Optimizing solution formulation to maximize oral absorption at early stages

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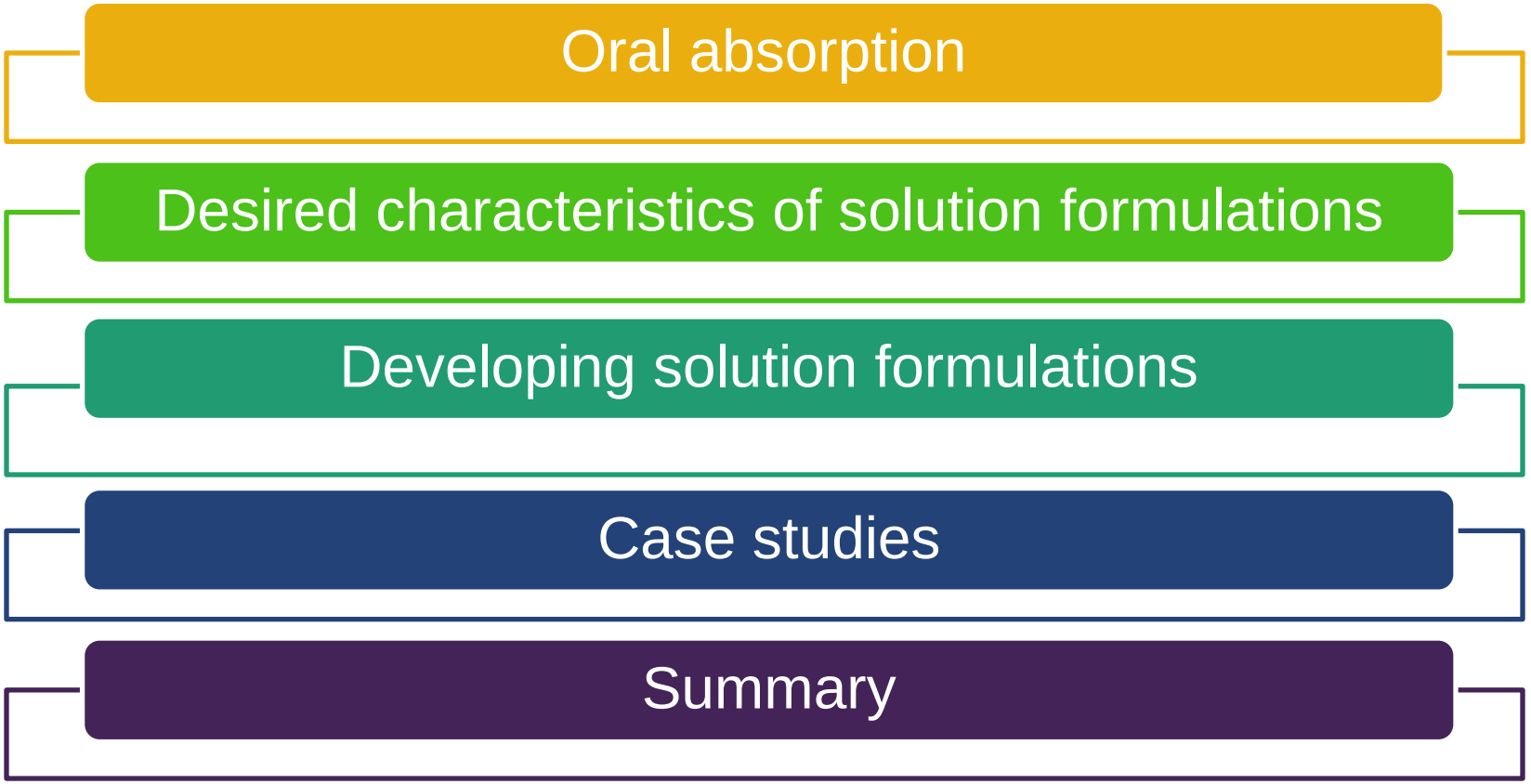
Outline



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Outline

- Oral absorption
- Desired characteristics of solution formulations
- Developing solution formulations
- Case studies
- Summary

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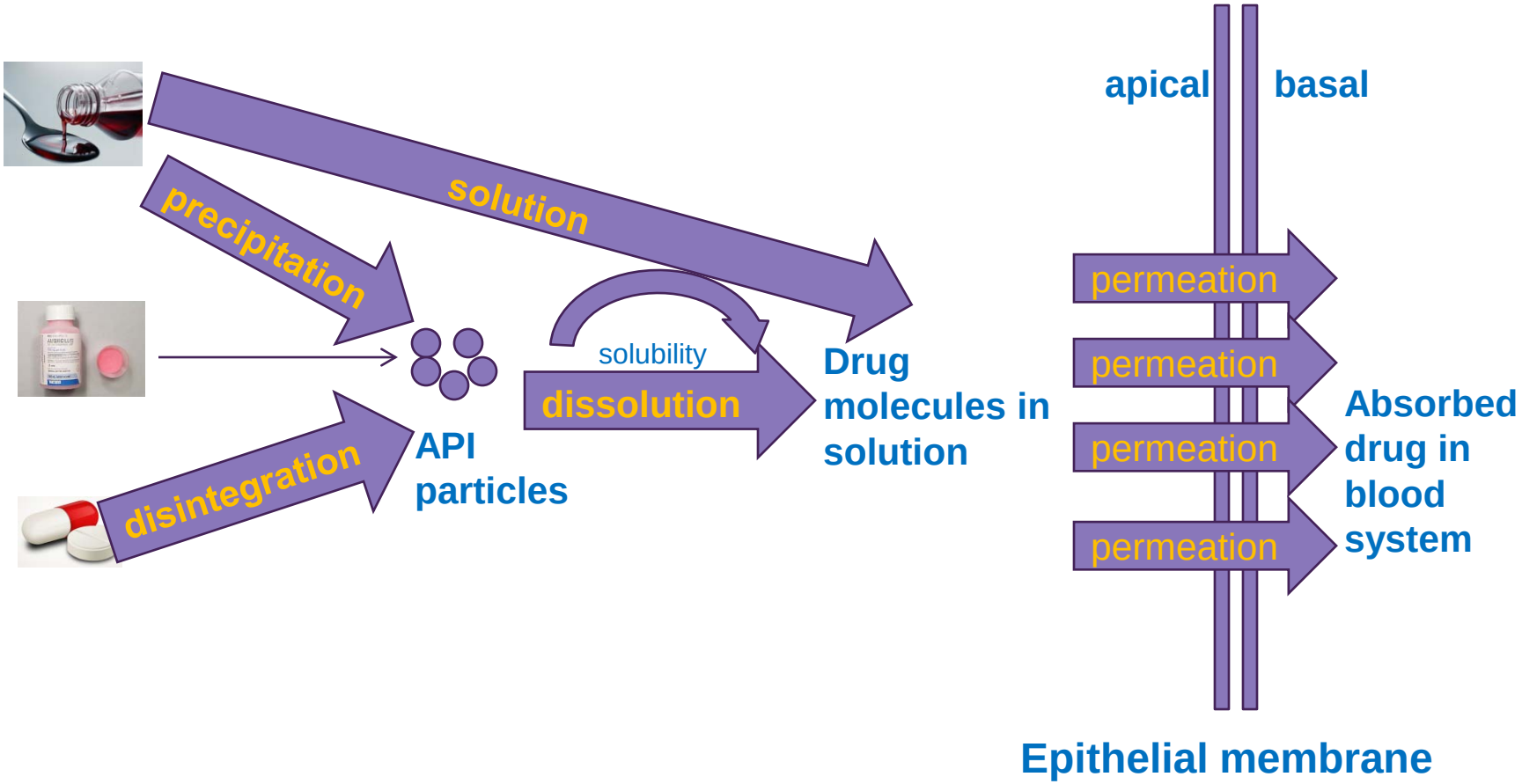
Oral absorption from a dosage



Gastrointestinal tract

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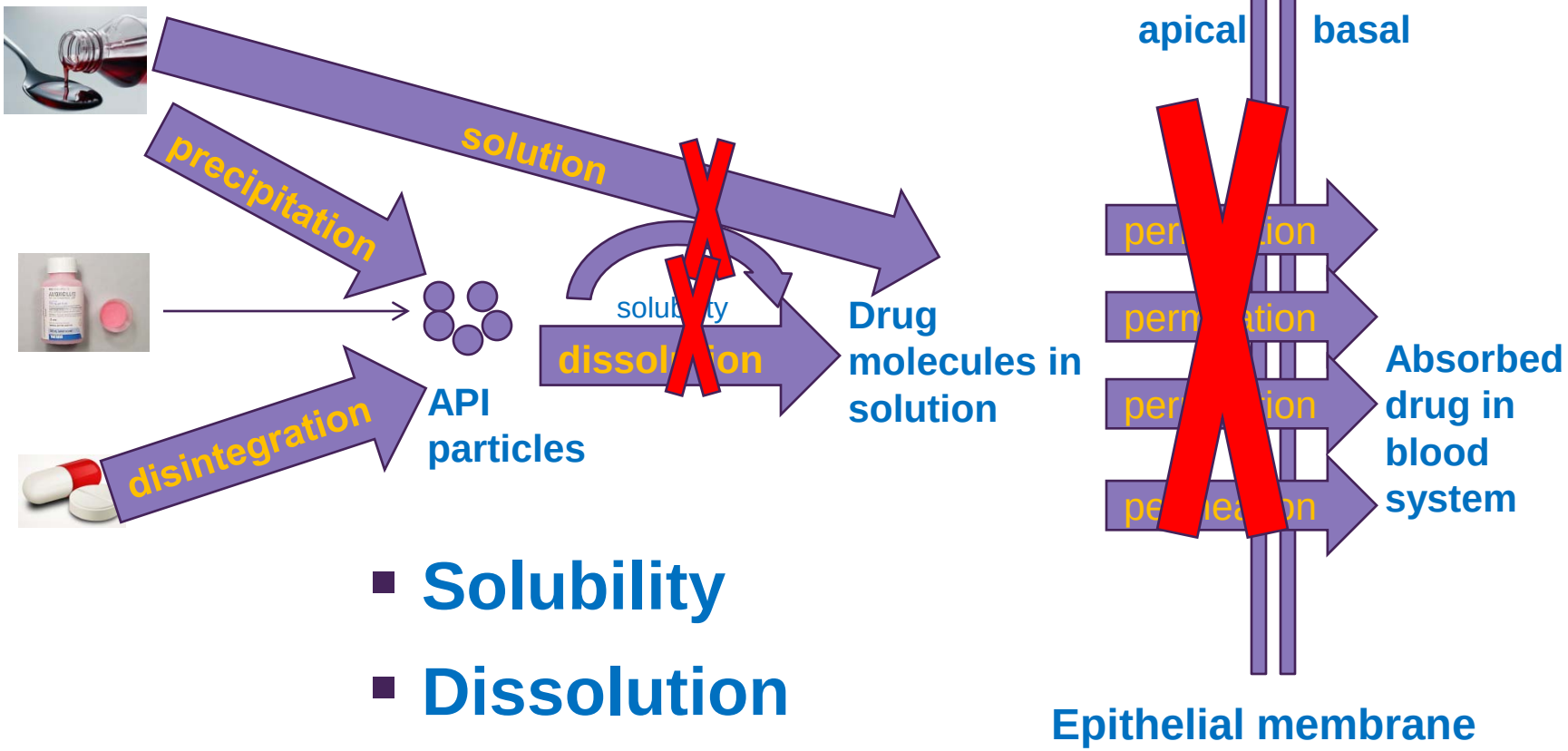
Limiting factors for oral absorption



- **Solubility**
- **Dissolution**
- **Permeability**

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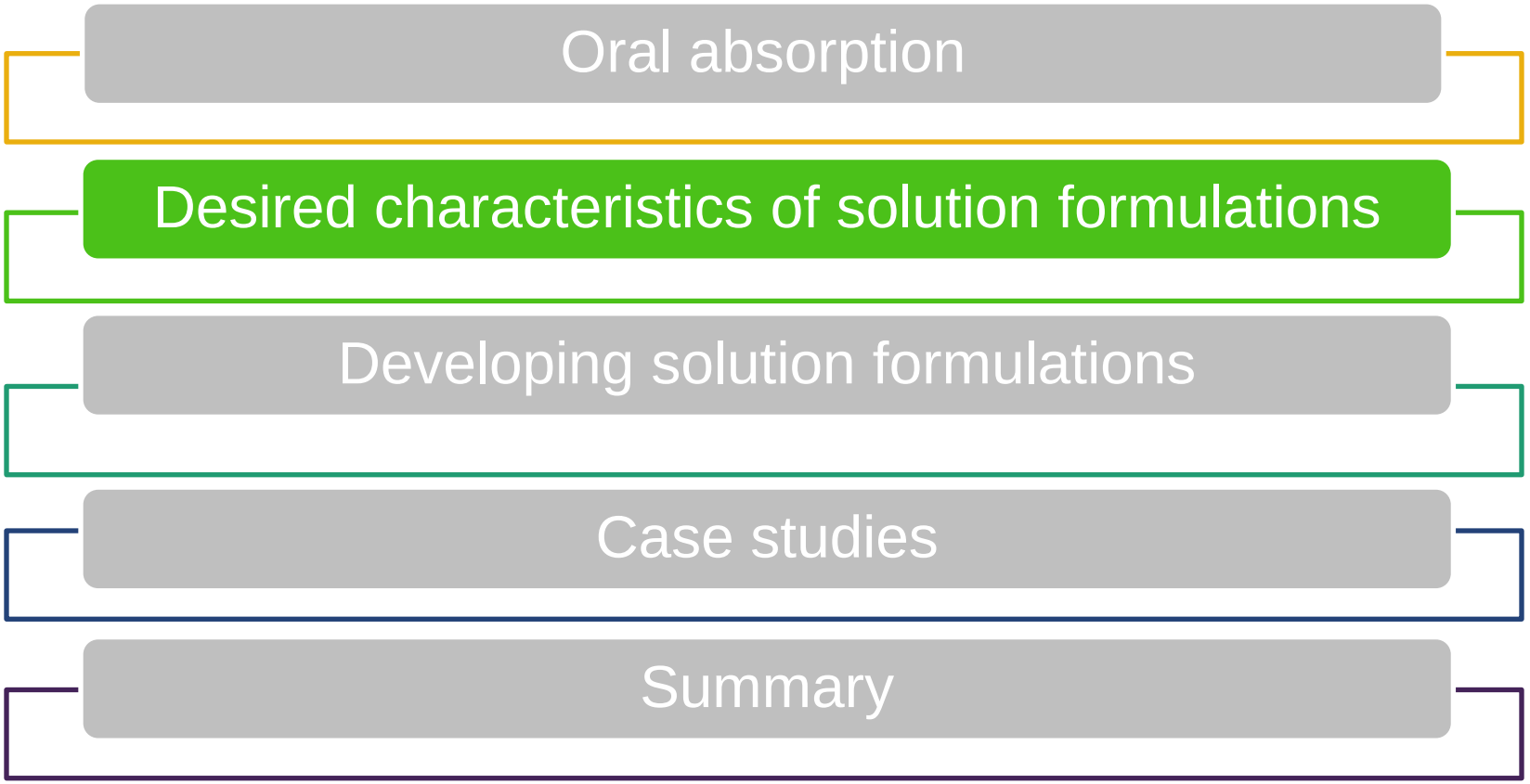
Outline



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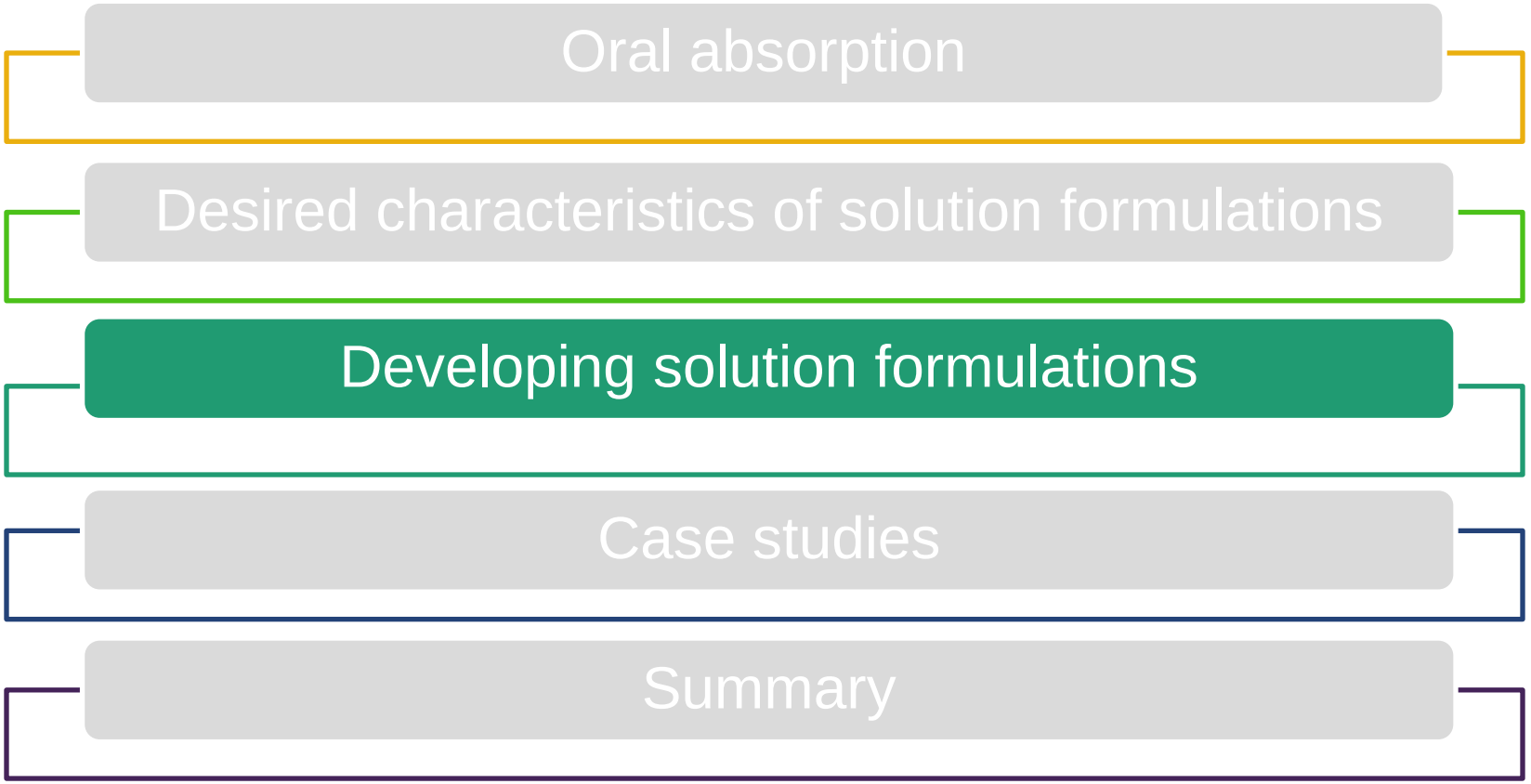
Desired characteristics for solutions

- **Desired characteristics**
  - Stay in solution along GI
  - Fast absorption
  - Maximum & consistent exposure
- **Advantages**
  - Widely used in pre-clinical and early clinical studies
  - Easy for accurate dosing
  - Dose flexibility
  - Same formulation for all species

Outline



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Developing solution formulations
Factors

- **Compound characteristics**
  - pKa
  - Solubility
- **Species and animal model**
  - Physiology parameters
  - Dosing volume
  - Duration of the study

Developing solution formulations Factors

- **Species and animal model**

Species	Typical weight (kg)	Stomach Volume (mL)	Stomach pH	Intestine volume (mL) (2)	Intestinal pH	Gastric-emptying time (6) (hr)	Plasma volume (mL) (2)
Mouse	0.025	0.4 (1)	3 (1)	1.5	<pH5.2 (1)	NA	1.0
Rat	0.25	3 (1)	2.5 (1)	11.3	<6.6 (1)	15-30 min	7.8
Dog	10	50	2.7-8.3 (6)	480	6.4 (2)	4	515
Monkey	5	100 (3)	1-3 (4)	230	5.6-9.0 (5)	2-4	224
Human	70	250	1.4-2.1(3)	1650	5.4-7.5(2)	2-4	3000

▪References: (1) McConnell, Emma L.; Basit, Abdul W.; Murdan, Sudaxshina . **Measurements of rat and mouse gastrointestinal pH, fluid and lymphoid tissue, and implications for in-vivo experiments.** J. Pharm. 2-4Pharmacol. 2008, 60 (1): 63-70; (2) **Davies** B, **Morris** T. Physiological parameters in laboratory animals and humans. Pharm Res. **1993** ,10(7):1093-5; (3) **Kararli** TT. Comparison of the gastrointestinal anatomy, physiology, and biochemistry of humans and commonly used laboratory animals. Biopharm Drug Dispos. **1995** ,16(5):351-80; (4) Kondo, H., Takahashi, Y., Watanabe, T., Yokohama, S., Watanabe, J., 2003. Gastrointestinal Transit of Liquids in Unfed Cynomolgous Monkeys. Biopharmaceutics & Drug Disposition; 24: 131-140.; (5) Dressman and Yamada, 1991; (6) Seshadri Neervannan. Preclinical formulations for discovery and toxicology: physicochemical challenges. Expert Opin. Drug Metab. Toxicol. 2006, 2(5): p718

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Developing solution formulations Factors

- **Route of administration**

Species	Oral	IV bolus	IV slow injection	Subcutaneous (SC)	Intraperitoneal (IP)
Preferred pH range	2-10	4-9	4-9	4-8	4-9
Dosing volume (mL)					
Mouse	10	10	25	5	10
Rat	10	5	20	5	10
Guinea-pig	10	5	20	5	10
Dog	5	1	5	1	3
Monkey	5	1	NA	1	3

Bolus injection is typically defined as administration over a short period of time (~1 minute)
Slow injection is defined as administration over a course of 5-10 minutes

Reference: Seshadri Neervannan. Preclinical formulations for discovery and toxicology: physicochemical challenges. Expert Opin. Drug Metab. Toxicol. 2006, 2(5): p718

Developing solution formulations
Factors

- **Excipients**
  - GRAS status
  - Tolerability: LD50, MTD/NOEL/NOAEL (mg/kg)
  - Source
    - Handbook of excipients
    - FDA inactive ingredient database (http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm)
    - FDA : Maximum Recommended Therapeutic Dose (MRTD) Database (mg/kg/day) (http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm092199.htm#P)
    - Supplier's data
  - Impact on absorption

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Developing solution formulations
Commonly used excipients

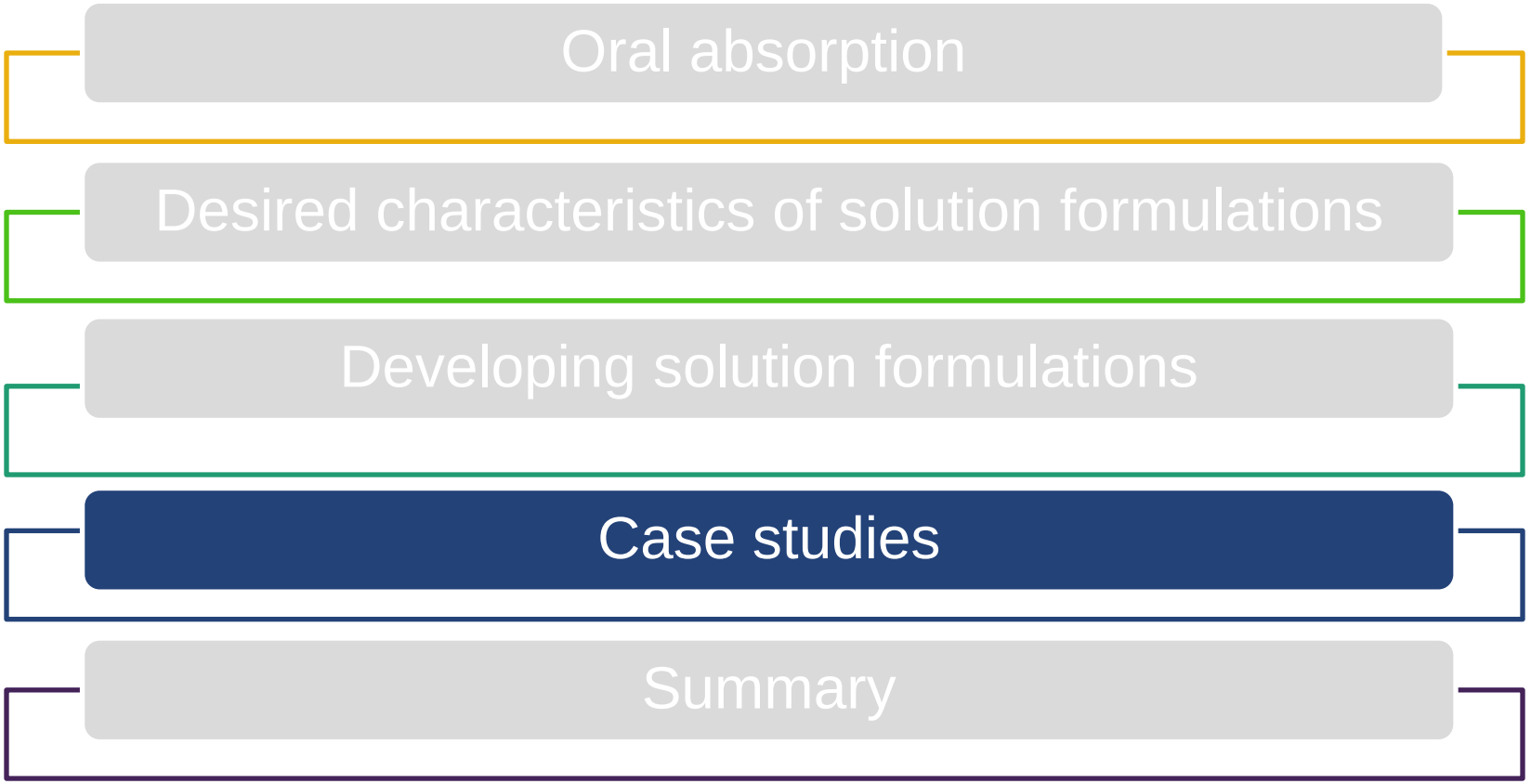
Category	Solvent or excipient with full name	Dosing route /common usage range
Aqueous	Water	oral, i.v.
	0.9% NaCl	i.v.
	D5W - 5% dextrose in water	i.v.
	Buffered solutions pH: 2 - 8	oral, i.v.
	NMP - N-methylpyrrolidon	10 - 20% (oral, i.v.)
Cosolvent	DMSO - dimethyl sulfoxide)	10 - 20% (oral or i.v.)
	Ethanol	10% (oral, i.v.)
	DMA - N,N-dimethylacetamide	10 - 30% (i.v.)
	PG - propylene glycol	30 - 60% (oral, i.v.)
	PEG400 - polyethylene glycol 400	40 - 100% (oral, i.v.)
	Transcutol - diethylene glycol monoethyl ether	30% (oral)
Cyclodextrin	HPβCD - hydroxyl-β-cyclodextrin	20 - 40% (oral, i.v.)
	SBECD - sulfobutylether-β-cyclodextrin	20 - 40% (oral, i.v.)
Surfactant	Posorbate 80 (Tween 80) - polyoxyethylene sorbitan monooleate 80	5 - 10% (oral, i.v.)
	Cremophor EL - polyoxyl-35 castor oil	5 - 10% (oral, i.v.)
	Cremophor RH40 - polyoxyl 40 hydrogenated castor oil	5 - 10% (oral, i.v.)
	Sodium cholate	10 - 20% (oral, i.v.)
	Pluronic F68 or Poloxamer 188 81% polyoxyethylene and 19% of polypropylene glycol	20 - 50% (oral, i.v.)
	Solutol HS-15 - macrogol-15-hydroxystearate	20 - 50% (oral, i.v.)
	VitE-TPGS 1000 - d-Î±-tocopheryl polyethyl glycol 1000 succinate	20 - 50% (oral)
	Gelucire 44/14 - lauroyl macrogol-32 glycerides	20 - 50% (oral)
	Labrasol - caprylocaproyl macrogol-8-glycerides	40 - 60% (oral); 20 - 40% (i.v.)
	Lecithin - phosphatidylcholin	20 - 50% (oral, i.v.)
Lipid	Soybean oil	50 - 100% (oral)
	Miglyol 812 - mid-chain triglyceride of caprylic/caprolic acid	60 - 100% (oral); 20 - 40% (i.v.)
	Labrafil 1944CS - polyxoyethyllated oleic glycerides	30 - 60% (oral, i.v.)
	Capmul MCM - medium chain mono- and diglycerides	30 - 60% (oral, i.v.)

Are solutions bioequivalent???

Note: usage range is based on mouse or rat model, single dosing at 10mL/kg

Ping Li, Luwei Zhao. Developing early formulations: practice and perspective. International Journal of Pharmaceutics. 2007, 341, p1-19

Outline



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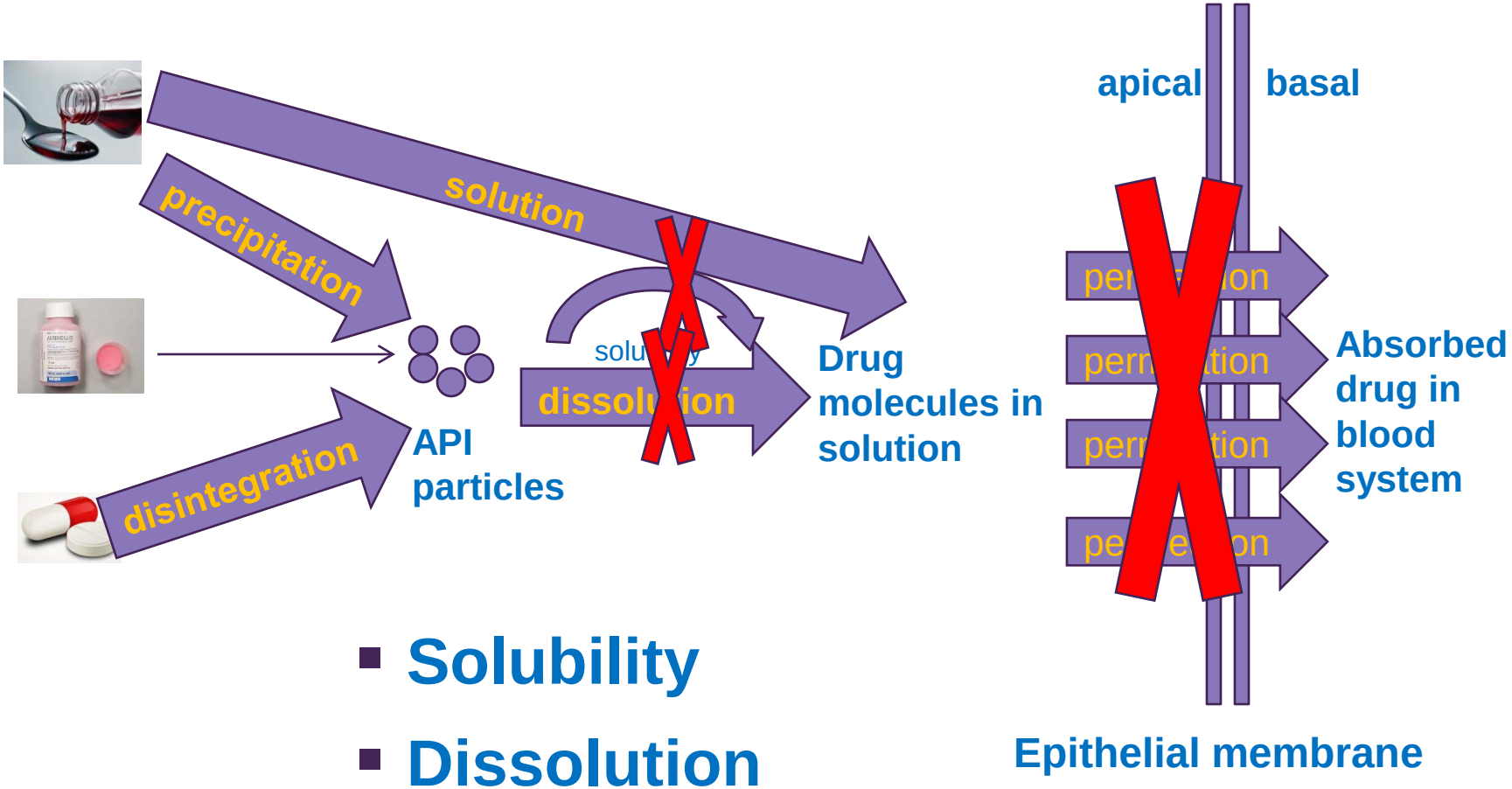
Limiting factors for oral absorption



- **Solubility**
- **Dissolution**
- **Permeability**

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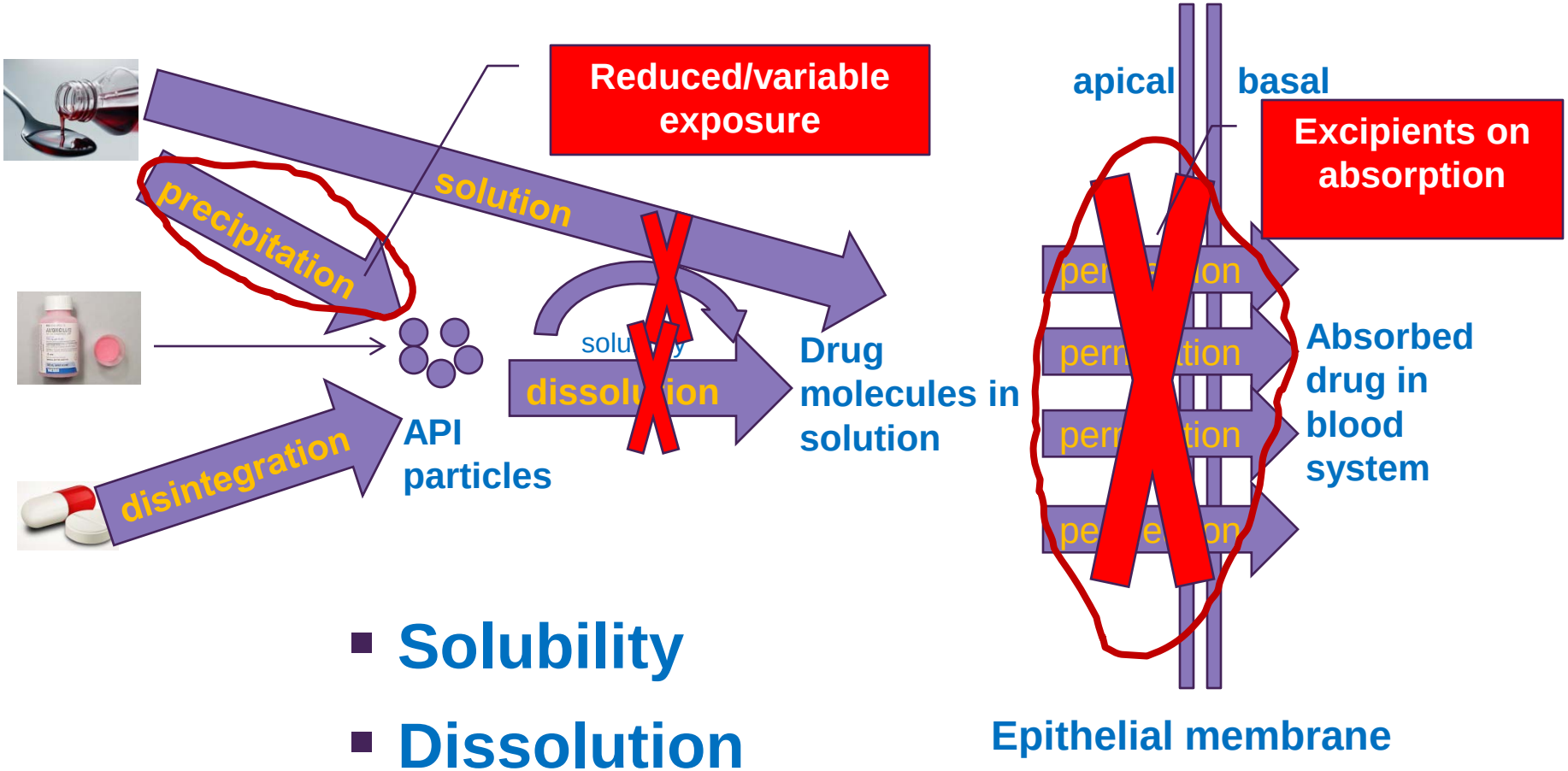
Limiting factors for oral absorption



- **Solubility**
- **Dissolution**
- **Permeability**

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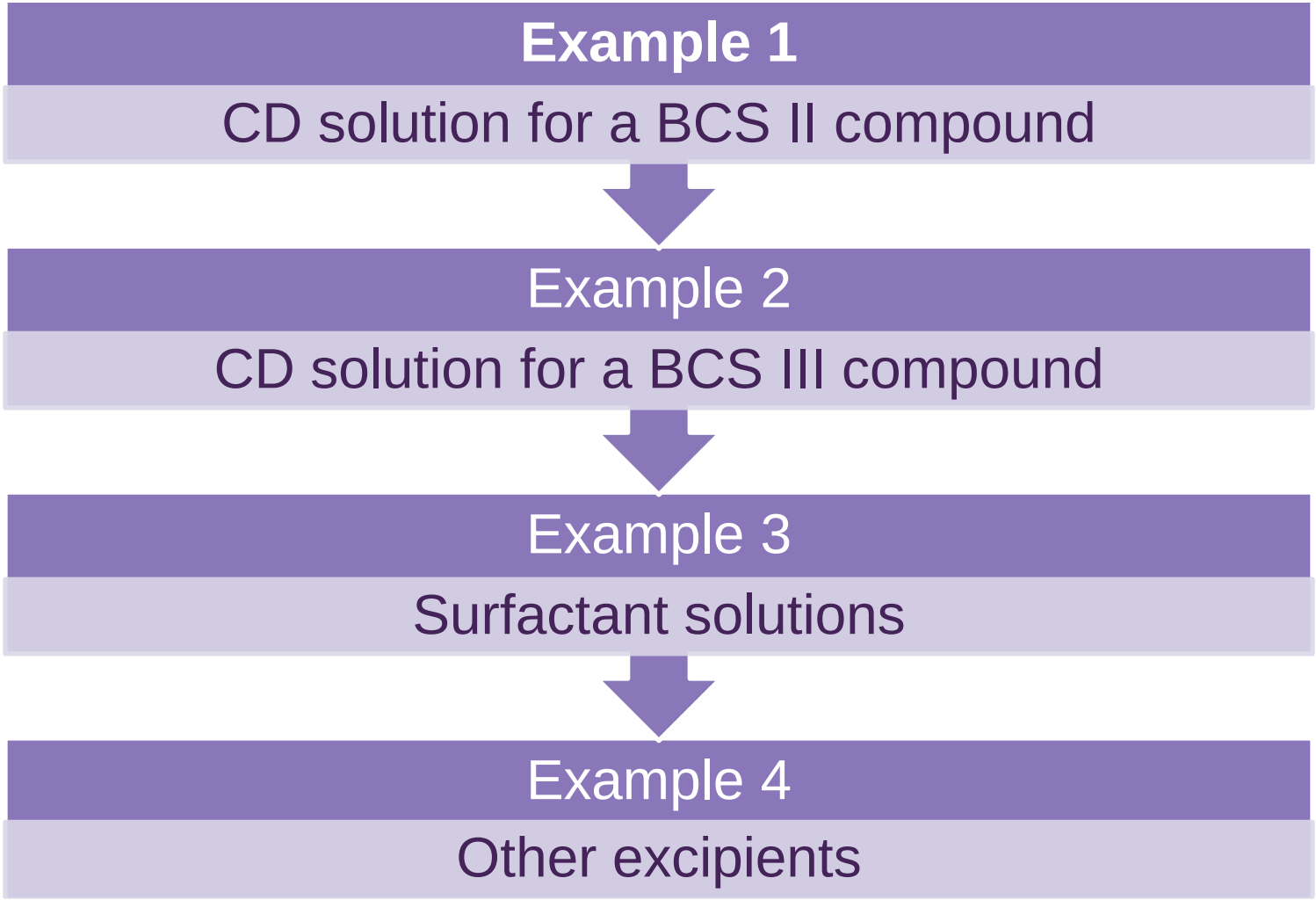
Case studies
Impact of excipients on oral exposure



Jan Bevernage , Joachim Brouwers , Marcus E. Brewster , Patrick Augustijns. **Evaluation of gastrointestinal drug supersaturation and precipitation: Strategies and issues.** International Journal of Pharmaceutics Volume 453, Issue 1 2013 25 – 35. http://dx.doi.org/10.1016/j.ijpharm.2012.11.026

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Case studies 1: CD solution
Enhanced exposure for a BCS II compound

- **Rat: CD solution to be the best formulation**
- **Dog: comparable**

Species	Formulation	Cmax (ng/mL)	AUC (ng*h/mL)
Rat	10% CD, pH 10	8500	20220
Rat	0.5% HPMC, pH 10	7343	10137
Dog	10% CD, pH 10	7920	29606
Dog	0.5% HPMC, pH 10	NA	30698

- In vitro dissolution

Formulation	16% CD, pH 10	40% CD, pH 10	20% CD, pH 10	0.5% HPMC, pH 10
% dissolved in FaSSIF pH 6.5	52	62	70	40

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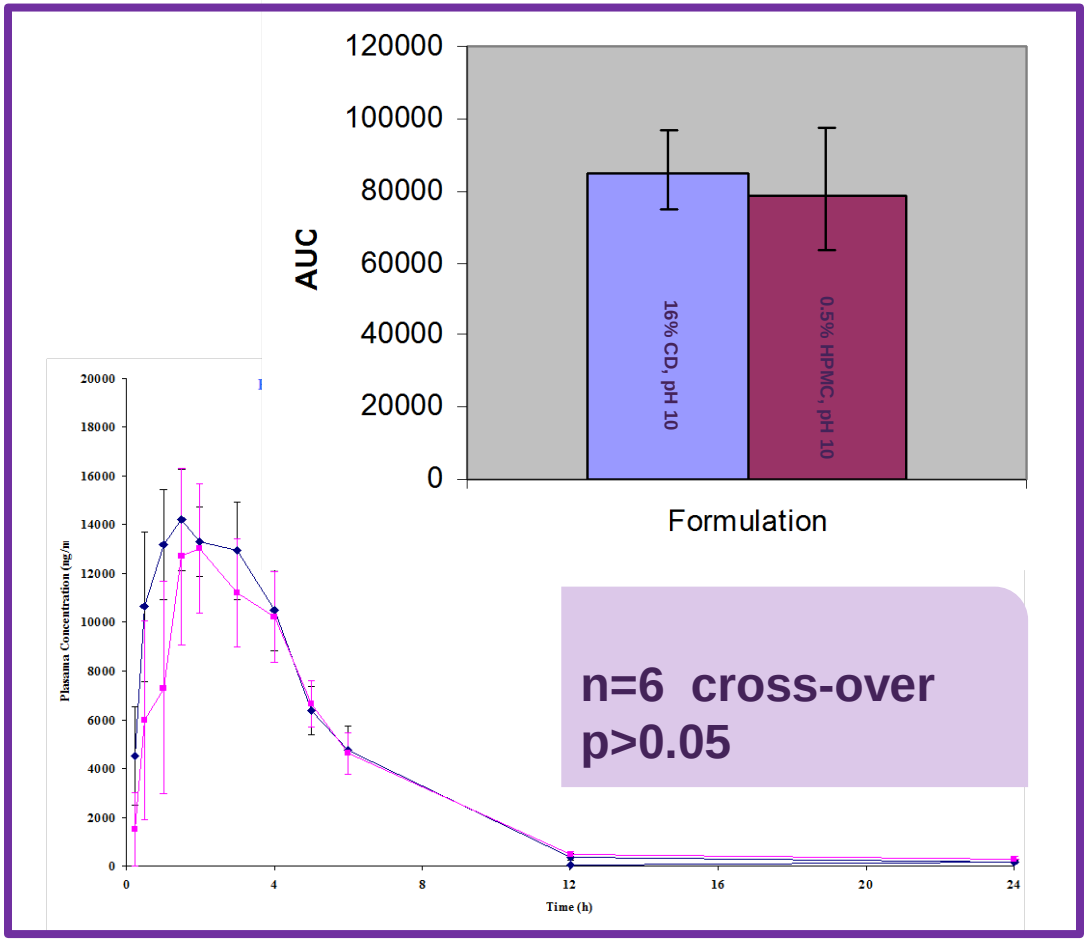
Case studies 1: CD solution
Enhanced exposure for a BCS II compound

- Less variable/more consistent exposure in dog



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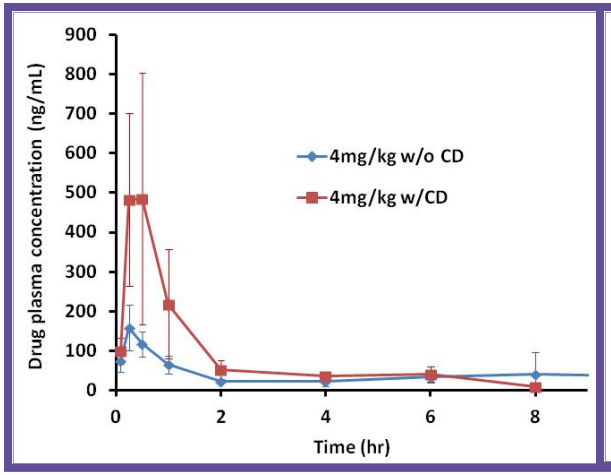
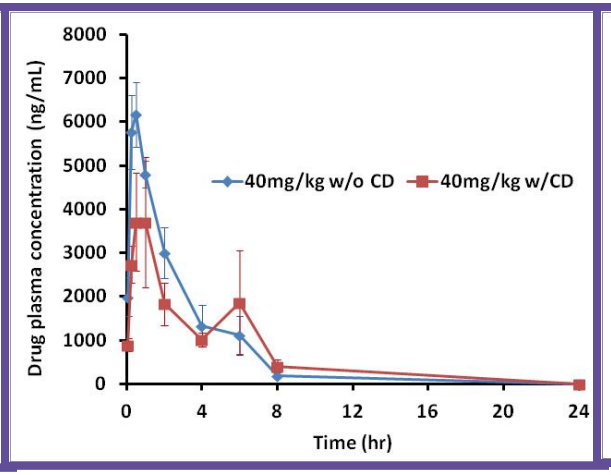
Case studies 2: CD solution
Reduced exposure for a BCS III compound

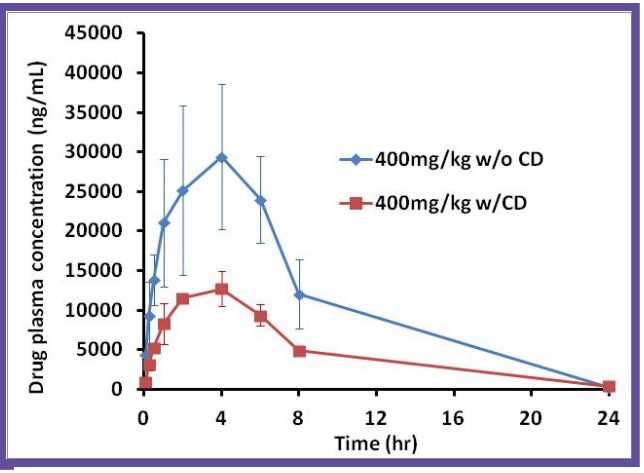
- **CD is chosen for stability reasons**

Low dose: faster & enhanced absorption

Higher dose: reduced absorption







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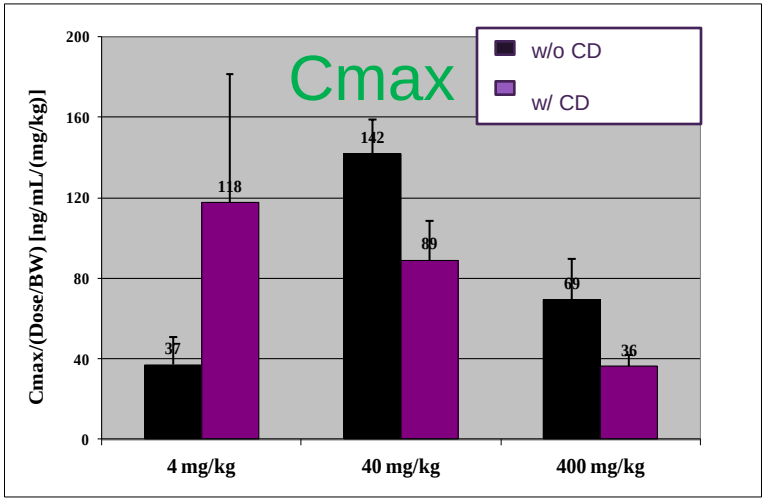
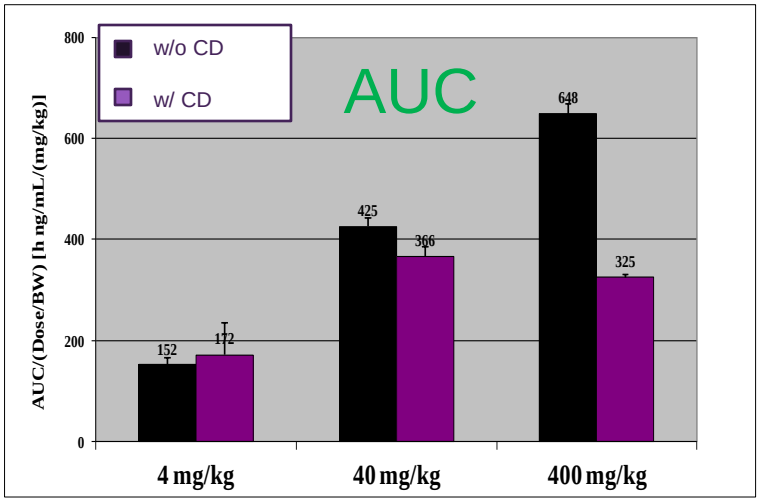
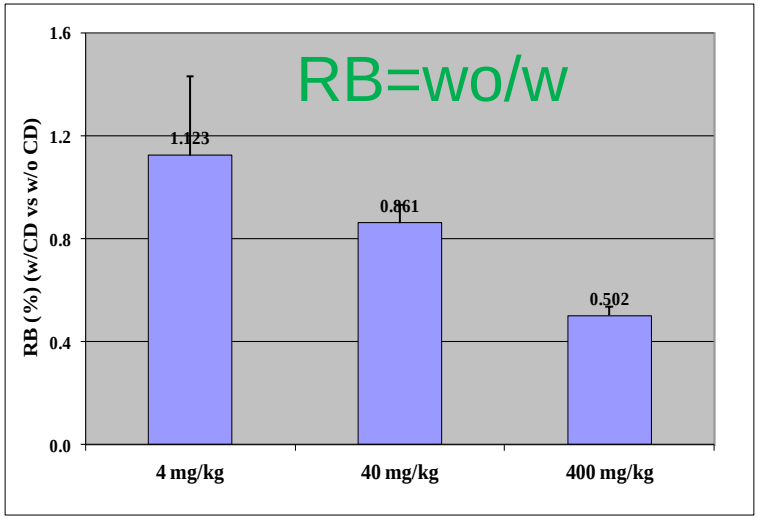
Case studies 2: CD solution
Reduced exposure for a BCS III compound







- 4mg/kg: CD ↑ C_{max} & AUC
- 40 & 400mg/kg: CD ↓ C_{max} & AUC

Dose (mg/kg)	Tmax h (w/o CD)		Tmax h (w/ CD)
4	0.25±0	<	0.333±0.144
40	0.417±0.144		0.833±0.289
400	4±2	>	3.33±1.15

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Case studies 2: CD solution
Reduced exposure for a BCS III compound

- **Why exposure ↓ at higher CD concentration?**
  - FaSSIF blank solubility: 3.6mg/mL
  - Solution formulation: Drug/CD at 1:3 molar ratio

$$f_{free} = \frac{1}{1 + K_{11} \bullet [CD]}$$

Media	SGF	FaSSIF
Binding constant (M^{-1})	37	332

Drug concentration (mg/mL)	HPBCD (mg/mL)	SGF	FaSSIF blank
		Free drug %	
0.4	4	91	54
4	40	51	10
40	400	9	1

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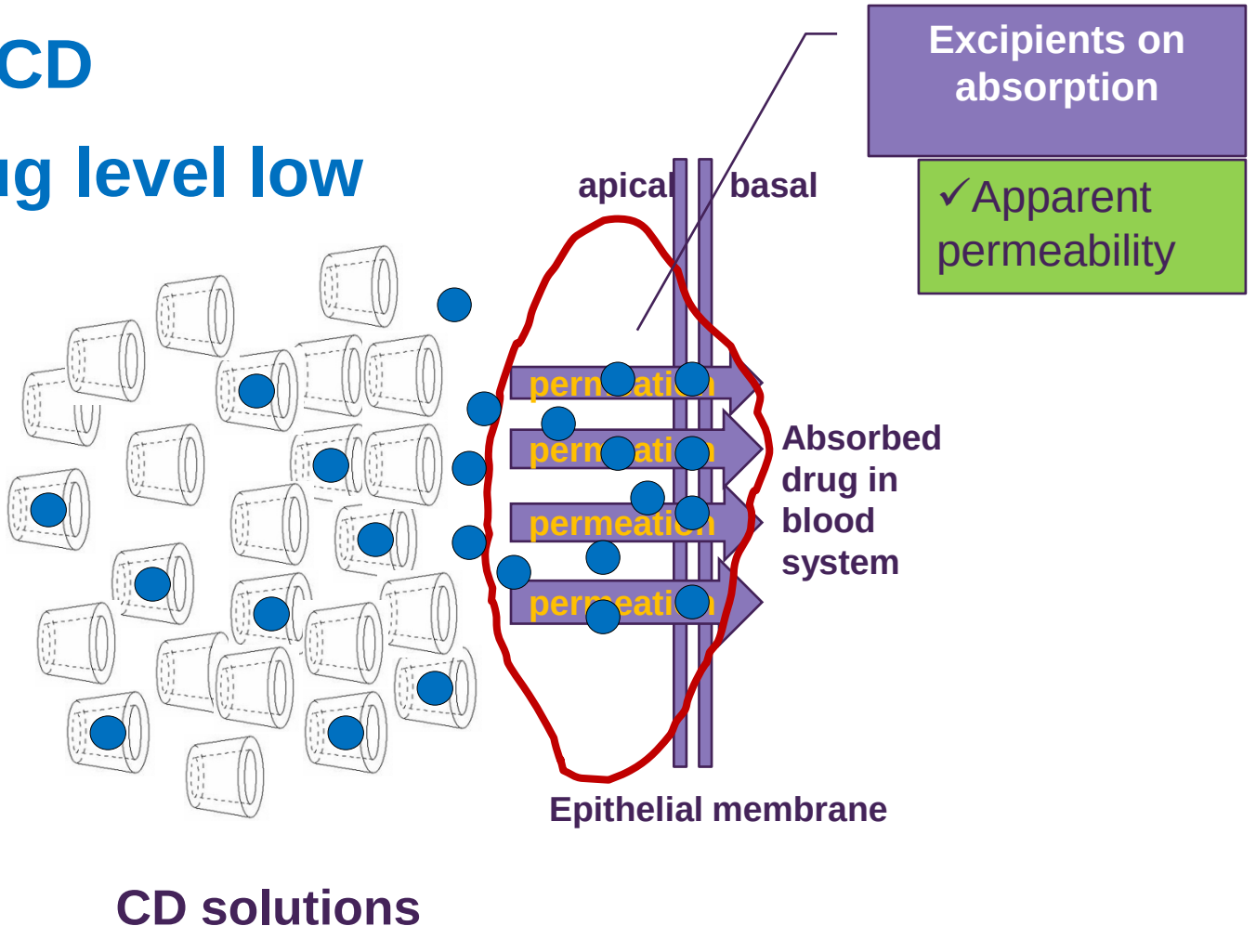
Case studies 2: CD solution
Reduced exposure for a BCS III compound

- **Excess CD**
- **Free drug level low**



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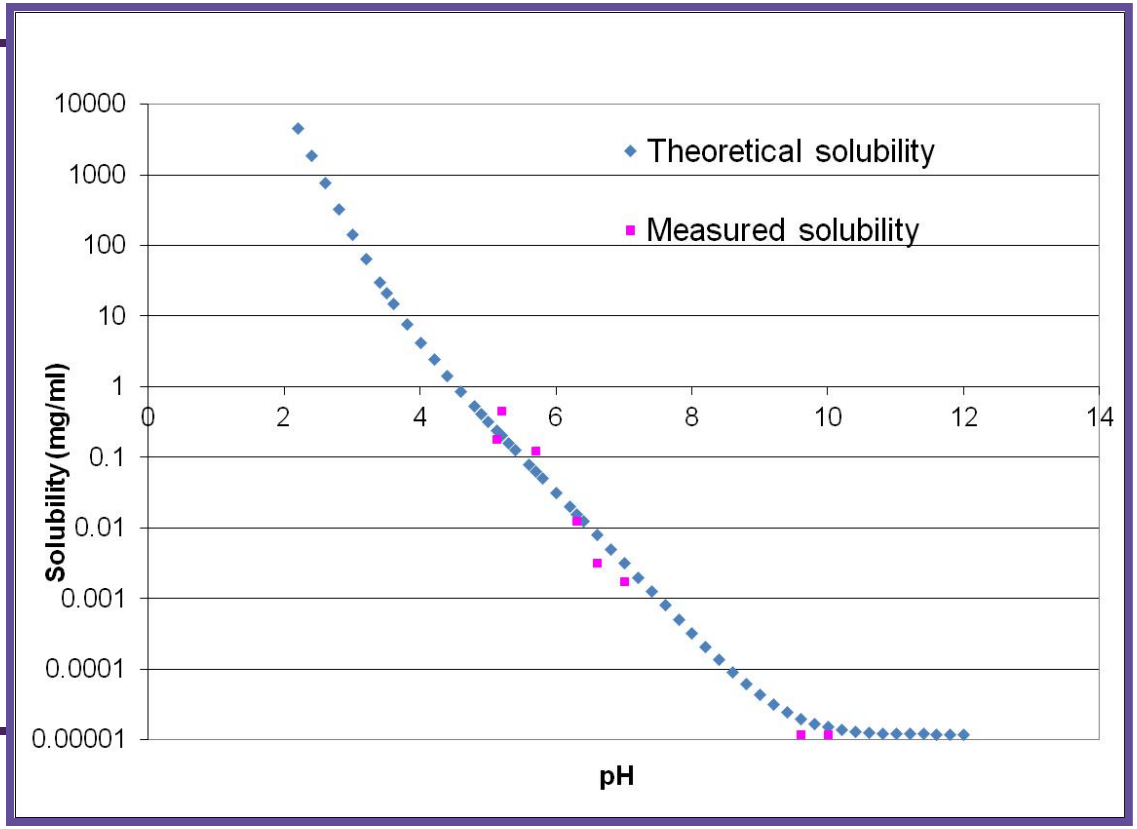
Case studies 1&2: CD solution Summary

- **For poorly soluble compounds**
  - Enhanced solubility/dissolution/exposure
  - Consistent exposure/reduced variability
- **Soluble compounds**
  - Cannot assume CD is not going to impact absorption for soluble compounds, e.g., BCS III
- **Impact on exposure**
  - Binding constants
  - Excess CD in formulation

Case studies 3: surfactant solutions
Reduced exposure for a BCS IV compound

- pKa: 9.42, 3.55, 2.08
- MWt: 450
- Log D: 2.69
- Solubility
  - SGF: >10mg/mL
  - FaSSIF: 0.07mg/mL
  - Phosphate buffer pH6.5: 0.02mg/mL
  - Water: 0.0000488 mg/mL
- Permeability
  - Low to moderate



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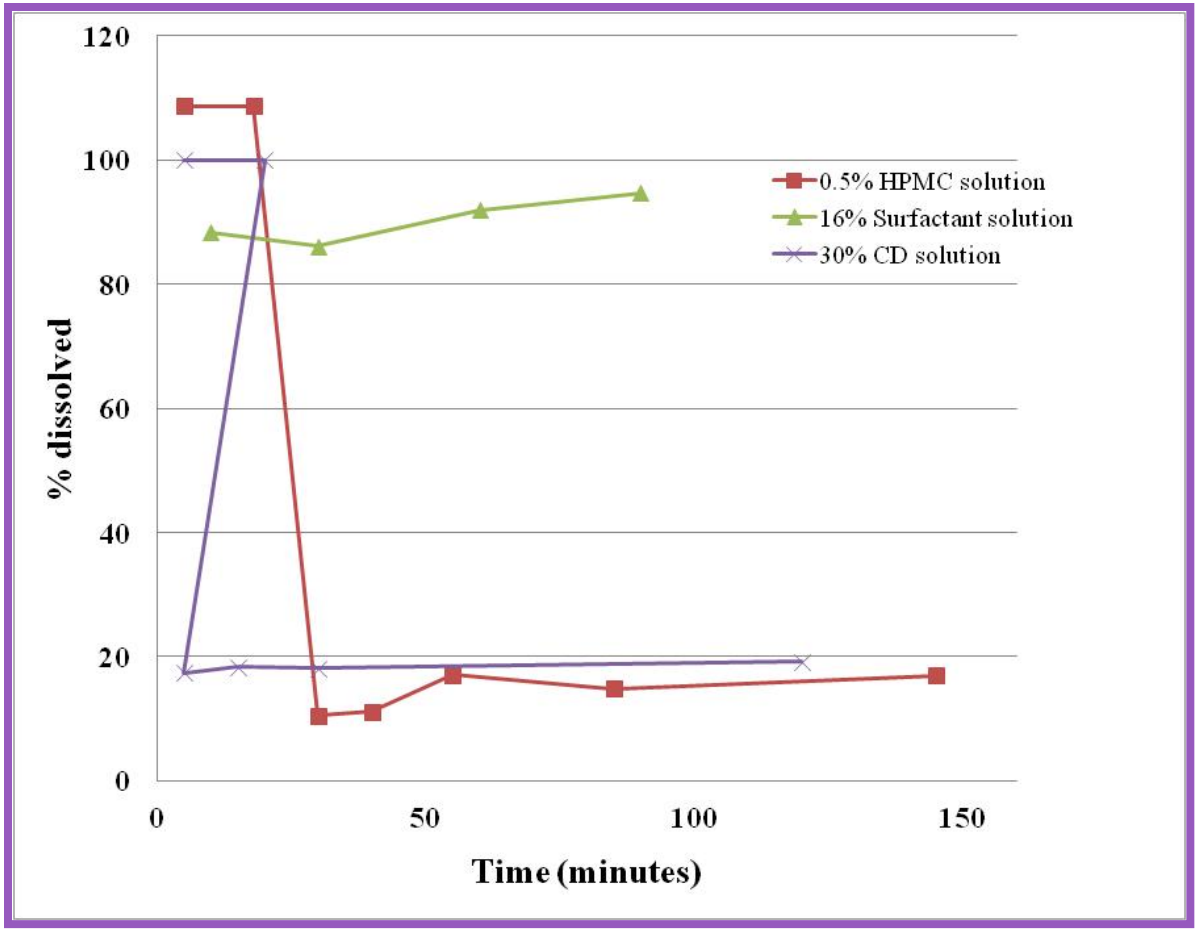
Case studies 3: surfactant solution Reduced exposure for a BCS IV compound

- **In vitro pH-shift**
  - CD is no good
  - The surfactant promising



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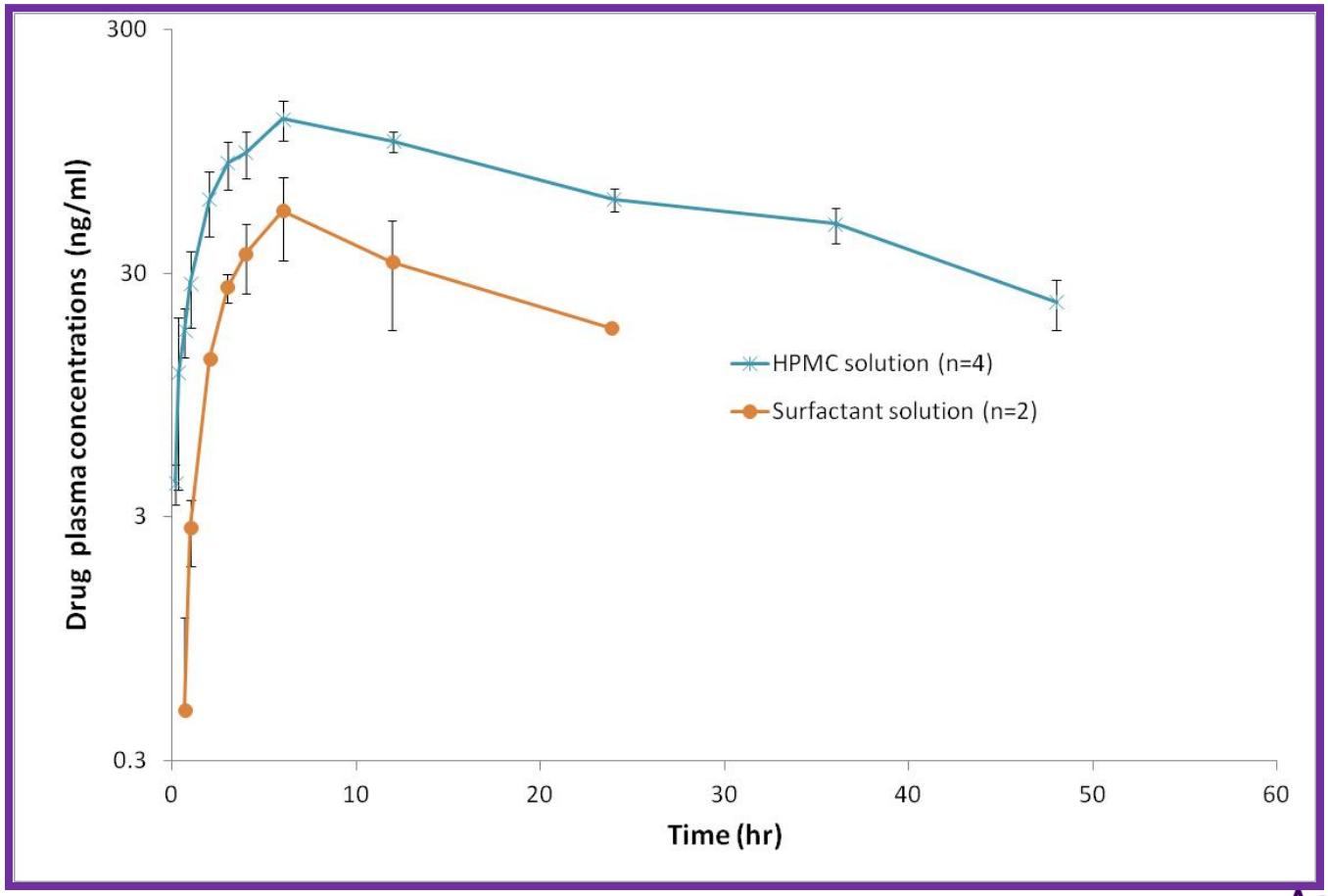
Case studies 3: surfactant solution Reduced exposure for a BCS IV compound

- **In vivo dog PK**
  - 10mg/mL surfactant solution < 10mg/mL in HPMC



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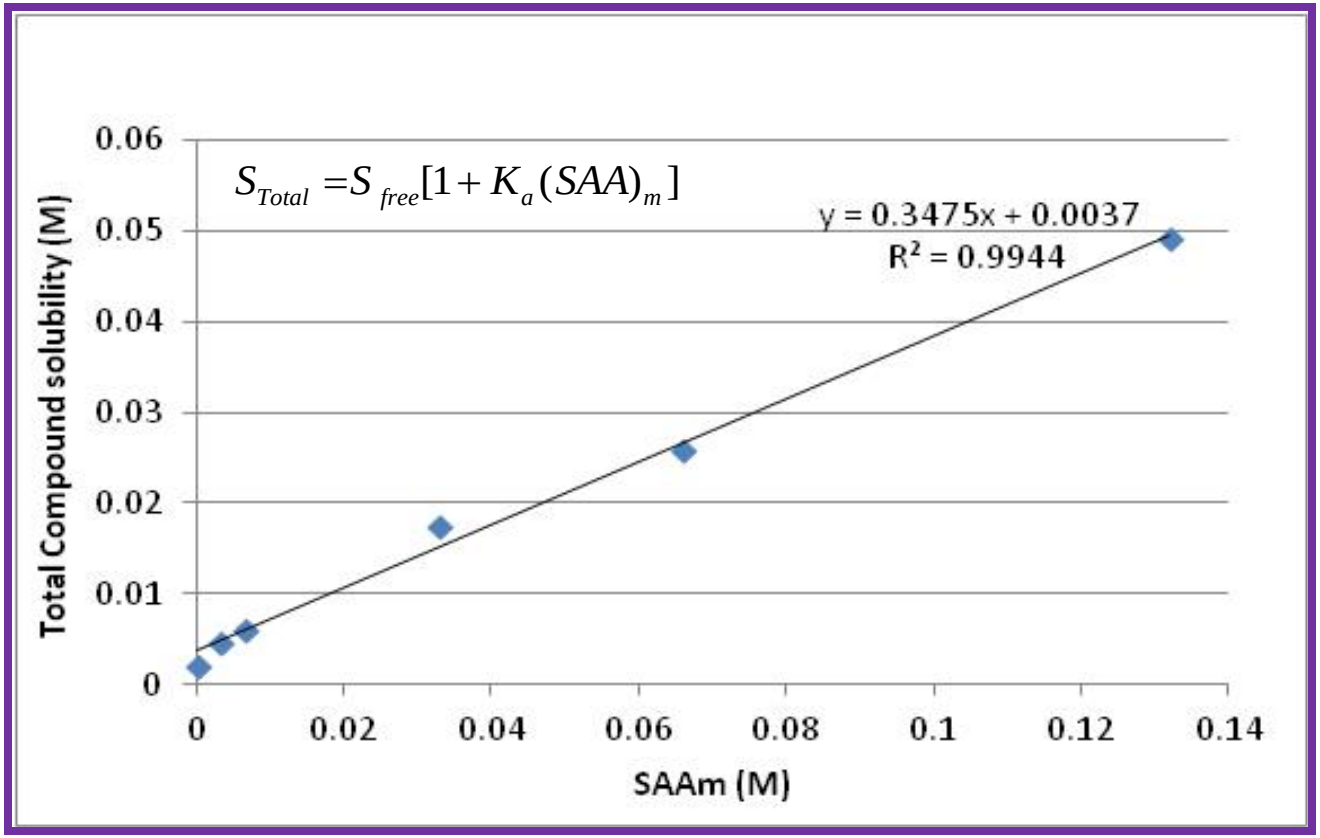
Case studies 3: surfactant solution Reduced exposure for a BCS IV compound

- **Ka: 165 M^{-1}**
- **At 10mg/mL, majority compound in the micells**



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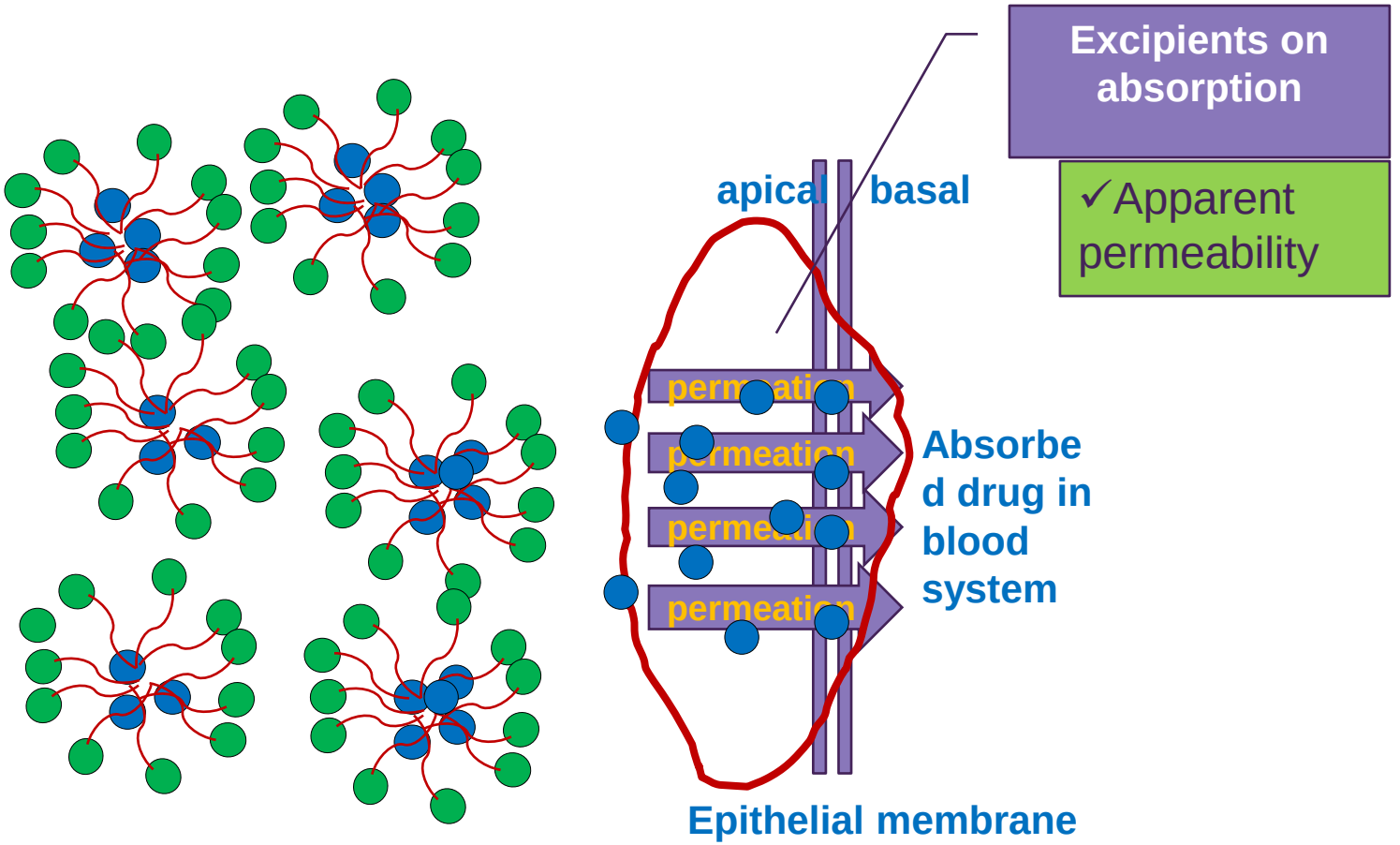
Case studies 3: surfactant solution
Reduced exposure for a BCS IV compound



Surfactant solutions

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Case studies 3: surfactant solution Modified exposure from literature

- **Cremophor EL/tween 80**

Agents	Test system	Effect(s)
Cremophor® EL		
Acf(N-Mef)NH_2	Caco-2 cells	2.6-fold reduced permeability
Digoxin	Human	Decreased lag time
Paclitaxel	Human	2.0-fold decreased AUC[a]
	Mouse	1.4-fold decreased AUC[b]
Saquinavir	Human	5.0-fold increased AUC
Phytomenadione	Human (infant)	Decreased PIVKA-II
Tween® 80		
Albendazole	Rat	1.9-fold increased AUC
Cyclosporin	Rat	33-fold increased bioavailability[c]
Danazol	Dog	16-fold increased bioavailability
Digoxin	Rat intestine	Increased uptake
Griseovulvin	Human	1.5-fold decreased AUC
Indomethacin	Rat	1.6-fold increased AUC
Itazigrel	Rat	1.5-fold increased absorption
Methotrexate	Mouse	2.0-fold increased AUC
Tetracycline	Rat intestine	2.7-fold increased absorption

a As compared with a Tween® 80 formulation.

b As compared with a formulation containing 7-fold less Cremophor® EL.

c As compared with a nanosphere formulation.

AUC = area under the plasma concentration-time curve; **PIVKA-II** = des-gamma-carboxyprothrombin.

Albert J. ten Tije, Jaap Verweij, Walter J. Loos and Alex Sparreboom. **Pharmacological Effects of Formulation Vehicles.** Clin Pharmacokinet 2003; 42 (7): 665-685

Case studies 4: other excipients
Reduced exposure from literature

- **Cosolvent: PEG 400**
  - Reduction in small intestinal transit time
  - Limit oral absorption
  - Nullify bioavailability benefit from solubilization

	Mean gastric residence time (MGRT) (min)		Mean small intestinal transit time (MSITT) (min)		Mean caecum arrival time (MCAT) (min)	
Volunteer	Control[a]	Test[b]	Control	Test	Control	Test
1	17	18	200	144	217	162
2	13	19	250	169	263	188
3	30	10	227	138	257	148
4	17	23	256	128	273	151
5	36	31	212	190	248	221
6	23	25	197	138	220	163
7	13	15	197	133	210	148
8	30	19	297	271	327	290
9	13	18	320	137	333	155
10	11	23	204	85	215	108
Mean	20	20	236	153	256	173
s.d.	9	6	44	49	45	50
P value	0.948		<0.001		<0.001	

[a] Control = orange juice preparation.
[b] Test = orange juice + PEG 400 preparation.

Control: 150mL of orange juice
Test: 150mL of orange juice containing 10g PEG 400

- **Other solution additives**
  - Mannitol/sorbitol: reduce bioavailability of drugs with low intestinal permeability in amounts sometimes used in oral liquid dosage forms

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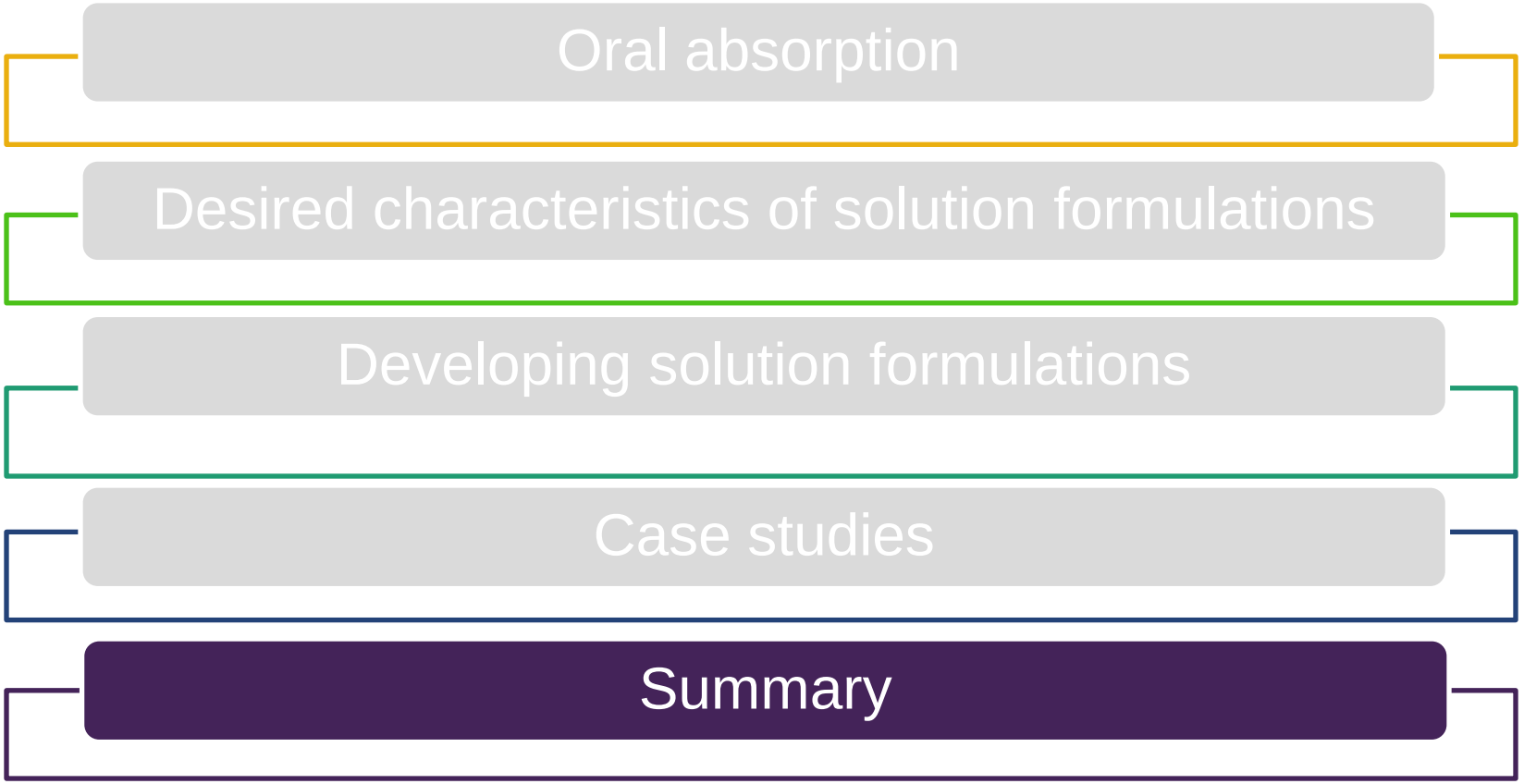

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Summary

- **Solution preferable at early stage**
- **Optimization**
  - In vitro/in vivo
  - Optimal amount/degree of supersaturation
  - % free drug at the absorption site
- **Precipitation inhibition**
  - Improve solubility (surfactant/CD)
  - Improve re-dissolution upon GI precipitation (surfactant/CD)
  - Inhibit precipitation to maintain super-saturation in GI tract (surfactant/CD/HPMC)
- **Impact of excipients on oral absorption**
  - Positive /Negative: solubility/dissolution/apparent permeability
  - Effect on GI transit

Are solutions bioequivalent???

Acknowledgement

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