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Advancing IVIVC in Lipid-Based Formulations: Addressing *In-vitro* Dissolution Challenges for BA Correlations

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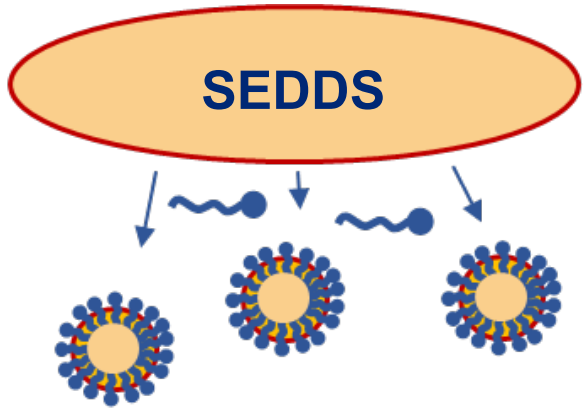
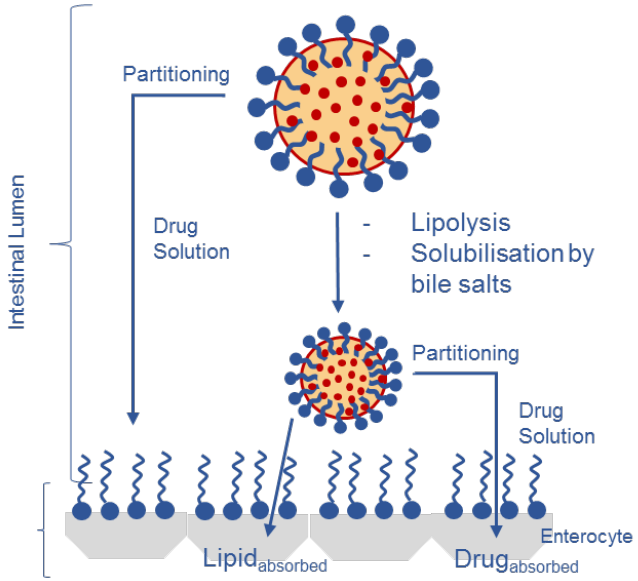
Self-Emulsifying Drug Delivery System (SEDDS)

SEDDS emulsifies upon contact with an aqueous environment

SEDDS **disperse** into macroemulsions, stabilized by surfactants.

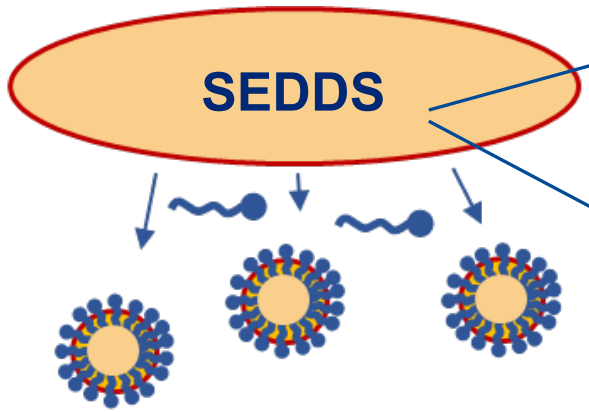


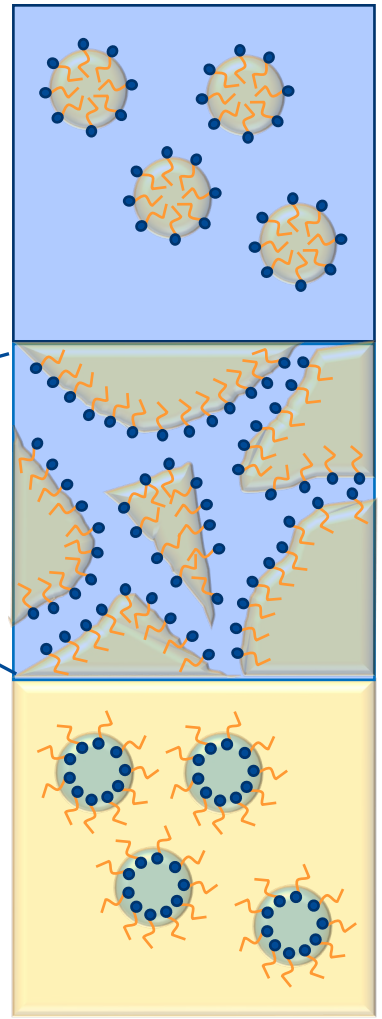
SEDDS emulsion droplets are then **digested**, and API is released and absorbed.



SEDDS formulations are truly bicontinuous

- **Surfactant HLB Balance**
- Mixing
- Dispersibility of Formulation



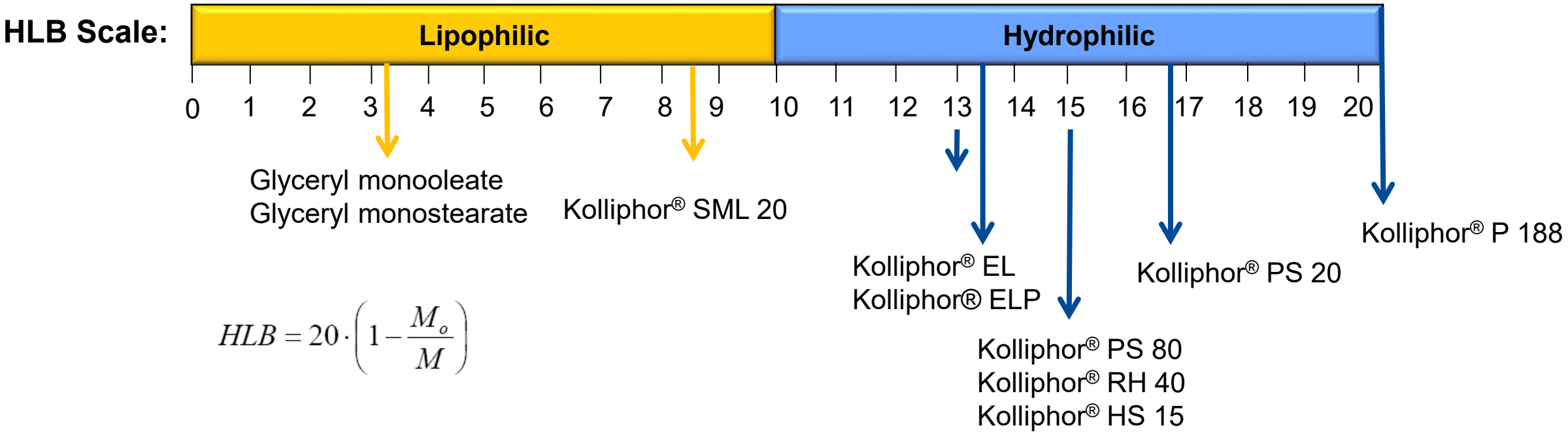


Oil-in-Water (O/W) Emulsion

Isotropic Bicontinuous Microemulsion

Water-in-Oil (W/O) Emulsion

Precise mixture of surfactants is required for SEDDS formulation



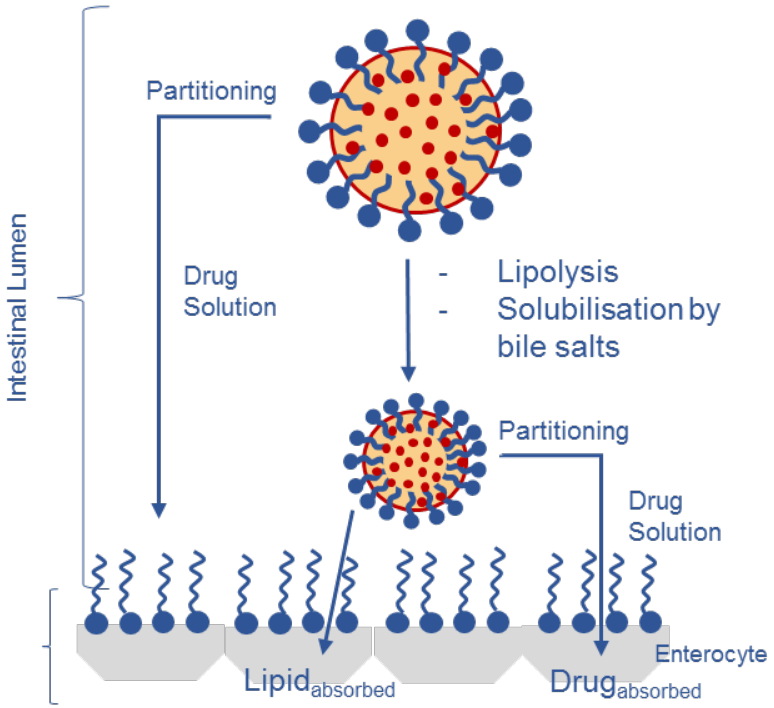
$$HLB = 20 \cdot \left(1 - \frac{M_o}{M}\right)$$

LBDDS typically require a **primary surfactant** (HLB > 10) and **cosurfactant** (HLB < 10).

The **mixture ratio** will affect properties like **droplet size.**

In the GIT, API absorption is controlled by SEDDS properties

SEDDS emulsion droplets are **digested**, and API is released and absorbed.



Controlled by:

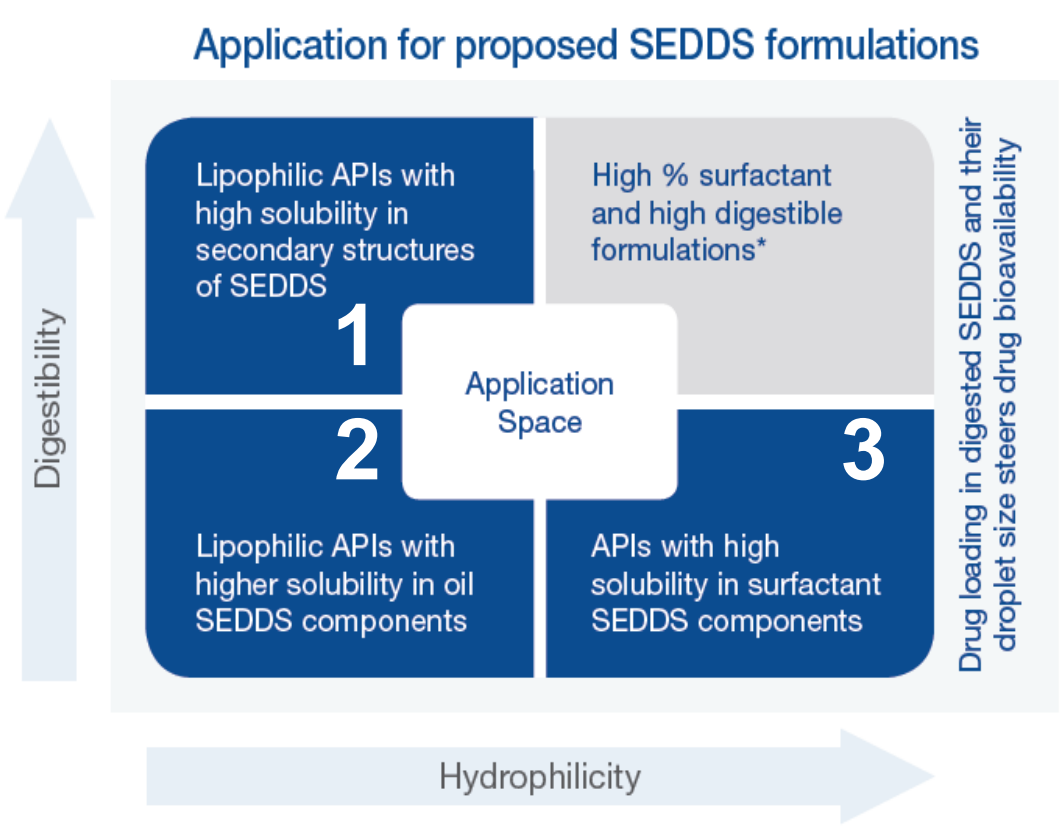
- **Oil Phase Type**
- **Surfactant Type/Characteristics**
- API concentration and recrystallization

low	**Digestibility** →	high

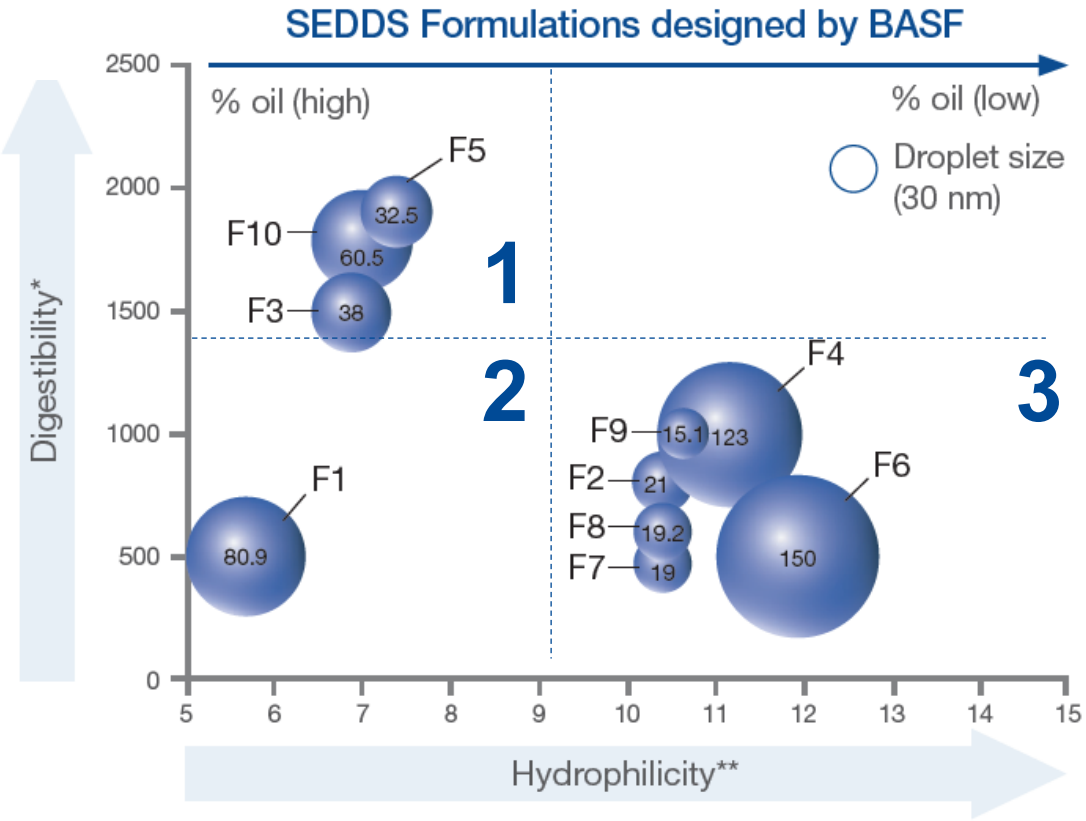
- Long-chain lipids
- Saturated-chain lipids
- Higher surfactant content
- Kolliphor® RH 40

- Short-chain lipids
- Unsaturated-chain lipids
- Higher oil content
- Kolliphor® EL

The Digestibility and Hydrophilicity of 10 BASF SEDDS Compositions Guides Their Application



* High % surfactant and high digestible formulations will not be stable in GIT conditions and hence not designed.



* Digestibility of formulation in GIT (based on lipolysis experiment) (Titrated free fatty acid; µmol)
** HLB value of system

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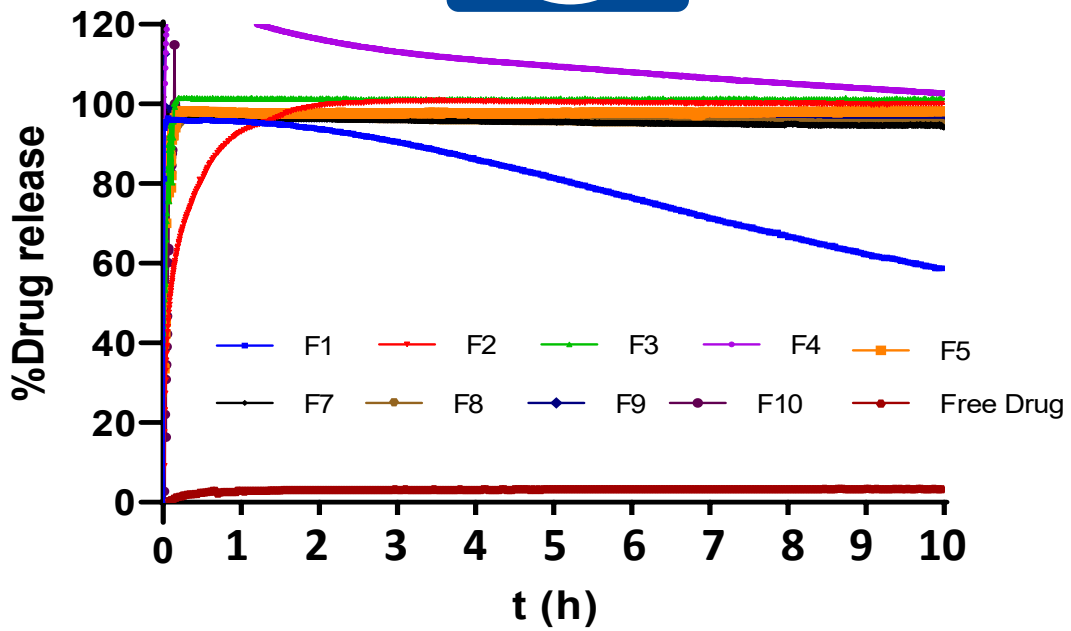
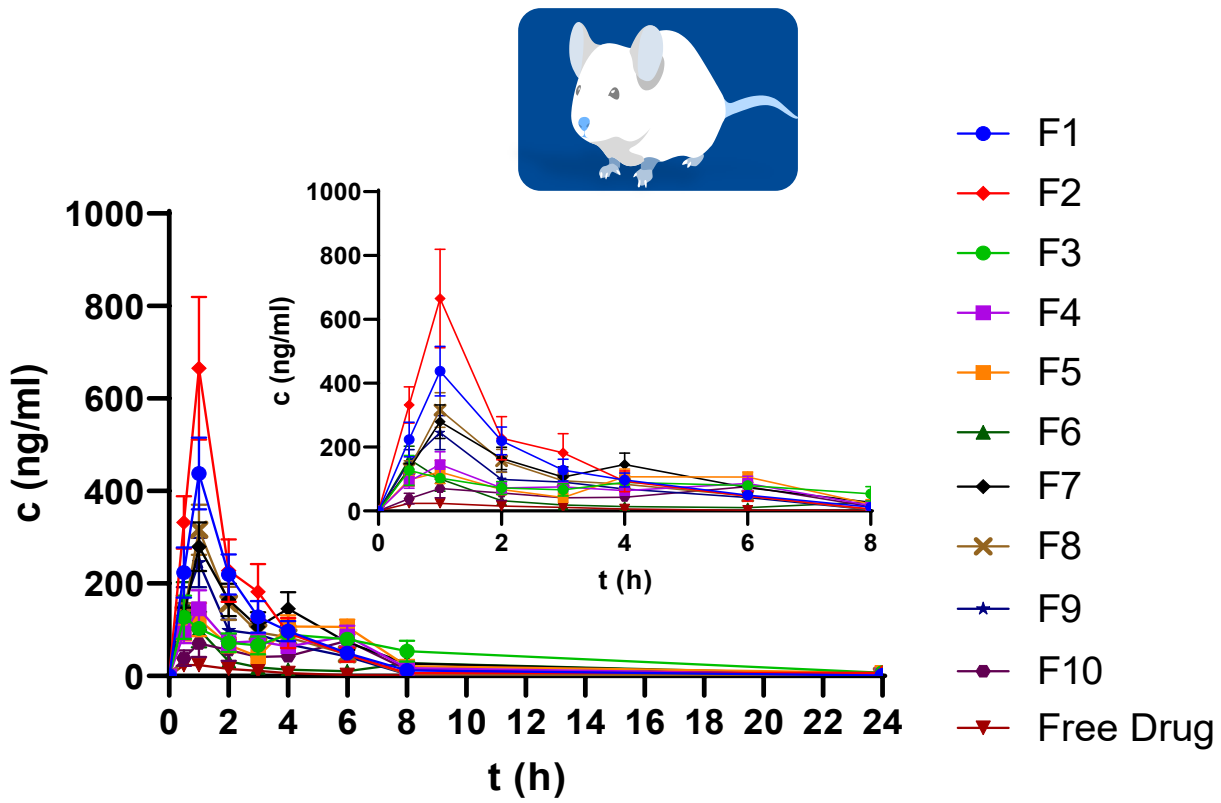
Standard *In Vitro* Dissolution of SEDDS Formulations Does Not Directly Correlate with *In Vivo* Absorption

In Vitro



In Vivo



SEDDS formulations showed improved *in vitro* dissolution of danazol in USP Type 2 apparatus **compared to free drug**, but this method has **poor *in vitro-in vivo* correlation** because of **limited *in vitro* discrimination of formulation behavior**

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In Vivo – In Vitro Correlation (IVIVC) Can Be Established Based On A Variety Of Parameters, Which Ultimately Determine the Level Of Correlation

- *In vitro–in vivo* correlation (IVIVC) is a **predictive model** describing the relationship between an *in vitro* property and a relevant *in vivo* response
- Depending on the designated level, **different parameters are used for correlation**.

Level	*In vitro*	*In vivo*	FDA Comments
A	Dissolution curve	Input (absorption) curves	The **most informative** and is recommended, **if possible**.
B	Statistical moments: MDT	Statistical moments: MRT, MAT, *etc*.	Level B correlations are **least useful** for regulatory purposes.
C	Disintegration time, time to 10, 50, 90% dissolved, dissolution rate, dissolution efficiency	c_{max}, t_{max}, K_a, time to 10, 50, 90% absorbed, AUC (total or cumulative)	Level C correlations **can be as useful as Level A correlations**. Level C correlations are used in the **early stages** of formulation development when pilot formulations are being selected
D			For determining a rank order and qualitative analysis

Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations, **1997**.

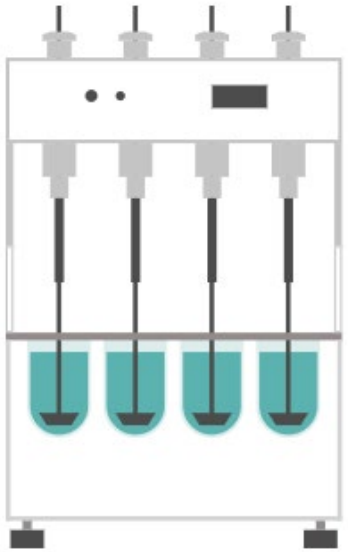
There Is No Specifically Recommended Method To Establish IVIVC Of SEDDS

- Scientist have tried *in vitro* dissolution using a USP apparatus 2, but the defined parameters **can not be used across formulations with different compositions**
  - **Neoral® formulation:** USP apparatus 2 is used with 100 mL dissolution media at various pH (pH 1.2, 4.5, and 6.8; vigorous shaking) to achieve level A correlation with dog PK data. (Ref: 10.1007/s12272-010-1116-2)
  - **Norvir® Ritonavir formulation:** USP apparatus 2 is used with 900 mL of medium with 0.7% SLS + water at 25 rpm to achieve level A correlation with clinical data. (Ref: 10.1016/j.ijpharm.2007.01.036)
  - **Kaletra® Lopinavir formulation:** USP apparatus 2 is used with 1000 mL of medium with 2.3% of sodium lauryl sulfate and pH 6.0 at 25 rpm to achieve Level A correlation (Ref: 10.1016/j.jpba.2008.02.014)
- **Biorelevant media is recommended over simple buffers**, in order to simulate GIT conditions critical to dissolution and absorption behaviors (*e.g.* fasted-state simulated intestinal fluid (FaSSIF), fed-state simulated intestinal fluid (FeSSIF)).
- **Sample collection process should include separation of carrier droplets from drug**, by passing the solution through a 0.22-μm or 5-μm filter, or using a size exclusion column. However, this is **not a robust or reliable process** because of the dynamic nature of SEDDSs droplet sizes.

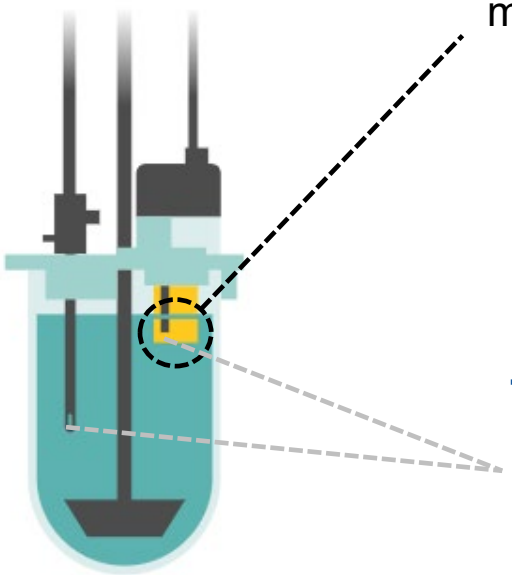
Ref: DOI: 10.1208/s12249-018-1239-1

Introduction of Pion MacroFlux™

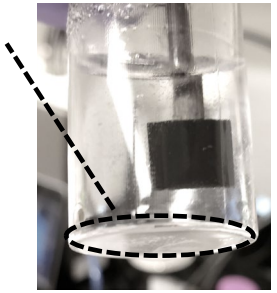
The MacroFlux system is designed for **real-time analysis of drug in multiple in vitro experiments** through fiber optic UV probes.



Each dissolution apparatus allows for **simultaneous dissolution and absorption monitoring**.



Synthetic lipidic membrane mimics the GIT membrane, and separates the **donor** (‘GIT’) and **acceptor** (‘blood’) chambers.

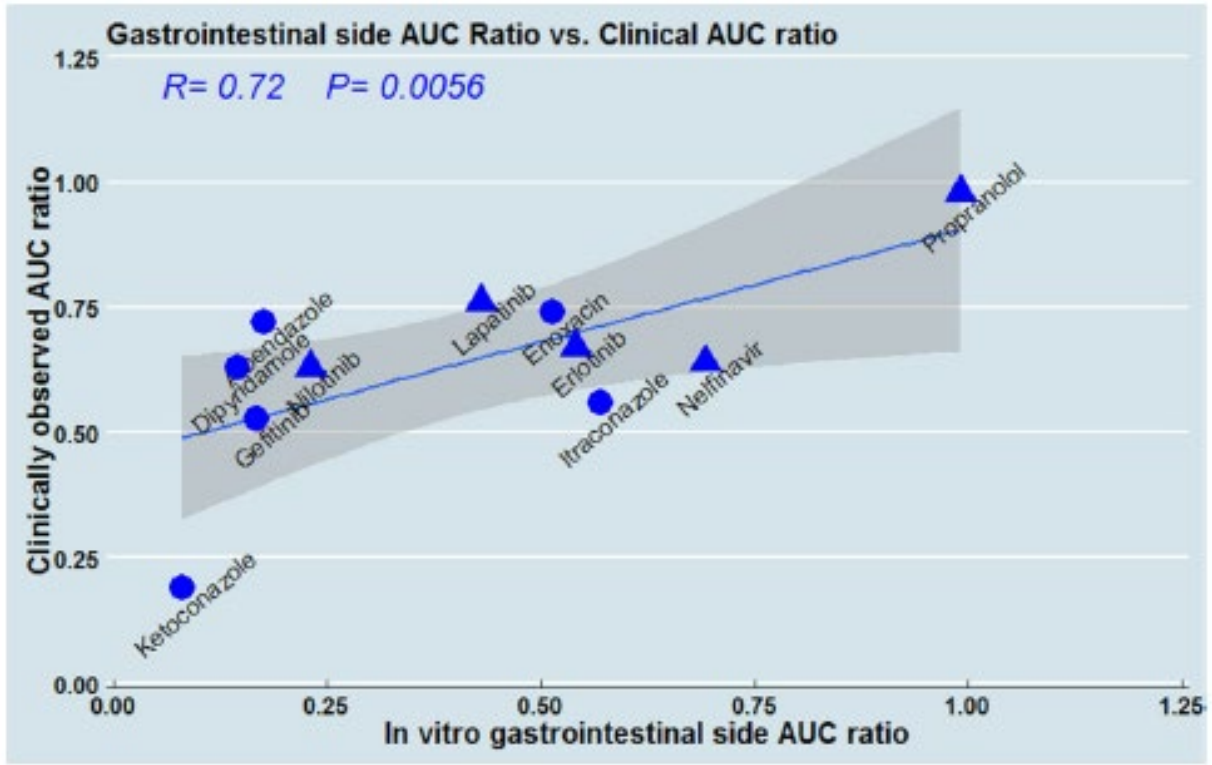


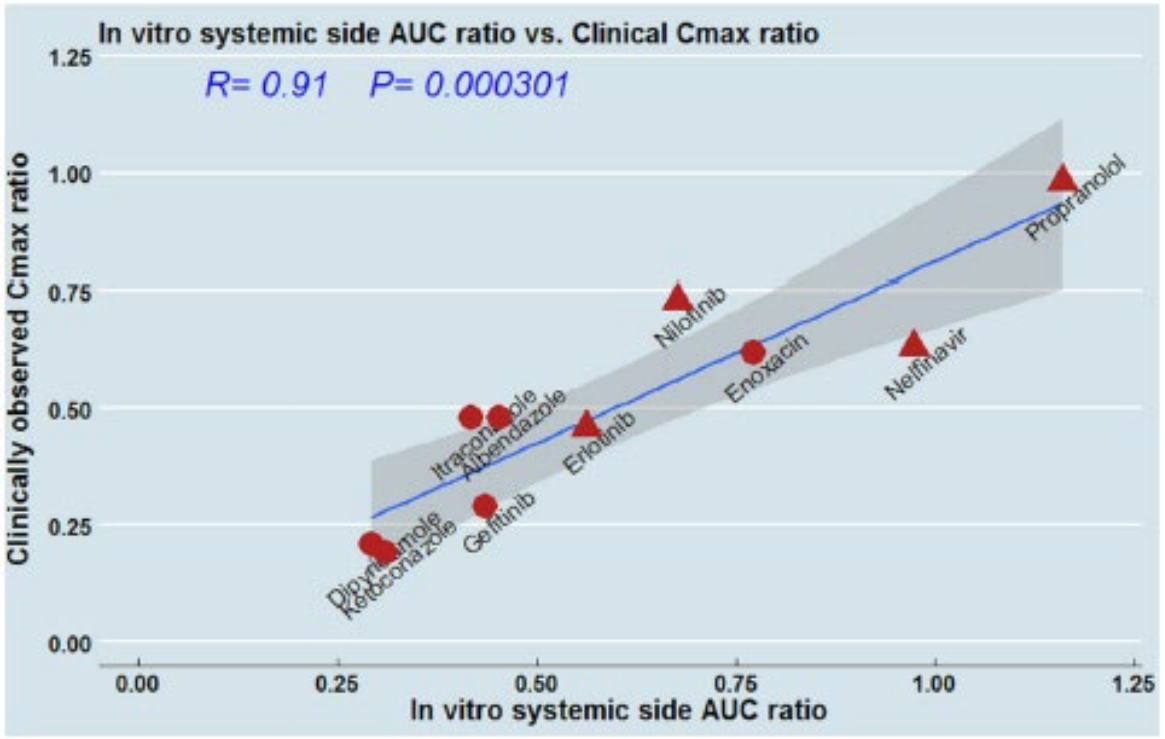
Two fiber optic probes allow for real-time, simultaneous analysis of **drug in donor and acceptor chambers**.

Figure adapted with permission from Pion

A Good Correlation was Reported

In Vitro Dissolution Permeation Data with Clinically Observed pH-dependent drug-drug interaction





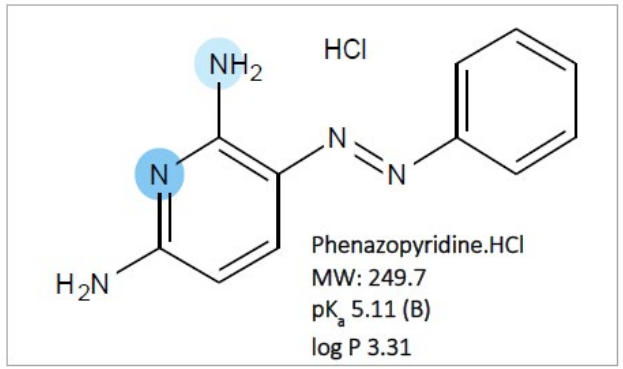
Triangle symbols indicate pH-dependent DDIs with PPIs, while point symbols represent pH-dependent DDIs with H2 antagonists.

The relationship between the gastrointestinal side AUC ratio from in vitro dissolution-permeation tests and the clinically observed AUC ratio is shown.

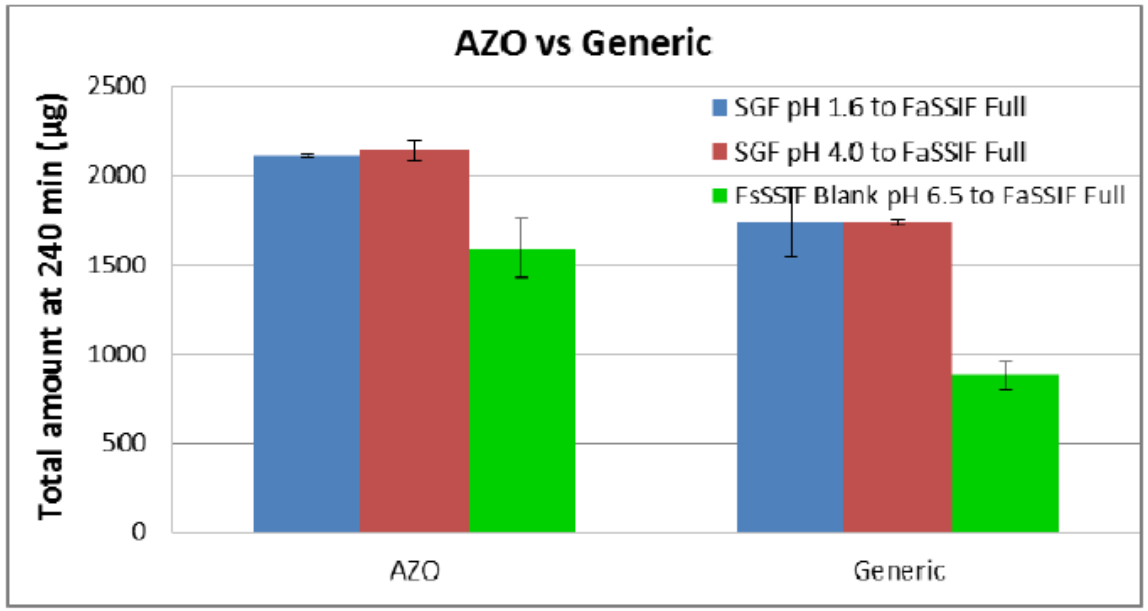
The correlation between systemic side AUC ratio from the *in vitro* dissolution permeation experiments and clinically observed Cmax ratio.

Ref. DOI: 10.1208/s12248-016-9972-4

Absorption Chamber Combined with USP II Dissolution Apparatus for Predicting Drug-Drug Interaction Risks from pH-Adjusting Agents



Phenazopyridine: an overview of its structure, physicochemical characteristics, and images of the examined drug products

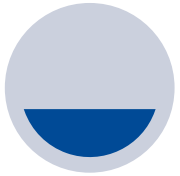


Total amount of PHZ in the receiver compartment for the Brand and Generic formulations, depending on initial pH conditions of SGF media

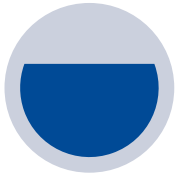
- No significant difference in flux depending whether conversion was from SGF1.6 or SGF4.0.
- A conversion FaSSIFblank ->FaSSIF was considered as a model for extreme gastric pH modification: AZO formulation dissolved only 90% dissolved vs the Generic form 65% dissolved after 250 minutes in FaSSIF

Ref: www.pion-inc.com Technical document TN5016 Rev A 06302017

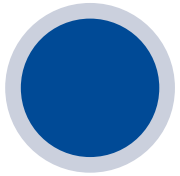
Prediction of Bioequivalence and Food Effect Using Flux- and Solubility-Based Methods for Complex Amorphous Solid Dosage Forms



Predict the food effect of formulations.



Predict the bioequivalence of formulations.



Compare the predictions with *in vivo* study results.

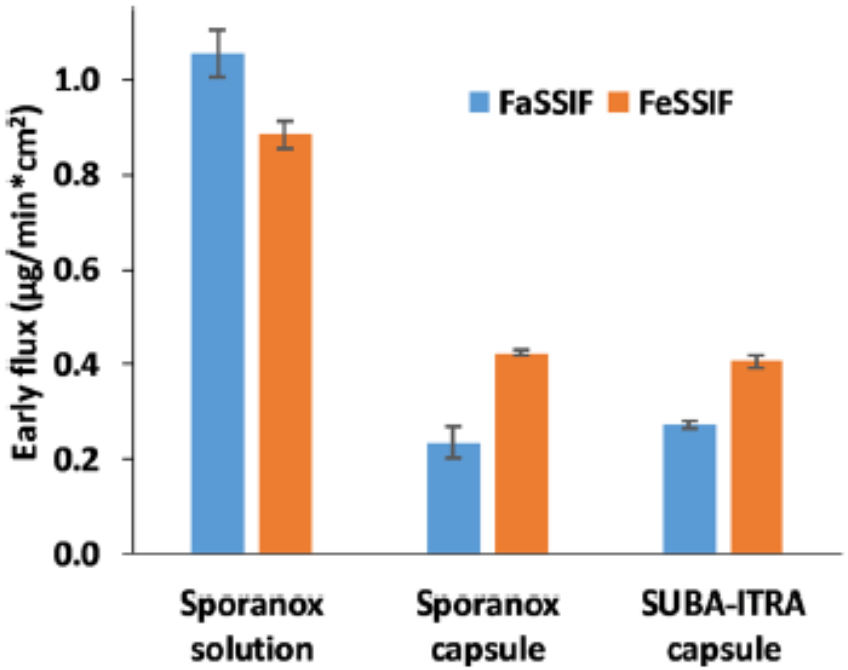
Case Study

Composition of Itraconazole Containing Marketed Formulations

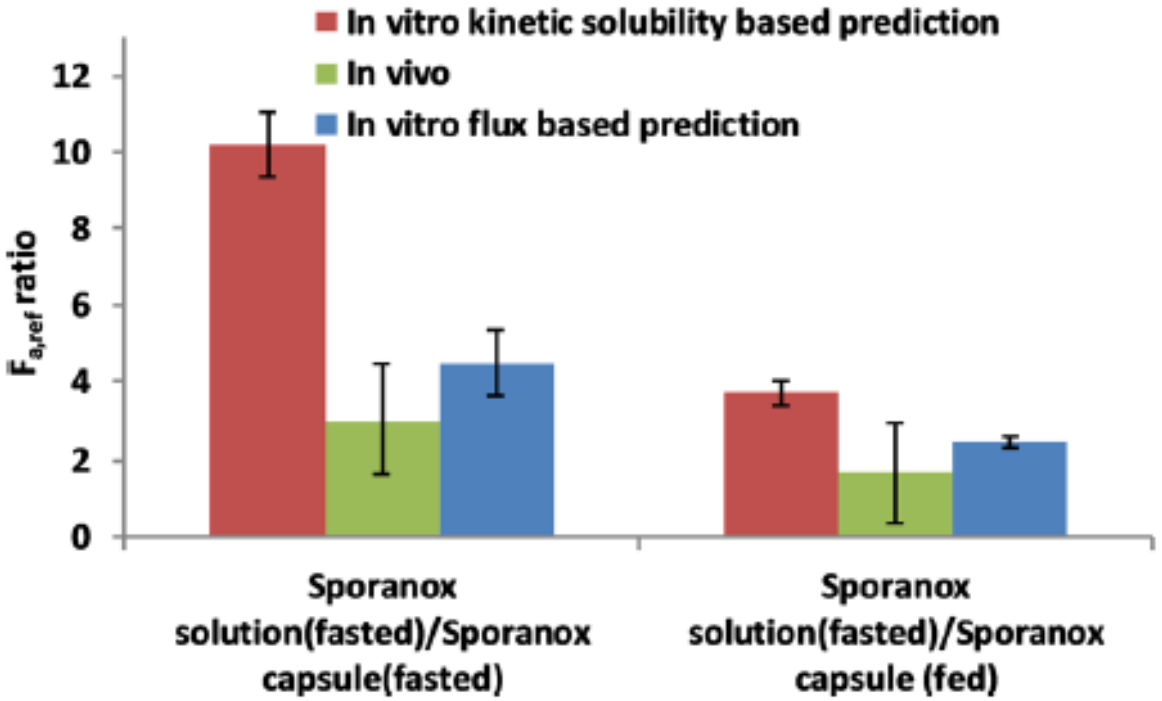
Formulation	Dose (mg/ capsule)	Main Additive	Load of additive
Sporanox solution	100 mg/10 mL	HP-β-CD	4000 mg/10 mL
Sporanox capsules	100	HPMC 2910	not published
SUBA-ITRA capsules	50	HPMC-P	75 mg/capsule

Ref DOI: 10.1021/acs.molpharmaceut.9b00406

Prediction of Bioequivalence and Food Effect Using Flux- and Solubility-Based Methods



Appearance profile of ITRA from Sporanox solution (100 mg), the Sporanox capsule (100 mg), and the SUBA-ITRA capsule (50 mg) in FeSSIF media.



Predicted fraction absorbed ratios for the comparison Sporanox solution and Sporanox capsule in fasted and fed conditions and in vivo data

Both kinetic solubility and flux-based prediction methods effectively identified a mild negative food effect for Sporanox solution and a notable positive food effect for the Sporanox capsule.

Ref DOI: 10.1021/acs.molpharmaceut.9b00406

SEDDS Formulations Show Complex Behavior in The MacroFlux™ Donor Chamber, but Only (Simply) Permeated Drug in the Absorption Chamber

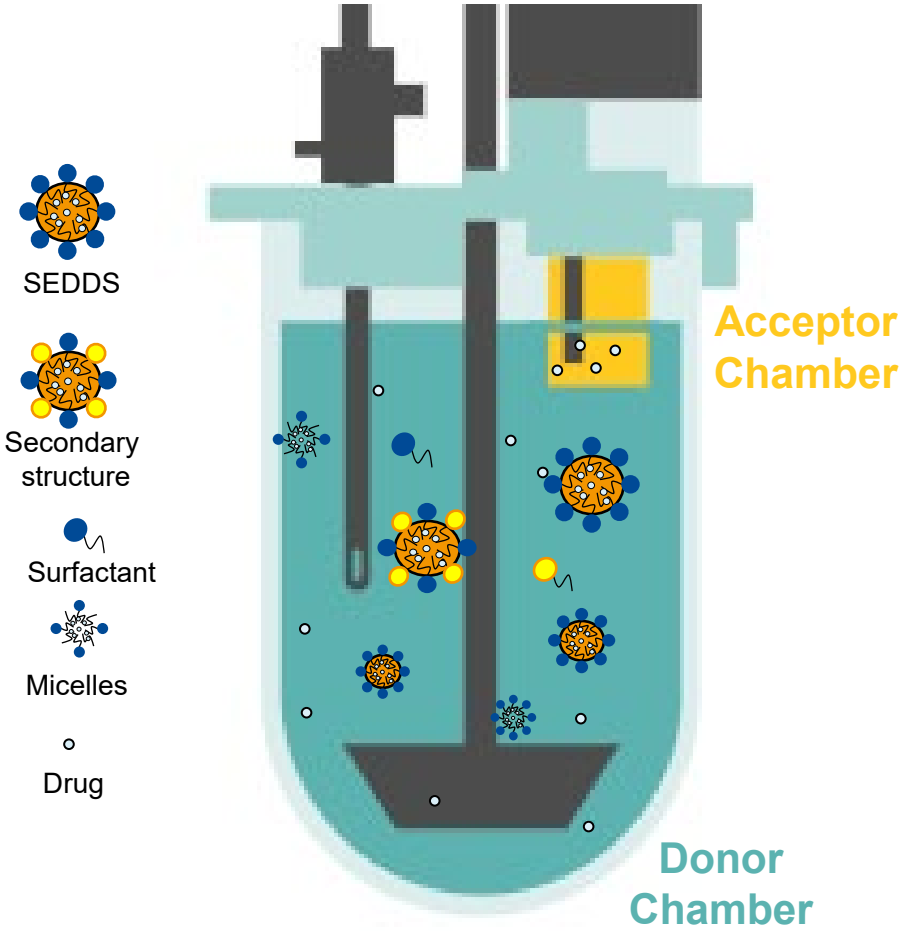
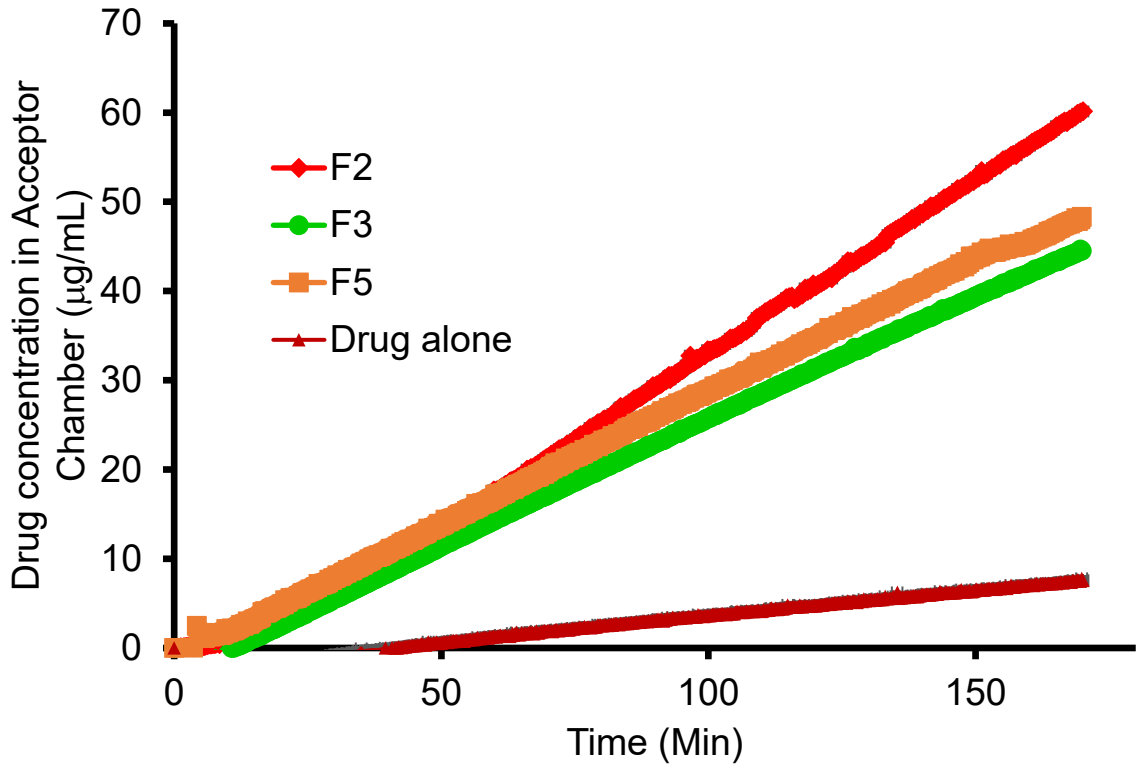


Figure adapted with permission from Pion

- SEDDS formulations **demonstrate complex *in vitro* performance** depending on multiple factors, including:
  - **Composition** of SEDDS Formulation
  - Rate of **dispersibility**
  - Effective SEDDS **droplet size**
  - **Digestibility** and **secondary structures**
  - **Drug solubilizing** properties and mechanisms
- *In vivo*, these complexities determine **drug uptake, rate of absorption, and absorption pathway(s)**.
- *In vitro,* the MacroFlux™ lipidic membrane resolves all of these complexities to a **single parameter monitored over time - absolute drug concentration in the absorption chamber**.

BASF's SEDDS Compositions Demonstrated Enhanced Flux And Permeation Of Danazol, As Compared To Drug Alone, and Gave Resolution Between Formulations



- **Drug flux was unique and resolved** for each SEDDS formulation.
- **Flux was directly proportional** to the **effective permeability** of the drug.
- For example, F2, F5, F3, and Free Drug are shown, with mean ± SD (n=3).

Formulation	Flux •10^{-3} (0-150 min) (µg sec^{-1} cm^{-2})	Permeability •10^{-5} (0-150 min) (P_e; cm sec^{-1})
F2	**13.0** ± 0.7	**16.3** ± 0.9
F5	**10.3** ± 0.1	**12.9**± 0.1
F3	**9.7** ± 0.7	**12.1** ± 0.8
Drug alone	**2.1** ± 0.2	**2.7** ±0.3

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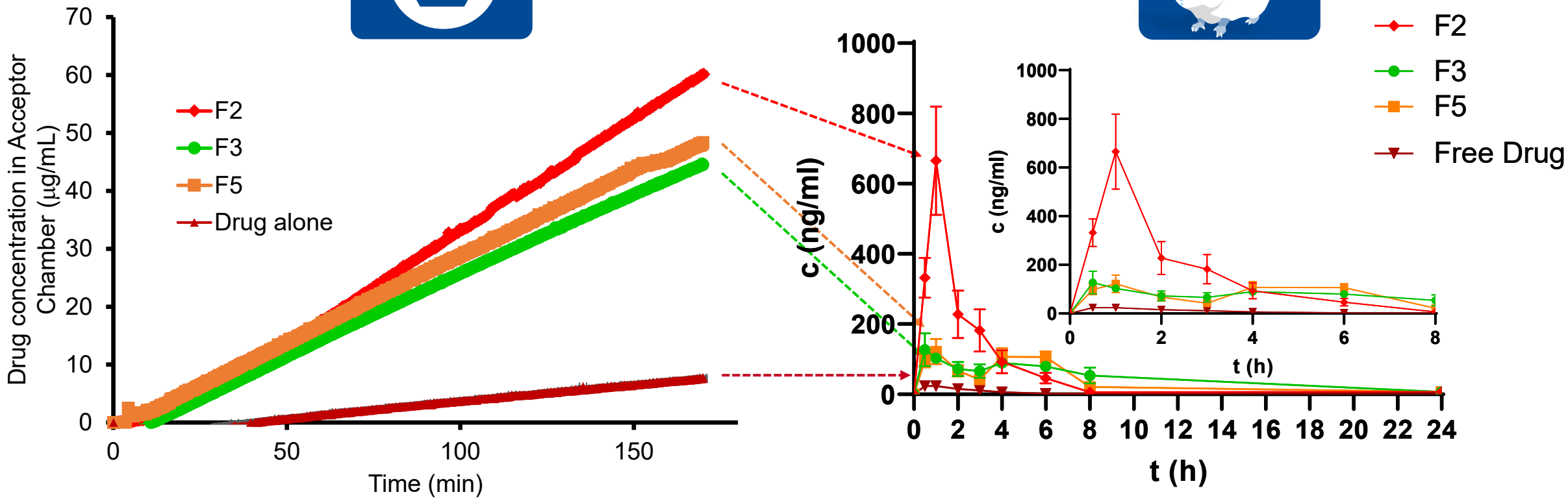
There is Strong Correlation Of MacroFlux *In Vitro* Permeation (Drug in Acceptor Chamber) And *In Vivo* Drug Absorption

MacroFlux™ *in vitro* **permeation** *data*

In Vivo data



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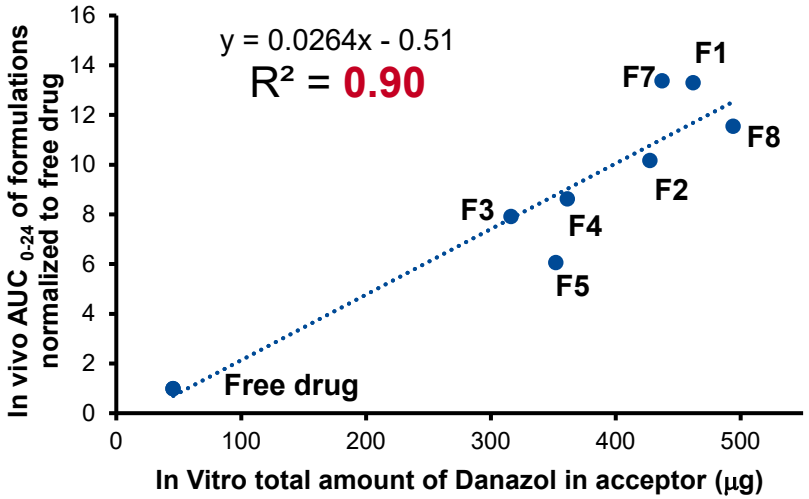
Excellent IVIVC (R^2 > 0.90) Achieved By In-House MacroFlux™ Studies

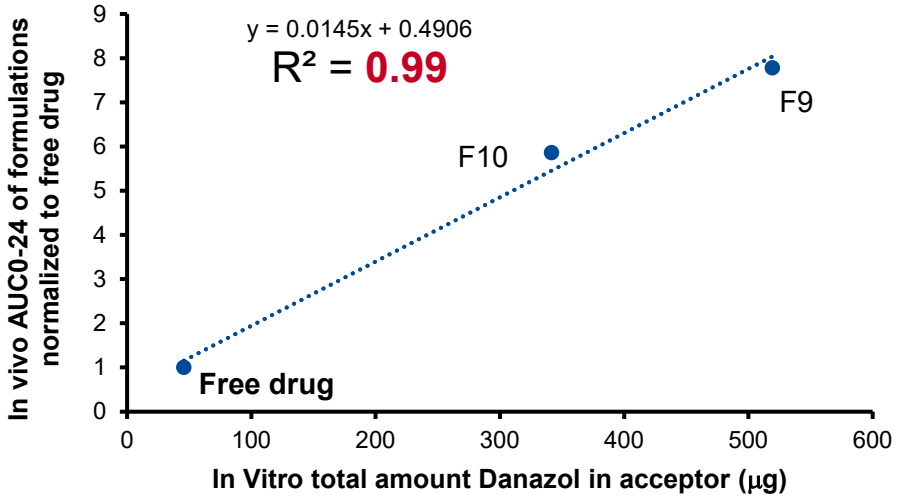
- Within a **single chemistry family** (*i.e.* GMO or Capmul), **excellent IVIV correlation** can be achieved
- **Different chemistries have different mechanisms** of interaction with biological membranes, cannot be correlated together
- In these formulations, **perfect rank-order matching was achieved across two chemistry sets** (GMO and Capmul)

GMO-based formulations*



in vivo AUC_{0-24h}	F1 =	F8 =	F7 >	F2 >	F4>	F3 =	F5 >>	Free Drug
in vitro MacroFlux	F1 =	F8 >	F7 =	F2 >	F4>	F3 =	F5 >>	Free Drug

Capmul MCM-based formulations



in vivo AUC_{0-24h}	F9 >	F 10 >>	Free Drug
in vitro MacroFlux	F9 >	F 10 >>	Free Drug

*Plus F1 formulation which was a Maisine-based formulation comprising of mono-, di- and triglycerides of oleic and linoleic acid (C18:1/C18:2)

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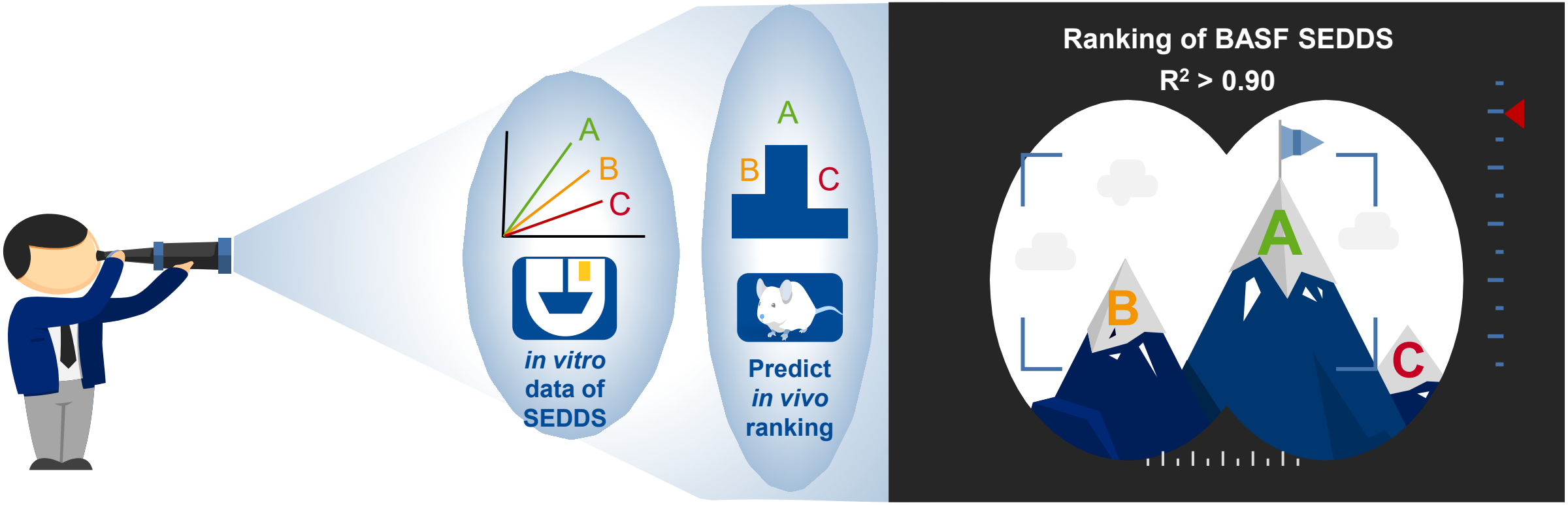


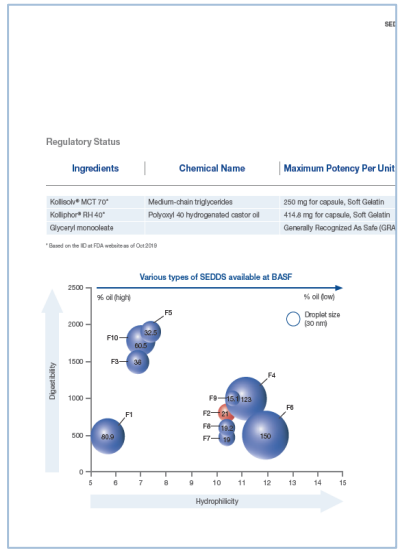
Methodological Constraints in Flux-Based Prediction Methods

- Reproducibility and Consistency Issues:
  - There is requirement of IQ/OQ/QP, positive and negative reference standard desired.
  - Stability of sink buffers and lipidic solution is not well established
- Compatibility of lipidic membranes with various dosage forms or excipients
  - Interaction of lipidic membranes with excipients can affect permeability
  - Compatibility issues with different dosage forms
- Complexity in analysis, especially in biphasic media
  - Challenges in analyzing drug behavior in biphasic media
  - Difficulty in interpreting results due to bubble formation or background noise
- Instrument calibration constraints
  - Need for reference permeation models to check reproducibility
  - Regular calibration required to ensure accurate measurements

SEDDS Formulations

- The formulation of **lipid-based drug delivery** formulations, specifically **SEDDS** is highly dependent on excipients selection and combination.
  - Proper balance of surfactants is needed to make stable, complex systems.
  - **Certain surfactants/ solvent combinations** are highly effective at making **SEDDS.**
  - We had created ten ready-to-use SEDDS formulations that can be utilized within a softgel formulation or liquid oral formulations

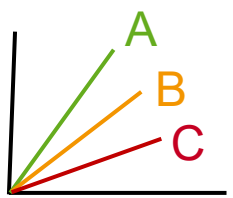
SEDDS Formulary



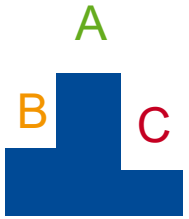
In Vitro Correlation with Bioavailability

1. A **reliable rank order of formulations** was established, serving as an indicator of bioavailability.
2. **Macroflux technology** can be effectively utilized to determine the rank order of formulations.
3. Alternative strategies for establishing bioavailability correlations in SEDDS formulations **remain an active area of research**. Advancing this focus could lead to the development of more effective and efficient in vitro tools for predicting bioavailability

Bioavailability prediction



in vitro **data of SEDDS**



Predict *in vivo* ranking

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Acknowledgements

- **Nitin Kumar Swarnakar**, BASF, North America
- **Ming Ji**, BASF, North America
- **Ronny Hoffmann,** & BASF R&D Team, Ludwigshafen, Germany
- **Professor Anette Müllertz**, University of Copenhagen
- **Balint Sinko and** the Pion Inc. Team

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