1) Formulations in Drug Discovery: Enabling Preclinical Pharmacokinetic, Pharmacodynamic and Toxicology Studies

2) Pediatric Formulations: Evolving Issue of To Use or Not to Use Preservatives

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Bay Area Discussion Group
December 1, 2011

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Last Year, January 20, 2010
Bay Area Discussion Group

Theory & Practice for Development of Enabling Formulations for Preclinical Studies

Sree Nadkarni, Ph. D.
FibroGen Inc. (at that time)
Now a consultant

http://www.caco-ba.org/htmls/Documents/Public%20References/2010Jan20_Joint_Meeting/Development%20of%20Enabling%20Formulations_Nadkarni.pdf

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Outline

- Concepts (1 slide)
- Introduction (4 slides)
- Molecule design (17 slides)
- Formulation
  - Parenteral (10 slides)
  - Oral (29 slides)
- Pediatric formulations: To use or not to use preservatives (4 slides)
- Conclusions (1 slide)

Concepts

1. “Drugs should be designed with delivery in mind” Takeru Higichi in Prodrugs: Some Thoughts and Current Issues, V. Stella, J Pharm Sci, 99, 12, 4755-4765 (2010)
2. Message to Medicinal Chemists on chemical structure
    - Ionizable group (pKa)
    - Handle for prodrug
    - Lack of planarity
3. Supersaturation vs equilibrium solubility
4. Minimize solvents

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Introduction

Ways to enable PK, PD and Tox Studies:

1. Molecule design
2. Formulation
3. Manufacturing process to make amorphous solids or nanosuspensions

Introduction- Ways to enable PK, PD and Tox Studies

1) **Molecule design**

If target oral delivery via the portal vein, then want water-soluble (dose in 250 mL pH 2-7) or soluble in intestinal fluid

Ref: Role of the Development Scientist in Compound Lead Selection, S. Venkatesh, J Pharm Sci 89, 2, 145-154 (2000)

Physical chemical properties of oral drug candidates in the discovery and exploratory development settings, W. Curatolo, PSTT, 1, 9, 387-393 (1998)

If targeting oral delivery via the lymphatic then want lipid-soluble ($\geq$ 50 mg/mL in long-chain triglycerides) and Log P $\geq$ 5

Ref: Lymphatic Transport of Drugs, W. Charman and V. Stella, CRC Press, 1992

Introduction- Ways to enable PK, PD and Tox Studies

2) **Formulation**

pH adjustment (only if molecule has pKa)

Co-solvent(s)

Surfactant(s)

Introduction- Ways to enable PK, PD and Tox Studies

3) **Manufacturing process to make amorphous solids or nanosuspensions**

Nanotechnology

Process: Spray-dry with surfactant or polymer
Melt extrusion
High pressure homogenization - nanosuspension

Principles: Equilibrium solubility
In-vivo solubility
Supersaturation
Precipitation upon dilution
Particle size reduction

NOT A FOCUS OF THIS TALK

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Molecule Design

Active Pharmaceutical Ingredient (API) in Discovery

1. My message to Medicinal Chemists on chemical structure
   - Ionizable group (pKa)
   - Handle for prodrug
   - Lack of planarity

2. If the molecule or scaffold has an ionizable group
   - pH-dependent solubility
   - Salt formation
   - In preclinical prefer free base or free acid, so the formulator can chose the counterion (HCl, Mesylate, NaOH, etc.)

3) Amorphous form is common in discovery (column purification)
   - Likely more soluble than crystalline form in development

API in Discovery

Message: In discovery measure solubility in: 1) SIF, 2) pH 2 and pH7

If the molecule has limited water-solubility, but is solubilized by simulated intestinal fluid (SIF):

1) Can have good oral bioavailability from
   - Aqueous suspensions (preclinical)
   - Conventional solid oral dosage forms (clinic, commercial)

2) Potential for positive oral food-effect

3) To prevent or minimize the food-effect may require an enabling technology (topic for another discussion)
   - Surfactant-containing formulation
   - Liquid-filled capsule process
   - Supersaturation
   - Amorphous solid

API in Discovery

- BCS (Biopharmaceutical Classification System)
- BDDCS (Biopharmaceutics Drug Disposition Classification System) high permeability if metabolized
- Definition of solubility: highest dose soluble in 250 mL pH 1-7.5
- Solubility is important relative to dose
- The speaker proposes to modify the definition of solubility to be measured in 250 mL of simulated intestinal fluid.

	High Solubility	**Low Solubility**
High Permeability Rate/ Metabolism	Class 1 High Solubility Extensive Metabolism	Class 2 Low Solubility Extensive Metabolism
Low Permeability Rate/ Metabolism	Class 3 High Solubility Poor Metabolism	Class 4 Low Solubility Poor Metabolism

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Simulated Intestinal Fluid (SIF)

Fasted: **5 mM total bile salts**

Fed: **15 mM total bile salts**

Component[a]	Concentration, mM
Sodium glycocholate	7.5 (3.7 mg/mL)
Sodium taurocholate	7.5 (3.9 mg/mL)
Lecithin (assume MW=800 g/mol)	3.75 (8.0 mg/mL)
Sodium phosphates, pH 6.5 [b]	50
Sodium chloride	80

[a] Water with sodium phosphate, 50 mM (pH 6.5) with the ionic strength adjusted to 0.15M with NaCl.
[b] Mixture of sodium phosphate monobasic sodium phosphate dibasic.

Similar composition: biorelevant.com; ePhares.com

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Aqueous Suspension Formulations

- **In the case where the API is solubilized in simulated intestinal fluid, an aqueous suspension may proved the need plasma exposure**

- Aqueous suspension: Water with 0.1% TWEEN 20 and 0.1% HPMC is a simple oral formulation

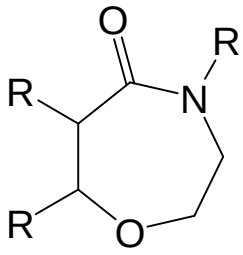
- In general for poorly water-soluble molecules, the oral bioavailability from an oral solution is better than from a suspension or a solid

Case Study #1

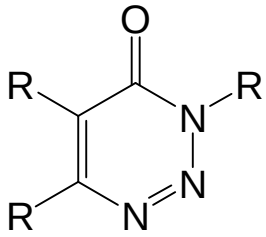
In the case on the next 2 slides

- The water solubility is ~ 10 µg/mL for all three scaffolds with no usable pKa

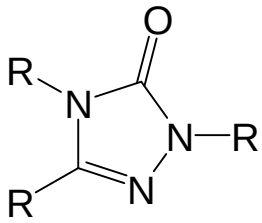
7-membered ring
non-planar scaffold



6-membered ring
planar scaffold



5-membered ring
planar scaffold



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Case Study #1 (cont.)

- In simulated intestinal fluid the solubility of the
  - 7-membered ring non-planar scaffold ~ 500 µg/mL
  - 6-membered ring planar scaffold is ~ 40 µg/mL
  - 5-membered ring planar scaffold is ~ 40 µg/mL

- Selected the 7-membered non-planar scaffold
- In the preclinical drug safety studies (toxicology) an aqueous oral suspension used in both rats and dogs

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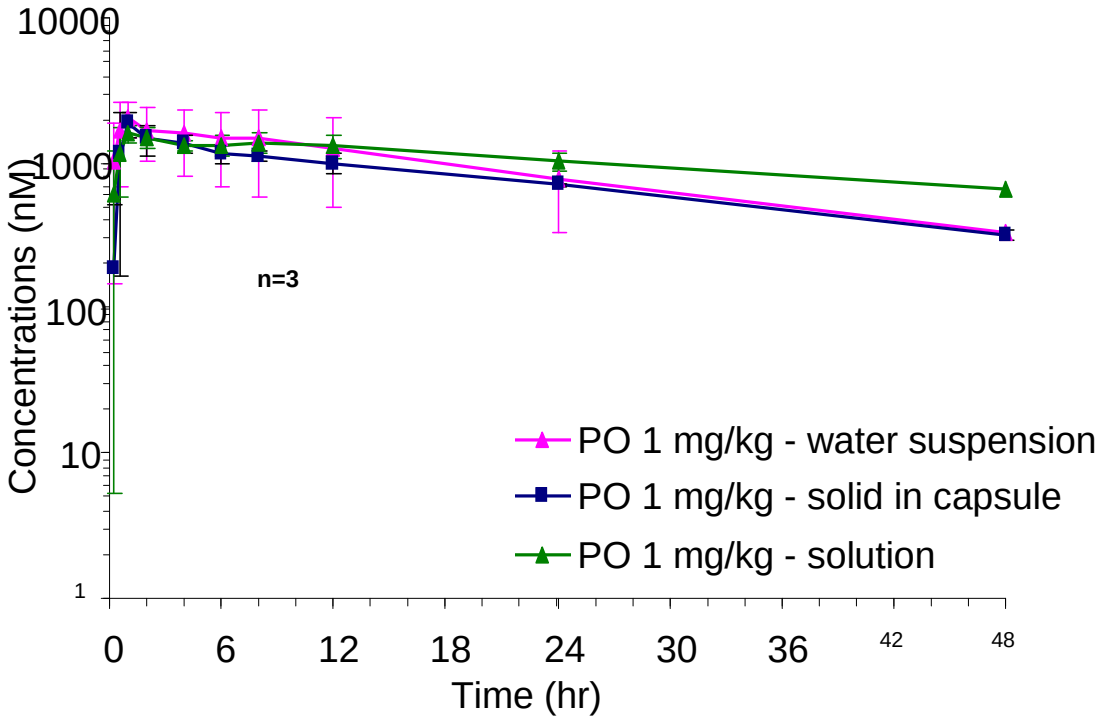
Case Study #1 (end)

PK-PO in Beagle Dogs at ~ 1 mg/kg



The observed oral bioavailability at 1 mg/kg in dogs was ~ 100% from co-solvent solution (5/30/45/20 NMP/PG/PEG/Water), aqueous suspension, and crystalline solid formulations.

API in Discovery - Prodrug

If the molecule has limited oral bioavailability due to low solubility in both water and in simulated intestinal fluid, and adequate plasma exposure is not achievable by formulation or process approaches (co-solvents, organic formulation, nano-suspensions, amorphous solids):

1) Prodrug strategy can be quite successful

2) Do not shy away from prodrugs in drug discovery

3) Need to have a “handle” for prodrug on the core scaffold

API in Discovery – Prodrug (added post)

Reference to books on prodrugs

•Prodrugs, Challenges and Rewards Part 1 and Part 2

STELLA, V.; BORCHARDT, R.; HAGEMAN, M.; OLIYAI, R.; MAAG, H.; TILLEY, J. (EDS.)
BOOK DOI: 10.1007/978-0-387-49785-3
PUBLISHER: SPRINGER NEW YORK
COPYRIGHT: 2007
ISBN: 978-0-387-49785-3 (ONLINE) 978-0-387-49782-2 (PRINT)
SUBJECT: BIOMEDICINE AND PHARMACOLOGY/TOXICOLOGY
LIST PRICE: $649.00
AAPS MEMBER PRICE: $486.75

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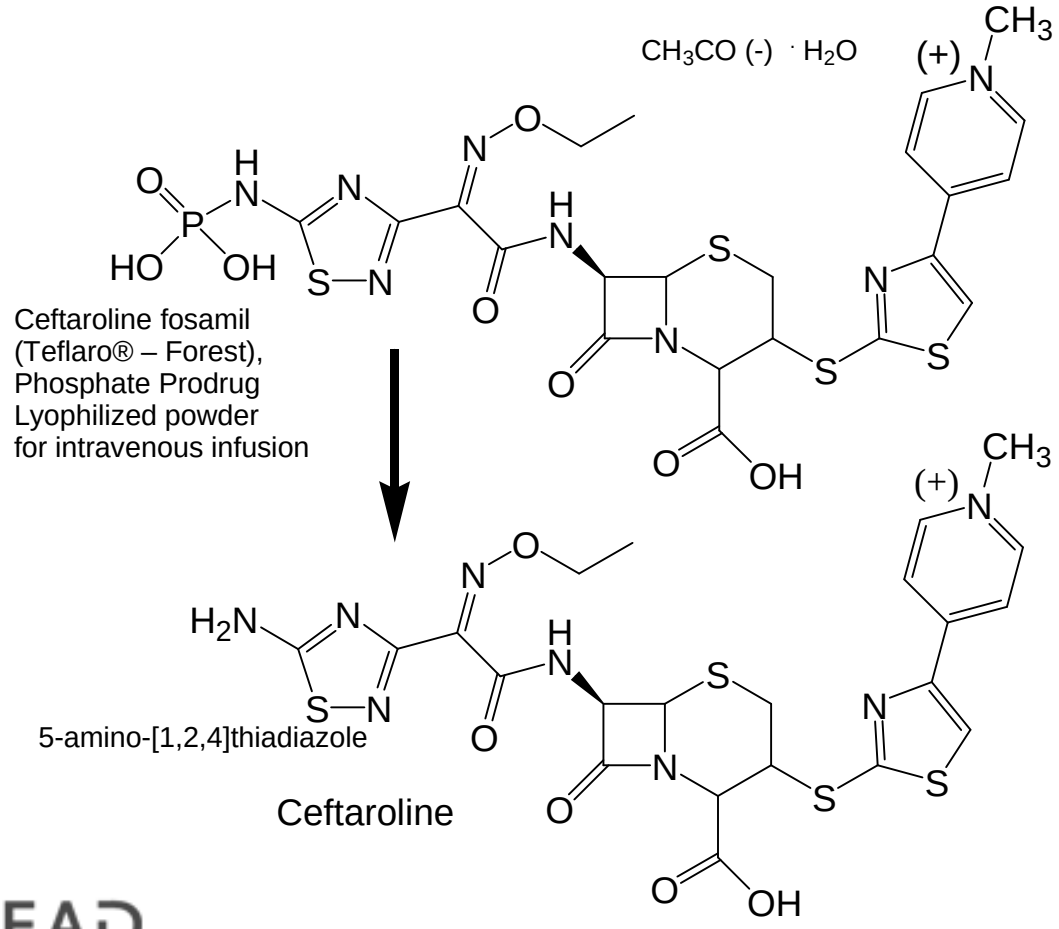
API in Discovery - Prodrug

- On the next 3 slides are examples of new prodrugs approved marketed in 2011
- Of the 14 new drugs marketed in first half of 2011:
  - 2 antibodies
  - 1 peptide/protein
  - 11 small molecules of which three (27%) are prodrugs:
  - Ceftaroline fosamil (Teflaro® – Forest), intravenous infusion
  - Azlisartan medoxomil (Edarbi® – Takeda), oral
  - Abiraterone acetate (Zytiga® - Centocor), oral

Ref: New Therapeutic Agents Marketed in the First Half of 2011:
Part I, Daniel A. Hussar, Pharmacy Today, Oct 2011;
Part 2, Daniel A. Hussar, Pharmacy Today, Nov 2011

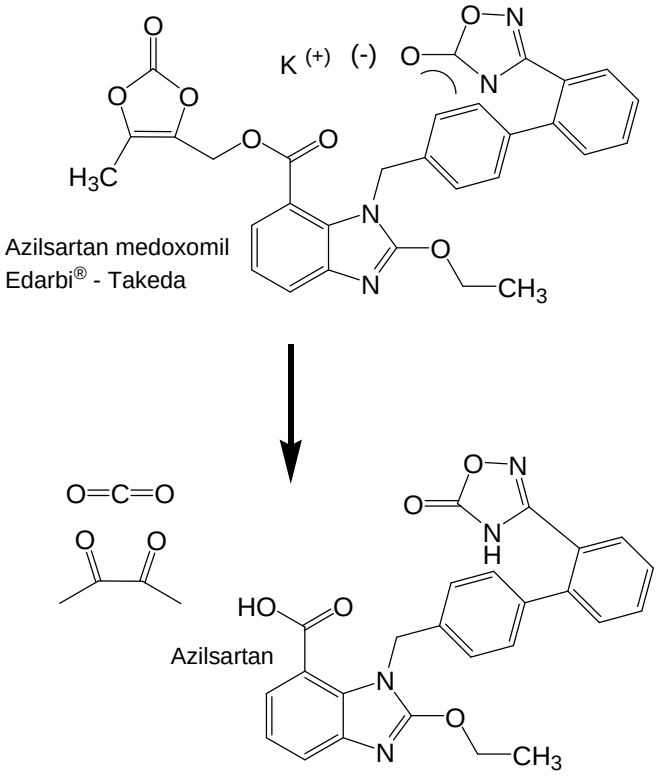
Prodrug Strategy – Recent Commercial Example

- Ceftaroline fosamil (Teflaro® – Forest), intravenous infusion
- Advanced-generation cephalosporin antibiotic
- Someone in discovery decided that ceftaroline needs to be prodrugged



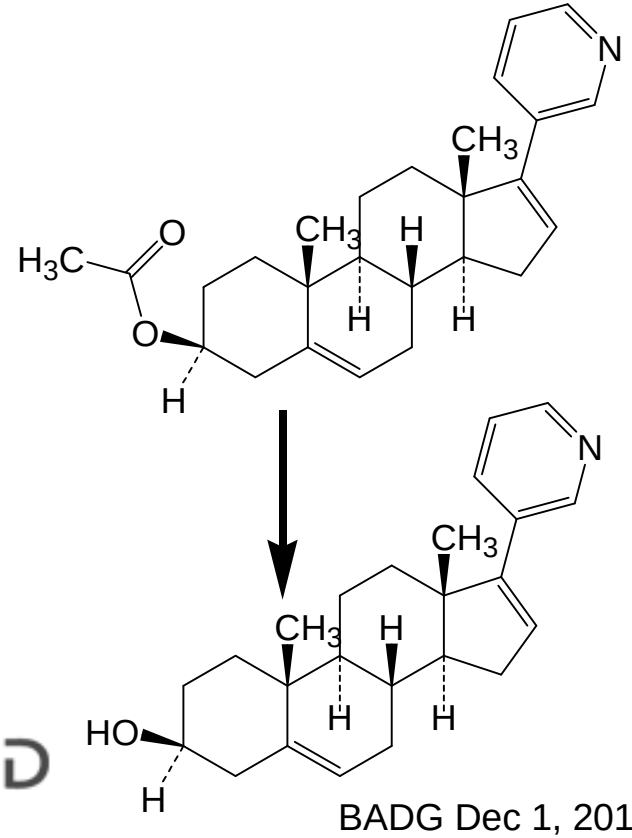
Prodrug Strategy – Recent Commercial Example

- Azlisartan medoxomil (Edarbi ® – Takeda), oral
- Angiotensin II receptor blocker (ARB)
- Hydrolyzed in the gastrointestinal tract to azilsartan, bioavailability is about 60%, and is not affected by food
- Someone in discovery decided that azilsartan needs to be prodrugged



Prodrug Strategy – Recent Commercial Example

- Abiraterone acetate (Zytiga® - Centocor)
- Oncology – Prostate cancer
- Abiraterone was poorly bioavailable, a prodrug was sought. Abiraterone acetate was found to be rapidly deacetylated to abiraterone *in vivo*. Ref: Nature Review Drug Discovery, 10(8), 573-571 (Aug 2011)



Abiraterone acetate
Zytiga® - Centocor
Log P = 5.1
Insoluble in water
Significant food effect

Abiraterone

Prodrug in Discovery– Enable Toxicology Studies Case Study #2

In the case on the next 2 slides

- Weak acid with heterocyclic nitrogen pK_a ~ 9.0
- Low intrinsic water-solubility pH < 9 = 12 µg/mL
- Not solubilized by SIF:, FeSIF = 10 µg/mL
- Phosphate prodrug has solubility of ~ 0.2 mg/mL at pH 2, and > 2 mg/mL in pH 7
- In the preclinical drug safety (toxicology) studies the prodrug is used with an aqueous-based oral solution in cyno monkeys

Prodrug in Discovery– Enable Toxicology Studies Case Study #2 (cont.)

Cyno Monkey PK-PO at 30 mg equiv/kg

Parent from Parent as nano-suspension

PO Cmax = 4.2 µM,

PO bioavailability = 8% ± 1%

Parent from prodrug as aqueous-based co-solvent

PO Cmax = 34 µM,

PO bioavailability = 36% ± 7%

Fold improvement of prodrug

PO Cmax = 8-fold

PO bioavailability = 4-fold

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Prodrug in Discovery– Enable Toxicology Studies Case Study #2 (end)

Dog PK-PO as sieved powder-in-capsule at 5 mg equiv/kg

Parent from Parent

PO Cmax = 0.15 µM,

PO bioavailability = 7% ± 6%

Parent from prodrug

PO Cmax = 2.7 µM,

PO bioavailability = 40% ± 13%

Fold improvement of prodrug

PO Cmax = 18-fold

PO bioavailability = 6-fold

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Formulation

Parenteral Routes

"Para" = other

"Enteral" = intestine

- Intravenous: Bolus up to 5-10 mL (humans)
  Infusion up 100's of mL (humans)
  Bolus and infusion up to 2 mL/kg (animals)
- Intramuscular: 2-5 of mL (humans)
  1 mL/kg (animals)
- Subcutaneous : Less local flow at the site of injection, the most challenging for small molecules, common for proteins and antibodies
  1-2 mL (humans)
  1 mL/kg (animals)

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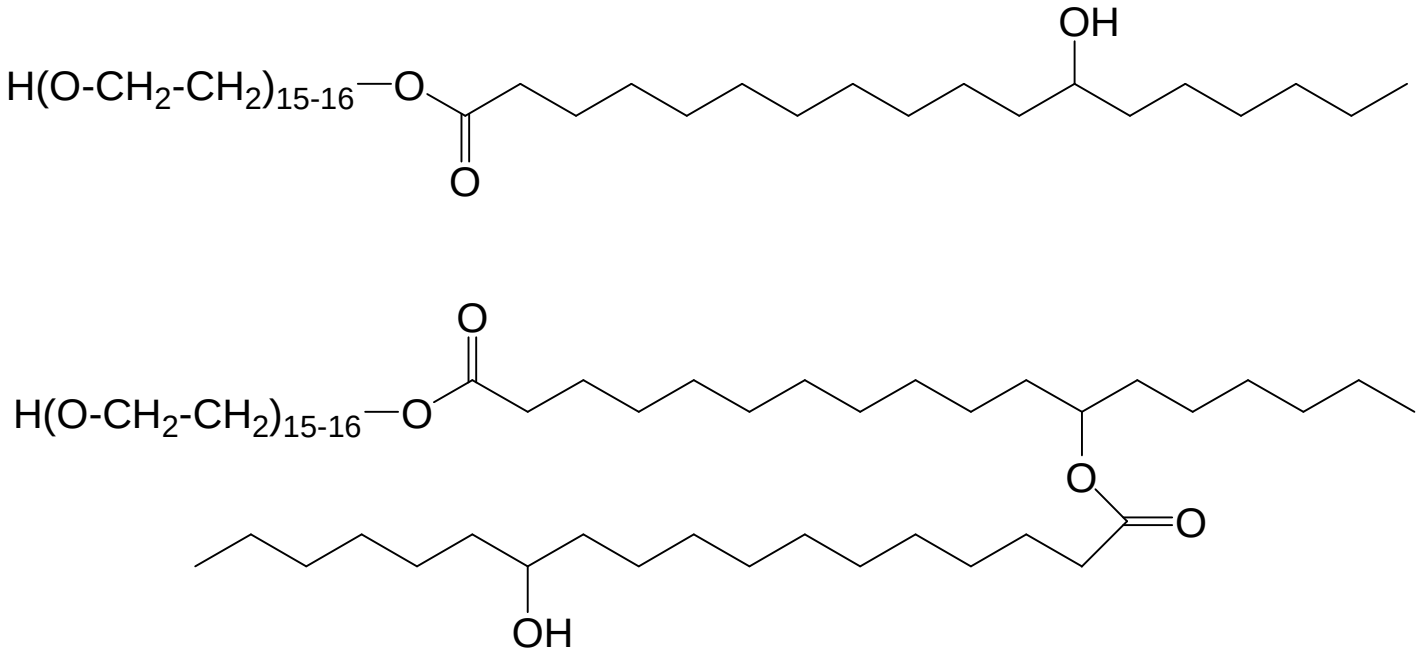
Parenteral Excipients - Classification

Oil-soluble solvents	Water-soluble solvents	Water-soluble surfactants	Complexation
Long-chain triglycerides Medium-chain triglycerides SABER (sucrose acetate isobutyrate)	PG **PEG 400** **Ethanol** Glycerin NMP DMA DMSO	Cremophor Polysorbate **Solutol HS-15** Phospholipids (lecithin) Poloxamers	Cyclodextrins **Captisol®** (SBE-β-CD)

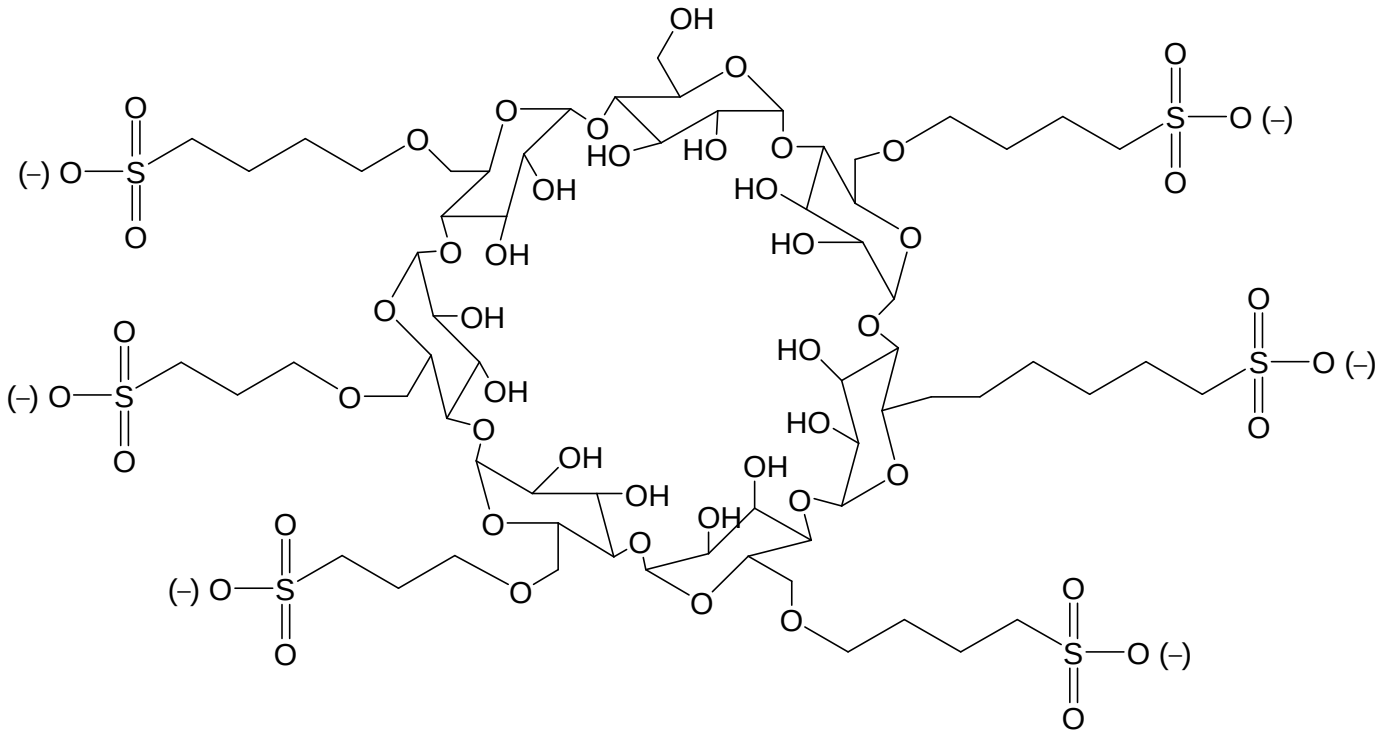
Parenteral Excipient: Solutol HS-15

Polyethylene glycol 660 12-hydroxystearate

Polyglycol mono- and di-esters of 12-hydroxystearic acid



Parenteral Excipient: Sulfobutylether-β-cyclodextrin (Captisol®)



Preclinical Intravenous Bolus

Bolus injection administered at 2 mL/kg

1) Equilibrium solubility

60% PEG 400

40% water, pH 3-10

Rats, Dogs, Cyno and Rhesus Monkeys

2) Supersaturation

5% Solutol HS-15

20% DMSO (drug dissolved at 5-x concentration)

75% water, pH 3-10

Tested only rats

Process: Dissolve drug in DMSO (or other solvent), then slowly add to the water with Solutol, sterile filter, administer within certain time period.

Concept: Create solubilizing conditions, then add drug

R.G. Strickley, L Liu and P. Lapresca "Preclinical Parenteral and Oral Formulations of Water-Insoluble Molecules" ISSX Meeting, 1999, Nashville, TN, USA

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Preclinical Intravenous Infusion

Infusion injection administered at 2 mL/kg
Rat, Dogs, Cyno and Rhesus Monkeys

1) 5% NMP or Ethanol
   30% PG
   45% PEG 400
   20% water, pH 3-10

   Keep ethanol ≤ 10%
   PG ≤ 30 (hemolysis)

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Preclinical Intravenous Mini-Bolus

Slow bolus injection administered at ≤ 1 mL/kg in rat

1) 10% Ethanol
   90% PEG 400

   Pharmacodynamic-IV efficacy

   Last resort to use 100% organic for intravenous

Parenteral Lipid Excipients

Concentrate to be diluted with provided diluent

- Phares' Instant Solubilization

  1) Lipid dispersion: Aqueous buffer pH 6.8 (0.01M histidine), 100 mg/mL phospholipid

  2) Transfer medium: Drug and phospholipid in a minimal amount of organic solvent EtOH, PEG 300, PG, DMSO or NMP

  Mix the two to ≤ 10% organic solvent, administer intravenous, intramuscular, subcutaneous, or intraperitoneal

- Available as "Lead Select I.V." - a kit for research compounds

P.V. Hoogevest and M. Leigh "Instant Solubilization of Poorly Water-soluble Drugs by *In-situ* Loading of Aqueous Phospholipid Dispersions Suitable for Parenteral Administration" PDA Journal Pharmaceutical Science and Technology. 60, 6, 366-377 (2006)

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Instant Solubilization

Placebo lipid dispersion is clear and translucent	Organic drug concentrate mixes with lipid dispersion	Drug partitions into the lipid phase within seconds	Drug loaded lipid dispersion is again translucent

Parenteral Lipid Emulsions

- Molecules that are soluble in triglycerides can be formulated for intravenous delivery by an oil-in-water emulsion
- Total Parenteral Nutrition (TPN): 10-30% triglyceride in water with 2.25-2.5% glycerol, 1.2-1.8% lecithin
- Liposyn® II (5% safflower oil, 5% soybean oil)
- Liposyn® III (10% soybean oil)
- Liposyn® III 30% (30% soybean oil)
- Intralipid 10% (10% soybean oil)
- Lipofundin MCT/LCT 10% (5% medium-chain triglyceride, 5% soybean oil)
- Lipofundin MCT/LCT 20% (10% medium-chain triglyceride, 10% soybean oil)

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Oral Excipients - Classification

Water-soluble solvents/excipients

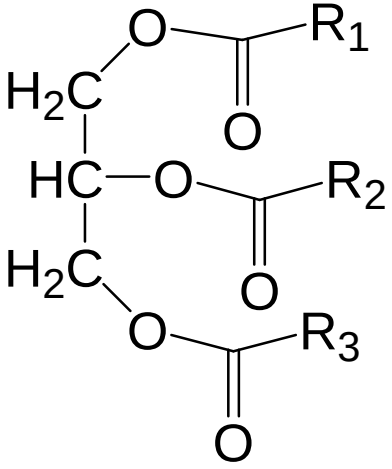
- Propylene glycol
- Polyethylene glycol (PEG 300, PEG 400)
- Ethanol
- Glycerin
- Sulfobutylether-β-cyclodextrin (Captisol®)

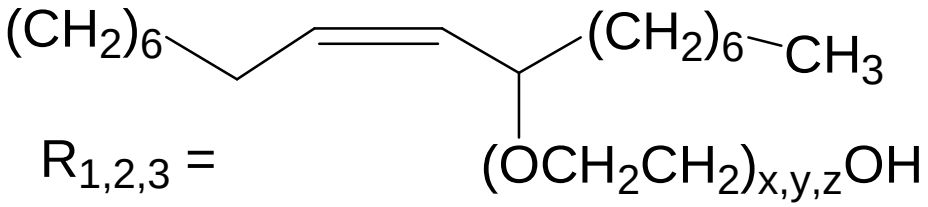
Surfactants

- Cremophor EL and Cremophor RH40
- Sorbitan esters (SPAN 20, SPAN 80)
- TWEEN 20 and TWEEN 80 (Polysorbates)
- TPGS
- Solutol HS-15
- Polyglycolyzed glyceride (Labrasol, Labrafil, Gelucire)
- Poloxamers

Oral Surfactant Excipients – Chemical Structure

Cremophor EL, Polyoxyl 35 castor oil, Super Refined® Etocas 35





R = Polyethylene glycol ricinoleate
x + y + z = 35
Cremophor EL (Polyoxyl 35 castor oil)

Complex mixture of 75%-83% relatively hydrophobic and 17%-25% relatively hydrophilic

Adapted from Strickley, "Solubilizing Excipients in Oral and Injectable Formulations" *Pharm. Res*. 21(2) 201-230 (2004)

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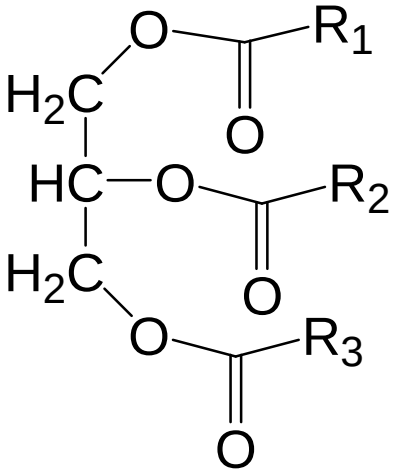
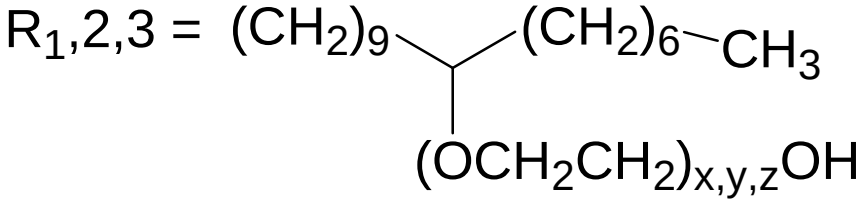
Oral Surfactant Excipients – Chemical Structure

Cremophor RH-40, Polyoxyl 40 hydrogenated castor oil





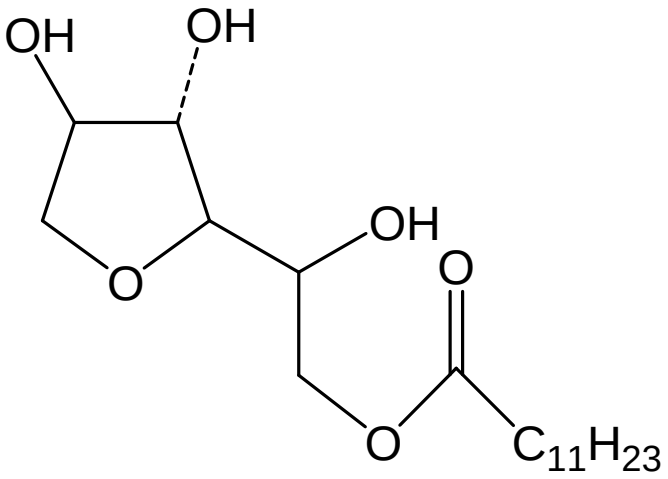
R = Polyethylene glycol 12-oxystearate
x + y + z = 40
Cremophor RH 40 (Polyoxyl 40 hydrogenated castor oil)

Complex mixture of 75%-83% relatively hydrophobic and 17%-25% relatively hydrophilic

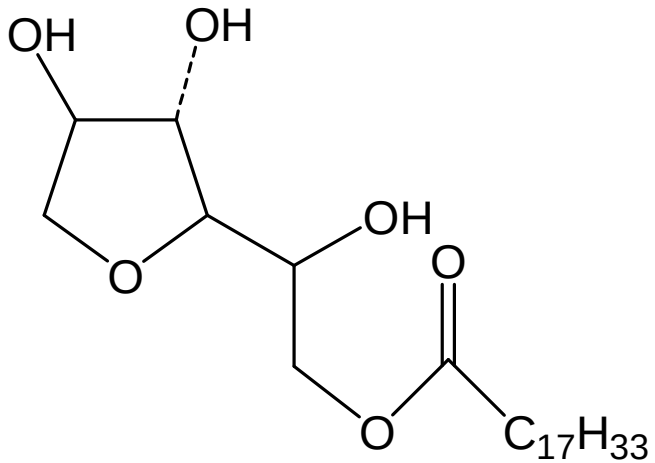
Adapted from Strickley, "Solubilizing Excipients in Oral and Injectable Formulations" *Pharm. Res*. 21(2) 201-230 (2004)

Oral Surfactant Excipients – Chemical Structure

Sorbitan monolaurate
(SPAN 20)



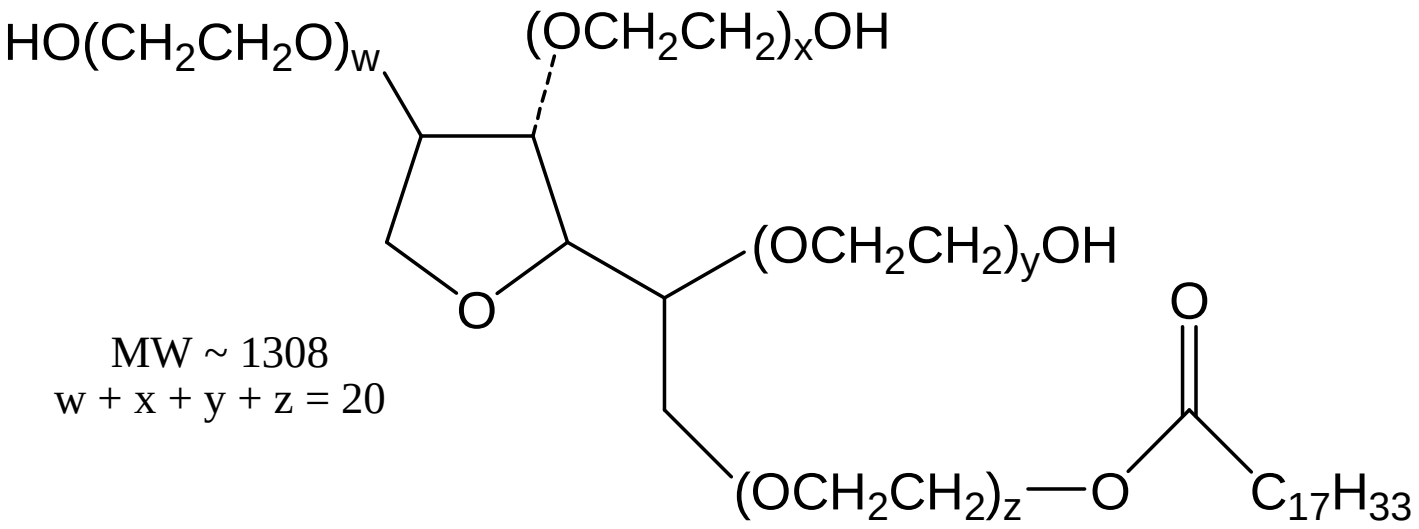
Sorbitan monooleate
(SPAN 80)



Adapted from Strickley, "Solubilizing Excipients in Oral and Injectable Formulations" *Pharm. Res*. 21(2) 201-230 (2004)

Oral Surfactant Excipients – Chemical Structure

Polysorbate 80, TWEEN 80
polyoxyethylene 20 sorbitan monooleate



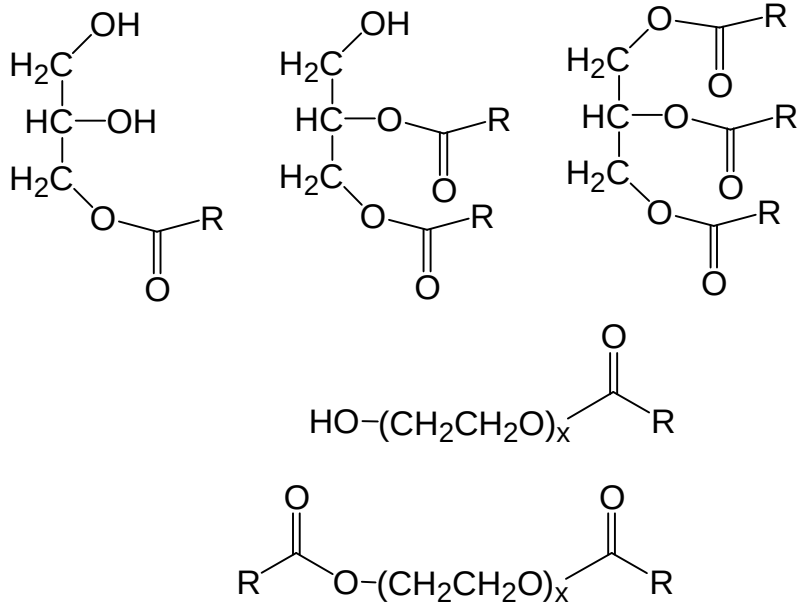
MW ~ 1308
w + x + y + z = 20

Adapted from Strickley, "Solubilizing Excipients in Oral and Injectable Formulations" *Pharm. Res*. 21(2) 201-230 (2004)

Oral Lipid Excipients – Chemical structure

Polyglycolyzed glycerides

Reaction between a Triglyceride and a PEG

Excipient name and/or common name(s)			Chemical structure
Mono-, di- and triglycerides and mono- and di- fatty acid esters of PEG (also contains glycerol and PEG)			
Example	x	R	
Softigen® 767	6	C_8, C_{10}	
Labrasol®[c]	8	C_8, C_{10}	
Labrafil® M-1944CS[d]	6	$C_{18:1}$	
Labrafil® M-2125CS[e]	6	$C_{18:2}$	
Gelucire® 44/14[f]	32	C_{12} C_{14}	

Adapted from R.G. Strickley, "Solubilizing Excipients in Oral and Injectable Formulations" *Pharm. Res*. 21(2) 201-230 (2004)

Oral Lipid Excipients - Classification

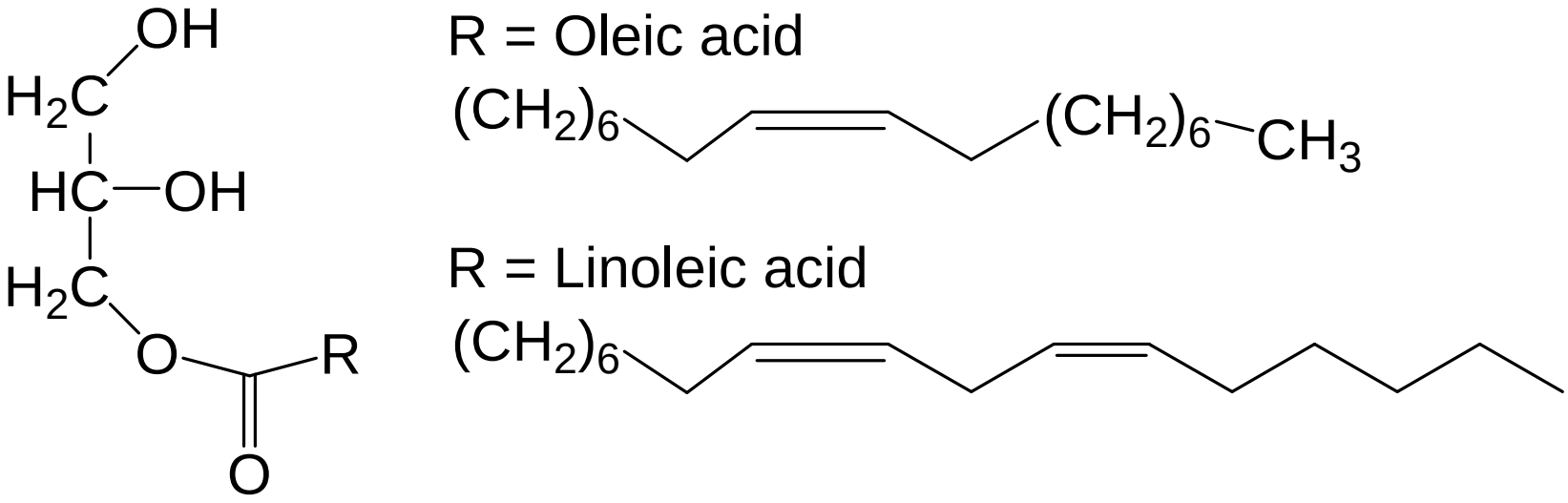
Water-insoluble

- Monoglycerides and diglycerides
- Long-chain triglycerides
- Medium-chain triglycerides
- Oleic acid
- PG esters
- PEG esters/diesters
- Vitamin-E
- Fatty acids

Oral Lipid Excipients – Chemical structure

Long-chain monoglycerides

Glyceryl monooleate (Maisine®)



Adapted from Strickley, "Solubilizing Excipients in Oral and Injectable Formulations" *Pharm. Res*. 21(2) 201-230 (2004)

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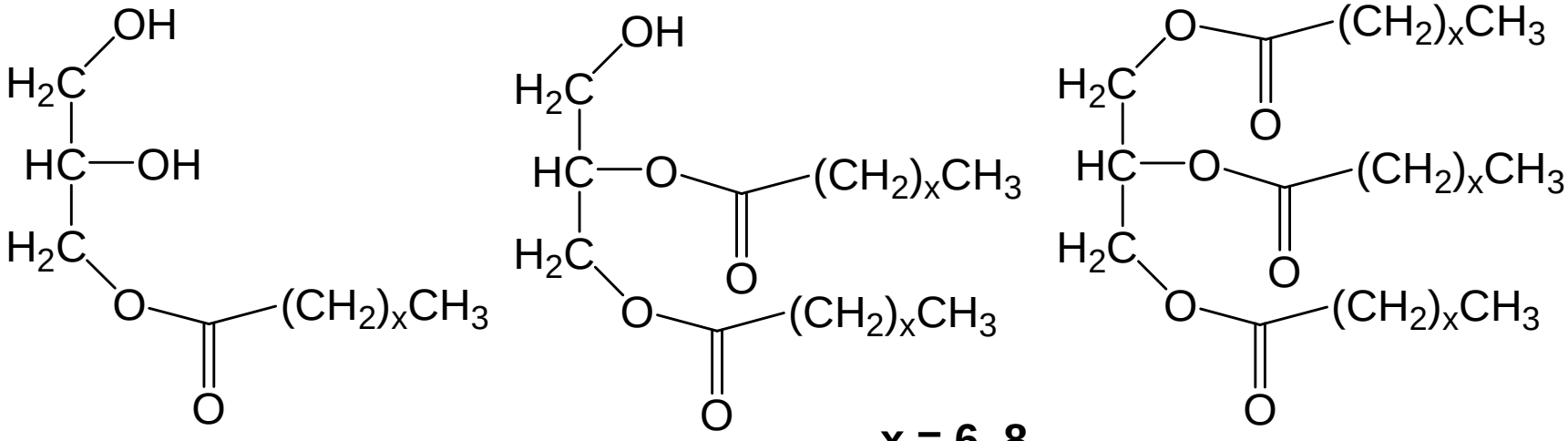
Oral Lipid Excipients – Chemical structure

Medium-chain mono-, di-, and triglycerides



x = 6, 8

Adapted from Strickley, "Solubilizing Excipients in Oral and Injectable Formulations" *Pharm. Res*. 21(2) 201-230 (2004)

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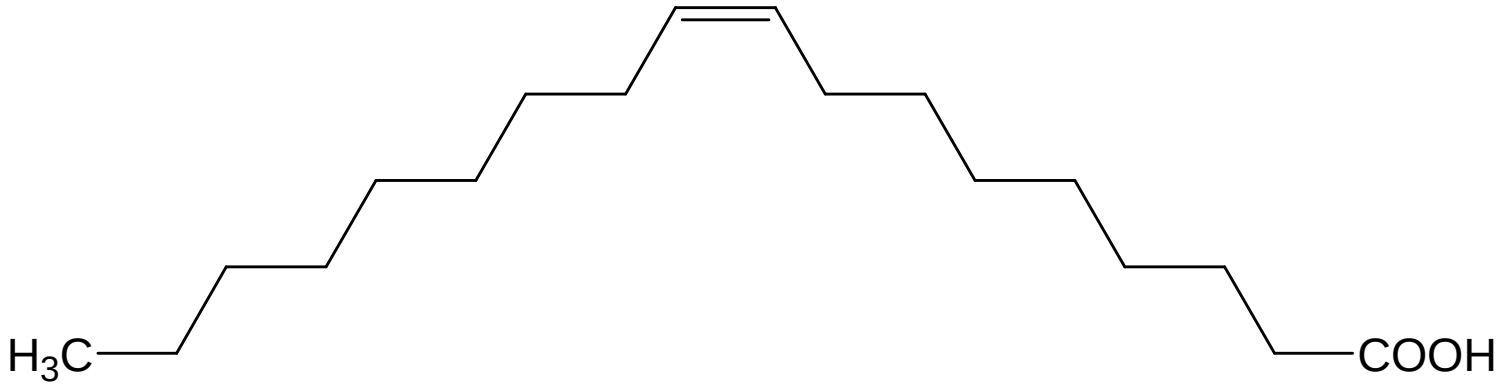
Oral Lipid Excipient – Chemical structure

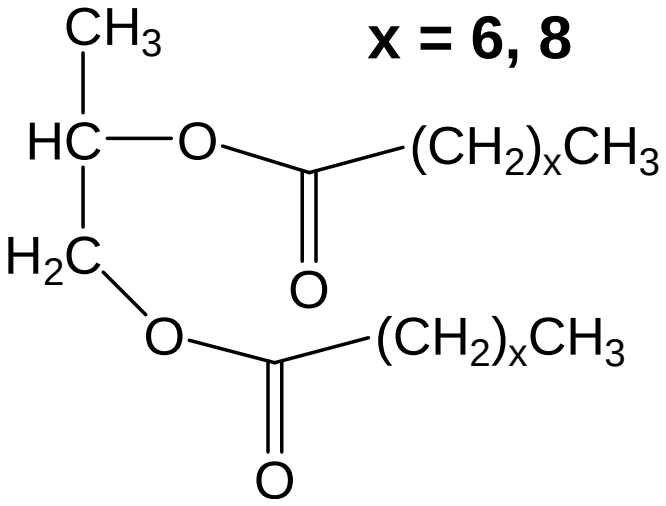
Most lipid excipients are non-aromatic (except Vitamin E)



Oleic acid is a liquid at room temperature

Oral Lipid Excipients – Chemical structure

Propylene glycol diesters of C_8 and C_{10} (PGC8)

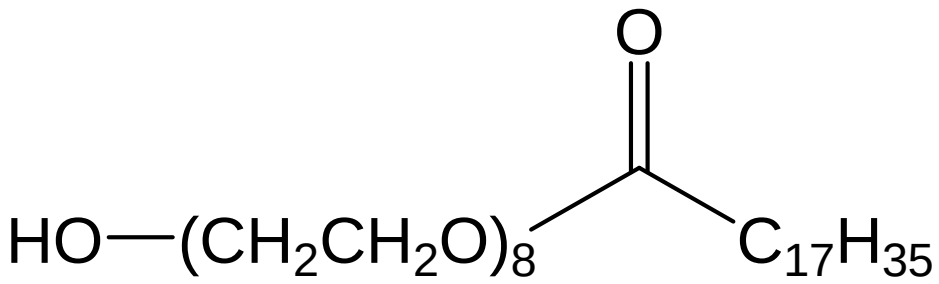


Oral Lipid Excipients – Chemical structure

PEG 400 Esters

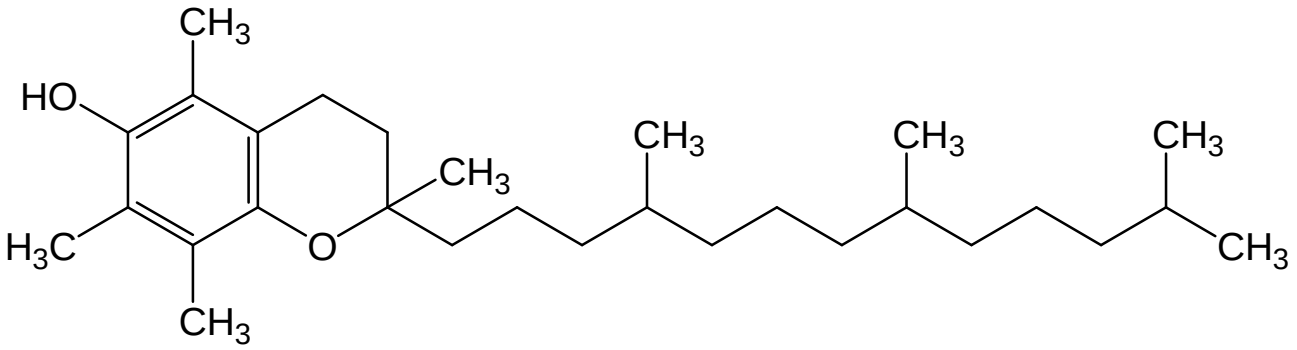
Polyoxyl 8 stearate

PEG 400 monostearate

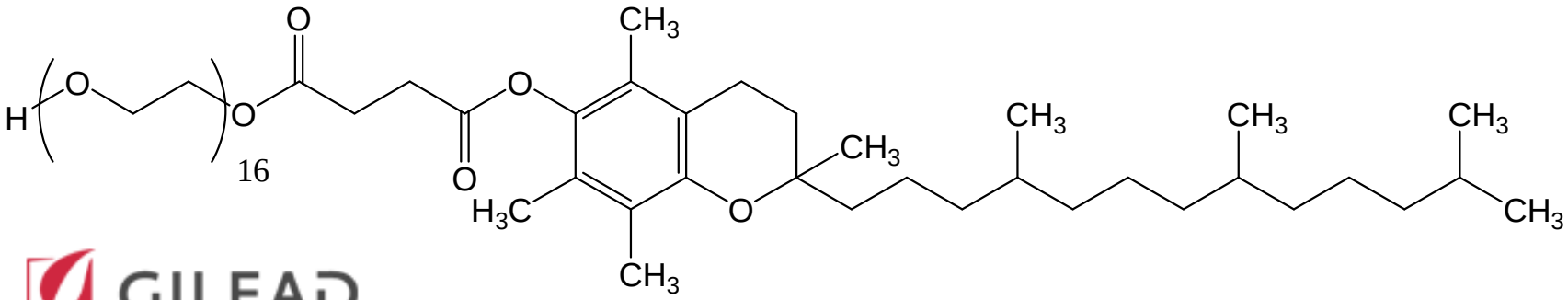


Oral Lipid Excipients – Chemical structure

Vitamin E is the common name for d-α-tocopherol
liquid at room temperature and is also an antioxidant



TPGS: d-α-tocopherol polyethylene glycol 1000 succinate
is water-soluble



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Oral Solutions - Preclinical

Some useful oral formulations in preclinical studies:

- Any parenteral (injectable) formulation
- 10% NMP. 15% Solutol HS-15 and 75% water, pH 2-10
- Water/PEG 400
- 0.1% TWEEN 20, 20% PG, 25% PEG 400 and 55% water, pH 2 (0.05M citric acid)
- 10% ethanol and 90% PEG 400
- 5% ethanol and 95% PG
- **5% ethanol, 10% water, 10% Solutol HS-15 and 75% PG**
- 10% ethanol, 10% PG, 40% Solutol HS-15 and 40% Labrasol (RSSEEDS)
- 15% RSSEEDS and 85% water, pH 2-10

Oral Solutions - Preclinical

Table 14 Flow chart of suggested order of solubilization approaches for oral liquid formulations: simple to complex	
Capsule	**Oral Solution**
Water-soluble organic solvent	Aqueous, pH 2-10
Long-chain triglyceride	Cosolvent (Aqueous/organic solvent), pH 2-10
Medium-chain triglyceride	Organic solvent(s) (100%)
Water-insoluble organic solvent	Aqueous with complexation, pH 2-10
Organic solvents and surfactant	Oil-in-water emulsion
Triglyceride and surfactant	Microemulsion
Microemulsion	SEDDS (self-emulsifying drug delivery system)
SEDDS (self-emulsifying drug delivery system)	SMEDDS (self-microemulsifying drug delivery system)

Formulation in Drug Discovery, R.G. Strickley, in *Annual Reports in Medicinal Chemistry Volume 43*, editors A. Wood and Manoj Desai, Chapter 24, pages 419-451, ISBN: 978-0-12-3743442-2, Elsevier Academic Press, Oxford, UK, 2008

Drug Safety - Toxicology

Oral Solutions - Preclinical

- Maximize oral bioavailability
- Aqueous: pH 2-10
- Organic: up to 100% organic solvent(s)
- Minimize volume
- Minimize excipient(s)

Species	Oral Dose Volume, mL/kg	Formulation
Canine	1-5	Aqueous
	≤ 2	Organic
Rodent	2-10	Aqueous
	≤ 5	Organic

Formulation in Drug Discovery, R.G. Strickley, in *Annual Reports in Medicinal Chemistry Volume 43*, editors A. Wood and Manoj Desai, Chapter 24, pages 419-451, ISBN: 978-0-12-3743442-2, Elsevier Academic Press, Oxford, UK, 2008

Drug Safety Studies (Toxicology)

- FDA:
- http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm

- Shayne Gad:
- S. C. Gad, “Nonclinical Vehicle Use in Studies by Multiple Routes in Multiple Species” International Journal of Toxicology, 25, 499-522 (2006)
- http://www.gadconsulting.com/index.htm
- http://www.gadconsulting.com/vehicles.htm
- http://www.gadconsulting.com/Vehicles%20for%20Animal%20Studies.xls

- The Roundtable of Toxicology
- http://www.toxconsultants.com/

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Oral Solutions - Preclinical

Table 15. Oral Formulations Used in Toxicological and Clinical Studies

Drug (Company)	Formulation	Species	Route/High Dose	Volume administered	Dose Frequency
Amprenavir	20/80 water/PEG 400, pH 2	Sprague-Dawley rats	Oral gavage/ 500 mg/kg	5 mL/kg/dose	BID 6 hours apart for 1 month
Amprenavir	PEG 400/TPGS/PG	Sprague-Dawley rats	Oral gavage/ 375 mg/kg	2-5 mL/kg	BID for 6 months
Amprenavir	PEG 400/TPGS/PG	dogs	Oral gavage/ 350 mg/kg	1-2 mL/kg	12 months
Amprenavir	Water and PEG 400	Cyno monkey	Oral gavage/ 200 mg/kg	1-2 mL/kg	BID 6 hours apart for 1 months
Ritonavir	5/95 EtOH/PG	Sprague-Dawley rats	Oral gavage	2 mL/kg/day	1 month
Ritonavir	5/95 EtOH/PG	Dogs	Oral gavage	2 mL/kg/day	1 month

The **5% ethanol and 95% PG** is a common formulation for toxicology studies
If the molecule precipitates upon dilution into an aqueous solution, then the formulation can be modified to contain a surfactant to
5% ethanol, 10% water, 10% Solutol HS-15 and 75% PG

Formulation in Drug Discovery, R.G. Strickley, in *Annual Reports in Medicinal Chemistry Volume 43*, editors A. Wood and Manoj Desai, Chapter 24, pages 419-451, ISBN: 978-0-12-3743442-2, Elsevier Academic Press, Oxford, UK, 2008

Recent Literature Example

A Formulation-Enabled Preclinical Efficacy Assessment of a Farnesoid X Receptor Agonist, GW4064, in Hamsters and Cynomolgus Monkeys, J Pharm Sci, 100:11, 4722-4733 (2011), P-C Chiang et al (Pfizer, St Louis). Lead author now at Genentech

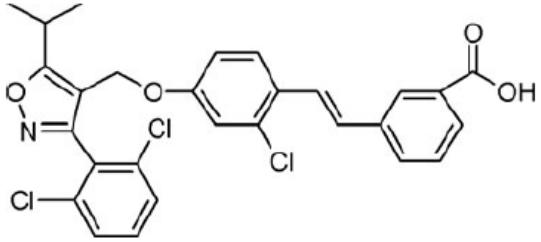

Figure 1. Structure of GW4064.

Water solubility:	2 ng/mL, weak acid pKa = 4.5
Preclinical oral formulation:	**5% Polysorbate 20**
SEDDS, 20 mg/mL	**5% HPMC (no information on grade)**
	35% Cremophor EL
	20% PEG 400
	10% Ethanol
	25% Capmul medium-chain monoglyceride
Dose volume:	5 mL/kg twice-a-day in hamsters (10 mL/kg/day)
	2.5 mL/kg twice-a-day in cyno monkeys (5 mL/kg/day)

Literature Example (cont.) – Solubility in Solvents

Table 2. Solubility of GW4064 in Different Excipients

Excipients	Solubility of GW4064 (mg/g) in Each Excipient
EtOH	~10
Glycerin	<5
Propylene glycol	<5
PEG 400	~50
Cremophor EL	>50
Tween 80	>50
Oleic acid	<3
Capmul MCM	~7

Preclinical oral formulation:
SEDDS, 20 mg/mL

5% Polysorbate 20
5% HPMC (no information on grade)
35% Cremophor EL
20% PEG 400
10% Ethanol
25% Capmul medium-chain monoglyceride

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Literature Example (cont.) – Formulation Criteria

- 28-day in-vivo toleration upon oral administration
- Does not cause soft stools upon oral administration
- **Provides transient in-vivo supersaturation upon dilution into aqueous environment**
- 28-day chemical and physical stability
- Good oral bioavailability – sufficient plasma concentration
- "This formulation was well tolerated by the animal and achieved exposures that allowed us to fully assess the effects of an FXR agonist"

Preclinical oral formulation:	5% Polysorbate 20
SEDDS	5% HPMC (no information on grade)
	35% Cremophor EL
	20% PEG 400
	10% Ethanol
	25% Capmul medium-chain monoglyceride

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Literature Example (cont.) – In Vivo Compatibility

Multiple formulations tested for adverse effects – oral

Soft stools were observed in 3 of 4 formulations (not specified)

Table 3. Vehicle Safety Study Results ($n = 3$ for Each Group)

Vehicle Tested	Dose Volume (b.i.d.)/Total Volume Dosed in 3 days	Adverse Effect Observed
Vehicle 1	0.5 mL/3 mL	Soft stool ($n = 3$)
Vehicle 2	0.5 mL/3 mL	Soft stool ($n = 2$)
Vehicle 3	0.5 mL/3 mL	Soft stool ($n = 2$)
Vehicle 4	0.5 mL/3mL	No

Literature Example (cont.) – In Vitro Supersaturation

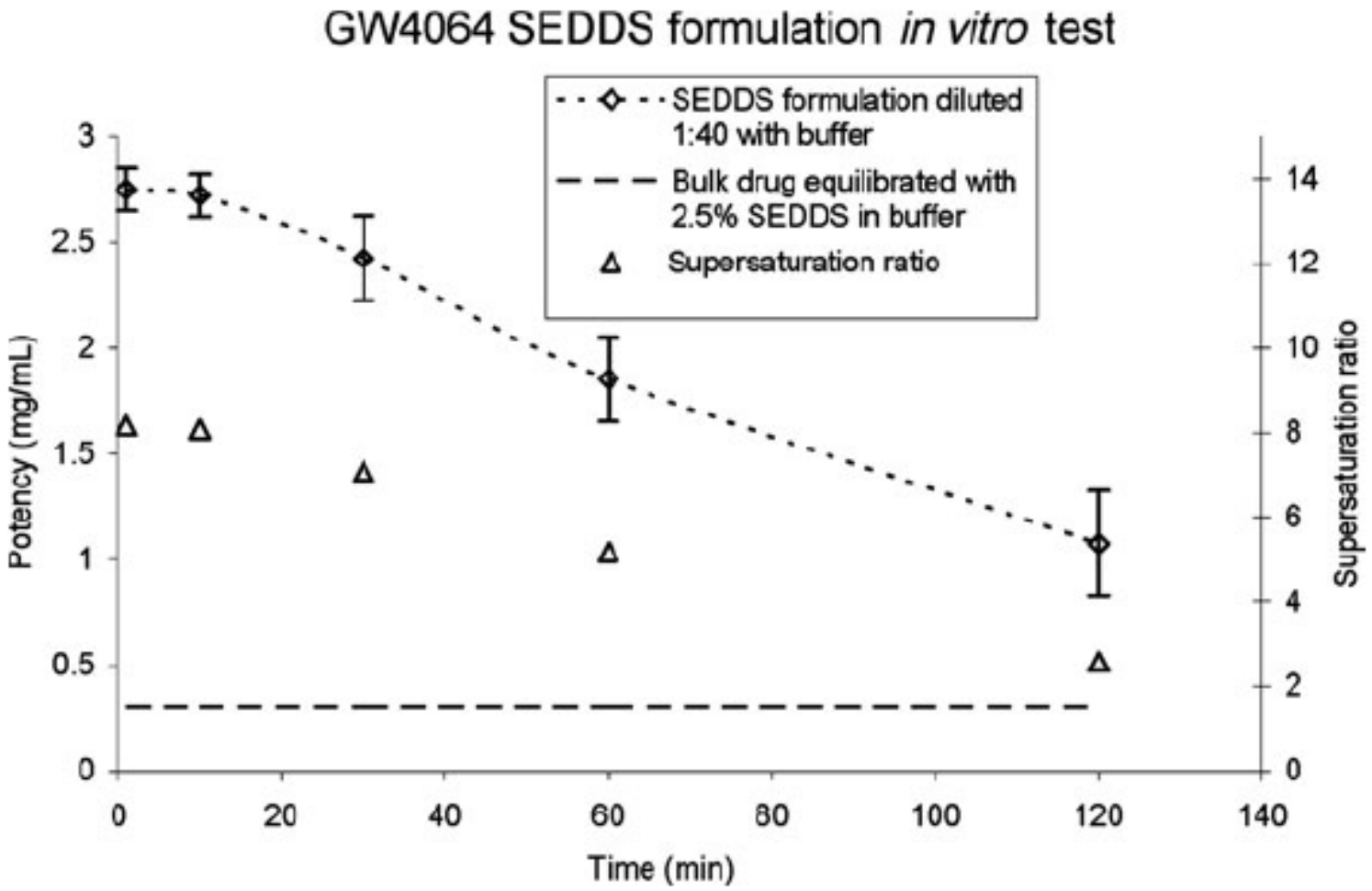

Figure 3. GW4046 SEDDS formulation supersaturation effect.

Literature Example (cont.) – In Vivo Hamster PK-PO

SEDDS versus Aqueous Suspension
Formulations 20 mg/mL

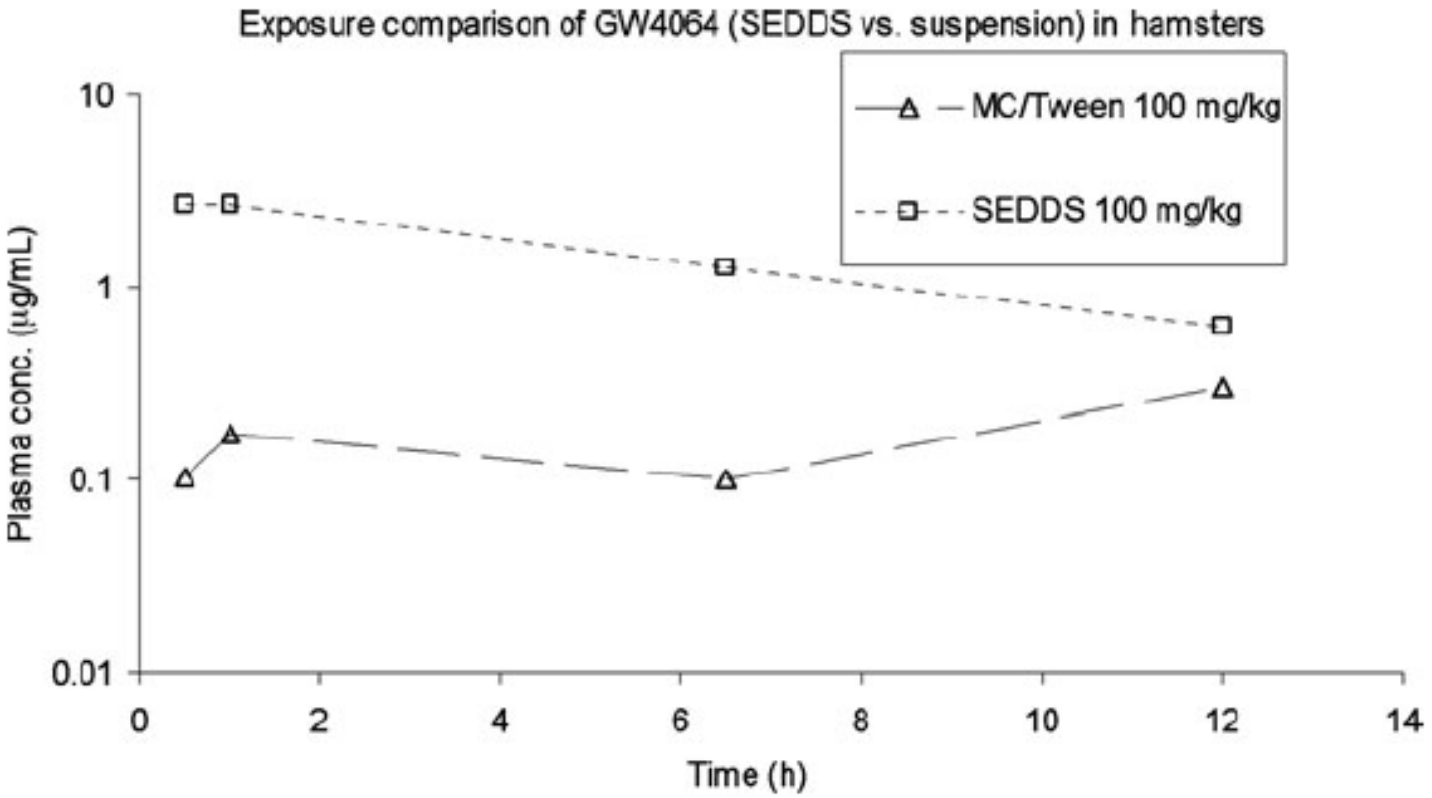

Figure 4. Plasma exposure comparison of GW4064 dosed in hamsters with two different formulations ($n = 8$ and samples were pooled).

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Literature Example (end) – In Vivo Cyno Monkey PK-PO

SEDDS versus Aqueous Suspension

Formulations 20 mg/mL

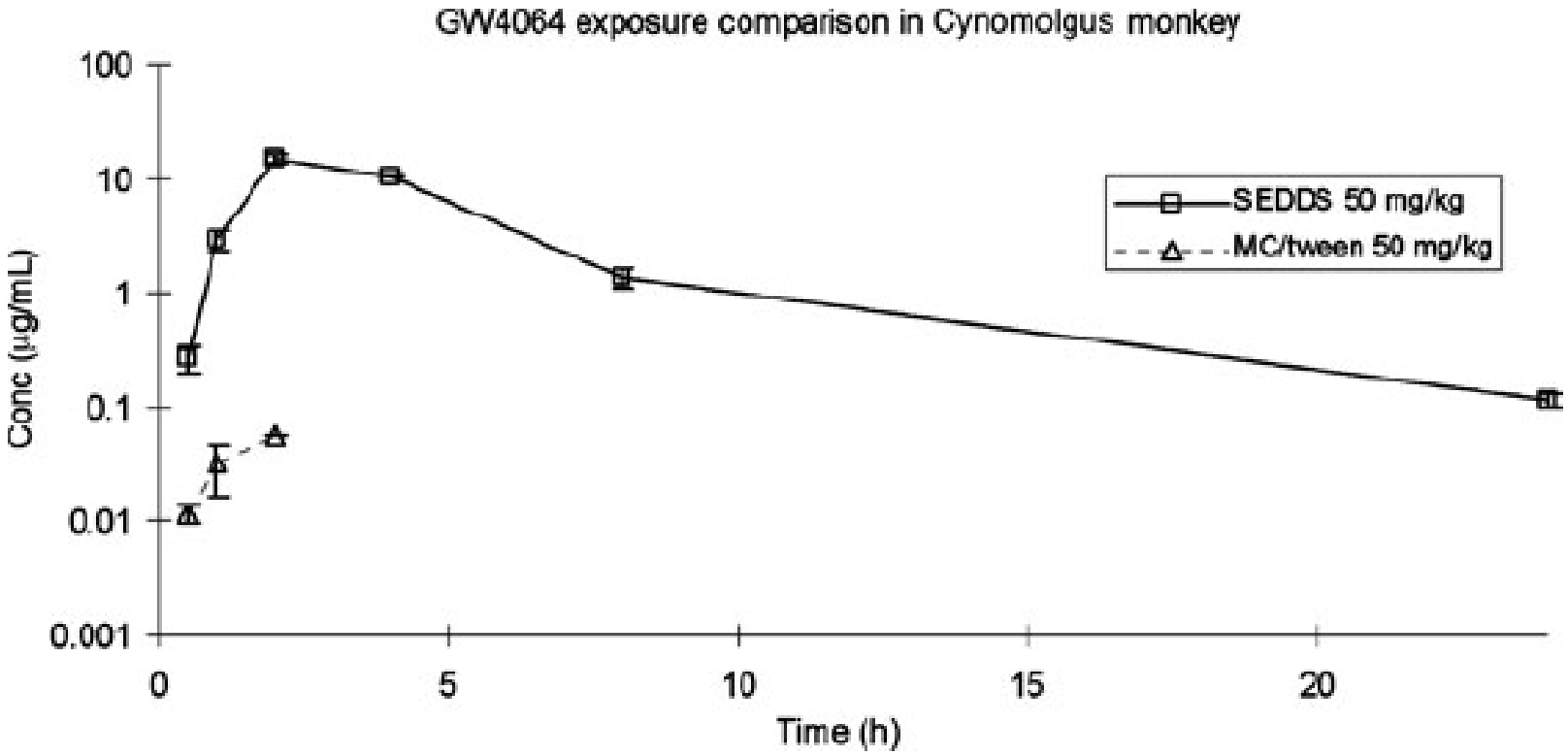


Figure 5. Plasma exposure comparison of GW4064 dosed in cynomolgus monkeys ($n = 3$).

Case Study #3

In the case on the next 2 slides

Low-water solubility with 2 weak base pK_a's 2.5 and 3.8

Intrinsic water solubility pH > 4 = 0.001 µg/mL

Salt Selection:

pH 1.5 (HCl) = 80 µg/mL

pH 1.5 (Mesylate) = 1000 µg/mL

Solubilized by SIF and cyclodextrin complexation:

FaSIF = 2 µg/mL (2000-fold)

FeSIF = 10 µg/mL (10,000-fold)

SIBLM = 80 µg/mL (80,000-fold)

Solubilized by 30% Captisol® = 20,000 µg/mL, pH 2-3 (HCl)

Process: **In-situ preparation of a supersaturated pH-adjusted solution**

Case Study #3 (cont.)

Formulations: Dog Tox-PO at 600 mg/kg/day

Powder in capsule twice-a-day, 1:1 mix of Mesylate salt and PGS

AUC = 350 uM*hr, Oral bioavailability = 18%

Rat Tox-PO at 10 mL/kg, 100 mg/mL, 1000 mg/kg

Aqueous supersaturated solution

pH 2.0 (0.05M sodium phosphate)

AUC = 960 uM*hr, Oral bioavailability = 11%

Process: **In-situ supersaturated solution** (Rat Tox-PO, 10 mL/kg)
Add mesylate salt to pH-adjusted aqueous suspension vehicle to make supersaturated solution up to 20 mg/mL for ≤ 200 mg/kg, suspensions for > 200 mg/kg and use within 20 minutes of preparation.

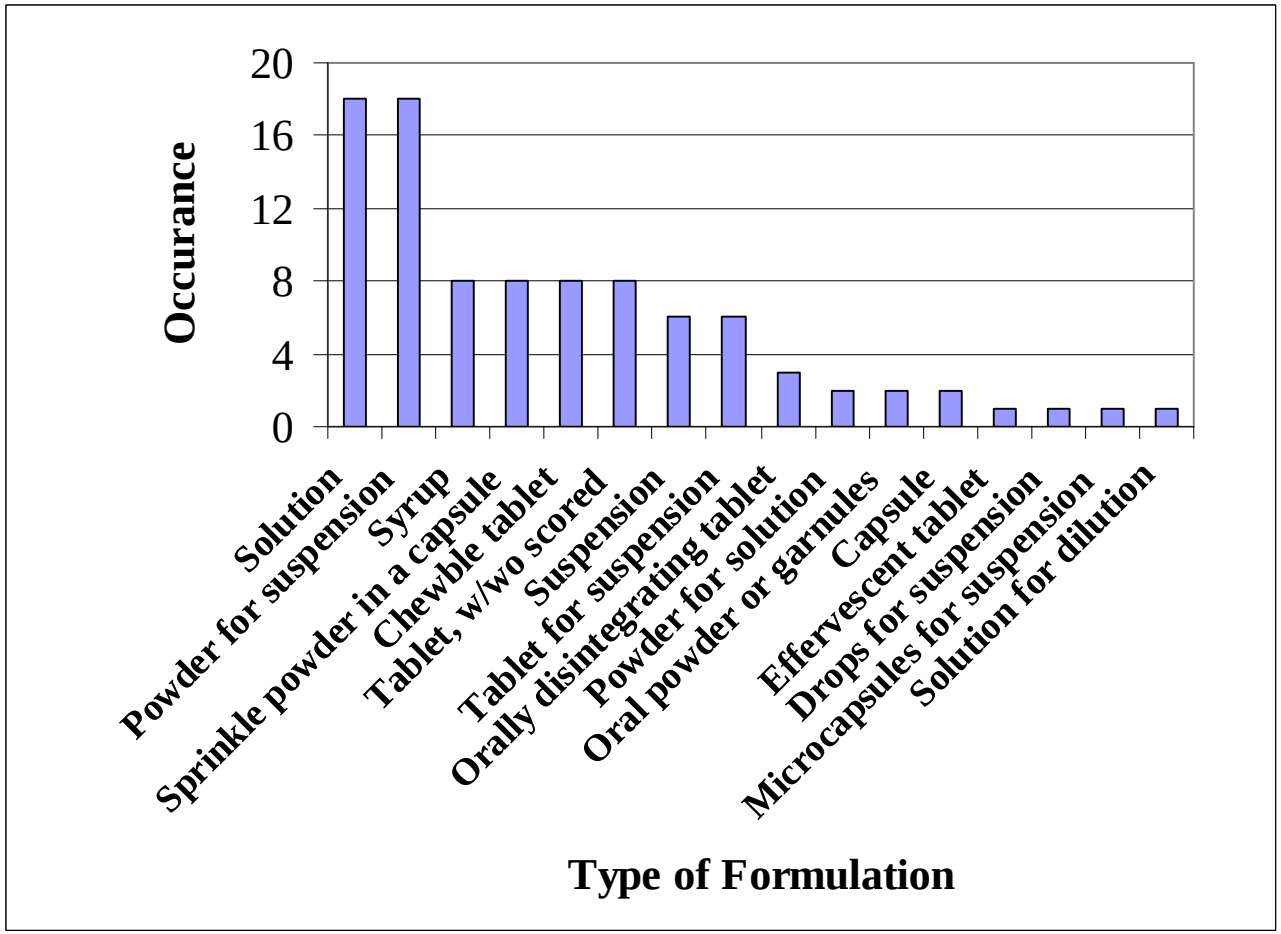
Case Study #3 (end)

Dog PK-PO, non-fasted, no pretreatment
Mesylate salt
Need AUC > 100 µM*hr

Dose (mg/kg/day)	Formulation	AUC (µM*hr)	Oral Bioavailability (%)
200	Aqueous suspension (Rat Form.)	20	3
100	Solution, 30% Captisol ®, pH 2	100	30
150	Powder-in-capsule qd	90	18
300		90	9
100	**Powder-in-capsule bid**	90	28
300		290	30
600		350	18

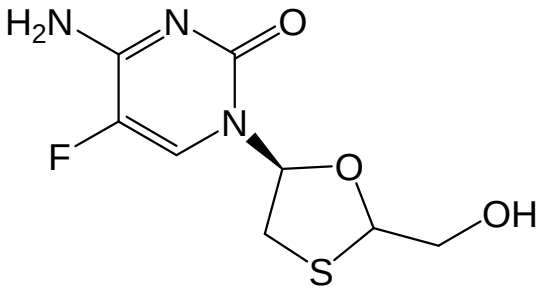
Pediatric Formulation

Pediatric Formulations



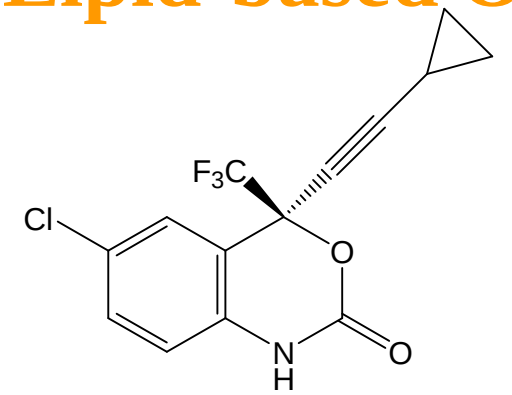
R.G. Strickley, et. al., Pediatric Drugs – A Review of Commercially Available Oral Formulations, J. Pharm. Sci., 97:5, 1731-1774 (2008)

Commercial Aqueous-based Oral Solution



Product	Strength, mg	Dose	Excipients	Storage
Emtricitabine/ Emtriva Oral Solution/ Gilead	10 mg/mL	Adults: 200-240 mg (up to 24 mL) Pediatrics: 3-6 mg/kg (1-24 mL) Once daily	**Water** EDTA **Methylparaben** **Propylparaben** Sodium phosphate PG Xylitol Cotton candy flavor Yellow dye	Refrigerated 2-8°C Room Temperature for up to 3 months

Commercial Lipid-based Oral Solution



Product	Strength, mg	Dose	Excipients	Storage
Efavirenz/ Sustiva Oral Solution/ Bristol Meyers Squibb	30 mg/mL	Adults: 600 mg (up to 20 mL) Pediatrics: 270-600 mg (9-20 mL) once daily	**Medium-chain triglyceride**	Room temperature

Pediatric Formulations – To Use or Not To Use of Preservatives

- Strong tendency to limit the amount of all excipients in pediatric formulations
- Special considerations for the use of preservatives
- Special considerations for neonates and infants
- There is no clear guidance on the use of preservatives in pediatric formulations
- *Current approach:*

  -Preservative free formulations whenever possible should be considered

  -When preservatives are required, justify the use, choice of preservative system, appropriateness
- **Any information would be most useful**
- **Good project for a student**

Conclusions

Enable PK, PD and Safety studies:

1. Molecular Design of the API
   - Soluble in water and/or simulated intestinal fluid (oral delivery)
   - pK_a for pH-dependent solubility and potential salt selection
   - Prodrug handle
2. Formulation

- Minimize solvent
  Wide variety of water-soluble solvents, surfactants, and lipids
- Websites and publications available on safety of excipients and examples of formulations

3. Team work

- Formulation personnel work with Medicinal Chemistry, Biology, Pharmacology, ADME/PK, Drug Safety (same as Dr. Sree Nadkarni in Jan. 2010)