Combined *in vitro* dispersion / digestion technique

Dr HDR Vincent Jannin, Research Director - Pharmaceuticals, July 2016

POORLY WATER-SOLUBLE DRUGS

Bioavailability enhancement

Brick dust or Grease ball

GATTEFOSSÉ

LIPID FORMULATION CLASSIFICATION SYSTEM

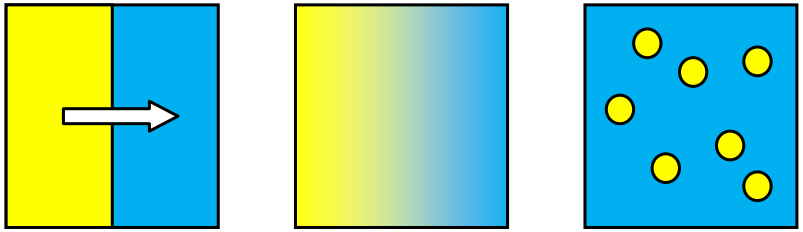
Formulation	Composition		Characteristics
Type I	Oils	100%	Non-dispersing, poor solvent capacity unless drug is highly lipophilic, requires digestion.
Type II	Oils Low-HLB surfactants	40-80% 20-60%	SEDDS without water-soluble components, turbid O/W dispersion, unlikely to lose solvent capacity on dispersion.
Type III	Oils High-HLB surfactants Hydro. cosolvents	<20-80% 20-50% 0-50%	SEDDS / SMEDDS with water-soluble components, clear or bluish dispersion, possible loss of solvent capacity on dispersion, less easily digested.
Type IV	Low-HLB surfactants High-HLB surfactants Hydro. cosolvents	0-20% 30-80% 0-50%	Micellar solutions, good solvent capacity for many drugs, loss of solvent capacity on dispersion, may not be digested.

GATTEFOSSÉ

Pouton, C.W. **2006**. Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. Eur. J. Pharm. Sci. 29, 278-287.

MECHANISMS OF SELF-EMULSIFICATION

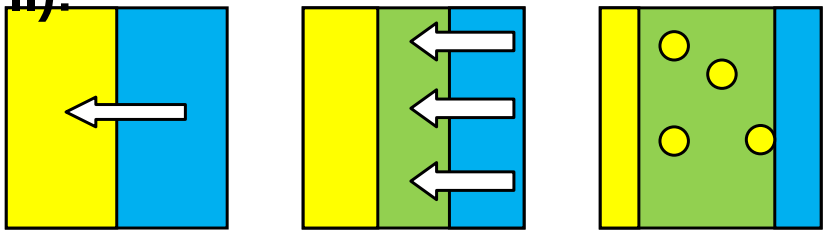
Oil / water-soluble surfactant mixture (Type III):



Aqueous phase
Lipidic phase
Hydrosoluble components ○

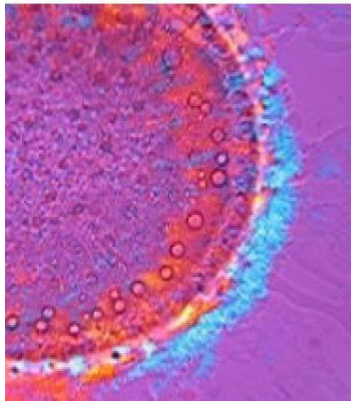
Mechanism of self-emulsification by diffusion and stranding

Oil / surfactant mixture with limited solubility in water (Type II):



Aqueous phase
Lipidic phase
Liquid crystalline phase

Mechanism of self-emulsification by formation of a lamellar liquid crystalline phase



Labrafil droplet (PLM)

EXAMPLES OF LIPID-BASED EXCIPIENTS

Excipient type		Example
Oils	Medium chain triglycerides / mono, diglycerides	Captex 300 (Abitec) / Capmul MCM (Abitec)
	Long chain triglycerides / mono, diglycerides	Corn oil, Soybean oil / Maisine 35-1 (Gattefossé)
Low HLB surfactant (HLB < 12)	Polyoxyethylene sorbitan trioleate	Tween 85 (Croda)
	Linoleyl polyoxyl-6 glycerides	Labrafil M2125CS (Gattefossé)
High HLB surfactant (HLB > 12)	Polyoxyl-35 castor oil	Kolliphor EL (BASF)
	Polyoxyl-40 hydrogenated castor oil	Kolliphor RH40 (BASF)
	Caprylocaproyl polyoxyl-8 glycerides	Labrasol ALF (Gattefossé)
Hydrophilic cosolvent	Diethylene glycol monoethyl ether	Transcutol HP (Gattefossé)

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Highly cited lipid-based excipients in Google Scholar

EXAMPLES OF MARKET REFERENCES

Form. type	Composition (excl. Antioxidants)	Drug products	Dosage form
Type I	Medium chain glycerides (MCT)	Lubiprostone (Amitiza, Sucampo) Calcitriol (Rocaltrol, Roche)	SGC SGC
Type I	Hydro. soybean oil, Hydro. vegetable oil, Soybean oil... (all LCT)	Isotretinoine (Accutane, Roche)	SGC
Type II	Oleyl polyoxyl-6 glycerides	Vitamin D3 (Uvedose, Crinex)	Ampoule
Type II	Alcohol, Linoleyl polyoxyl-6 glycerides, Corn oil	Cyclosporine A (Sandimmune, Sandoz)	SGC
Type III	Alcohol, Propylene glycol, Corn oil, Polyoxyl-40 hydrogenated castor oil	Cyclosporine A (Neoral, Sandoz)	SGC
Type III	Caprylocaproyl polyoxyl-8 glycerides	Enzalutamide (Xtandi, Astellas)	SGC
Type III	Lauroyl polyoxyl-32 glycerides, PEGs, HPC, Na starch glycolate	Fenofibrate (Lipofen, Kowa Pharm.)	HGC
Type III	Oleic acid, Polyoxyl-35 castor oil, Propylene glycol (PG)	Lopinavir + Ritonavir (Kaletra, Abbott)	SGC
Type IV	d-α-Tocopheryl polyethylene glycol 1000 succinate, PG, PEG 400	Amprenavir (Agenerase, GSK)	SGC

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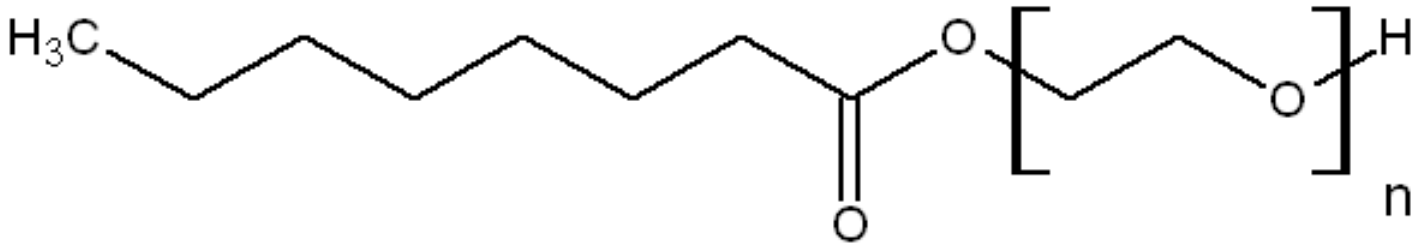
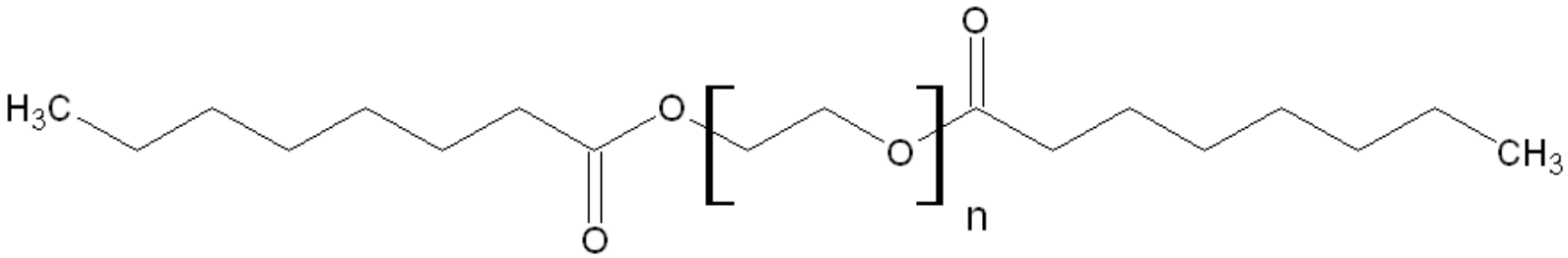
SGC = Soft Gelatin Capsules, HGC = Hard Gelatin Capsules / Data from www.rxlist.com

PEG ESTERS



PEG-n monoester



PEG-n diester

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PEG ESTERS

	Gelucire® 48/16 pellets
Synthesis	Stearic & palmitic acids + PEG-32 (MW=1500)
Compendial names	Polyoxyl stearate (Type I) USP-NF Polyethylene glycol monostearate (JPE) Macrogol stearate (Type I) EP (pending)
LFCS type	Type IV
Functionality	Solid surfactant Practical HLB = 12

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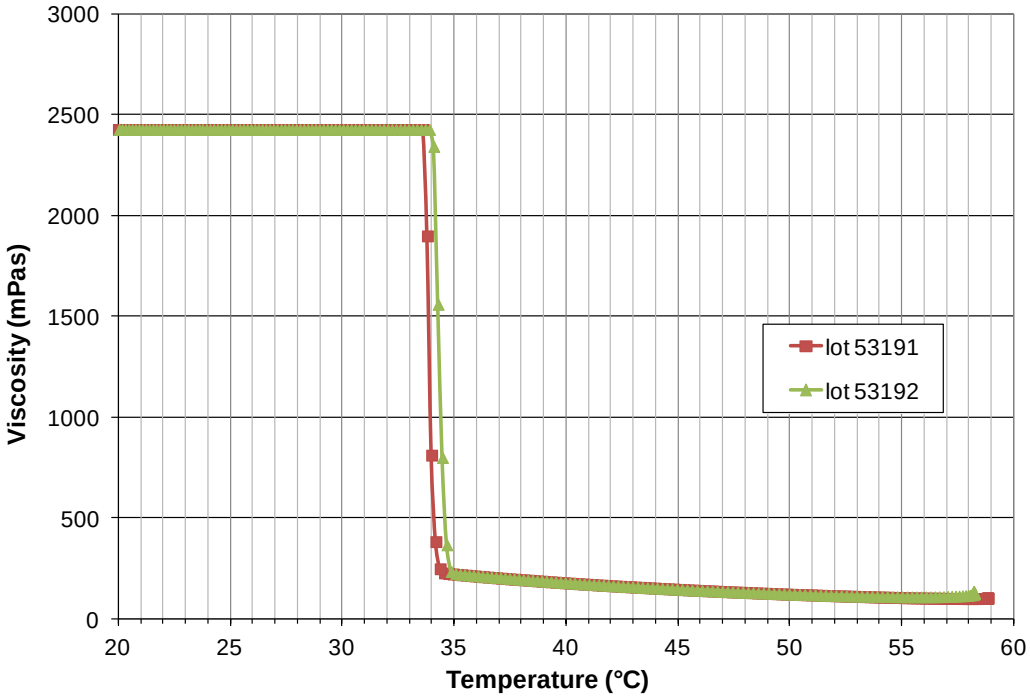
GELUCIRE 48/16 PROPERTIES

Drop point (° C)	48.4 ± 0.1
Melting point (° C) – onset temperature by DSC	45.4 ± 0.2
pH – 10% in purified water	5 ± 1
CMC (mg/L)	153 ± 31
Particle size (nm) – 1g/200mL of water at 37° C, DLS	7 ± 1



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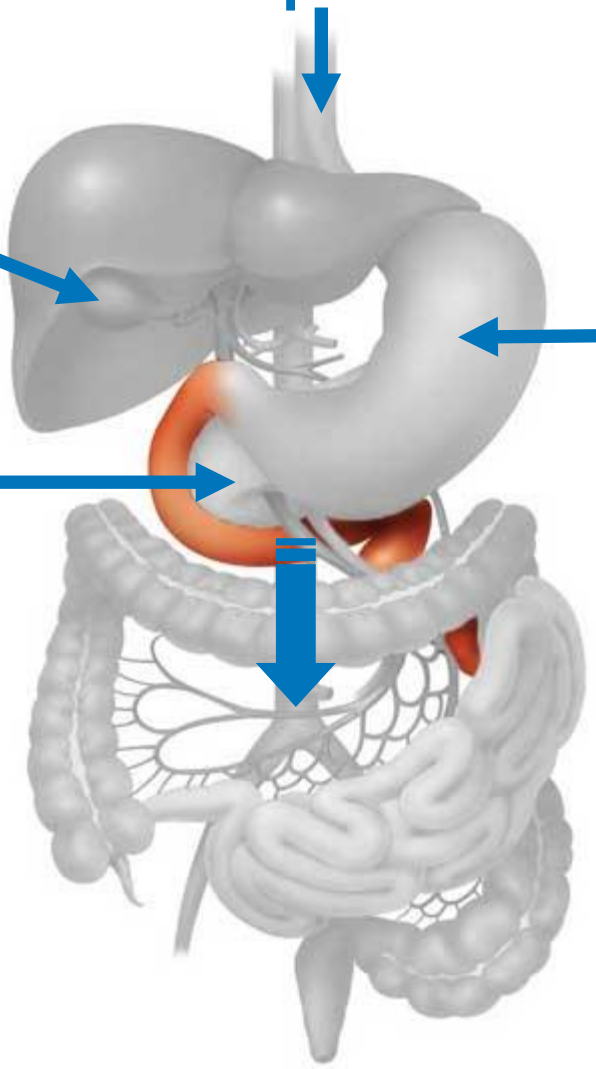
IN VITRO DIGESTION

SELF formulation protocol

Lipid digestion

GASTROINTESTINAL TRACT



Bakala N'Goma, J.C., Amara, S., Dridi, K, Jannin, V., Carrière, F. **2012**. Understanding lipid digestion in the GI tract for effective drug delivery. Therapeutic Delivery, 3(1) 105-124.

LFCS CONSORTIUM

- The Lipid Formulation Classification System Consortium is a non-profit organization that sponsors and conducts research on lipid systems for the oral administration of poorly soluble drugs.
- The primary objective is to develop guidelines that rationalize and accelerate the development of promising drug candidates:
  - identification of key performance criteria
  - validation and publication of universal SOP
  - dialogue with pharmaceutical regulatory bodies

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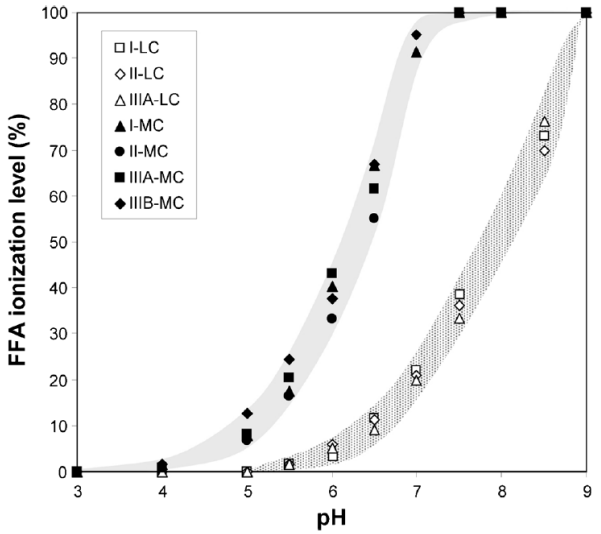
IN VITRO DIGESTION: LFCS CONSORTIUM

- Lipolysis medium, pH 6.5 (fasted):

Tris-maleate	2 mM
$CaCl_2$, $2H_2O$	1.4 mM
NaCl	150 mM
NaTDC	3 mM
PC	0.75 mM
Milli-Q water	qs



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Sassene, P.J., Kleberg, K., Williams, H.D., Bakala-N'Goma, J.C., Carrière, F., Calderone, M., Jannin, V., et al. **2014** Toward the Establishment of Standardized In Vitro Tests for Lipid-Based Formulations, Part 6: Effects of Varying Pancreatin and Calcium Levels. AAPS J. 16. 1344-1357

Bakala-N'Goma, J.C., Williams, H.D., Sassene, P., Kleberg, K., Calderone, M., Jannin, V., Igonin, A., et al. **2015** Toward the Establishment of Standardized in Vitro Tests for Lipid-Based Formulations. 5. Lipolysis of representative formulations by gastric lipase. Pharm. Res. 32. 1279-1287

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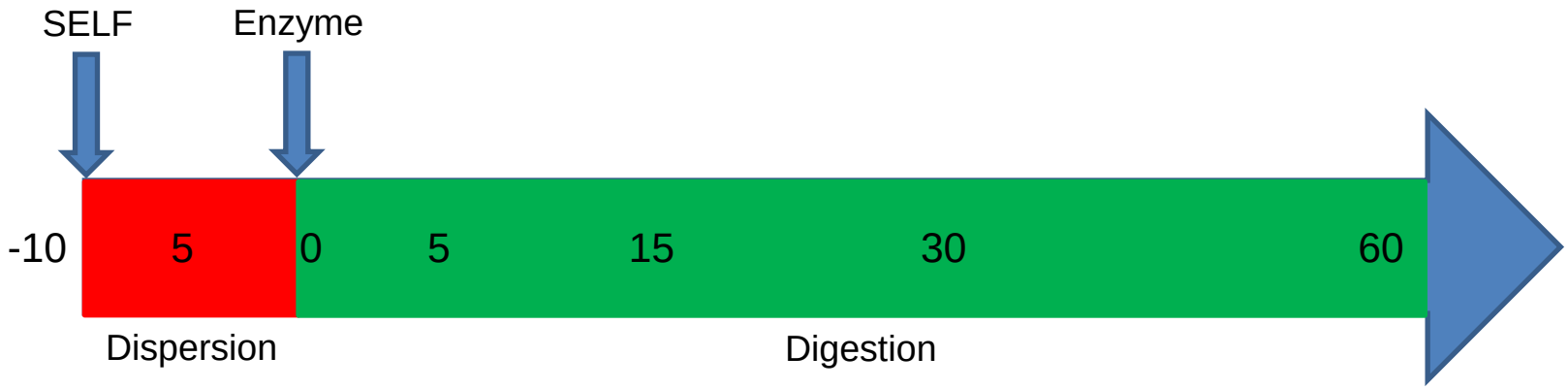
IN VITRO DIGESTION: LFCS CONSORTIUM

- Protocol:
  - 1 g lipid formulation in 36 mL lipolysis medium
  - Stirring at 450 rpm
  - Addition of 4 mL of pancreatin solution
  - pH regulation with NaOH 0.2 or 0.6M



Williams, H., Anby, M.U., Sassene, P., Kleberg, K., Bakala N'Goma, J.C., Calderone, M., Jannin, V., et al. **2012**. Toward the establishment of standardized in vitro tests for lipid-based formulations, Part 2: The effect of bile salt concentration and drug saturation level (dose) on the performance of Type I, II, IIIA, IIIB and IV formulations during in vitro digestion. Mol. Pharm. 9. 3286-3300

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IN VITRO DIGESTION: LFCS CONSORTIUM

- Enzyme: pancreatin (contains PPL & CEH)
  - 1 g of pancreatin powder in 5 mL of lipolysis buffer
  - Magnetic stirring for 10 minutes
  - Centrifugation: 10 minutes, 2 800 g, 5°C
  - Aliquot the supernatant for lipolysis testing
- Sample preparation:
  - Sample 1 mL in the pH-stat vessel
  - Immediately add an enzyme inhibitor: 5 µL of (100 mg 4-bromobenzeneboronic acid (BBBA) in 0.5 mL of methanol)
  - Centrifugation: 30 minutes, 21 000g, 37°C
  - Aliquot the supernatant and dilute with an appropriate solvent prior to analysis

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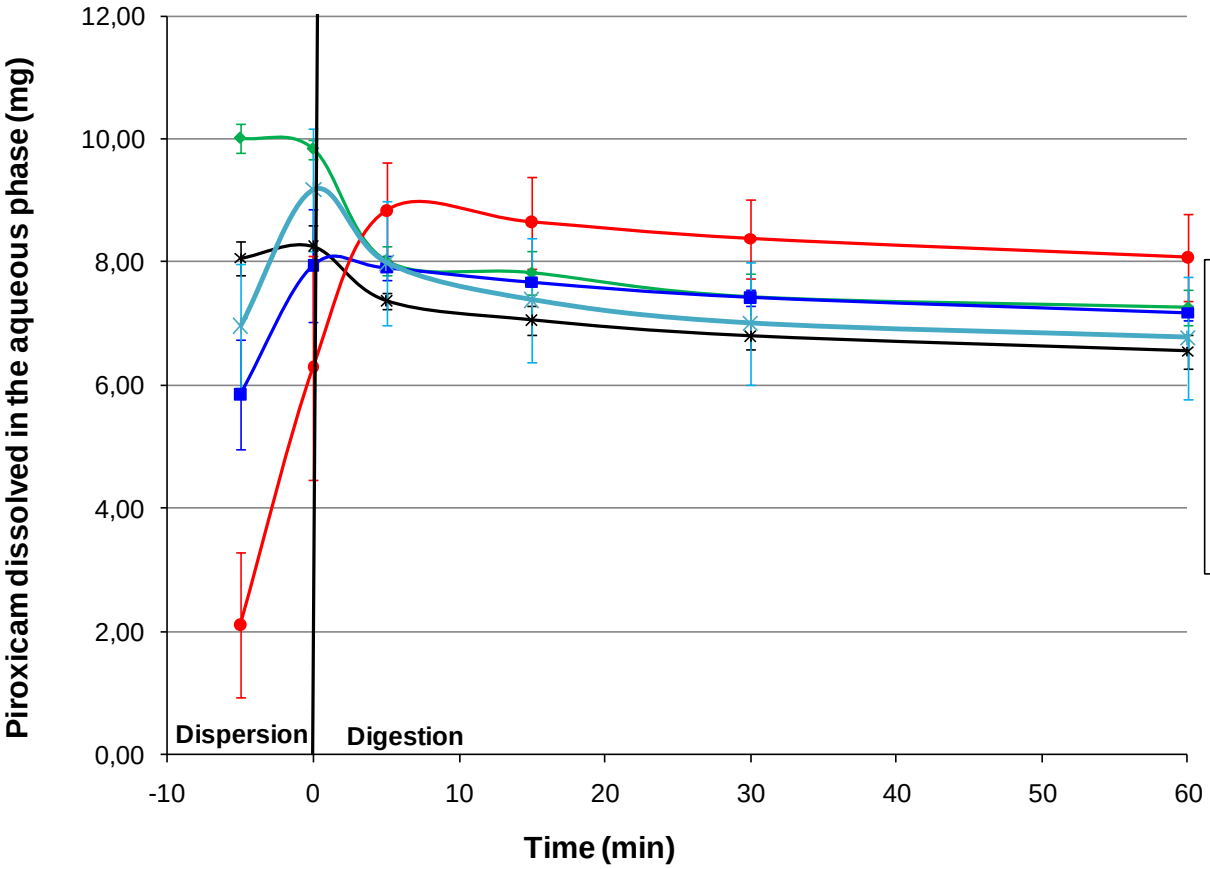
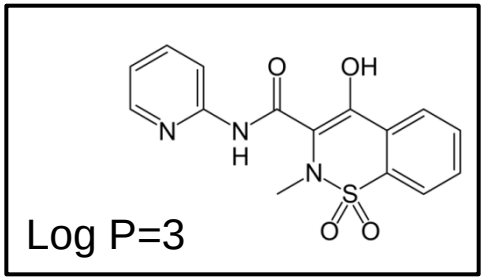
IN VITRO DIGESTION: PIROXICAM



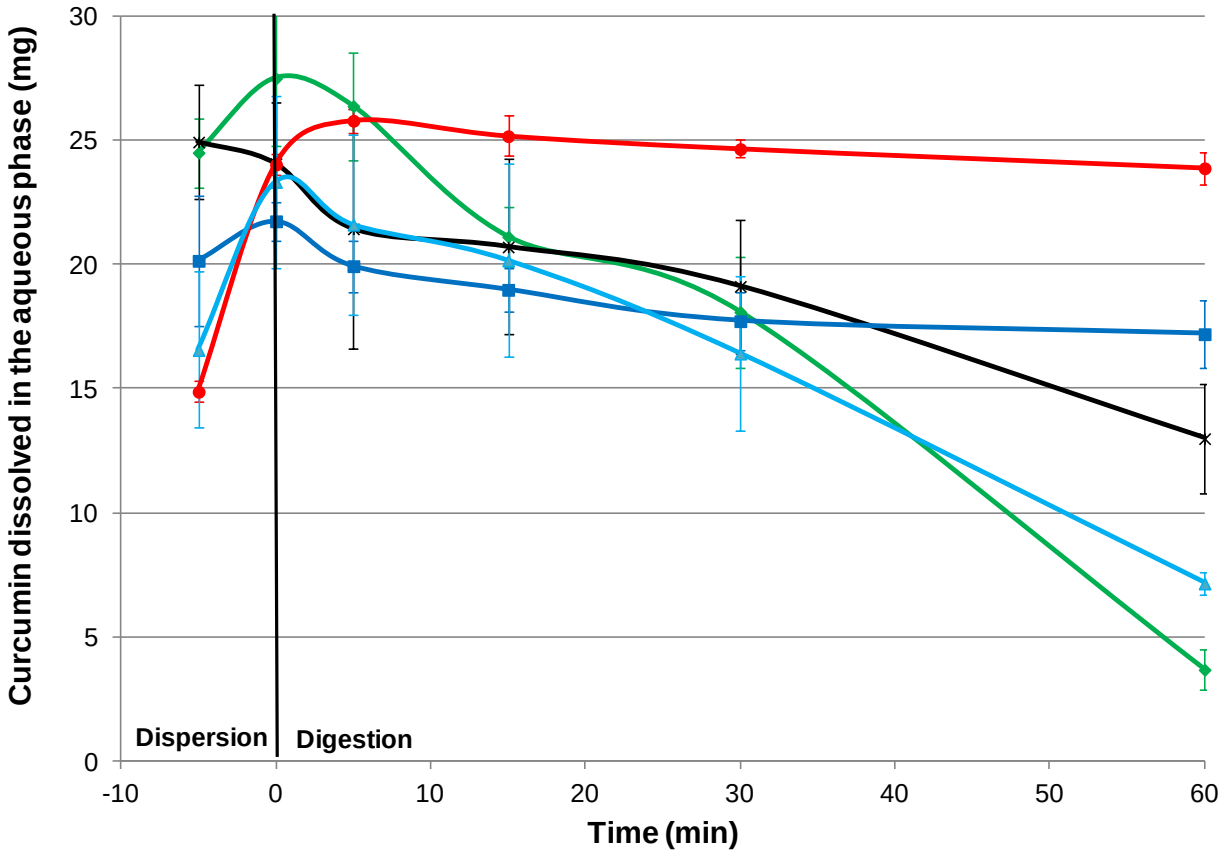


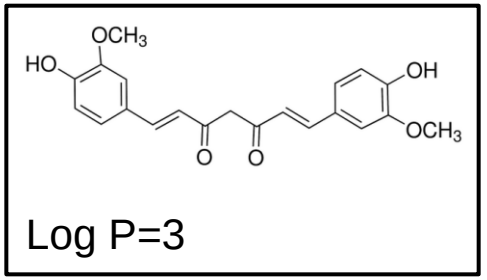
	%sat / AUC
Labrasol ALF	67% / 676
Tween 80	54% / 611
Cremophor RH40	35% / 665
Gelucire 48/16	59% / 742
Gelucire 44/14	90% / 637

Same dose for all formulations = 10 mg/mL

Jannin, V., Chevrier, S., Michenaud, M., Dumont, C., Belotti, S., Chavant, Y., Demarne, F. **2015** Development of Self Emulsifying Lipid Formulations of BCS class II drugs with low to medium lipophilicity.
Int. J. Pharmaceut. 495, 385-392

IN VITRO DIGESTION: CURCUMIN





	%sat / AUC
Labrasol ALF	43% / 1103
Tween 80	34% / 1495
Kolliphor RH40	72% / 1614
Gelucire 48/16	49% / 2198
Gelucire 44/14	67% / 1163

Same dose for all formulations = 30 mg/mL

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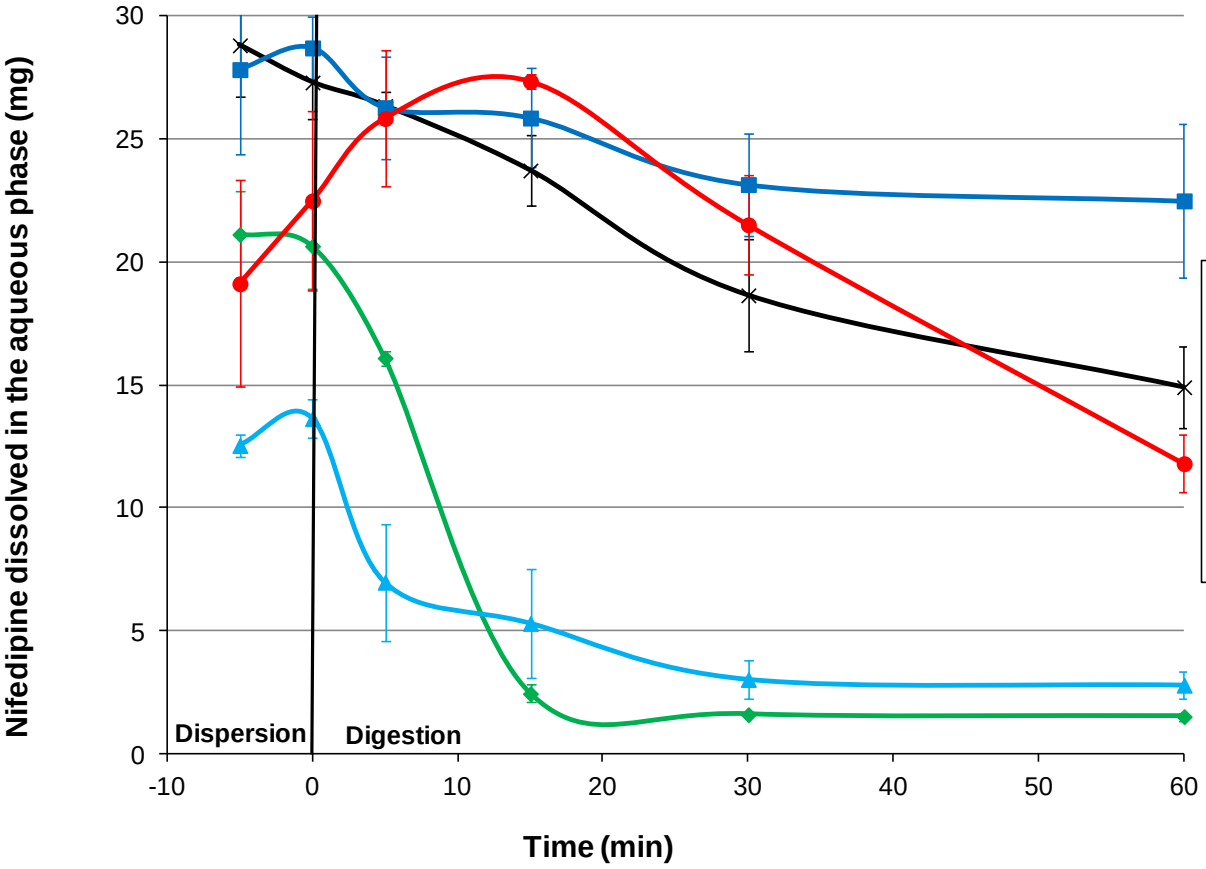
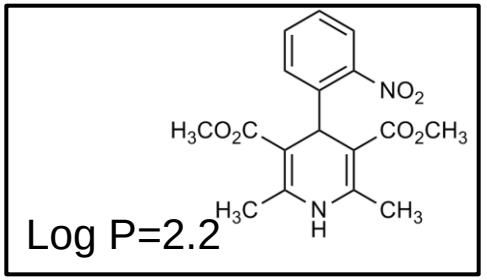
IN VITRO DIGESTION: NIFEDIPINE





	%sat / AUC
Labrasol ALF	42% / 307
Tween 80	79% / 1652
Kolliphor RH40	77% / 2124
Gelucire 48/16	51% / 1606
Gelucire 44/14	73% / 347

Same dose for all formulations = 30 mg/mL

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ADVANTAGES OF LIPID-BASED SYSTEMS

- Enhancement of bioavailability by:
  - Dissolution of active substances in the dosage form
  - Maintaining the drug in solution (supersaturation is possible) in the gastro-intestinal tract
  - Stimulation of biliary secretion
  - Facilitation of the drug permeability through the intestinal epithelium (local supersaturation induced by lipid metabolites absorption)
  - Stimulation of chylomicrons secretion, enhanced passage through the lymphatic pathway
  - Mitigation of food effect

GRATEFUL ACKNOWLEDGEMENTS TO

- Gattefossé R&D
  - Stéphanie Chevrier, BSc
  - Yann Chavant, MSc
  - Cécric Miolane
  - Christophe Voutsinas, BSc
  - Nicolas Ritter, MSc
  - Jean-David Rodier, Ing
  - Bruno Mahler, Ing
  - Sylvie Fernandez, PhD
  - Frédéric Demarne, PhD
- Gattefossé R&D interns
  - Héloïse Cavey, PharmD
  - Caroline Bruley, PharmD
  - Claire Devaux, PharmD
  - Silvia Belotti, PhD
  - Eleonora Dellera, PhD
  - Camille Dumont, Ing
  - Matthieu Michenaud, PharmD
  - Hamza Benhaddou, PharmD
- EIPL, CNRS Marseille
  - Frédéric Carrière, PhD