Opportunities & Challenges with IR-MR Lipid Based Formulations (LBFs)

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Outline

01 Lipid Based Formulations & Softgels

02 MR/ER Softgel Formulations

03 Formulation Challenges

04 Analytical Challenges

05 Food Effect & IVIVC

06 Conclusion

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LBFs (Self Emulsifiable - Type I to IV) Have the Ability to Solubilize Lipophilic Compounds, Increase Absorption & Improve Delivery

	Type I	Type II	Type IIIA	Type IIIB	Type IV	Hydrophilic solvent
Composition	100% glycerides	40-80% glycerides; 20-60% hydrophobic surfactant	40-80% glycerides; 20-40% hydrophilic surfactant; 0-40% hydrophilic cosolvent	0-20% glycerides; 20-50% hydrophilic surfactant; 20-50% hydrophilic cosolvent	30-80% hydrophilic surfactant; 0-50% hydrophilic cosolvent; 0-20% hydrophobic surfactant	100% cosolvent
Dispersion	Limited or no dispersion	Moderate dispersion to form an emulsion	Rapid dispersion to form micro/ nanoemulsion		Spontaneous dispersion to form micelles	
Digestion	Digestion required	Likely to require digestion	May need digestion	Digestion likely not needed	Digestion likely not needed	
System	**Solutions**	**SEDDS (>250 nm)**	**SMEDDS (100-250 nm)/ SNEDDS (20-100 nm)**		**Non-oil micellar system**	
Examples	**Valproic acid (Depakene®) BCS I/II**; **Ergocalciferol (Drisdol®) BCS III**	**Ranitidine (Zantac®) BCS III**; **Cyclosporin A (Sandimmune®) BCS II**	**Ritonavir (Norvir®) BCS IV**	**Cyclosporin A (Neoral®) BCS II**	**Bexarotene (Targretin®) BCS IV**; **Cyclosporin A (Gengraf®) BCS II**	**Talazoparib (Talzenna®) BCS II/IV**

Over 70 Rx products approved, representing all classes of drugs to date

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Ref:
Pouton CW. Eur J Pharm Sci. 2006 Nov;29(3-4):278-87.
Huang Y Acta Pharm Sin B. 2021 Aug;11(8):2469-2487.

Select Examples of FDA Approved Drugs with LBF in Softgels Including Suspension Fills

HORMONAL DISORDER
- Calcifediol ER softgel/**Rayaldee®**
- Vit D analog; **BCS II/IV**
- Approved 2016
- ***Suspension based ER softgel***

INFECTIOUS DISEASE
- Ritonavir /**Norvir®**
- Protease inhibitor
- **BCS IV**
- Approved 1996

IMMUNOLOGY
- Voclosporin/**Lupkynis®**
- Immunosuppressant
- **BCS II**
- Approved 2021

WOMEN'S HEALTH
- Estradiol & Progesterone/**Bijuva®**
- Hormones; **BCS II/IV**
- Approved 2018
- ***Suspension***

RESPIRATORY
- Nintedanib/**Ofev®**
- TK Inhibitor; **BCS II**
- Approved 2014
- ***Suspension***

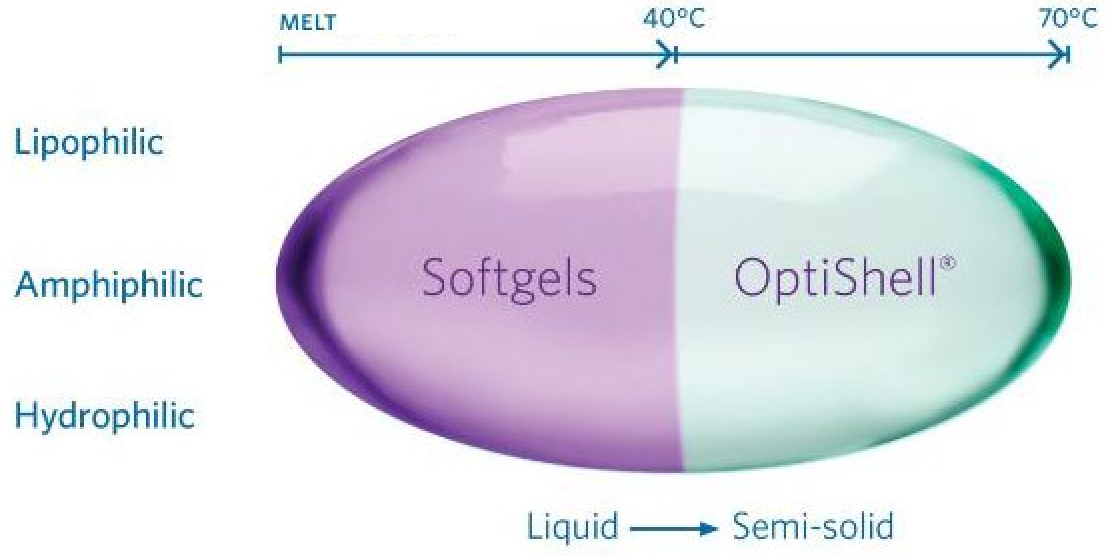
TRANSPLANT MEDICINE
- Cyclosporine/**Neoral®**
- Immunosuppressant
- **BCS II**
- Approved 1995

MEN'S HEALTH
- Testosterone undecanoate/**Jatenzo®**
- Hormone
- **BCS II**
- Approved 2019

ONCOLOGY
- Midostaurin/**Rydapt®**
- Kinase inhibitor
- **BCS II**
- Approved 2017

DYSLIPIDEMIA
- FFA formulation of EPA & DHA / **Epanova®**
- **BCS II**; Approved 2014
- ***Delayed release coated***

MR/ER Lipid Based Formulations Using Non-Gelatin (OptiShell®) Softgels



SHELL COMPOSITION	**Gelatin**	**Carrageenan** and modified starch
FILL TEMPERATURES	**Lower** (up to 40° C)	**Higher** (70 - 80° C)
FILL FORMULATIONS	**Solutions** and **suspensions**	**+ Semi-solid** and **highly viscous** fills
EXCIPIENTS RANGE	Wide	Wider
pH LEVELS	**Slightly acidic to neutral**	**Slightly acidic to alkaline (up to pH 12)**

- OptiShell® (Carrageenan based) is developed as an **alternative to traditional gelatin softgels**
- It utilizes **plant-based materials**, addresses dietary & ethical concerns with animal-sourced gelatin
- **First semi-solid ER fill containing Calcifediol (Rayaldee®) in softgel** delivered by OptiShell® is FDA approved in **2016**

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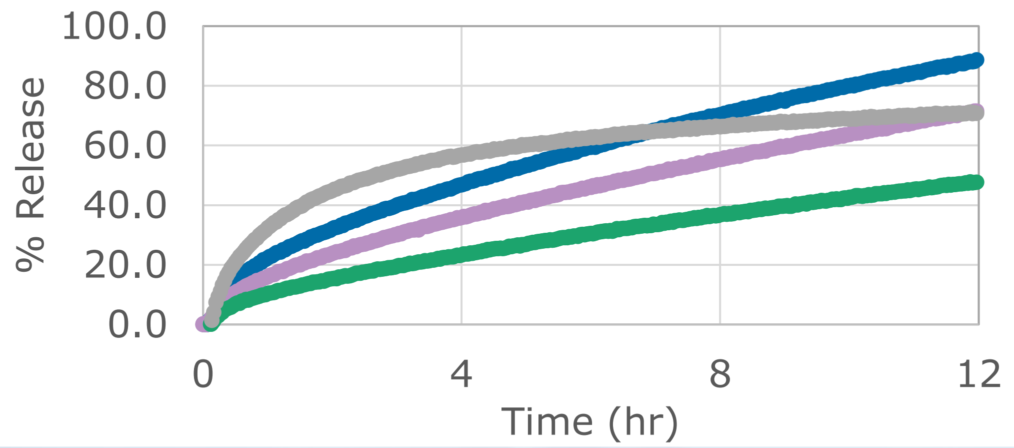
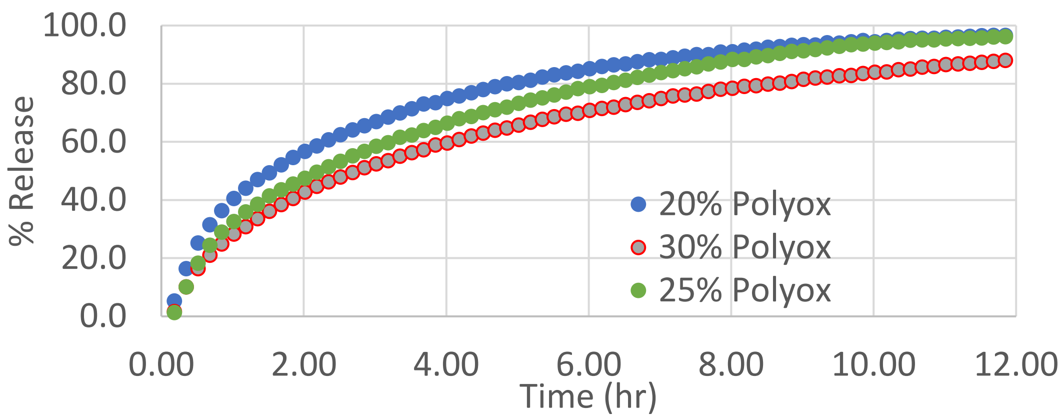
Modified Release Fill Matrix Types Suitable for Encapsulation

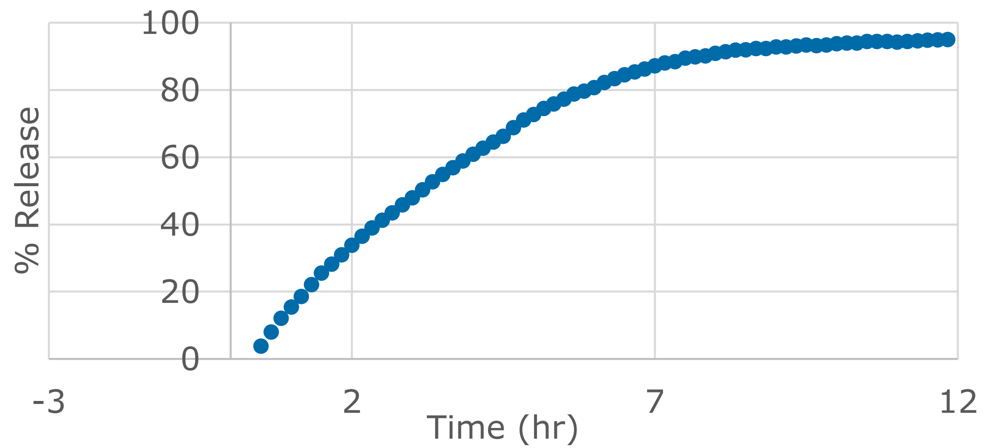
Combination of Lipid-Cellulose Matrices



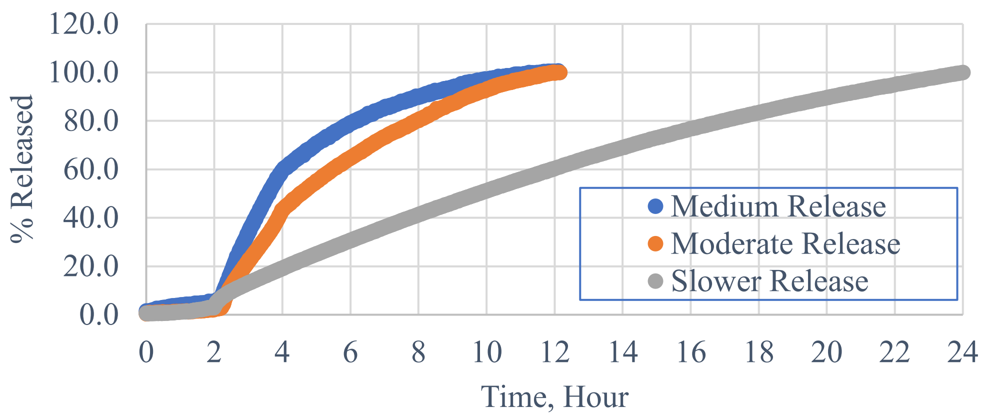
PEO Based ER Matrices



Lipid Based ER Matrice



Enteric Shell & Sustained Release Fill (Dual Control)



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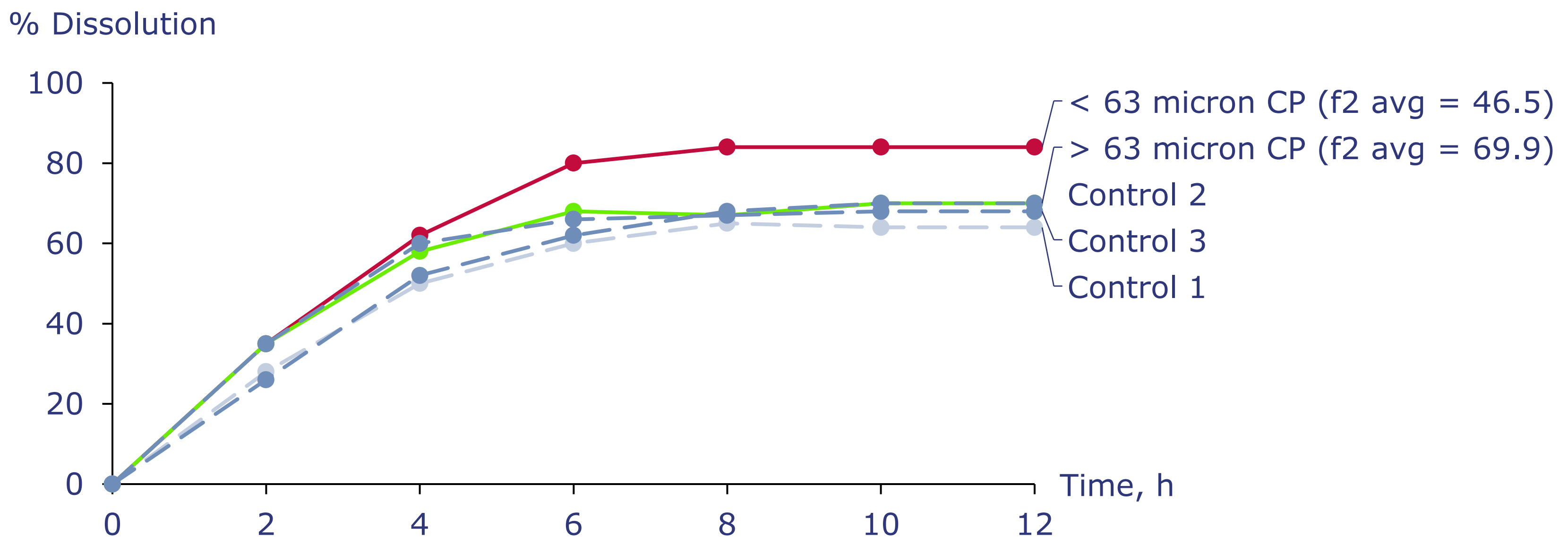
Effect of Cellulose ER Polymer Particle Size on Dissolution from ER-LBF Softgel

- LBF-MR fill matrix with low & high particle size containing cellulose polymer were filled into softgels
- Release profile determined using fiberoptic probes

	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Analyte	Model drug	Model drug	Model drug	Model drug	Model drug
Cellulose polymer (CP)	Unaltered (control)	Unaltered (control)	Unaltered (control)	Polymer with <63 µm (small particle size)	Polymer with >63 µm* (large particle size)

* Process not optimized; presumably smaller particles of polymer remained on top of mesh



Altering the polymer particle size while keeping all other excipients & manufacturing parameters constant, dissolution is significantly different (f2<50) with change in particle size

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Delayed Release (DR) Softgels for Lipid Based Formulations

Comparison of Enteric Coated vs Pectin Based OptiGel® DR Softgels

	Enteric Coated	OptiGel® DR
Protecting Acid-sensitive APIs	Yes	Yes
Reducing Gastric Reflux & Irritation	Yes	Yes
Enhancing Absorption of Certain APIs	Yes	Yes
Manufacturing	Multistep & complex	Single step & simple

Pectin is a **natural polymer** in IIG & used in Rx products

OptiGel® DR **(gelatin+pectin)** - **Single step** manufacturing process

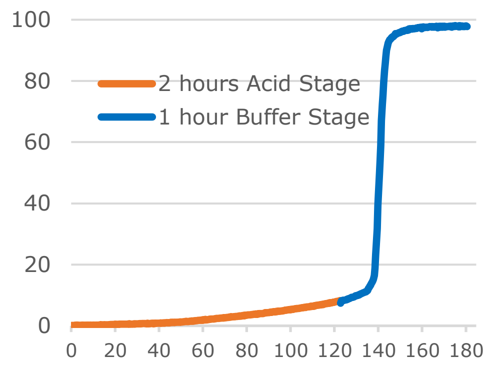
Excellent capsule **robustness**

First enteric/delayed release Rx softgel, **Stavzor®**; using gelatin-acrylate; FDA approved-2008

First Rx delayed release coated softgel, **Epanova®**; FDA approved-2014

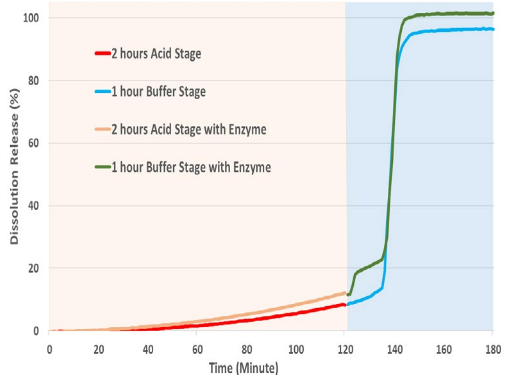
Delayed Release Softgels: Testing Dissolution in Various Media Beyond USP/EP is Critical to Demonstrate Robustness

2-Stage Dissolution



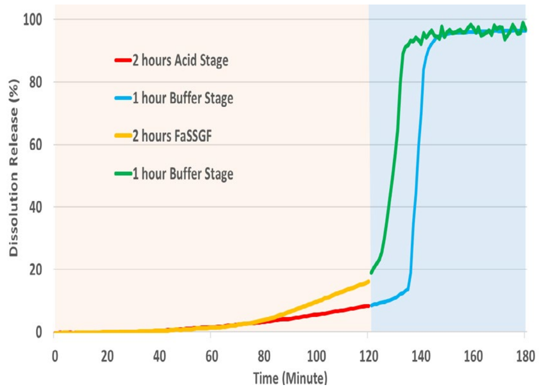
- Softgel **stayed intact in acidic medium** & **then ruptured** followed by immediate released of content in buffer

2-Stage: With or Without Enzyme



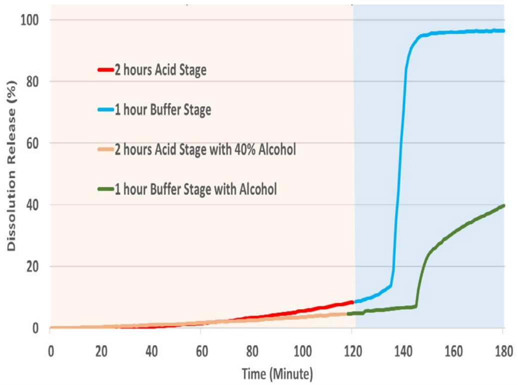
- Softgels **stayed intact in pH 1.2** medium with & without pepsin for 120 min, **then ruptured & released within 25 min in buffer**.
- **No significant effect** on enteric performance with enzymatic medium

Fasted State Simulated Gastric Fluid



- Softgels **stayed intact in FaSSGF** medium for 120 min **then ruptured & released content within 25 min in pH 6.8 buffer**

Alcohol-Containing "Dose Dumping" Medium



- Alcohol-containing (40% ethanol) had no impact in acidic media (**no dose dumping effect**) which is desired but slowed the release in buffer

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Key Formulation & Manufacturing Challenges

Poor solubility & solubilization
Screening with lipid excipients

API migration into shell
Select shell-compatible lipids, excipient combinations that prevent API migration

Lipid oxidation or fill degradation
Add antioxidant; minimize heat, light, avoid oxygen exposure

Phase separation / crystallization
Use co-solvents + surfactants and suspending agents and conduct challenge studies

API precipitation in GI fluids
Use surfactants & develop SEDDS or SMEDDS

Incompatibility between fill & shell
Pre-screen fill-shell; optimize water & plasticizer

Viscous fill variability
Apply precise temperature controls; use heated tanks & stirrers

Emulsion/suspension stability/fill homogeneity
During scale up, bulk fill holding & encapsulation

- Overcoming poor solubility, GI precipitation & phase separation requires tailored use of excipients, surfactants, SEDDS/SMEDDS & stable co-solvent blends
- Preventing drug migration, oxidation & solvent loss demands strategic excipient & antioxidant selection, shell pre-screening & tight process controls
- Monitor droplet size, crystallinity & peroxidation during stability studies

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Formulation Strategy: Fill & Shell

Reference & Characterization
- Source multiple RLD batches
- Measure fill weight

Disintegration & Dissolution
- Dissolution and rupture test
- Develop early dissolution profiles

API & Excipient Profiling
- Perform API assay & RS on RLD
- Dispersibility & digestibility

Excipient Risks
- Quantify antioxidant
- Select matchable excipient grades

Shell Composition & Analysis
- Identify gelatin type- IEP and GPC
- Analyze bloom strength & MW

Shell Excipient Profiling
- Quantify plasticizer
- Evaluate water content in shell

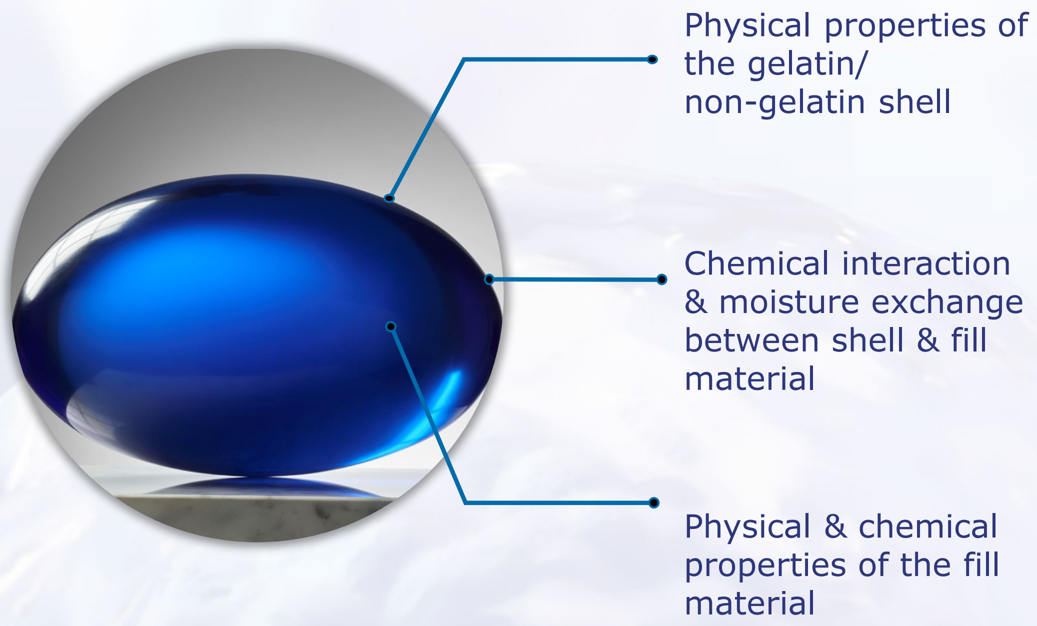
Shell–Fill Compatibility
- Perform API migration assay on washed shells
- Compare cross-linking with disintegration

Final Optimization
- Set shell–processing parameters
- Validate shell stability across shelf life

Note:
For generic development, important to match the functional performance of the RLD, excipient selection must consider both biopharmaceutical impact & global regulatory acceptability

IR-MR Lipid Based Formulations - Analytical Challenges

Developing a Discriminating Dissolution Method Requires Understanding of Shell & Fill Interactions



Challenge	Proven Solutions
Compounds with little to **NO UV** chromophores	Alternative detection techniques (e.g. CAD, ELSD & LC-MS)
Low-dosage API with **LOW UV** chromophores	Optimized sample prep to enhance sensitivity, derivatization & applying alternative detection like LC-MS
Excipients that **interfere with UV** detection	Selective extraction techniques to isolate API from excipients, exploring non-UV detection
Complex lipid matrices affecting sample preparation	Advanced sample prep methods, including whole softgel digestion, liquid nitrogen softgel crack extraction & liquid-liquid extraction

Case Study 1: Cross-Linking - Enzyme & Surfactant Addition

Challenges

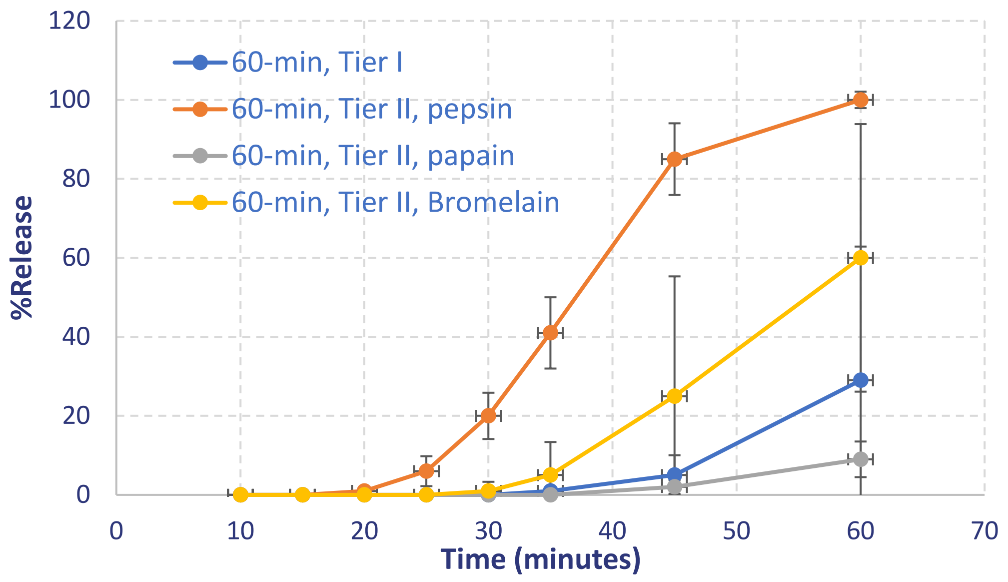
- Softgel **rupture is delayed** by pellicle formation on the external gelatin surface resulting in lower and/or incomplete dissolution

Approach

- Enzymatic media – types of enzyme
- **Time of surfactant addition to enzymatic media**
- pH of media
- Assessment & validation of Tier II method prior to implementation
- Expose capsules to formaldehyde to force cross-linking of gelatin as a part of assessment

Results

60-min exposure time, Tier II Enzyme Study



Key Insights

- Media is pH 4.5; **pepsin outperformed** papain & bromelain, designated by USP at this pH range
- **Selection of appropriate enzyme & time when surfactant is added is critical**

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Case Study 2: Discriminatory Dissolution Method for Omega-3 Fatty Acid Release from Delayed Release Softgel

Challenge

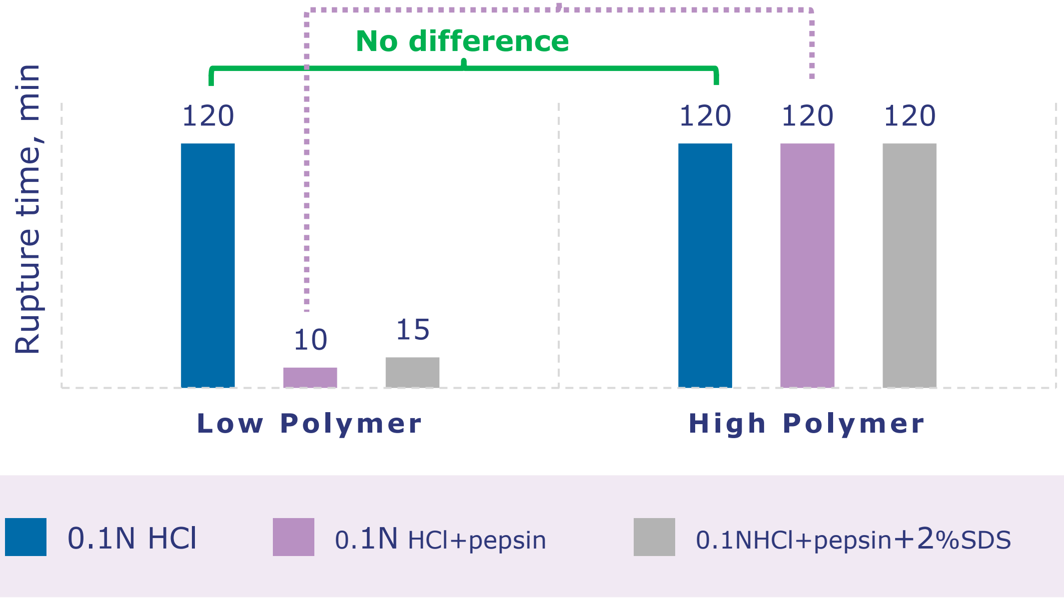
- **Failure to discriminate** omega-3 fatty acids release in USP/EP media -0.1N HCl media for DR softgels with different polymer (pectin) levels

Approach

- USP App II Dissolution at 37ºC
  - Paddle speed: 75 rpm
  - Media (900 mL):
    - 0.1N HCl
    - 0.1N HCl, pepsin 700,000 Units/L
    - 0.1N HCl, pepsin 700,000 Units/L, 2% SDS

Results

Significant difference with enzyme addition



Key Insights

- Softgels with 50% less polymer ruptured in 10–15 min in pepsin media vs. 2 h in USP/EP media
- High polymer softgel was unaffected by pepsin
- **Include discriminatory dissolution media to test robustness of the product**

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Case Study 3: Impact of Temperature & Solid Lipid Matrix on Dissolution - Need for Optimizing Processing Temperatures

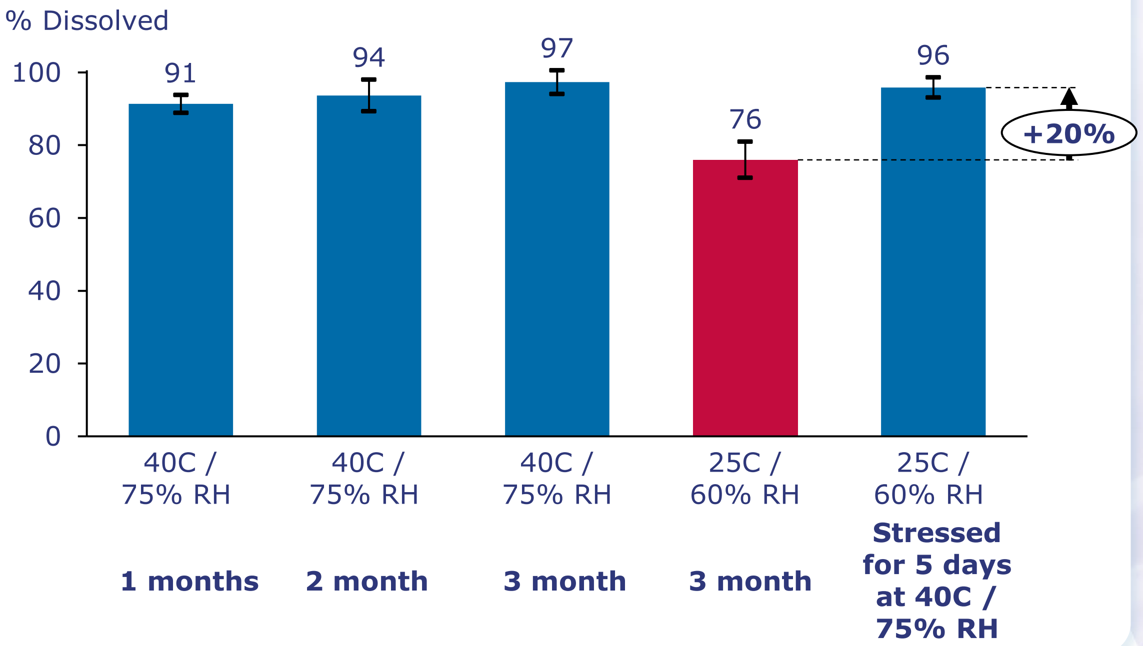
Challenges

- Lipid based suspension **fill material with wax type** excipient

Approach

- Dissolution was satisfactory at 40° C /75% RH **but OOS at 25° C/60% RH after 3 months** due to solidified lipid matrix that delayed the release
- Storing the RT samples at 40° C for 5 days & tested dissolution again with passing results

Results



Key Insights

- Modified the fill holding temperature to prevent solidification of the lipid matrix
- Fill manufacturing & fill holding temperature is critical in maintaining a fine balance between CU & dissolution

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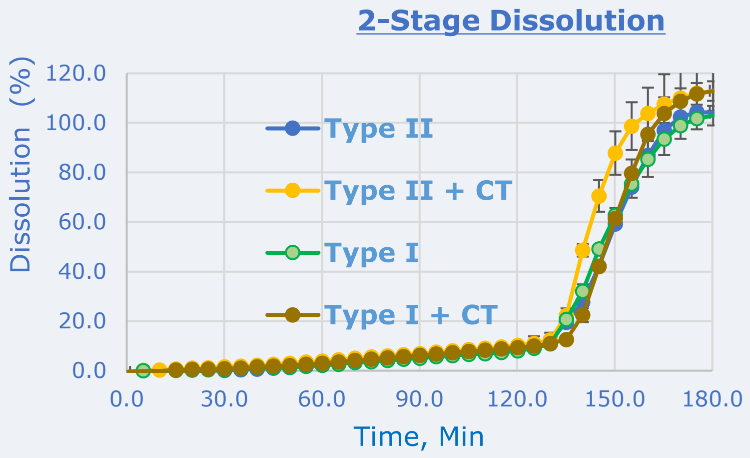
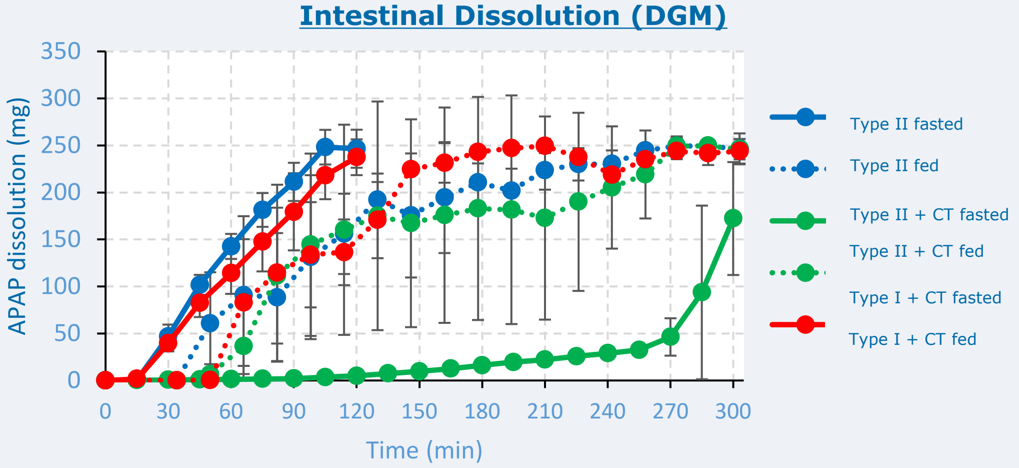
Case Study 4: Conventional Dissolution (USP/EP) vs. Dynamic Gastric Model (DGM) to Predict in-Vivo performance



No discrimination identified with the different shell formulation with standard USP/EP method



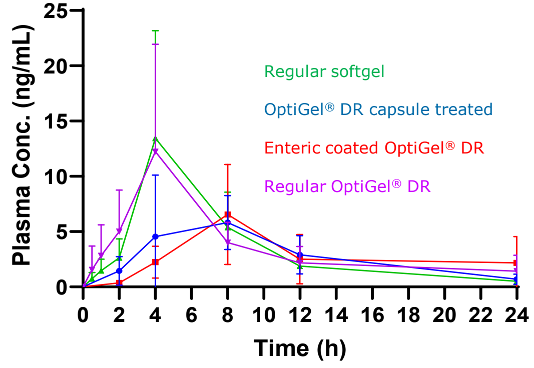
Results

- USP/EP enteric test couldn't differentiate the 4 types of softgels
- DGM successfully identified the variations among the 4 enteric softgels
- Only Type II & Type II + CT managed to endure the high shear conditions of the antrum while in a fasted state using DGM

Key Insights

- USP/EP enteric/DR methods are not discriminatory compared to DGM method

Animal PK Study



- Study in fasted monkeys (n=6)
- OptiGel® DR softgels showed delayed plasma peak at 4–8 h
- No API detected at 1 h, confirming gastric resistance of DR softgels

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Why IVIVC Is Challenging For LBFs

In vitro gaps: Current tests don't capture dynamic GI processes like pH shifts, bile flow, or lipolysis

Food effect variability: Fed vs. fasted states impact LBF performance, but hard to replicate in vitro

Formulation heterogeneity: Diverse LBF types complicate standardized dissolution testing

Translation challenge: Animal-validated models often fail to reflect human GI physiology

The % of solubilized drug in FaSSIF/FeSSIF can be correlated with the amount of drug absorbed in vivo. Multiple examples showed Level A IVIVC [1]

Drug	In Vitro Dissolution	In Vivo	IVIVC
Cyclosporin (SMEDDS)	Dissolution at pH 1.2, 4.5, 6.8	Dog bioavailability	Strong Level A correlation between in-vitro and in- vivo fraction absorbed.
Ritonavir (SEDDS)	Dissolution in SLS (0.3–1%)	Human BA	Strong Level A IVIVC across SLS levels.
Lopinavir (SEDDS)	Dissolution at pH 6.0 with 2.3% SLS	Human PK	High IVIVC; linear correlation
Arundic Acid (Type I)	Dissolution at pH 8.0 & 6.8 with 2% SDS	Human PK	IVIVC achieved; pH 6.8 showed better correlation.
Fenofibrate (SMEDDS) [2]	Dissolution in FaSSGF & FaSSIF	Human PK	In silico model matched Cmax/AUC (within 0.8–1.25 range); supports IVIVC
Fenofibrate (suspension) [2]	Improved solubility over unformulated drug	Variable in vitro to in vivo	**No IVIVC**

Lipolysis-based models are more predictive for digestion-dependent formulations.
But IVIVC is more variable & influenced by species, bile flow & fed/fasted conditions [1]

Drug	In Vitro Lipolysis	In Vivo	IVIVC
Halofantrine	sSNEDDS performed superior to precipitating API	sSNEDDS, showed similar BA to precipitating formulation	**No IVIVC**
Griseofulvin	Rank: MCT > LCT > SCT > H_2O	In vivo data matched in vitro rank order	Strong correlation
Cinnarizine	Higher BA for ASD	Crystalline & ASD in SNEDDS yield similar in vivo results	**No IVIVC**
Dexamethasone	MCT = LCT = SCT	Rank order: MCT = LCT = SCT	**No IVIVC;** weak correlation in fasted state
Danazol	Rank: LC-SMEDDS > MC-SMEDDS	Rank order matched: LC > MC > SCT	**No IVIVC**
Probucol	Release rate: SMEDDS > SNEDDS > pure oil	Bioavailability matched: SMEDDS > SNEDDS > API	IVIVC obtained; strong correlation
Vitamin D_3	Rank: MCT > LCT > SCT	In vivo rats matched rank; bile cannulated rats did not	**No IVIVC;** bile-dependent variation affected correlation

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Ref:
[1] Kollipara S, Gandhi RK. Acta Pharm Sin B. 2014 Oct;4(5):333-49
[2] Fei Y, Dressman JB, et al. Eur J Pharm Biopharm. 2013 Nov;85(3 Pt B):1274-84

Calcifediol/Rayaldee® ER Capsules (Softgels & Hard Capsules)

Formulation Lessons from Marketed Softgel Product

Formulation Overview

Sensitivity to heat, light, and oxidation during manufacturing & storage

Encapsulation in opaque gelatin shells to protect from light exposure

Use of stabilizers & antioxidants to enhance shelf-life

Release Profile

The extended-release profile is achieved via lipid-cellulose based matrix

Generic Consideration

Generic calcifediol must replicate the reference product’s extended-release profile across various pH & biorelevant media

Understanding of the lipid-cellulose matrix & its effect on release kinetics is critical

FDA expects BE under both **fasting** & **fed** states, even without food effect noted in labeling

Being an ER formulation **dose dumping risk** must be evaluated

Food Effect & Implications for Generic Product Development – Recommended Bioequivalence Study Designs

Drug	DP Label	BE Study	Key Considerations
Midostaurin	Take with food	Fasted/Fed	Significant food effect; fasted & fed study required with PK endpoints
Testosterone Undecanoate	Take with food	Fasted/Fed	Significant food effect; fasted & fed study required
Nintedanib	Take with food	Fasted/Fed	Moderate food effect; fasted & fed study required

FDA product-specific guidance

- Midostaurin Oral Capsule, May 2022
- Testosterone Undecanoate Oral Capsule, Mar 2021
- Nintedanib Esylate, Sept 2015

High-risk products
… (BCS-II) have complex formulation and/or manufacturing methods, such as solid dispersions, ***microemulsions***, co-processed drug substances, ***lipid-based formulations***… For these high-risk products, ***BE studies should be*** conducted under ***both fasting and fed conditions***, irrespective of the drug product labelling with regard to food intake

ICH HARMONISED GUIDELINE BIOEQUIVALENCE FOR IMMEDIATE RELEASE SOLID ORAL DOSAGE FORMS M13A, JULY 2024

- Understanding formulation–food interactions is key
- Conduct **solubility vs precipitation** of the formulations **in biorelevant** media
- Employ **biorelevant media dissolution media** to better simulate GI conditions
- **Integrate in vitro data with PBPK** models to account for metabolism, food interactions to improve IVIVC predictability
- **In vivo validation** - Conduct in vivo studies in animals to validate in vitro findings and establish stronger correlations

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SMEDDS Enhances IVIVC in Preclinical Models, but Human Variability Challenges Translation for Cyclosporine LBFs

Dissolution data

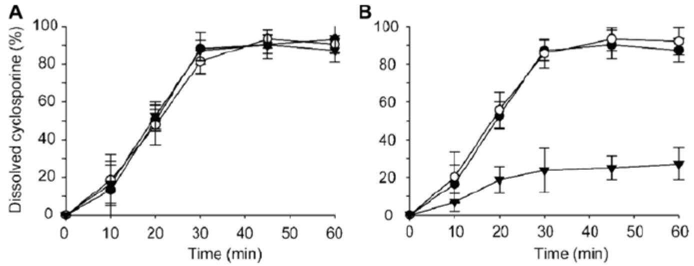


Fig. 1. (A) Dissolution of cyclosporine from test SMEDDS formula at pH 1.2 (●), pH 4.5 (○) and pH 6.8 (▼) dissolution medium. (B) dissolution of cyclosporine from the test (●), the reference I (○) and the reference II (▼) at pH 6.8 dissolution medium.

Dog PK data

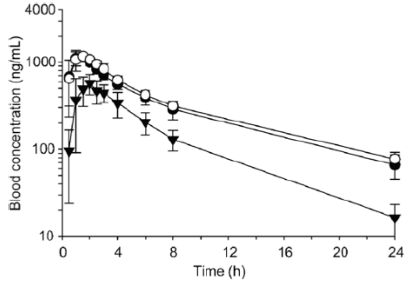


Fig. 2. Whole blood concentration-time profiles of cyclosporine after single oral administration of the test (●), the reference I (○) and the reference II (▼) against dogs at a dose of 100 mg (n=6).

IVIVC

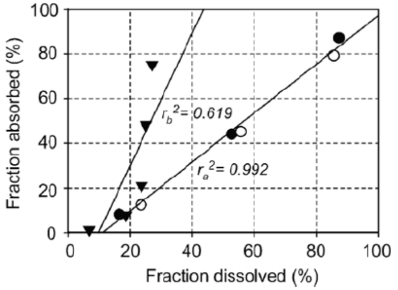
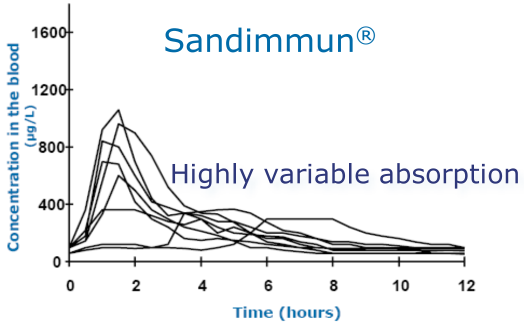


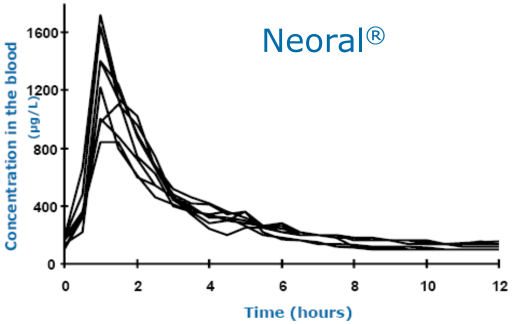
Fig. 3. Relationship between *in vitro* the fraction dissolved and *in vivo* the fraction absorbed; r_a^2 (correlation factor) was acquired from the pooled data of the test (●) and the reference I (○), and r_b^2 was acquired from the data of the reference II (▼) alone.

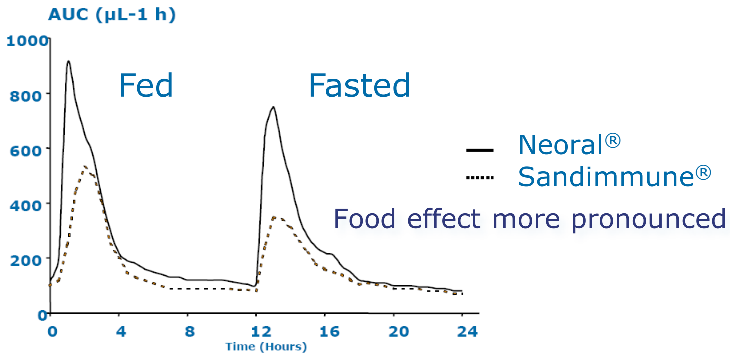
Legend: Reference I = Neoral® (SMEDDS) | Reference II = Cyclosporin SEDDS with mean droplet size > 2µm

versus

Human PK data







IVIVC in Preclinical Model
Dog PK & in vitro dissolution of SMEDDS show a strong Level A correlation ($r^2 > 0.9$), suggesting predictive power [1]

Human Data
Variability in Neoral® absorption (fed vs. fasted, age, transplant type), with meta-analysis showing persistent variability despite improved bioavailability over Sandimmune® [2] *Gengraf® - AB rated generic to Neoral® resulted in 39% organ transplant reject vs 25% for Neoral®.*

Why It Matters
SMEDDS improves consistency over non-SMEDDS, but human physiological variability challenges IVIVC translation, risking underexposure or toxicity [2] ***IVIVC MUST BE CONSIDERED ON A CASE-BY-CASE BASIS particularly for NTDs***

Ref:
[1] Arch Pharm Res Vol 33, No 11, 1835-1842, 2010
[2] Int J Immunopathol Pharmacol. 2010 Oct-Dec;23(4):1177-83.

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Key Takeaways

- Lipid-based IR/MR systems are versatile
- Broad utility for complex APIs covering BCS II, III & IV
- Promising technology for **targeted protein degraders** & potentially for **macromolecules**
- Understanding of formulation (fill & shell), analytical, process manufacturing & food effect is key for successful generic development
- Need for better IVIVC predictive tools for LBFs

Lipid based formulations offer strong potential for generics — success depends on early, strategic resolution of formulation & development challenges

Proposed Research Areas for FDA on IVIVC for LBFs

Gap	**Current IVIVC guidance treats products with LBFs same as non-LBFs** • The FDA's research should focus on developing & validating advanced in vitro models, integrating PBPK modeling, exploring mechanistic insights with novel technologies, addressing physiological & formulation challenges & standardizing methods.
Research Areas	• **Advanced In Vitro Lipolytic-Permeability-Microsomal Metabolism Models**: Develop & validate in-vitro models that mimic human GI physiology & lipid digestion, drug release & absorption • **Simulating GI Conditions**: pH-Stat lipolysis models mimicking GI & intestinal phases that account for pH gradients, enzymatic activity, bile salts, transit times, gastric retention (fed state), emptying should be studied • **Address Any Limitations** associated with current IVIVC predictive systems like DGM ™, TIM™, Gastroplus™, Symcyp™, STELLA®, Simcyp™, PK-Sim® software & encourage their use • **Impact of Food:** Lipid digestion and lipid digestion products like mono & diglycerides & fatty acids on drug solubilization & integrate PBPK models with in vitro digestion data • **Fund Studies Using PBPK–Food Interaction Modeling** to support risk classification of LBFs based on suspension vs solution formulations & for narrow therapeutic index (NTI) drugs • **Define Decision Trees** or scoring systems for food-effect study requirements based on excipient class, lipid type, or dispersion behavior **for both solution & suspension** formulations & for NTI drugs • **Revise IVIVC Guidelines:** Develop standardized in vitro digestion protocols validated for human data, ensuring consistency across studies to enhance IVIVC predictability for LBFs

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Thank You!
Questions?

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