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Lipid Based Oral Drug Delivery System (LBODDS)

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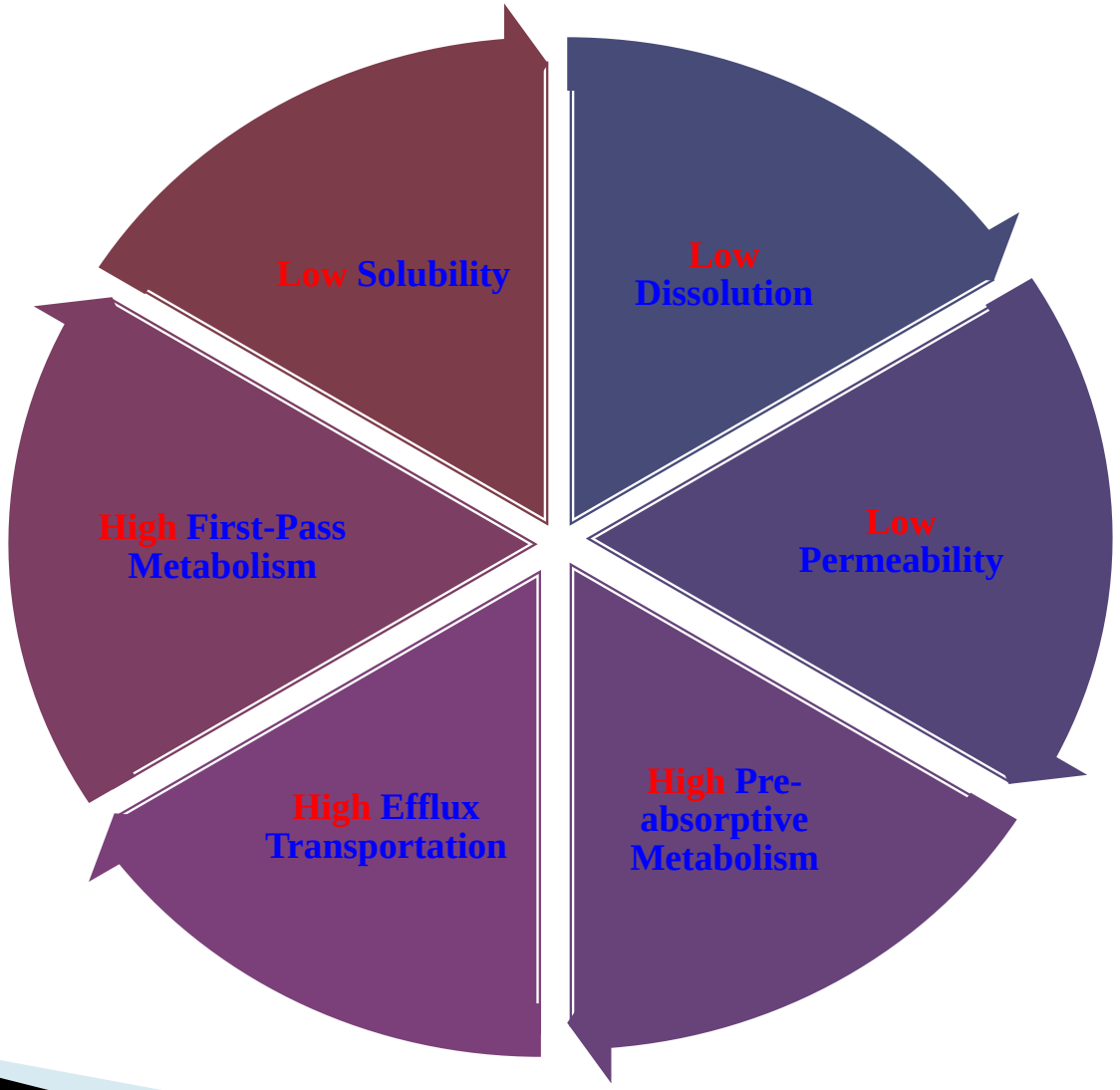
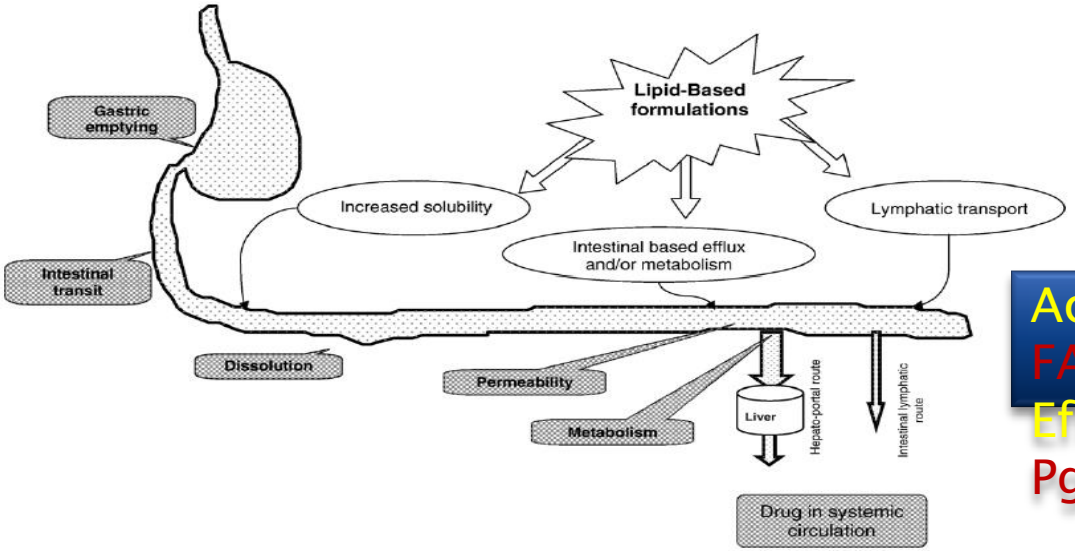
LBODDS???

- An emerging platform for oral delivery of drugs with poor aqueous solubility
- Utilization of lipid as a carrier for the delivery of poorly water soluble, lipophilic drugs
- BA enhancement & normalization
- Targeted lymphatic delivery

Why Low Bioavailability ???



LBODDS: Advantages



Active uptake transporters:
FATP4/SRB1
Efflux transporters:
Pgp/BCRP/MRP

High Fat Meal → Biliary or Pancreatic secretion → Prolonged GI Transit time → Lymphatic transport stimulation → Changes in mesenteric /liver blood flow → Increased Intestinal Wall Permeability & reduced metabolism & efflux activity → Enhanced BA

800-100 cal:
50-65 %fat
25-30 %carb
15-20 %protein

Lipid Delivery: Is this Really New???

- A BIG NO (X)
- Long been practiced
- Vegetable dressings with olive oil, cheese or mayonnaise
- Enhance absorption of water-insoluble vitamins/nutrients
- Eg.: Fat-soluble vitamins, carotenoids like beta-carotene, lutein, etc.

LBODDS: Commercial Products

Country	Product %	No. of Products
UK	2%	21
US	3%	27
Japan	4%	8

Sl no.	Generic name	Brand name/company	Dosage form	Use	Lipid components
1.	Amprenavir				succinate
2.	Bexarotene				
3.	Calcitriol				oconut oil, Fractionated
4.	Carvedilol phosphate				able oil
5.	Ciprofloxacin				
6.	Clofazimine				d, ethyl vanillin, gelatin, ophenone, parabens,
7.	Cyclosporin				es, polyoxyl 40
8.	Cyclosporin				M-2125CS)
9.	Dronabinol	Marinol/Roxane and Unimed	SG capsule	Anorexia or nausea	Sesame oil
10.	Dutasteride	Avodart/GSK	SG capsule	For benign prostate hyperplasia	Mixture of mono- and diglycerides of caprylic/capric acid
11.	Enalapril maleate-Felodipine	Lexxel/Astra Zeneca	ER tablets	Anti-hypertensive	Polyoxyl 40 hydrogenated castor oil
12.	Fenofibrate	Lipofen/Kowa Pharmaceuticals America, Inc.	Hard gelatin capsule	Lipid regulating agent	Gelucire 44/14 (lauroyl macrogol glyceride type 1500)
13.	Isotretinoin	Accutane/Roche	SG capsule	Anti-comedogenic	Bees wax, hydrogenated soyabean oil flakes, hydrogenated vegetable oils, soyabean oil
14.	Lopinavir and Ritonavir	Kaletra/Abbott	Tablet, SG capsule	HIV antiviral	Sorbitan monolaurate (span 20) Oleic acid, polyoxyl 35 castor oil (Cremophor EL)
15.	Mesalamine	Pentasa/Shire US Inc	Controlled-release capsules	GI anti-inflammatory agent	Acetylated monoglyceride, castor oil
16.	Omega-3-acid ethyl esters	Lovaza/ GlaxoSmithKline	hard gelatin capsule	Anti-hypertriglyceridemia	α-tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil)
17.	Paricalcitol	Zemplar/Abbott Laboratories	SG capsule	For secondary hyperparathyroidism	Fractionated medium-chain triglycerides of coconut oil or palm kernel oil
18.	Progesterone	Prometrium/Cardinal Health Encapsulation Tech.	Capsules	For endometrial hyperplasia	Peanut oil
19.	Saquinavir	Fortovase/Roche	SG capsule	HIV antiviral	Medium-chain mono- and diglycerides, dl-α-tocopherol
20.	Sirolimus	Rapamune/Wyeth-Ayerst	Oral solution	Immuno-suppressant	Phosal 50 PG (phosphatidylcholine, mono- and diglycerides, soy fatty acids, ascorbyl palmitate), polysorbate 80
21.	Tipranavir	Aptivus/Boehringer/ Ingelheim	SG capsule	HIV antiviral	polyoxyl 35 castor oil (Cremophor EL), Medium-chain mono- and diglycerides
22.	Tolterodine tartrate	Detrol LA/Pharmacia	ER hard gelatin capsule	Overactive bladder muscarinic receptor antagonist	Medium-chain triglycerides, Oleic acid
23.	Tretinoin	Vesanoid/Roche	SG capsule	Anti-neoplastic	Bees wax, hydrogenated soybean oil flakes, hydrogenated vegetable oils, soybean oil
24.	Valproic acid	Depakene/Abbott	SG capsule	Anti-epileptic	Corn oil

Lipids: Advantages

- Physicochemical diversity
- Biocompatibility
- Ability to enhance oral BA through lymphatic delivery

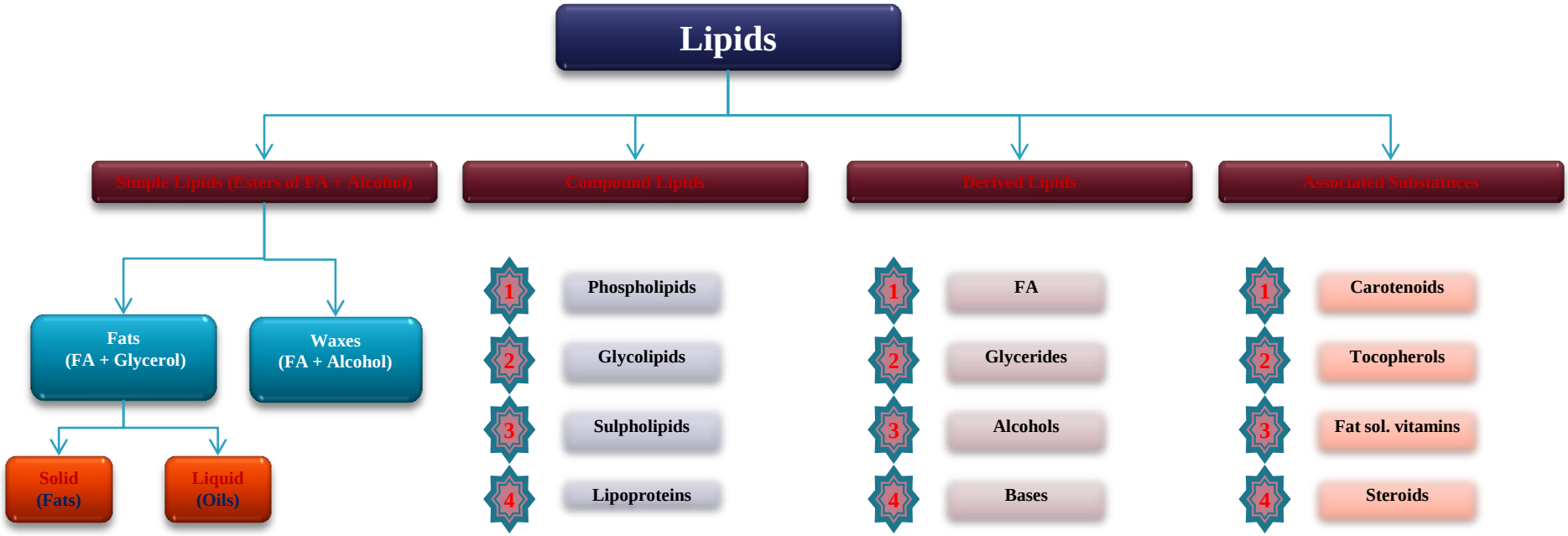
Lipid Delivery: Challenges!

- Complex physicochemical properties
- Challenges in stability & manufacturing
- Limited solubility of some poorly water-soluble drugs in lipids
- Pre-absorptive gastrointestinal processing
- Lack of knowledge about the in vivo behavior and influence of co-administered drugs/lipids
- Lack of predictive in vitro and in vivo testing methodologies

Well…I'm a Formulator… What should I Know about LBODDS???

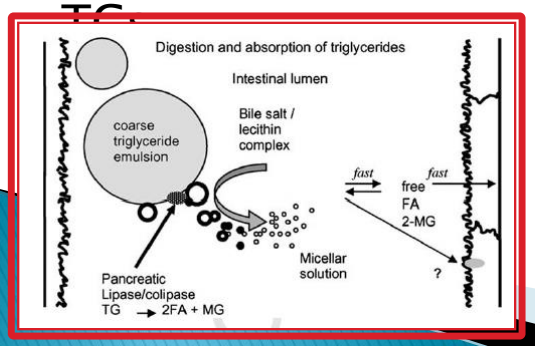
- In-depth knowledge of the GI digestive process of lipid
- Ability to interpret biopharmaceutical properties of lipid formulations
- Designing knowledge of relevant in vitro tests to mimic the physiological environment for the lipid formulation
  - Biorelevant dissolution media
  - In vivo colloidal behavior of the LBODDS

Lipids: Classification

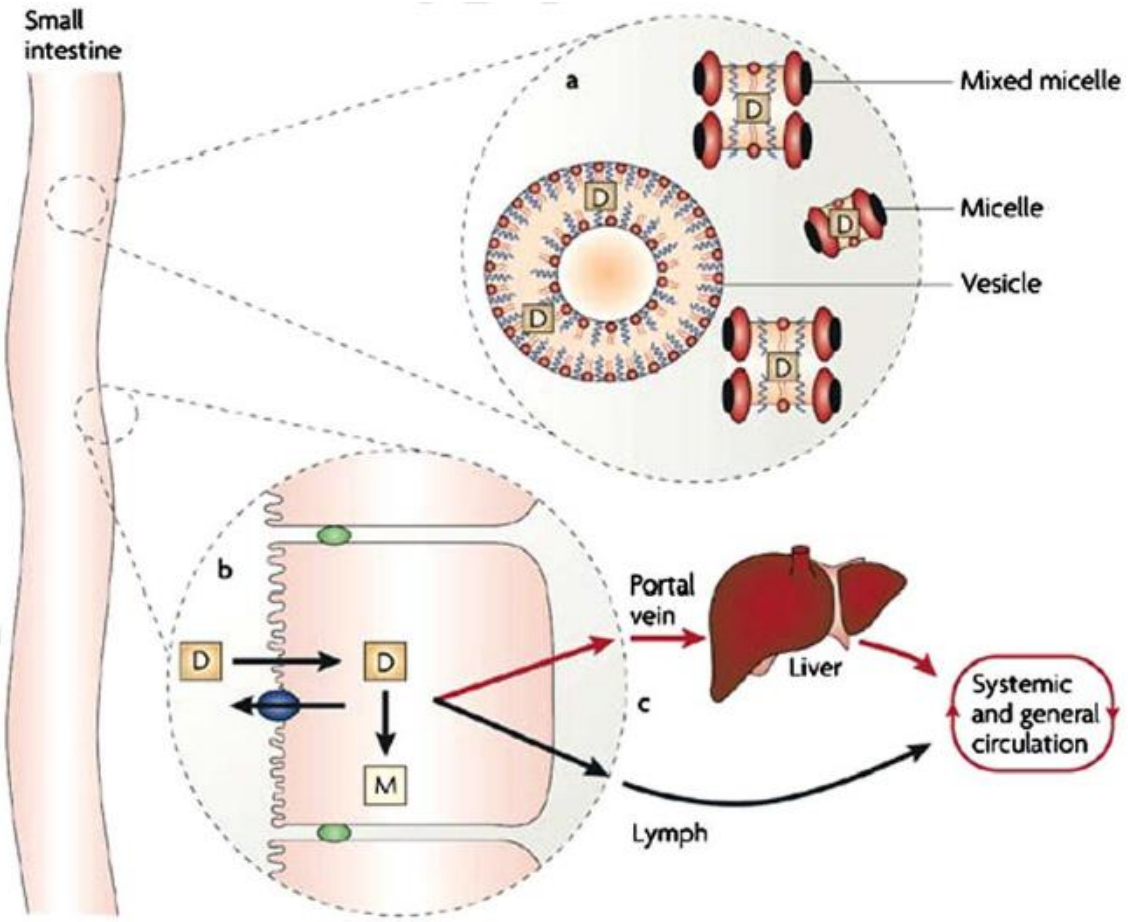


Lipids: In-vivo Fate

Digestive Phase	Absorption Phase	Circulatory Phase
Autocatalytic Process	Carrier Process	Size-selective Process
1. Physical breakdown of lipids into coarse emulsion 2. Hydrolysis of TGs into FAs and MGs 3. Mixed-micelle formation with bile salts and/or vesicle formation of FAs + TG	1. Entry into enterocyte by passive diffusion, facilitated diffusion and active transport 2. Formation of TG & PL from absorbed FA & MG 3. Formation of chylomicron and storage in golgi apparatus 4. Exocytosis into extracellular phase	1. Lipophilic drugs with logP > 5 with TG solubility > 50 mg/ml enters lymphatic delivery 2. Chylomicrons are big in size and access lymphatic transport 3. FFA < 12 carbon absorbed by portal and more than that by lymph



Lipids: In-vivo Fate

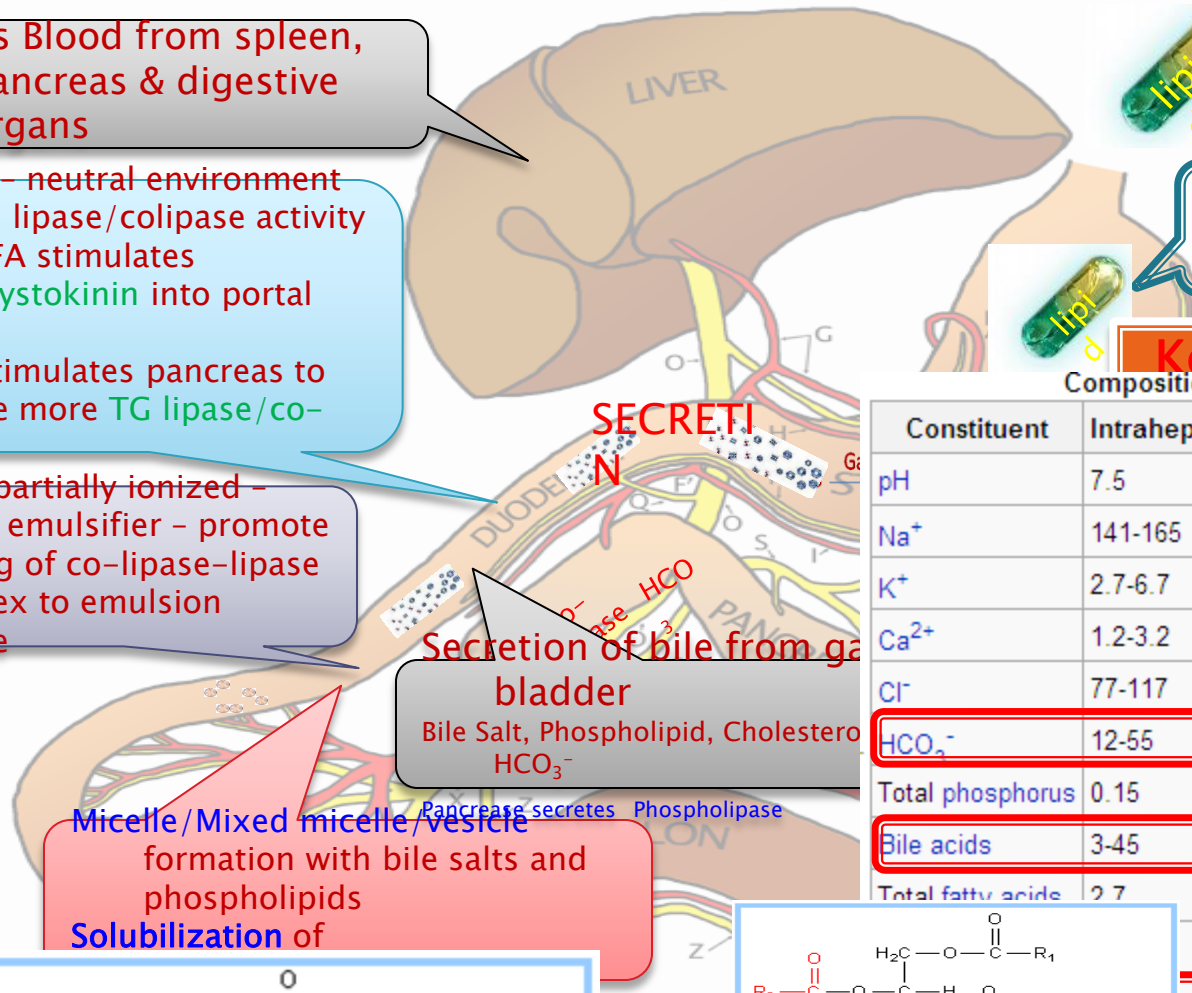


Lipid's Fate: Digestive Phase

Drains Blood from spleen, pancreas & digestive organs

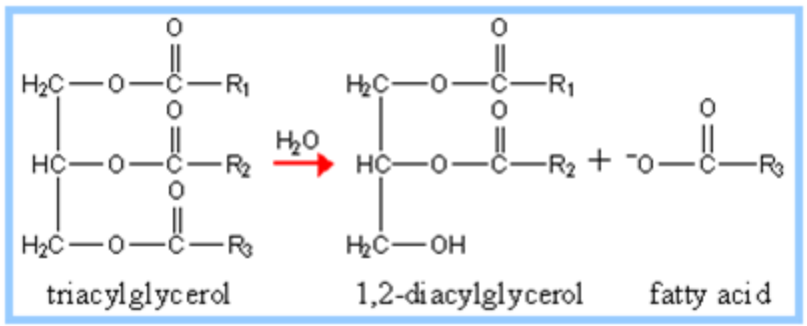
1. HCO3 – neutral environment – max. lipase/colipase activity
2. More FA stimulates cholecystokinin into portal circ.
3. This stimulates pancreas to release more TG lipase/co-lipase

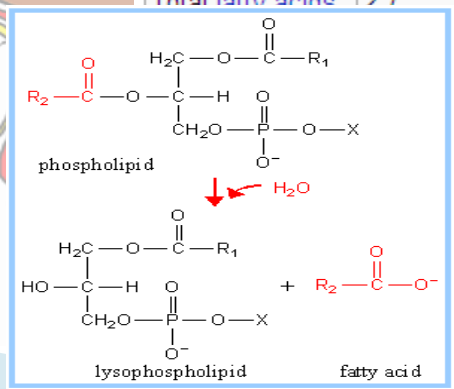
FA & MG – partially ionized – potent emulsifier – promote binding of co-lipase-lipase complex to emulsion surface



Micelle/Mixed micelle/vesicle formation with bile salts and phospholipids

Solubilization of





1. Antral contraction shear
2. Retropropulsion
3. Gastric emptying

Key Points to Ponder

Composition of bile

Constituent	Intrahepatic	In gallbladder	Unit
pH	7.5	6.0	
Na^+	141-165	220	mM
K^+	2.7-6.7	14	mM
Ca^{2+}	1.2-3.2	15	mM
Cl^-	77-117	31	mM
HCO_3^-	12-55	19	mM
Total phosphorus	0.15	1.4	g/L
Bile acids	3-45	32	g/L
Total fatty acids	2.7	24	g/L
		3	g/L
		34	g/L
		6.3	g/L
		4.5	g/L

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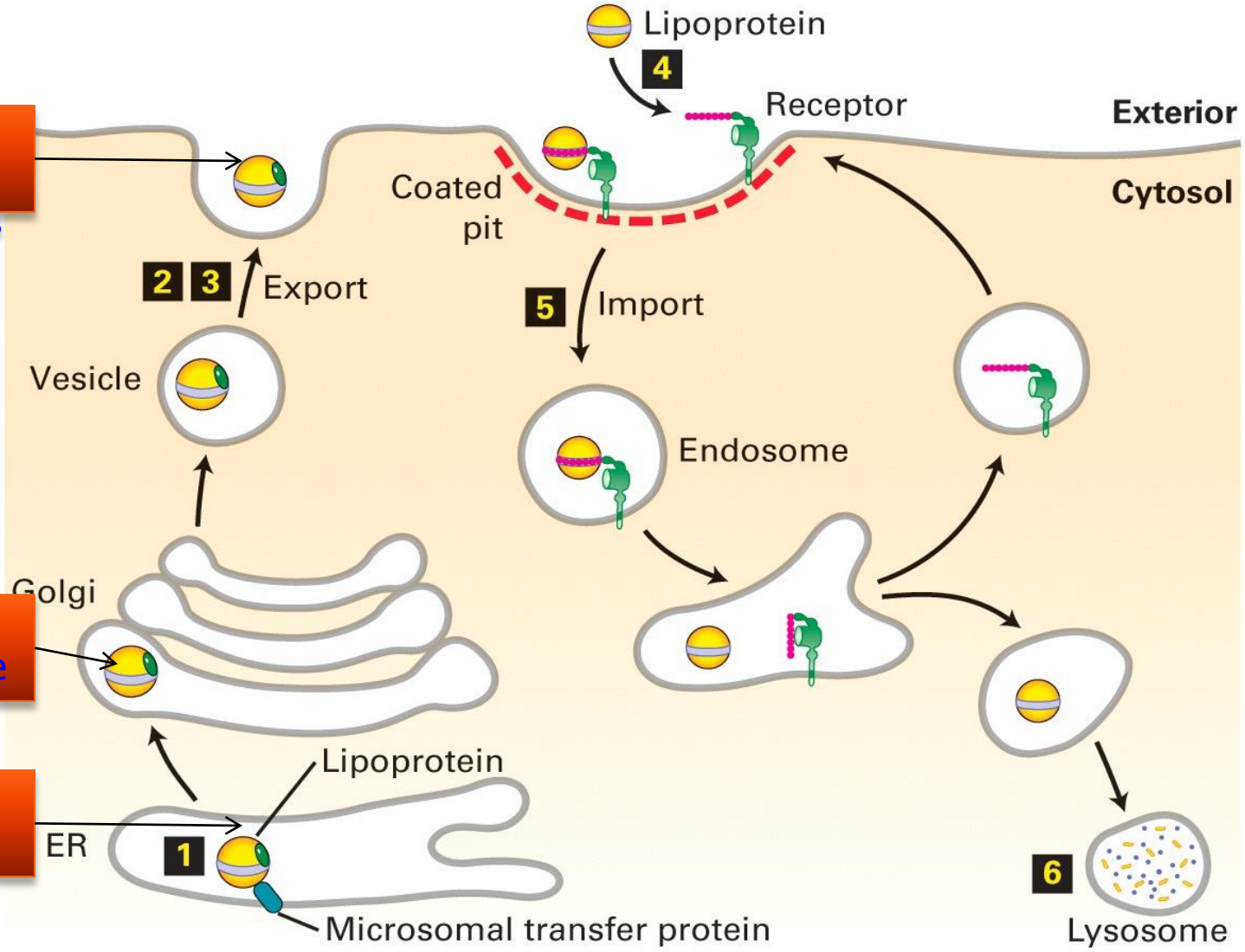
Lipid's Fate: Absorptive Phase

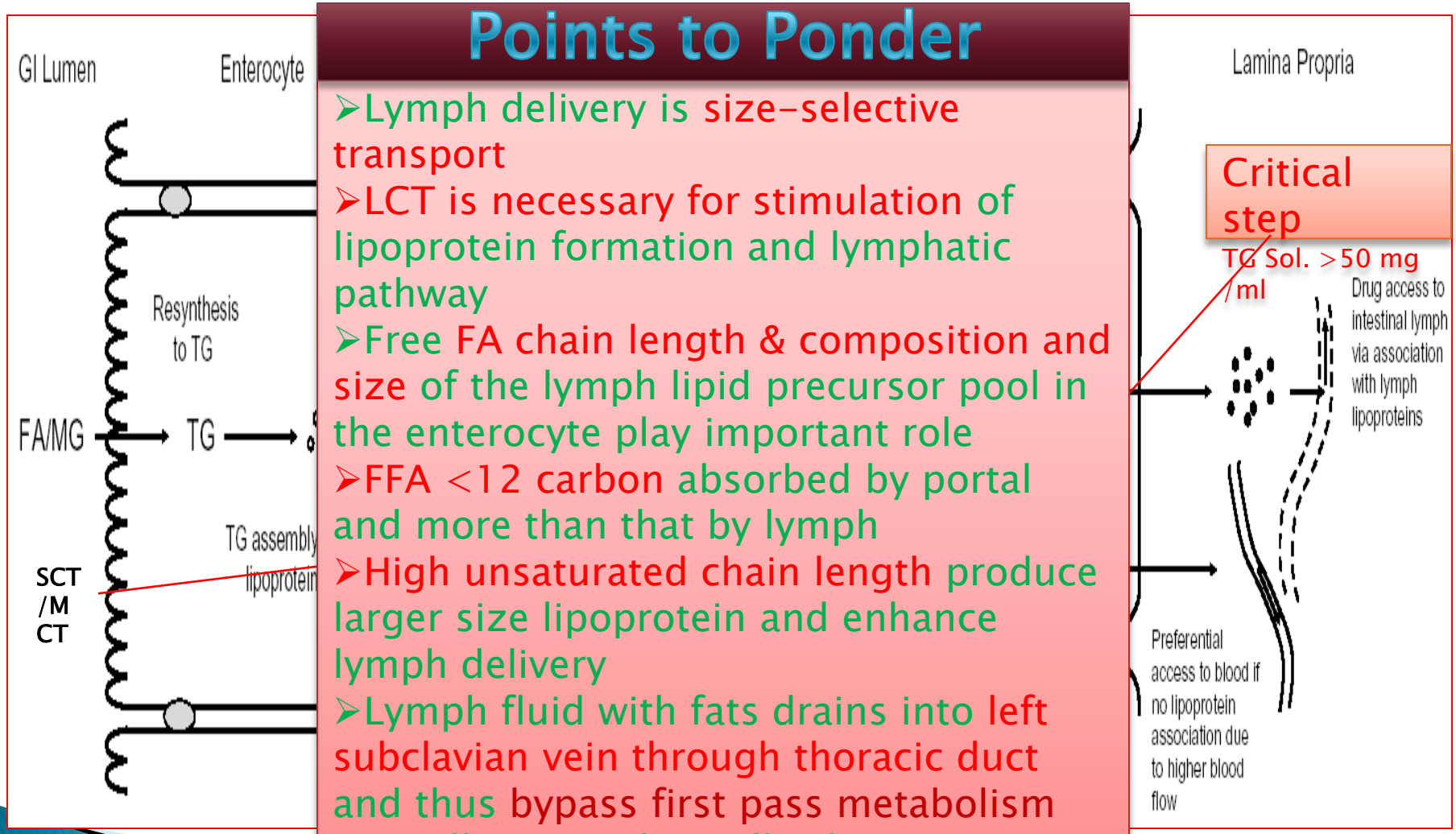
Chylomicron Exocytosis

Chylomicron Storage

Chylomicron Formation



Lipid's Fate: Circulatory Phase



Points to Ponder

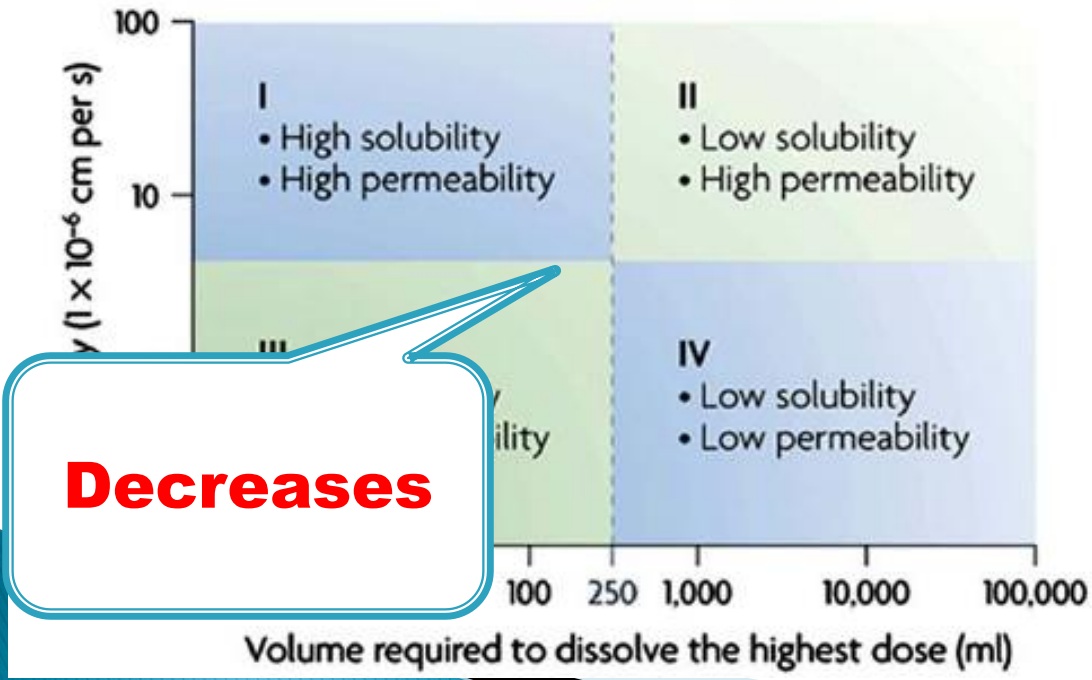
- Lymph delivery is size-selective transport
- LCT is necessary for stimulation of lipoprotein formation and lymphatic pathway
- Free FA chain length & composition and size of the lymph lipid precursor pool in the enterocyte play important role
- FFA <12 carbon absorbed by portal and more than that by lymph
- High unsaturated chain length produce larger size lipoprotein and enhance lymph delivery
- Lymph fluid with fats drains into left subclavian vein through thoracic duct and thus bypass first pass metabolism
- Micelles/mixed micelles become monomers in the blood due to large volume dilution, but chylomicrons stay

Effect of Food on BA

No Effect

Solubility definition in the USP

Description forms (solubility definition)	Parts of solvent required for one part of solute	Solubility range (mg/ml)	Solubility assigned (mg/ml)
Very soluble (VS)	<1	>1000	1000
Freely soluble (FS)	From 1 to 10	100–1000	100
Soluble	From 10 to 30	33–100	33
Sparingly soluble (SPS)	From 30 to 100	10–33	10
Slightly soluble (SS)	From 100 to 1000	1–10	1
Very slightly soluble (VSS)	From 1000 to 10,000	0.1–1	0.1
Practically insoluble (PI)	>10.000	<0.1	0.01



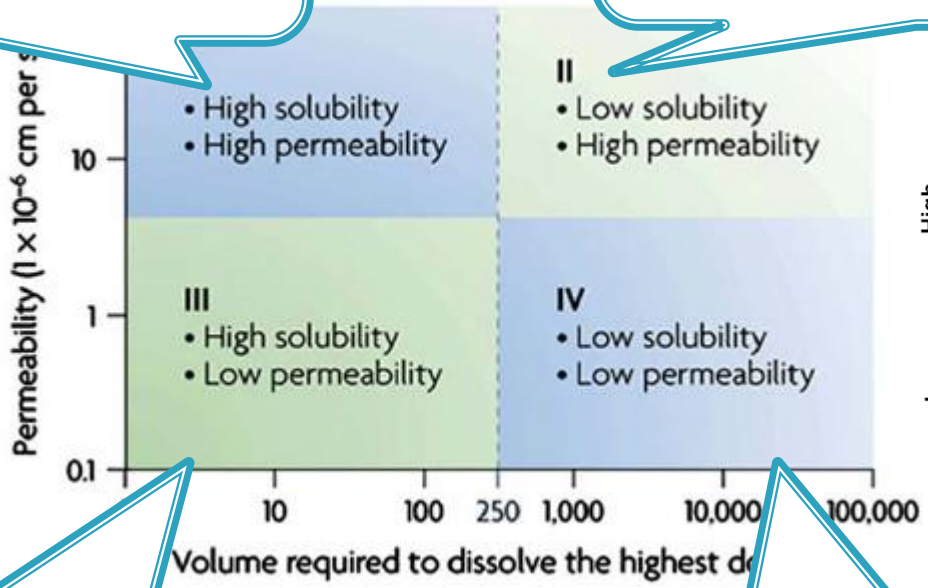
Decreases

Decreases?

What's the Rationality???

No Effect: (No action)
1. Passive diffusion thro' membrane
2. Saturate cellular transporter (efflux/absorptive)
3. Minimal transporter drug interaction

Increased: (Dual action)
1. Passive diffusion thro' membrane
2. Enhanced solubility
3. Saturation of efflux transporter by enhanced solubility

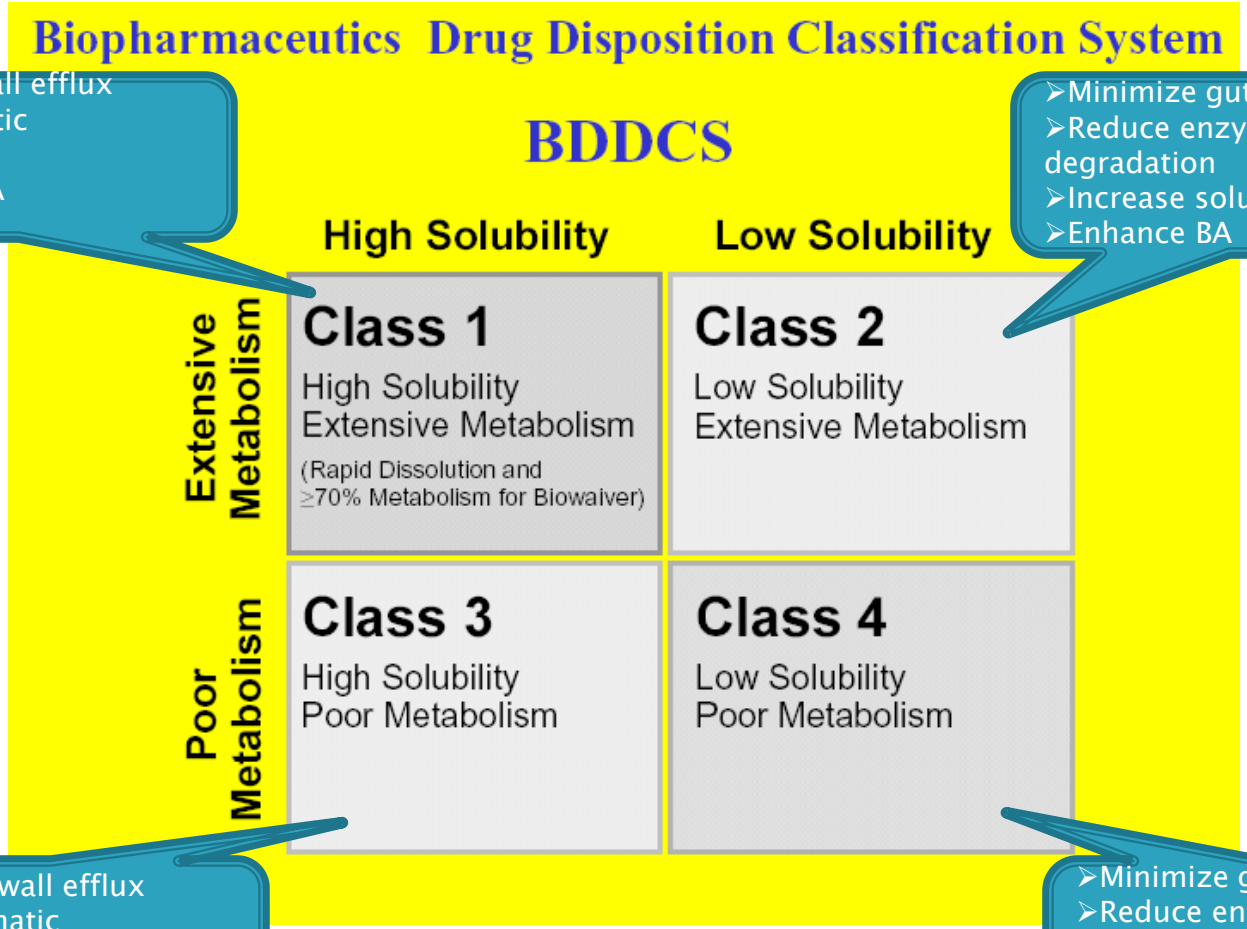


	High Solubility	Low Solubility
High Permeability	**Class 1** Transporter effects minimal	**Class 2** Efflux transporter effects predominate
Low Permeability	**Class 3** Absorptive transporter effects predominate (but can be modulated by efflux transporters)	**Class 4** Absorptive and efflux transporter effects could be important

Decreased: (inhibition)
1. Inhibition of uptake transporters (these drugs need this transporter for permeability due to poor permeability)

Decreased?: (inhibition)
1. Inhibition of uptake transporters (these drugs need this transporter for permeability due to poor permeability)

Effect of LBODDS on BA



- Minimize gut wall efflux
- Reduce enzymatic degradation
- No change in BA

- Minimize gut wall efflux
- Reduce enzymatic degradation
- Increase solubilization
- Enhance BA

- Minimize gut wall efflux
- Reduce enzymatic degradation
- Enhance BA

- Minimize gut wall efflux
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