DEVELOPMENT DELIVERY SUPPLY

Catalent®

Redefining Possibilities with Lipid-based Formulations from Pre-Clinical to Commercial and Harnessing Softgels for Drug Delivery

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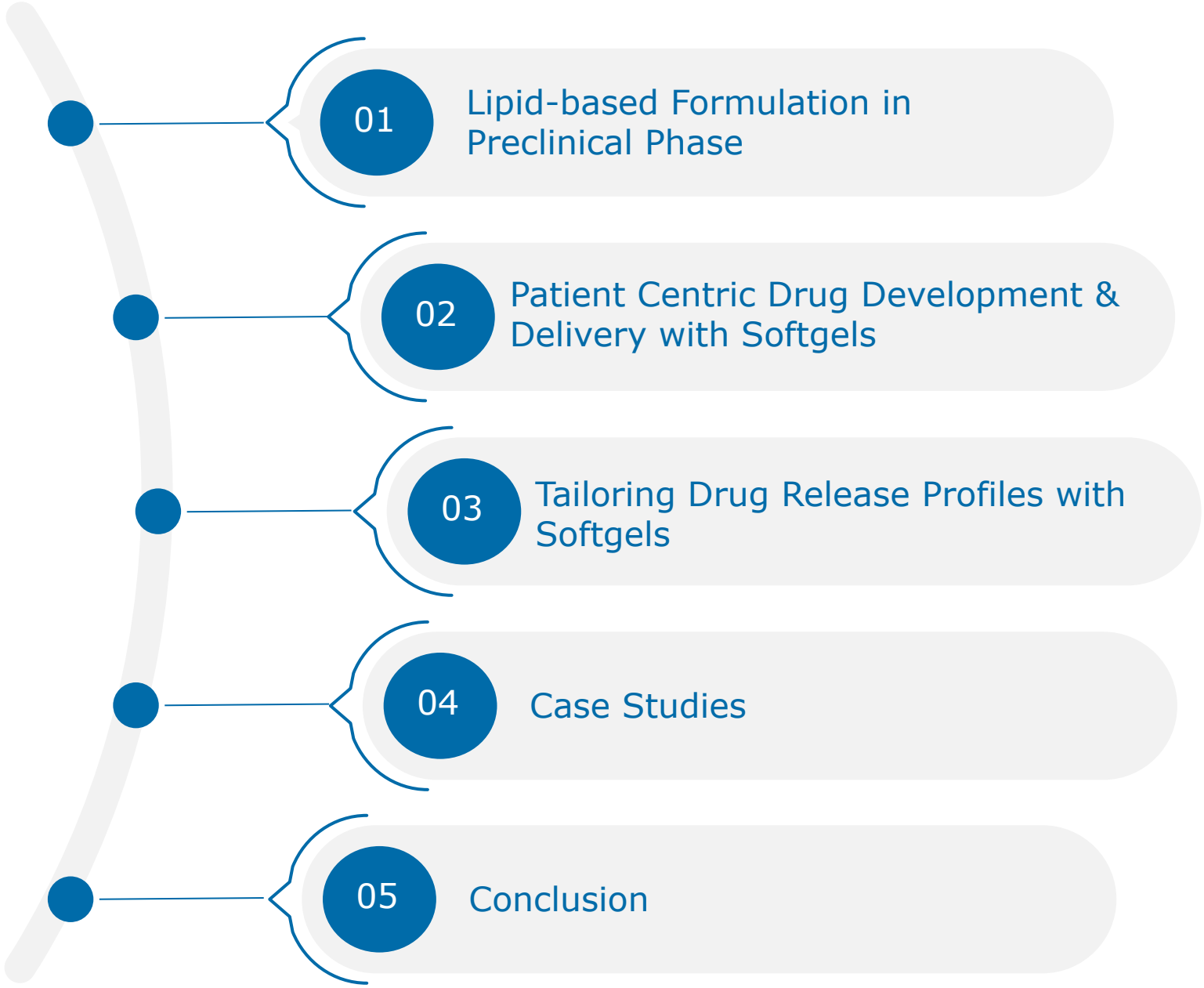
CATALENT PHARMA SOLUTIONS

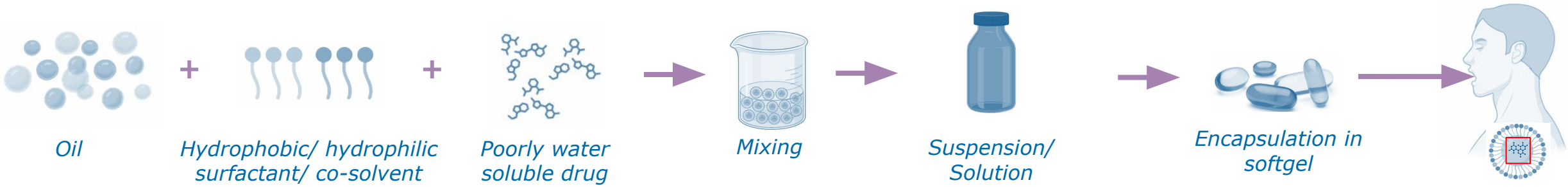
JULY 25,2023

more products. better treatments. reliably supplied.™

AGENDA



What Is a Lipid-based Formulation (LBF) ?



- A type of drug delivery system that typically comes in a **liquid** or **semi-solid** form
- The API is usually **dissolved** or **suspended** within the lipid-based ingredients, with little to no water involved in the formulation
- Characteristically a **homogeneous mixture**, although it can form an emulsion when it is well dispersed in an aqueous solution
- LBFs are often **encapsulated in softgel** as final dosage form for ease of oral delivery

Why Do We Develop Oral LBFs?

LBFs Can Address a Variety of Challenges

API Challenges

- Liquid state
- Highly potent API/ low dose
- Physical instability
- Chemical instability

Processing Challenges

- Powder/tableting issues
- Scalability issues
- Potent powder handling & operator safety

Clinical Challenges

- Dose flexibility
- Patient compliance
- Bioavailability improvement

Economic Challenges

- Speed to clinic
- Speed to market
- Lifecycle management

LBFs provide versatility to optimize drug performance, meeting patient & sponsor needs

How Formulation Complexity Evolves Over the Early Phases

	EXPLORATORY/ DEVELOPABILITY	GLP TOX	FIRST-IN-HUMAN
TYPE OF STUDIES	• PK – Candidate Selection • PK – Delivery Tech. Selection • Efficacy • Toxicity: Dose Range Finding	• Toxicology (2 species) • Genotoxicity • Toxicokinetics • Safety Pharmacology • Reproductive Toxicology	• Safety • Dose range • Side effect/toxicity • Pharmacokinetics
DOSE	1-50 mg/kg	≤ 1000 mg/kg (or up to 50-fold margin exposure)	≤ 10 mg/kg (typical)
FORMULATION FOCUS	**Exposure** of the drug to assess **efficacy** of the drug	To **push the limits of exposure** to elucidate **toxic effects** to assess the **safety** of the drug	Develop **Target Product Profile**
FORMULATION COMPLEXITY	**Solubility** (versus stability) is key focus; format should allow for quick/flexible dosing	• **Solubility & stability** needed for longer studies • Tolerability of formulation at **high doses** over **extended dosing**	• Formulation/enabling technology is selected for solubility & stability • **Dose delivery may be simplified** for flexible dosing as compared to later phase

High dose levels for GLP tox studies may require alternative formulation strategies such as LBF

Same Formulation for Toxicology & Clinical Studies?

GLP Tox Formulation

Solubility/permeability limited compounds **require unique formulations to achieve high dose**

(100x higher dose exposure needed)

Systemic **exposures achieved will often (and should) exceed clinical exposures** at max human dosages

≠

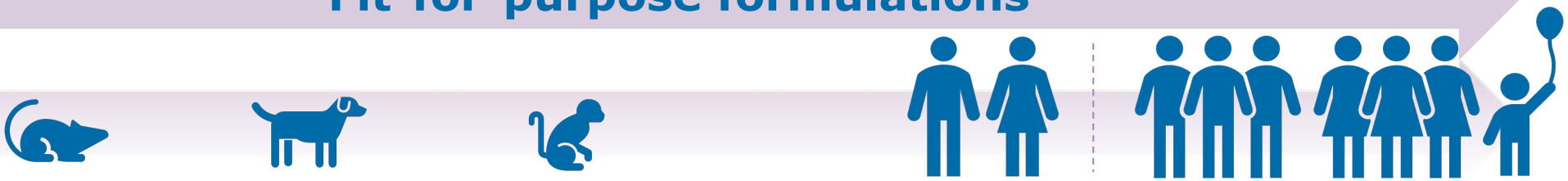
Clinical Formulation

Solubility/permeability limitations **may not be relevant to doses/exposures to be evaluated in humans**

(100x lower dose compared to tox)

Clinical formulation may therefore contain fewer or even completely different excipients than tox formulation

Fit-for-purpose formulations



GLP tox formulation may resemble clinical formulation, but doesn't need to be the same - the choice of formulation depends on the specific requirements of the study

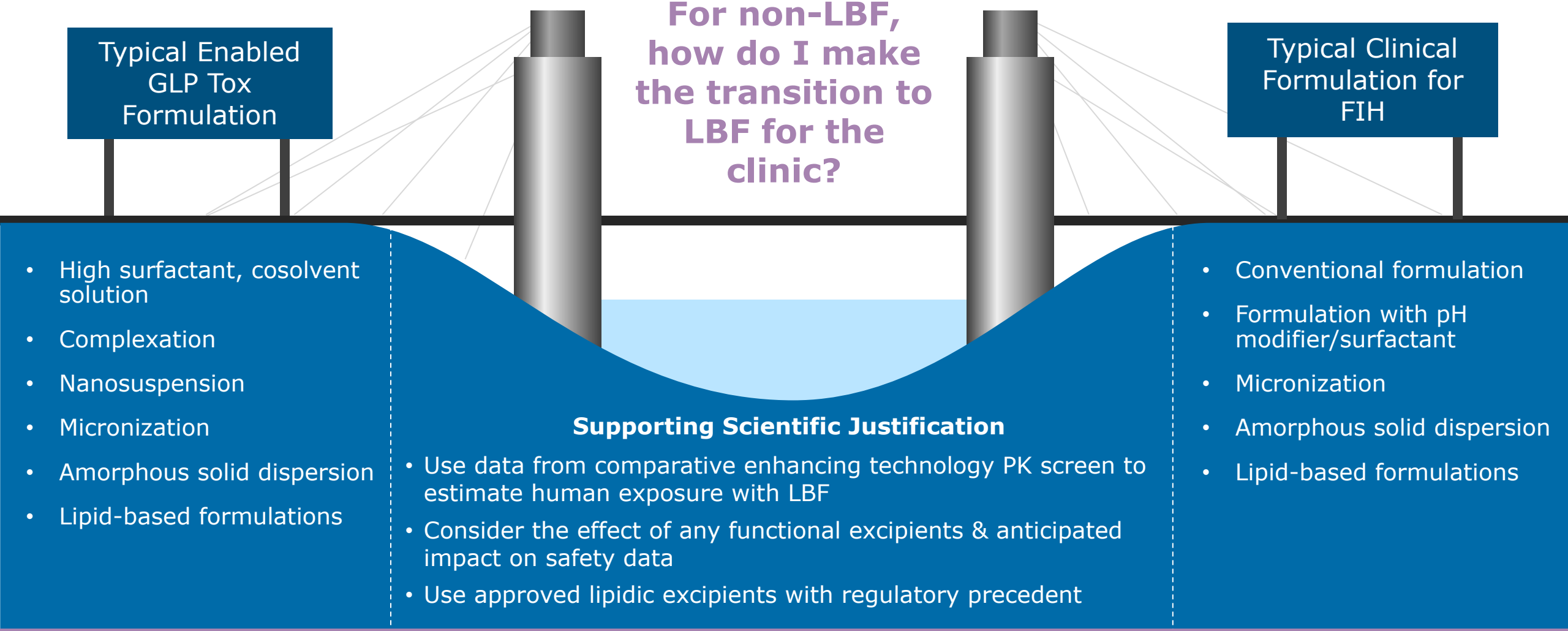
Understanding the Inherent Challenges in Developing LBF for Dosing in Animal Studies

Key Challenges	How to Overcome
Interspecies difference in physiology • Influences the emulsification & digestibility • Sensitivity to large amounts of lipid intake • Oral dose volume restrictions	• PBPK modeling & tailored *in vitro* lipolysis tools • (i) Consider relevant species & select excipients based on tolerability; (ii) Predilution of the formulation when needed • Reduction of dose volume
API in lipidic system • Max drug loading less than required tox dose • Excipient levels may exceed toxicity levels for species • Solubility-limited absorption at high doses	• Lipid suspension; use digestible formulation to promote *in situ* drug solubilization into mixed micelles • Co-dosing of amorphous solid dispersions (ASD) with LBF to leverage supersaturation benefit of ASD *

* Müllertz A. Combining lipid based drug delivery & amorphous solid dispersions for improved oral drug absorption of a poorly water-soluble drug. J Control Release. 2022 Sep;349:206-212.

LBF can potentially address these challenges through judicious selection of formulation components

Beyond Preclinical: Bridging the Gap to Transition to a Viable Clinical Formulation

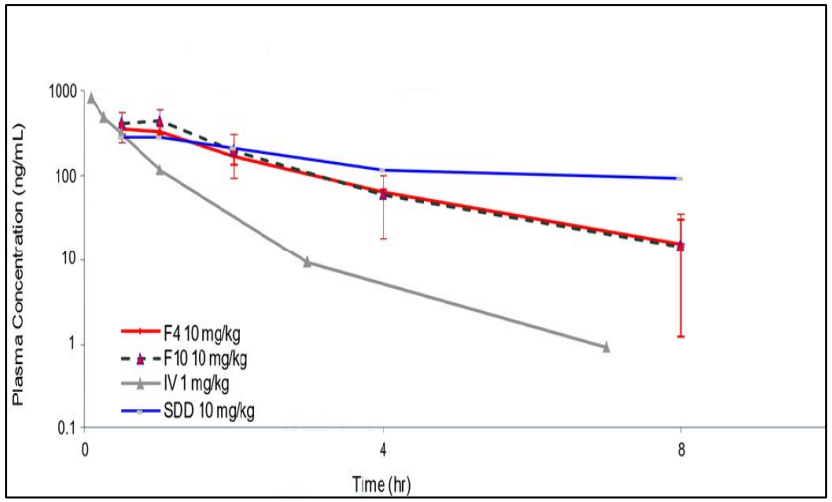


Tox studies may require aggressive formulations but may be simplified for the clinic. Don’t overcomplicate clinical formulation approach due to the needs of high tox dose

Case Study 1 Seamless Transition from ASD in GLP Tox Study to LBF for Clinical Study

Challenge	**Preclinical**	• Exposure levels of up to **100 mg/kg** for GLP tox studies, a customer turned to ASD • **High %CV** during PK profiling at lower concentrations (10 mg/kg) with ASD
	API	• **Light & oxidation sensitivities**
Solution	**Preclinical to clinical transition**	• Estimated max clinical dose = 10 mg • LBF can enhance solubility & bioavailability at this dose level • Comparable C_{max} & AUC to ASD, with **lower %CV** (LBF: 7.5 vs. ASD: 21.6)
	API	• No **content uniformity concerns** • Can mitigate light & oxidation sensitivities
Result	**Manufacturing**	• **Conveniently manufactured** as a liquid fill in softgels
	Patient	• Ease of administration and precise dosing
	Dose-ranging	• **Successful ascending dose** studies with LBF at 2, 5, 10, and 25 mg • **Dose linearity** was achieved in Ph 1

Rat PK Profile at 10 mg/kg



Formulation	PK Profile (10mg/kg)		
	AUC last (ng*hr/mL)	Cmax (ng/mL)	Cmax/AUC Ratio (%)
LBF F_4 (lead)	906 (%CV7.5)	372 (%CV16.7)	41.1
LBF F_{10}	1058 (%CV42.8)	462 (%CV35.6)	43.7
SDD (Spray dried disp.)	1218 (%CV21.6)	325 (%CV32.9)	26.7
IV (1 mg/ml)	540 (%CV12.2)	N/A	N/A

Case Study 2 Comparative PK Study of LBF *vs*. Dry Powder Blend in Capsule Shows Better Exposure & Reduced Variability

Challenge

- **DCS 2b molecule**, with poor solubility
- Absorption variation in test subjects

Solution

Softgel	Composition
	Compound X
	Capmul MCM EP
	Labrasol ALF
	Tween 80
	Peceol
	d-alpha tocopherol

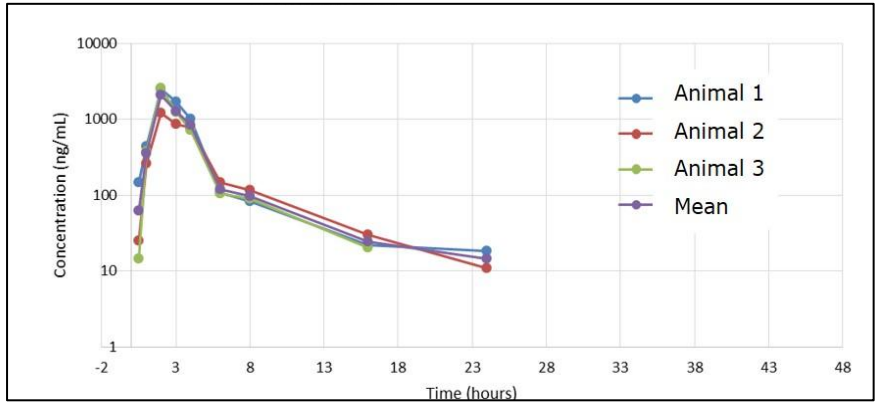
Hard Gelatin Capsule	Composition
	Compound X
	Lactose Monohydrate
	Microcrystalline Cellulose
	Hypromellose 2910
	Croscarmellose Sodium
	Purified Water

- LBF prototype was developed with good physical (no phase separation, no API precipitation under dispersion in biological fluid) & good chemical stability

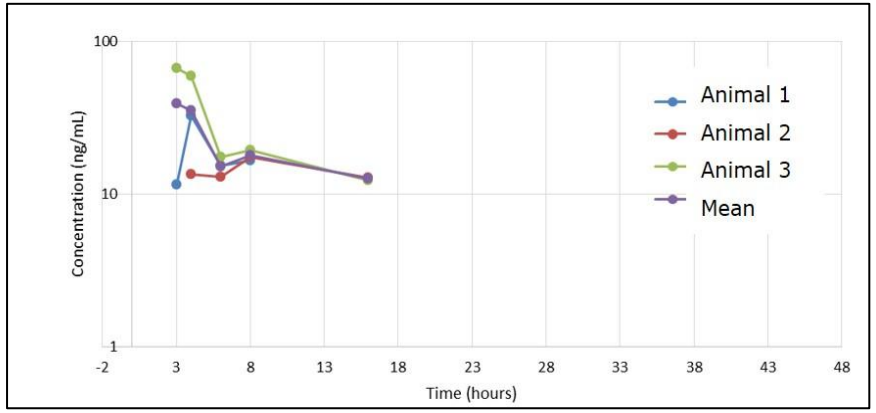
Result

- A quick screening method was used to develop safer lipid-based formulations with high solubilization capacity
- These early lipid formulation prototypes supported proof-of-mechanism to demonstrate drug exposure in animal PK studies
- LBF was also tested in human and the final formulation decision was based on reduced patient-to-patient variability in human PK

LBF encapsulated in softgel



Dry powder blend in capsule



Benefits of LBF

~**16x** higher AUC & ~**25x** higher C_{max}!

Case Study 3 Comparative PK Study of LBF *vs*. Spray Dried Dispersion Shows Superior Exposure with LBF

Challenge

- **DCS 4 molecule**, low solubility, low permeability

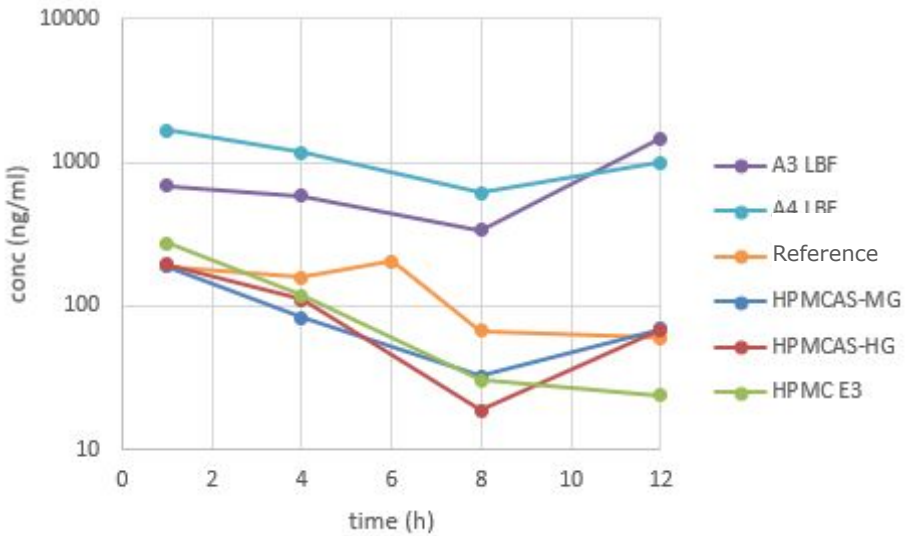
Solution

- Different solubility enhancement technologies were screened (LBF and Spray dried dispersion-SDD)
- 2 LBFs and 3 SDDs prototypes were evaluated in mice

Result

- Both LBFs showed superior bioavailability compared to SDDs and controlled powder API
- A4 LBF was chosen to continue as first-in-human clinical formulation and showed enhancement in bioavailability

Mice Plasma Exposure at 50 mg/kg



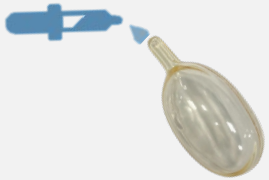
Type	Description	C_{max} (ng/ml)	Ratio to ref	AUC_{0-8} (ng*h/ml)	Ratio to ref	AUC_{0-12} (ng*h/ml)	Ratio to ref
-	Reference	205	1,00	1,26	1,00	1,75	1,00
SDD	HPMCAS-MG	188	0,92	0,73	0,58	0,94	0,53
SDD	HPMCAS-HG	194	0,95	0,81	0,65	0,99	0,56
SDD	HPMC E3	272	1,33	1,02	0,82	1,13	0,65
LBF	**A3**	**686**	**3,35**	**4,10**	**3,26**	**7,68**	**4,39**
LBF	**A4**	**1653**	**8,07**	**8,58**	**6,84**	**11,79**	**6,74**

Shared Attributes Between LBFs Offer a Practical Pathway for Converting Between Dosage Forms

Early start!

Lipid in bottle

Hand-filled softgels



Automated encapsulation

Late-Stage Discovery (PK/Efficacy)

Preclinical Studies (Pharmacology/ GLP Tox)

Ph 1 Clinical Formulation (GMP)

Ph 2 Clinical & beyond (GMP)

- Phase appropriate
- Evolution of data
- Patients or healthy volunteers?
- Molecule liabilities
- Packaging & labelling complexity?

With the constantly evolving nature of LBFs, formulators can effortlessly adapt & refine formulations & dosage form with seamless scalability

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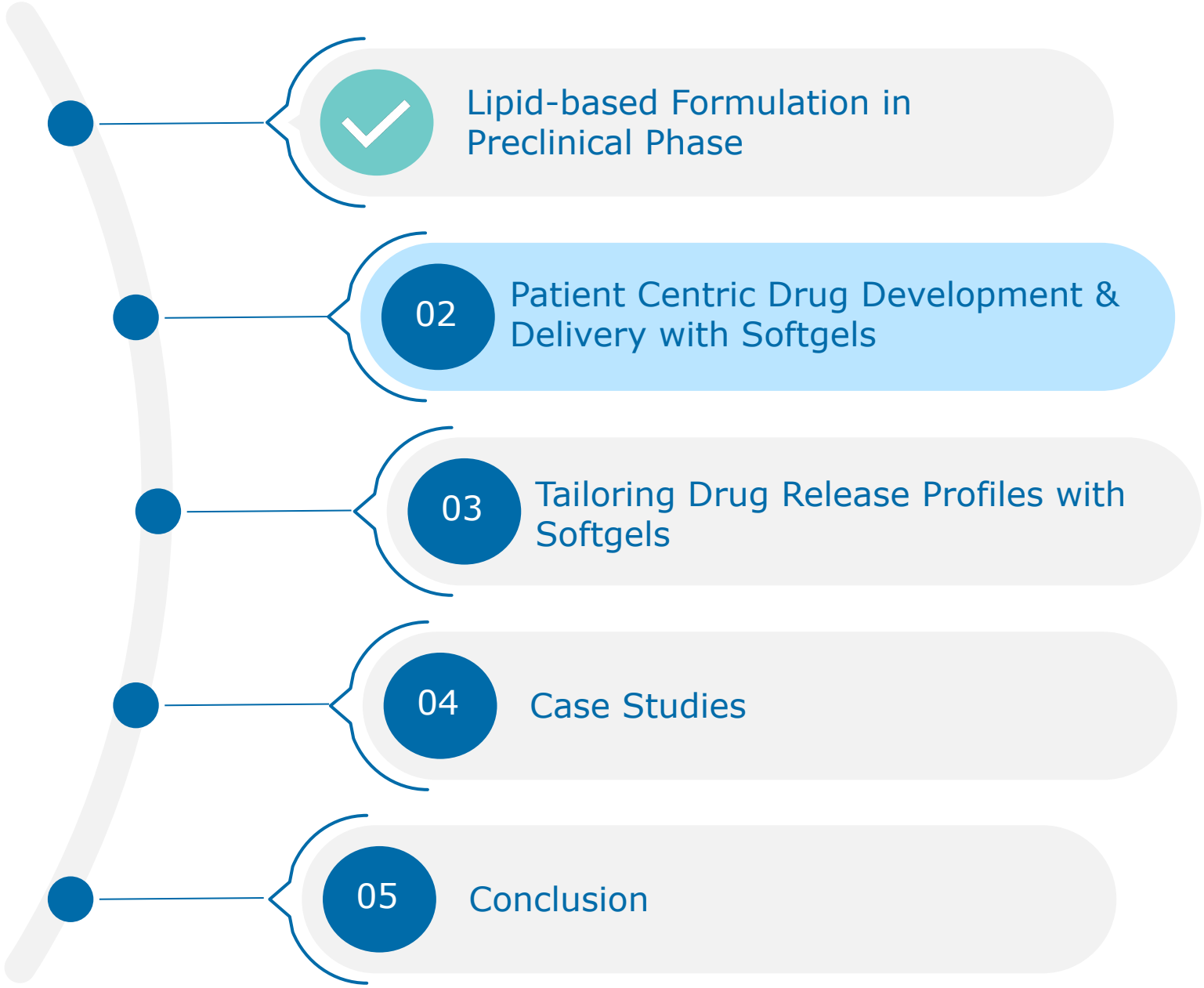


Patient Centric Drug Development & Delivery

Appropriate Dose Form Design Can Improve Patient Compliance & Outcomes

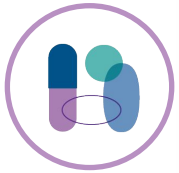
Patient Centric Drug Product Design

The process of **identifying** the comprehensive **need** of individuals or the **target patient population**, and utilizing the identified needs to design pharmaceutical drug products that **provide the best overall benefit over the intended duration of treatment**

Factors in Patient Centric Drug Development

Patient Factors

- Age (paediatric, geriatric)
- Ability to swallow
- Socioeconomic status
- Cognitive abilities



Therapy Related Factors

- Route of administration
- Frequency & timing of administration
- Pill burden
- Administration setting
  - *Self administration*
  - *Caregiver*

Disease Related Factors

- Acute *vs*. chronic
- Co-morbidities
- Disease specific challenges
  - *e.g., decreased dexterity in RA patients*

Softgels provide a versatile platform for the development of a variety of dosage forms to meet both patient and product needs

Patient Focused Drug Product Design Key Steps

1. Get the **RIGHT PATIENT INSIGHTS**
2. Get the **RIGHT MOLECULE**
3. Get the **FORM** of the molecule right
4. Get the **FORMULATION** right
5. Get the **DOSAGE FORM** right
6. Get the **PACKAGING & LABELING** right

Dosage Form Design

Softgel Is a Dosage Form of Choice to Deliver Drugs Through Multiple Routes of Administration

Oral

Indications

- Anti-cancer
- Hormones
- Potent drugs
- Controlled substances
- Immune suppressants

Examples

- Navelbine
- Calcitriol
- Bexarotene
- Dutasteride
- Enzalutamide
- Estrogen-pro gestin combo
- Testosterone
- Progesterone

Ophthalmic

- Anti-inflammatory
- Anti-bacterial
- Antiobiotic

Nasal

- Decongestant volatile oils for inhalation

Topical

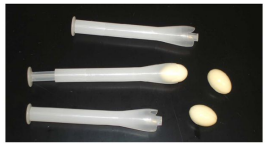
Indications

- Scar treatment
- Skincare and haircare cosmetics

Examples

Vaginal

- Anti-fungal suppositories



- Miconazole
- Fenticonazole

Rectal

- Suppositories for hemorrhoids
- Artemisinin suppositories

Softgels Are Gaining Popularity as a Means of Delivering Medication in a Patient-centric Manner

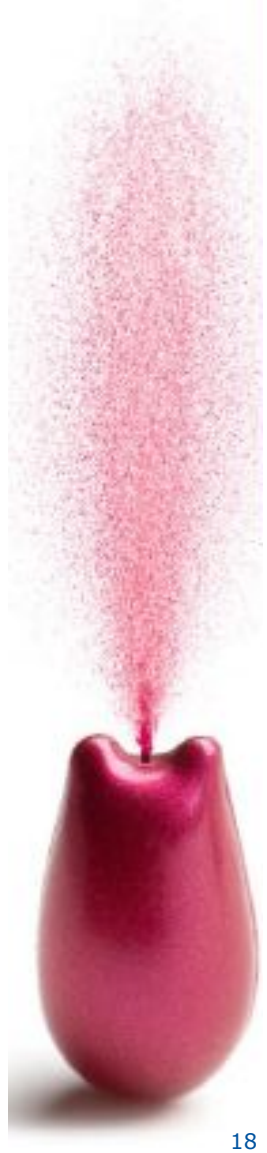
Types of delivery	Application/Indication
Immediate release	▪ Anti-cancer ▪ Hormones ▪ Potent drugs ▪ Controlled substances ▪ Immune suppressants ▪ Cardiovascular ▪ Protease inhibitors etc.
Controlled release/ extended release	▪ CR theophylline softgel ▪ ER calcifediol using OptiShell® capsule technology - FDA approved
Delayed release/enteric softgels without coating	▪ For omega-3 oils ▪ Odiferous oils ▪ Rx products including peptides and proteins
Coated enteric softgels	▪ Rx omega-3 oils (FDA approved) ▪ Proteins and peptides
Dual chamber softgels	▪ Topical/cosmetic applications
Abuse deterrent softgels	▪ Suitable for drugs with potential for abuse
Macromolecule delivery softgels	▪ For enhanced macromolecule permeability
Tablet-in-capsule	▪ Patient compliance to deliver synergistic drugs (Products in Development)
Seamless softgels	▪ For complex release profiles in stick pack/another softgel (Commercial)
Dual controlled release softgels	▪ For complex release profile needs

Softgels for Oral and Nasal Delivery

Softgels can deliver Rx products that are oxygen, *moisture & light sensitive* for **oral pre-gastric delivery** and **nasal delivery** to avoid first pass effect

Unit dose oral/nasal spray

- Sore throat relief in a portable targeted spray capsule to reach the back of the throat
- Relieves pain on contact
- Able to combine with other actives for multi-symptom relief
- Flavored and sugar free



Softgels Extend to Innovative Packaging Design Options

Dual Chamber Softgel: Cosmopod® Technology

Seamless Softgel: OptiGel™ Micro in Stick Pack

	Dual Chamber Softgel: Cosmopod® Technology	Seamless Softgel: OptiGel™ Micro in Stick Pack
1	Combine 2 aesthetically different products, combined at point of use	Unique delivery form
2	Creates "all in one" experience for a multi-purpose product	Easier to swallow
3	Separate and mix incompatible actives at point of use	Release of contents controllable by modified release/ enteric coating
4	Enables the consumer to create the perfect mix prior to application	Ideal to vary dose by number of capsules (e.g., in a sachet)
5	Eco-friendly - biodegradable Vegicaps® capsule shell made from plants	Various color and size options

Stick Packs – Packaging Features

Formats

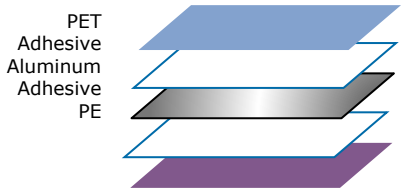
Width [mm]	18	23	25	28	30	32	35	40
Length [mm]	50 - 120							

Filling weights from 100 mg to 10 g

Foil

Different foil materials applicable

Most often used foil: PET/Alu/PE



Sizes

18x65 23x70 23x80 18x90 23x105 40x120

Cuts

Fancy Cut: a scratch/score in the upper length sealing

Laser Cut: a laser perforated foil/foil

Softgels Transform More Molecules into Better Treatments

BETTER ADHERENCE & COMPLIANCE

- Reduce patient pill burden & dose frequency
- Simplify dosing regimes for combination and poly-therapies
- Address patient specific requirements: pediatrics, geriatrics
- Reduced side effects *(avoidance of food effects)*

PATIENT PREFERENCE & CONVENIENCE

- Rapid onset of action with fast dissolve dosage forms
- Simplified medication regimes
- Patient preferred dose forms
- Easier swallowability
- Taste masking

Important to understand stakeholders' needs & match them with appropriate softgel delivery solutions to give the therapy the best potential for success

Evolution of Softgel-Drug Delivery Portfolio

Right Technology to Enhance Patient Usability

Gelatin Softgel

Non-gelatin Softgel

Capsules							Chewable/Lozenge		Capsules		Twist-off/Spray	
Macro-molecule	Abuse Deterrence	Seam-less	Delayed release	Coated	Standard Rx/CH	Reduced Fill	Chewable	Lozenge	Standard CH	Standard Rx	Twist-Off	Squeeze Spray
												
OptiGel® Bio	OptiGel® Lock	OptiGel® Micro	OptiGel® DR	Coated enteric softgels	IR Softgels	OptiGel® Mini	EasyBurst™	SoftDrop™	Vegicaps®	OptiShell®	CosmoPod™	CosmoSpray™
Multiple Rx peptide/ protein-based products in development	Narcotic Rx in development	Rx products **commercialized in Japan**	**Commercialized for VMS** & multiple Rxs in development	**FDA approved** (development for protein delivery ongoing)	Enhanced bioavailability **Commercialized**	Enhanced swallowability **Commercialized**	Enhance flavors **Commercialized**	Chewable		Highly suitable for potent and low dose drugs **Commercialized**	Topical products **Commercialized**	Portable, easy to use, ease of dose titration

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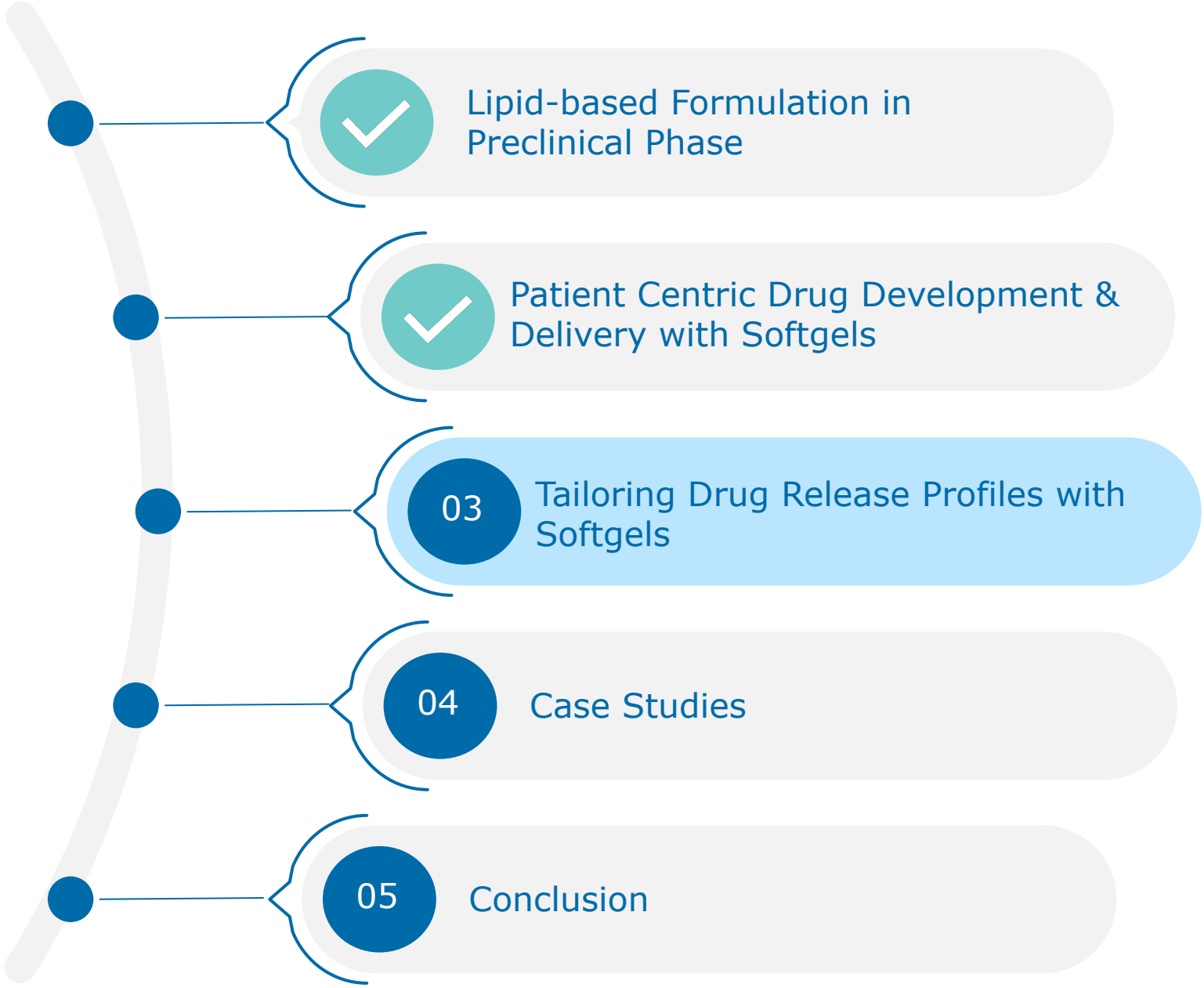
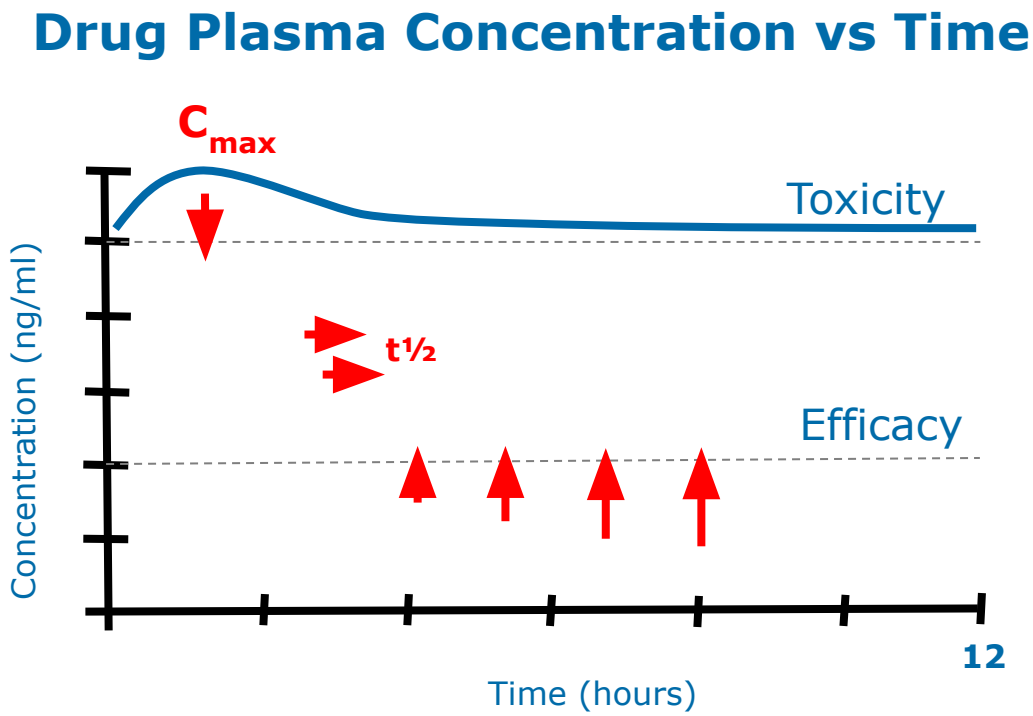


When Do You Need Controlled Release?

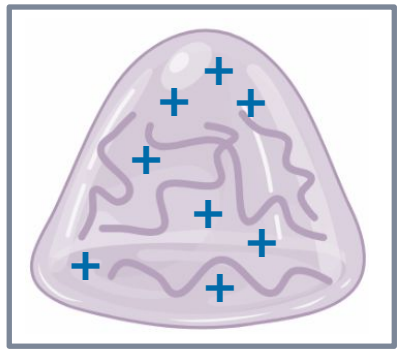
- To avoid C_{max} related side-effects
- Too short half-life ($t_{1/2}$)
- To maintain concentration above efficacious level
- To reduce dosing interval/enhance patient compliance



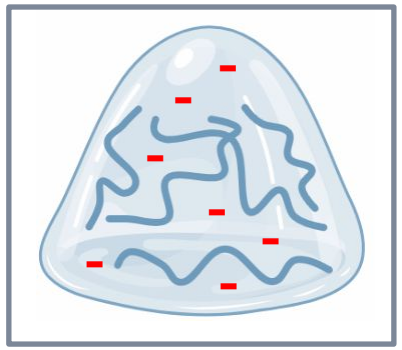
OptiGel® DR Softgel - Combination of Pectin and Gelatin

Incorporates Delayed Release Profile in the Shell with Proprietary Pectin + Gelatin Blend

Gelatin



Pectin

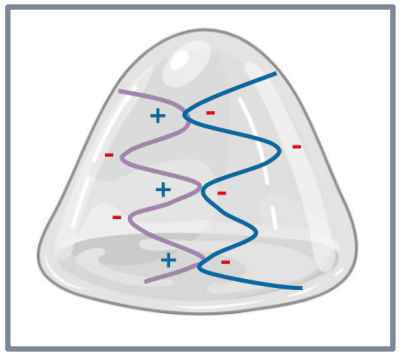


Water

Plasticizer

Heat

Gelatin-Pectin Coacervate



Graphics created with BioRender.com

Electrostatic attraction between **cationic groups on gelatin** & **anionic charged groups on pectin** leads to formation of **complex coacervates**

Thes complex coacervates are **insoluble in acidic pH**, but **soluble in basic pH**

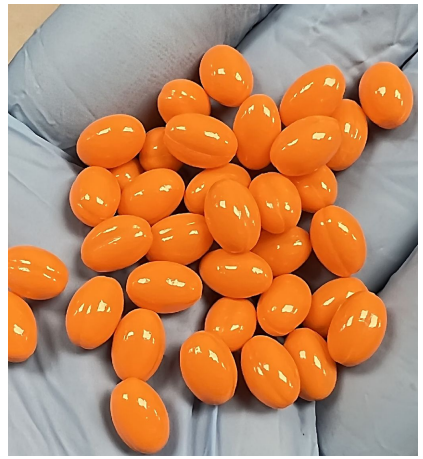
Enables a range of APIs into formulation with a **one-step manufacturing process** without the need for coating

The reversibility of this interaction at specific pH range imparts the enteric/delayed release properties on OptiGel® DR softgels

Optigel® DR Softgels

Differentiated Delayed Release Technology without the Need for Coating

Enhanced Bioavailability	• **Enhances absorption** of API that may be degraded in stomach acid and/or that requires larger or multiple capsules to achieve target dose • Eliminates/**minimizes gastric reflux**
Greater Compatibility	• Allows for a **broader range of APIs** (like thermolabile APIs) to be encapsulated versus coated softgels
Consistent Performance	• OptiGel® DR softgel's functional performance is **more reliable than coated softgels**



Opaque OptiGel® DR Capsules

Clear OptiGel® DR Capsules

Quality Target Product Profile (QTPP) for a Modified Release (Controlled & Delayed) Softgel

QTPP Elements	Target	Performance
Dose form	Uncoated softgel	✔ Extended release softgel
Strength	Meet label claims	
Enteric property	Consistent and robust	✔ Robust performance in other test media, beyond 0.1N HCl followed by testing at pH 6.8 phosphate buffer
pH dependency	Independent	✔ No rupture in pH 4-5 > 1 hr ✔ Pass rupture test at pH 6.8
Sustained property	>12 hr	✔ > 12 hr ✔ Up to 24 hr with the modified release fill matrix
Physical form of the fill matrix	Semi-solid, viscosity	✔ Flowable at 20-70 deg C ✔ Encapsulatability
Stability	Good chemical, physical & thermal stability	✔ Good chemical, physical & thermal stability up to 24 months
Manufacturing process	Minimal complexity	✔ Single step process with no scalability issue

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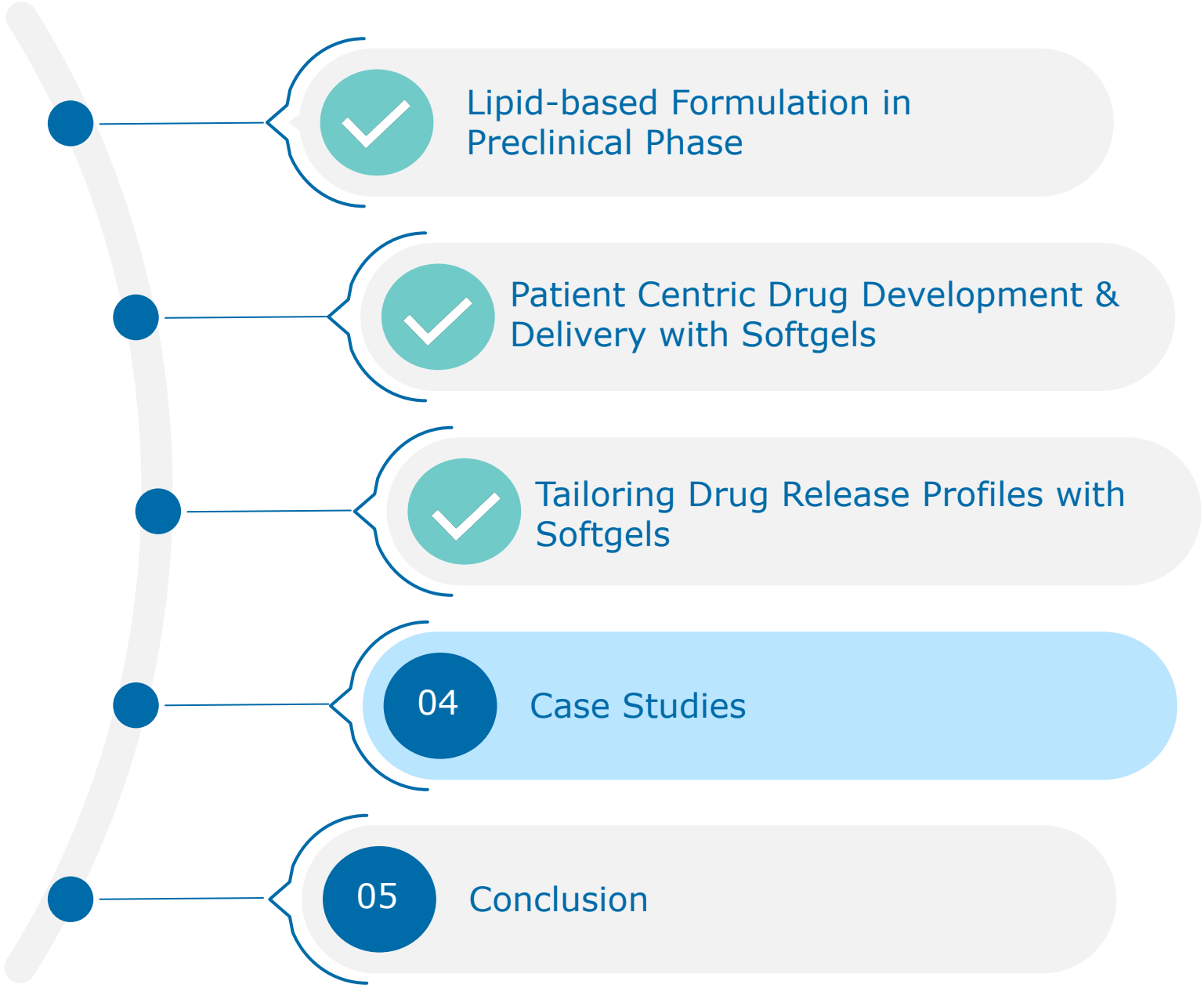
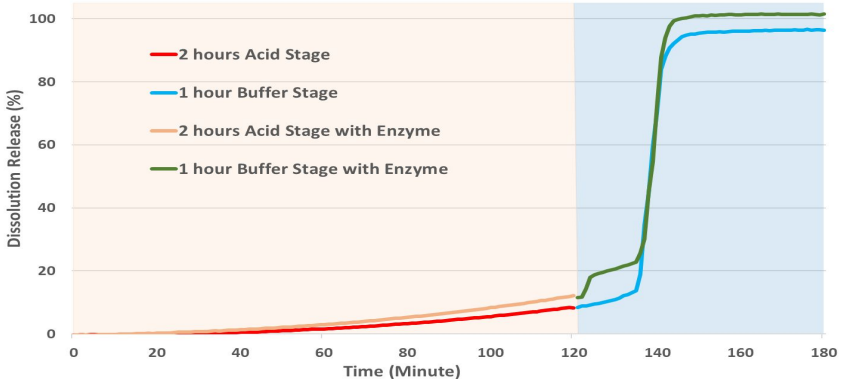
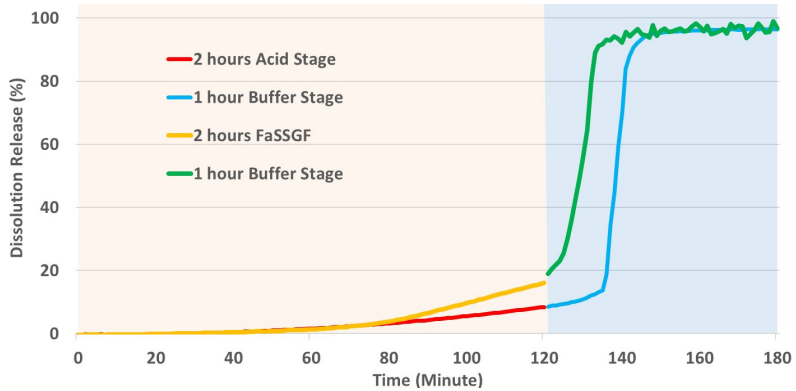
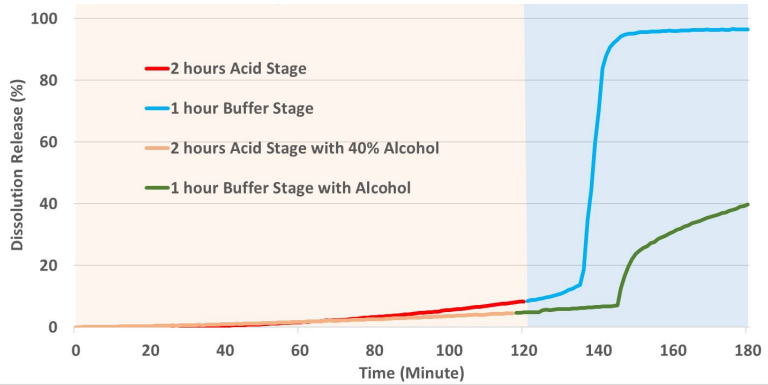


OptiGel® DR Capsules

In-Vitro Two-stage Dissolution Profile of Model Drugs







Medium

Acid stage: 0.1N HCl pH 1.2 with and without enzyme
Buffer stage: Phosphate buffer pH 6.8

Equipment

USP Apparatus II 75RPM @ 37 °C

Medium

Acid stage: FaSSGF
Buffer stage: Phosphate buffer pH 6.8

Equipment

USP Apparatus II 75RPM @ 37 °C

Medium

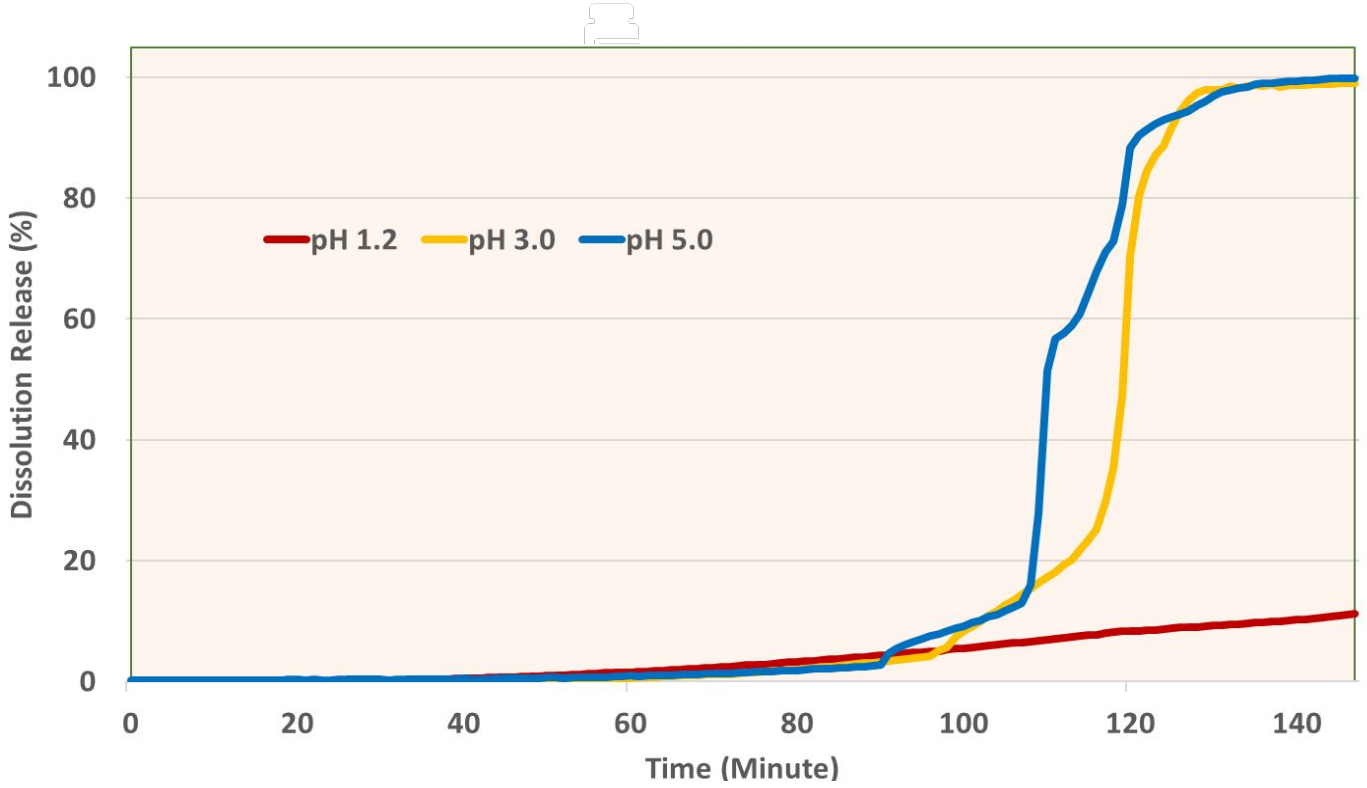
Acid stage: 0.1N HCl pH 1.2 with 40% alcohol
Buffer stage: Phosphate buffer pH 6.8 with alcohol

Equipment

USP Apparatus II 75RPM @ 37 °C

OptiGel® DR Capsules

In-Vitro Two-stage Dissolution Profile of Model Drug in higher pH media



Medium

Acid stage: pH1.2, pH 3.0, pH 5.0

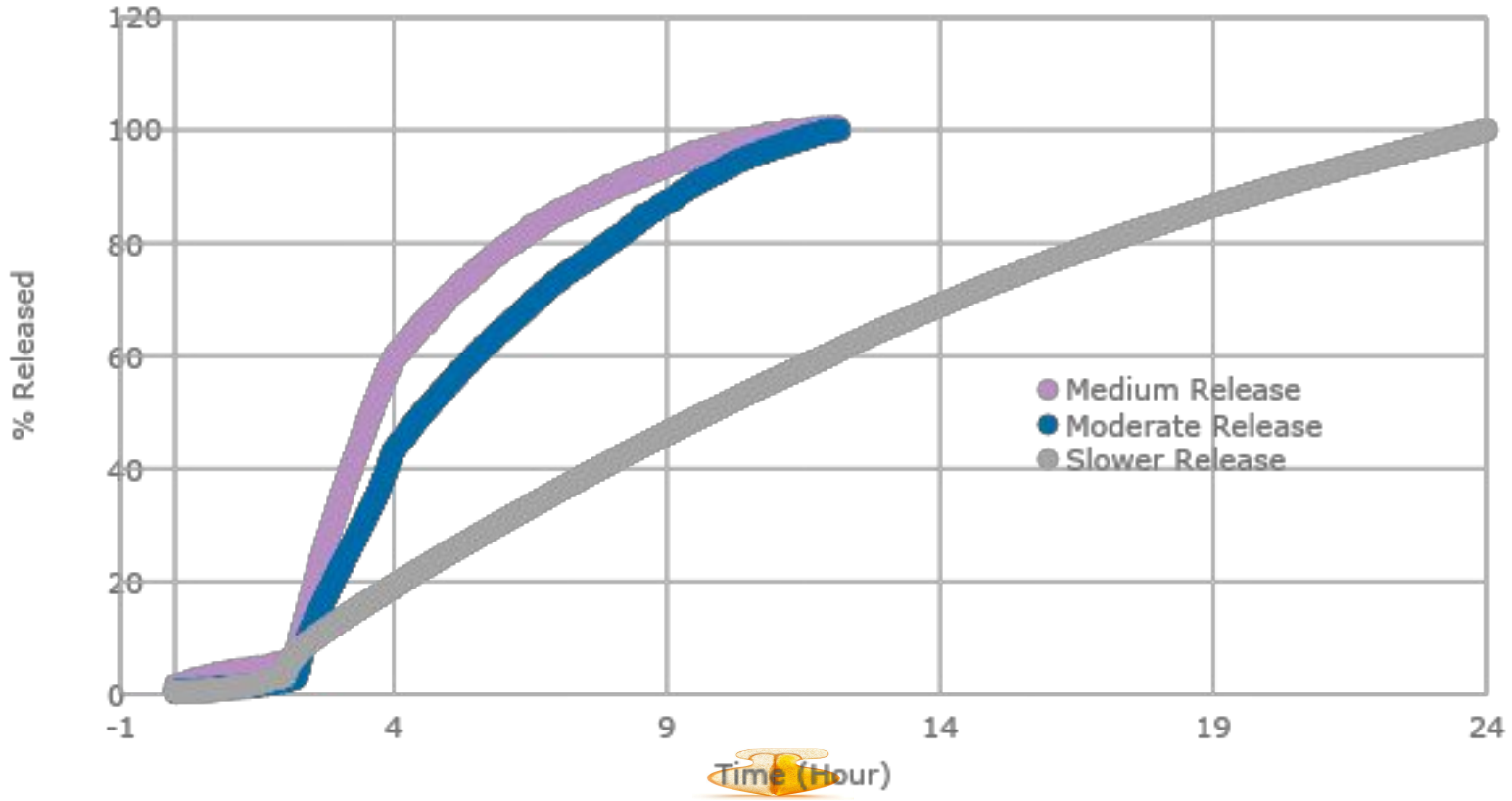
Equipment

USP Apparatus II
50RPM @ 37 °C

OptiGel® DR softgels stayed intact in pH 3.0 and 5.0 media for at least 90 min and higher pH resistance is a desirable attribute needed for delivering to lower GIT

Dual Controlled Release

Delayed Release Shell Combined with Control Released Fill Matrix



Protect peptides or other low pH sensitive actives through pectin shell that is further modified to remain intact until it reaches **pH 6.0 or >**

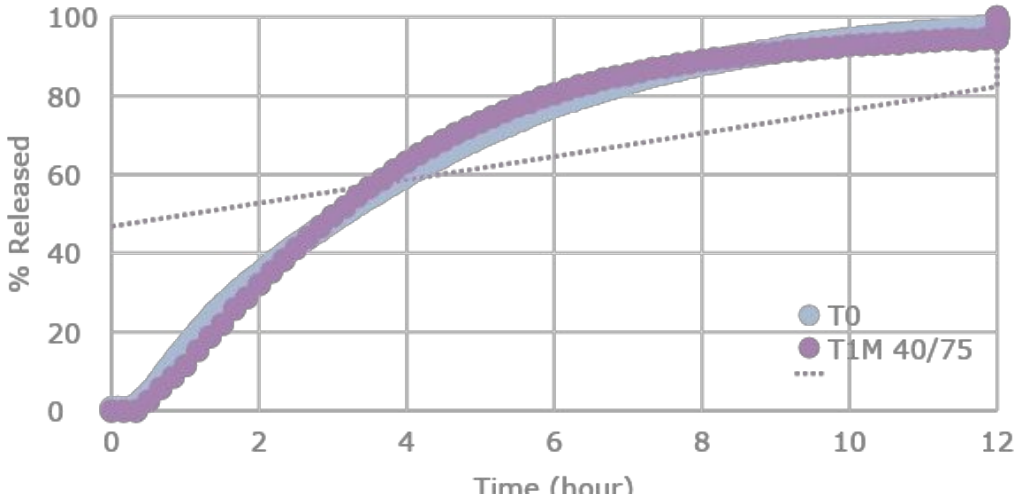
By changing the fill matrix composition, drug release can be prolonged from **IR** to **12hr to 24hr**

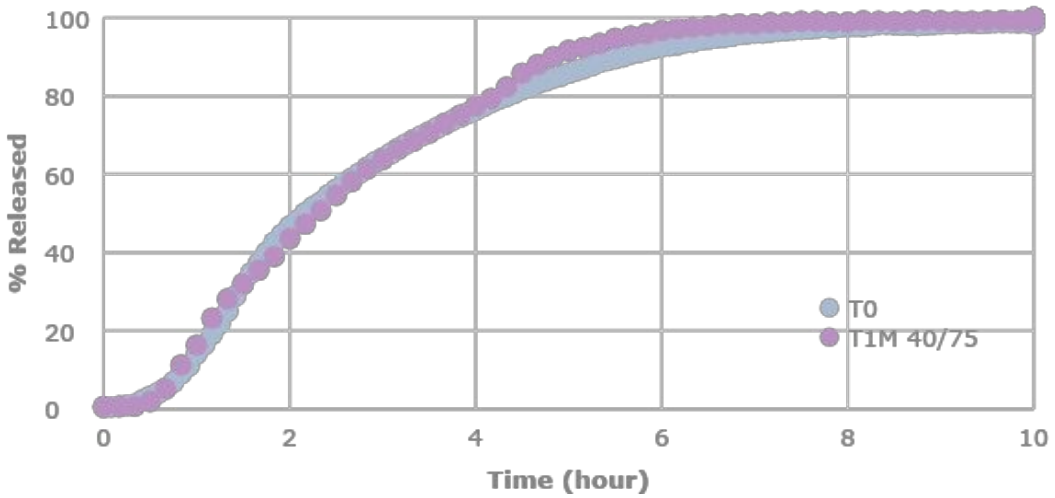
CR fill matrix extends the release making it potentially suitable for delivery to **lower intestine/ colonic delivery**

Extended-release dissolution profile of a model drug

Modified Release Fill Matrix

Dissolution Profile of Model Drugs from OptiShell® Capsule





Fill formulation

Model drug embedded in Hydrophilic (Polyox) fill matrix

Medium

Water

Equipment

USP Apparatus II 75RPM @ 37 ˚C

Fill formulation

Model drug embedded in Hydrophilic/hydrophobic mix (Cellulose) fill matrix

Medium

Phosphate Buffer pH 7.2

Equipment

USP Apparatus II 75RPM @ 37 ˚C

Tablet-in-Capsule Technology
Consumer Benefits & Applications

Multiphase softgels with pre-formed tablet or capsule in a liquid-filled soft capsule

An Optimum Solution for Multiple Categories

- Heart Health
- Cough and Cold
- Digestive
- Joint Health

Product Features & Benefits

1. **Allows to combine single or multiple actives** with different release profiles and release sites
2. Helps improve adherence in elderly by **reducing pill burden**
3. Potential solution to combine active ingredients with chemical incompatibility and/or homogeneity concerns
4. Potential for new IP
5. Highly differentiated products

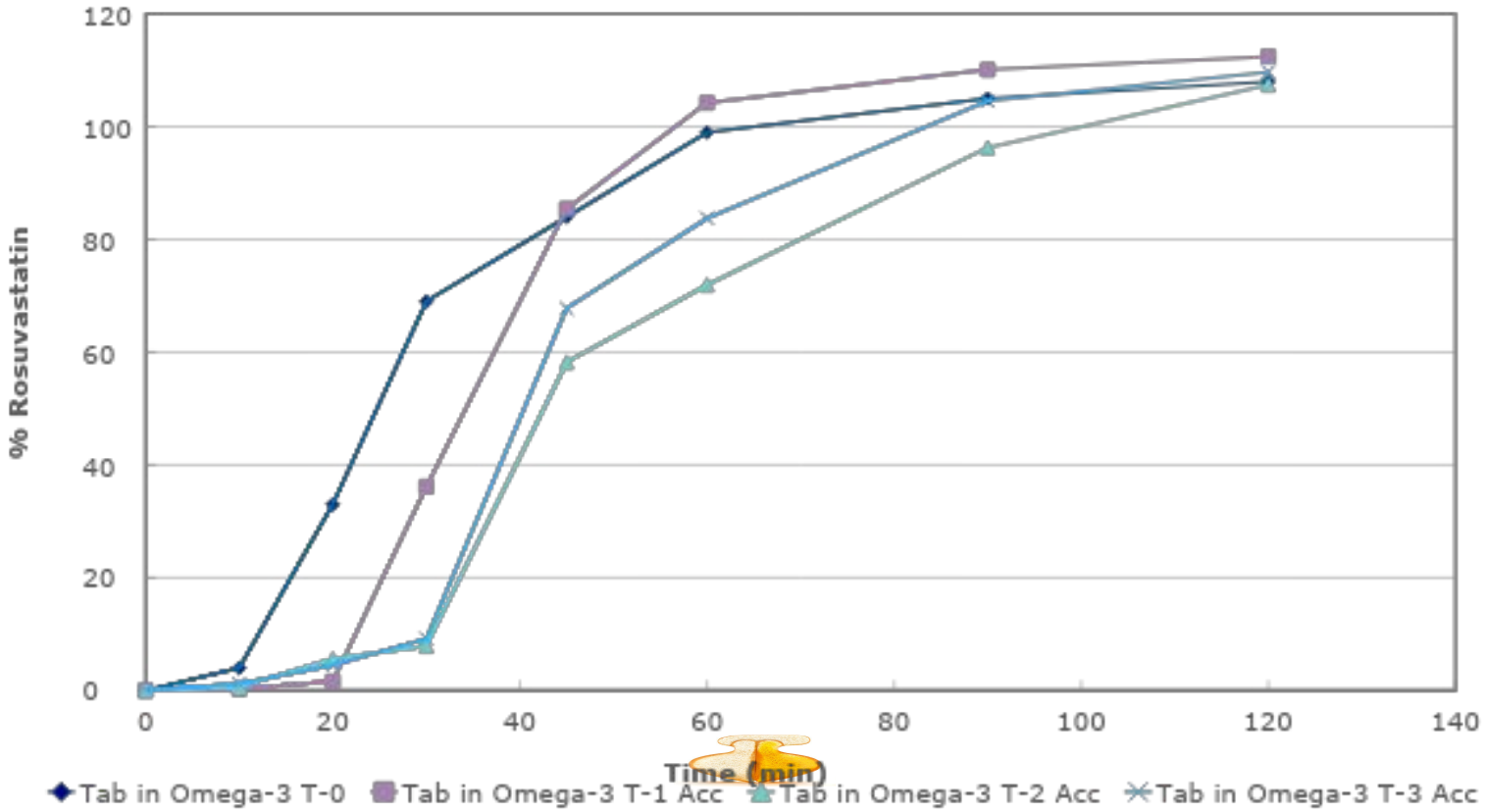
Tablet-in-Capsule Examples

Omega-3 capsules were manufactured encapsulating Rosuvastatin 10 mg, Atorvastatin 10 mg and Aspirin 81 mg tablets in them

Tablet-in-Capsule

Dissolution Profile of Rosuvastatin Tablets Encapsulated in Omega-3 Oil

Dissolution of Rosuvastatin Tablets in Omega-3 Oil Capsules

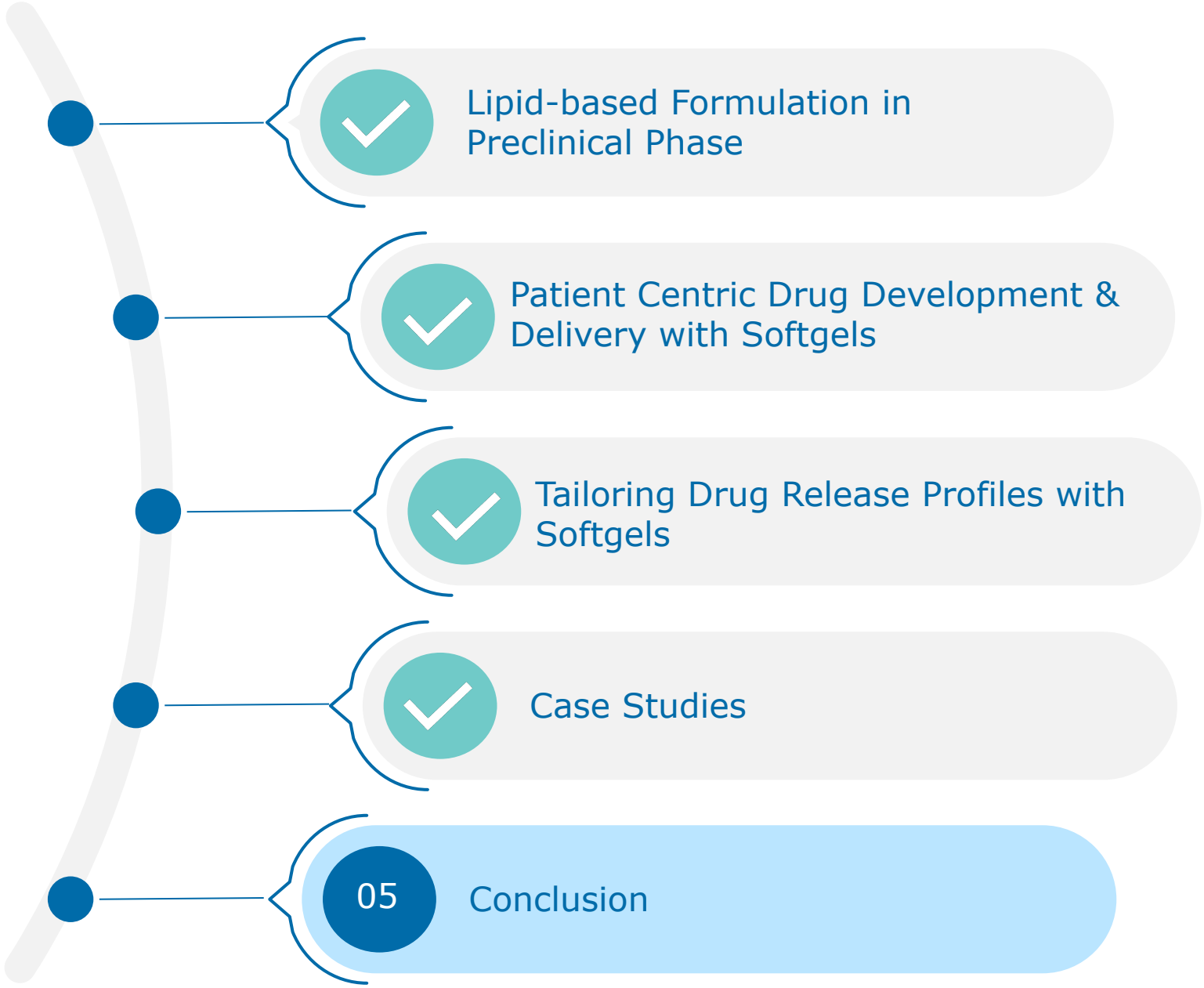


Dissolution of Rosuvastatin tablet affected mainly by the capsule rupture

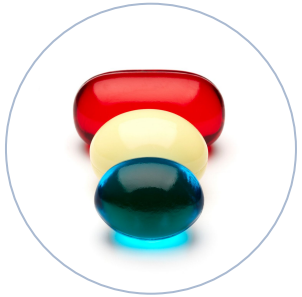
Very little difference in actual dissolution of tablet after shell rupture

Delay in shell rupture due to cross-linking of gelatin which can be overcome or minimized with the use of enzymes or different gel formulations

AGENDA



Conclusions



Lipid-based formulations can be tailored to meet the specific intent of the preclinical & clinical phase studies. The toxicology and clinical formulations should be fit-for-purpose.

Versatility of softgel as a dosage form facilitates patient centric dosage form design and drug delivery

Softgels provide **convenient dosing** options that can incorporate **controlled release mechanisms** that improve patient compliance

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Q&A

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