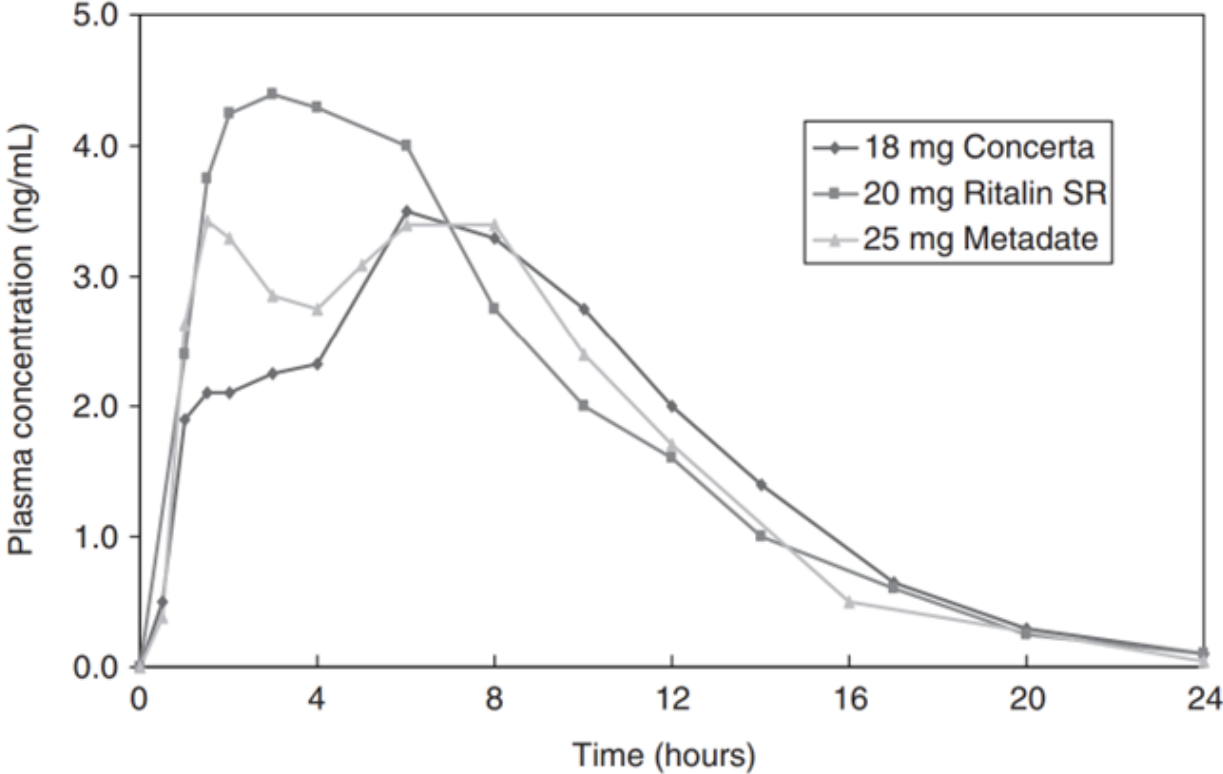
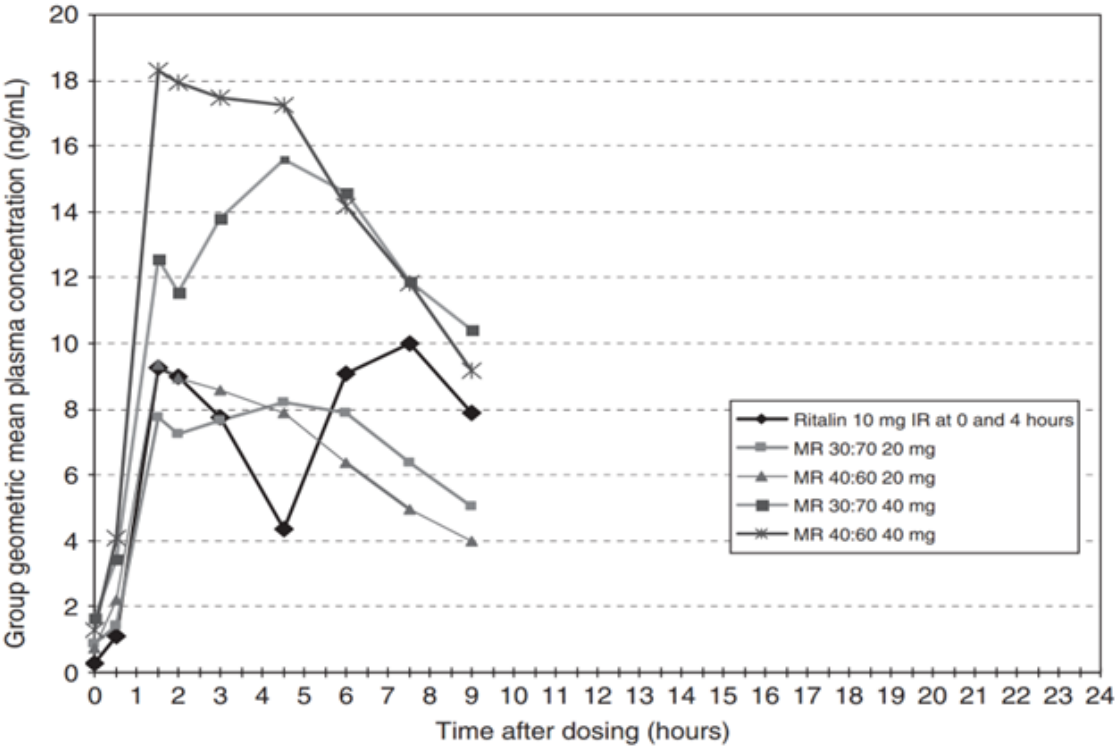
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Case Study #2: Chronotherapy for ADHD

DRUG	<ul style="list-style-type: none">• 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

- Requires frequent dosing given short half life
- Need to maintain plasma levels during day and avoid midday dosing for grade school 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



Conclusion

- 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!

To learn more about Adare's patient-centric technologies,
please contact us at busdev@adareps.com



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