« Development and characterisation of self-emulsifying pharmaceutical formulations of hydrophobic active ingredients of natural origin. »

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CONTEXTE[1,2]

Oral route is primarily used for drug administration. However, oral administration is becoming increasingly limited due to the lipophilicity of drugs. Indeed, nearly 40% of new drug candidates are considered to have poor water solubility, leading to low bioavailability. Lipid-based formulations are a formulation strategy that can enhance the oral bioavailability of poorly water-soluble drugs.

OBJECTIVE

The goal of this thesis is to develop and characterise two self-microemulsifying drug delivery systems (SMEDDS) each containing a lipophilic drug of natural origin.

DEFINITIONS [2,3,4,5]

1 Self-microemulsifying drug delivery system (SMEDDS)

- Lipid-based formulations
- When administered orally, SMEDDS comes into contact with the water in gastrointestinal fluids.

→ Formation of thermodynamically stable microemulsions

Composition

- **Active ingredient** → Lipophilic (log p≥ 2); Soluble in the mixture of oil, Surfactant, Co-Sufactant; Narrow therapeutic index
- **Oil** → - Medium Chain triglycerides (TG) (C6-C12) → Systemic action; - Long chain TG (>C12) → Mesenteric lymphatic system
- **Surfactant** → Reduces interfacial tension; Ideally HLB >12 → Emulsion O/W; Non-ionic surfactant → Less toxic
- **Co-Surfactant** → Soluble in oil; Reduces interfacial tension; Often medium-chain alcohols: C3-C8

INTERESTS [2,6]

1 Enhancing bioavailability of the drug

→ Increasing solubility of the lipophilic drug

→ Increasing intestinal permeability

→ Allowing lymphatic transport

2 Mimic food effect

→ Release of bile & lipase

→ Lipids digestion

3 Easy storage

→ Thermodynamically stable

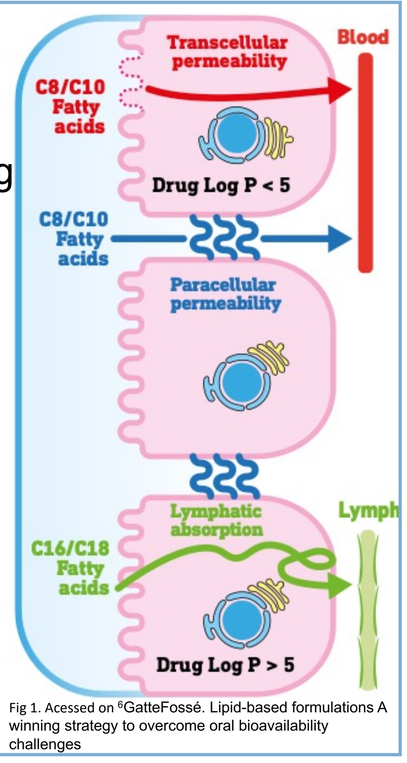
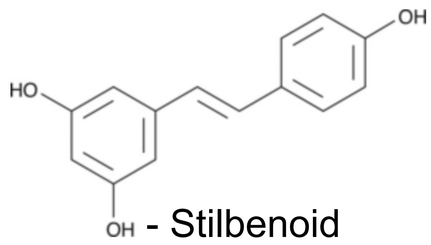


Fig 1. Acessed on [6]GatteFossé. Lipid-based formulations A winning strategy to overcome oral bioavailability challenges

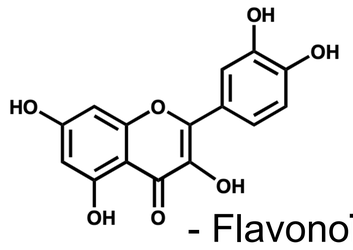
TARGETED MOLECULES[7,8,9,10]

1 Trans- Resveratrol



- Stilbenoid
- Log p = 3,1

2 Quercetin



- Flavonoïd
- Log p = 1,8

STEPS[6,11,12,13]

1 Analytical experiment : HPLC

→ Development → Validation

→ Forced degradation (light, H_2O_2, temperature, pH)

2 Active Ingredients Characterisation

→ Differential Scanning Colorimetry (DSC) : Thermal stability

→ X-Ray Diffraction (XRD) : Observe amorphous / crystallin form

3 Cellular culture

→ MTT test (CACO-2): Cytotoxicity of API's evaluation

4 SMEDDS formulations developpement

→ Solubility test of APIs in excipients

→ Miscibility test of APIs in excipients

→ Dispersibility test of the mixture (APIs + excipients)

➔ Pseudo-ternary diagram

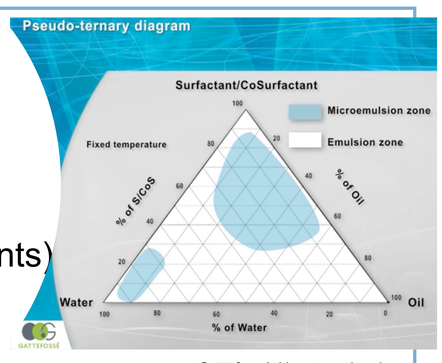


Fig 2. Accessed on [13]*Gattefossé.* How to make phase diagrams.

5 Test of SMEDDS formulations

→ Lipids digestion

→ Dissolution test - Dissolution Bath USP II :Quantifying drug dissolution

→ Permeability test : - PAMPA
- CACO-2

→ SMEDDS characterisation : - Dynamic Light Scattering (DLS)
- Hot Stage Microscopy (HSM)
- Scanning Electron Microscopy (SEM)
- Differential Scanning Calorimetry (DSC)

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