PRO AGRO LECTORIUM

Enhancing antimalarial drug bioavailability via eutectic synergy with natural excipients

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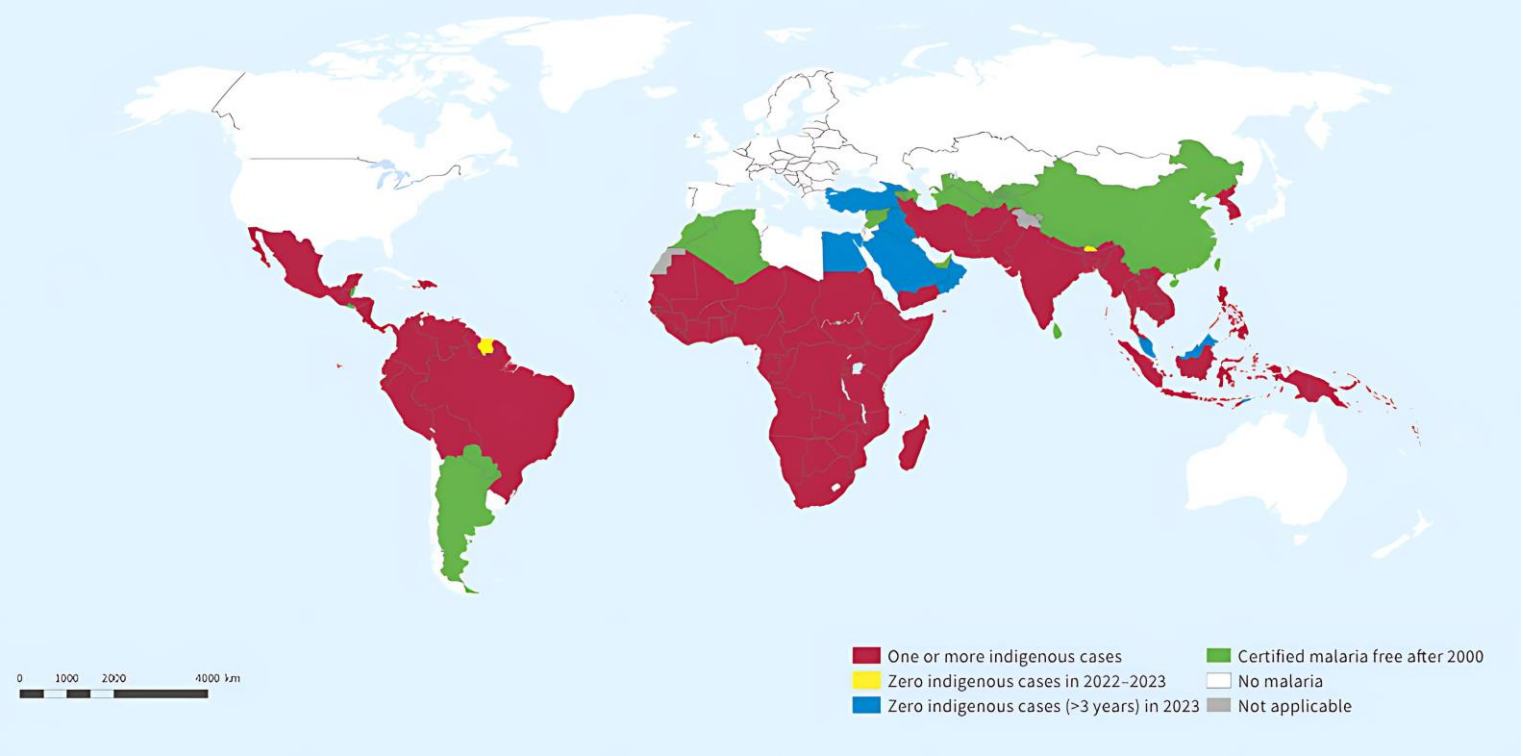
Malaria

- **Malaria** is a life-threatening **infectious disease**, potentially affecting nearly half of the world's population and causing **hundreds of thousands of deaths** each year



263 million cases

597 000 deaths

83 countries

*World malaria report **2024**

Malaria

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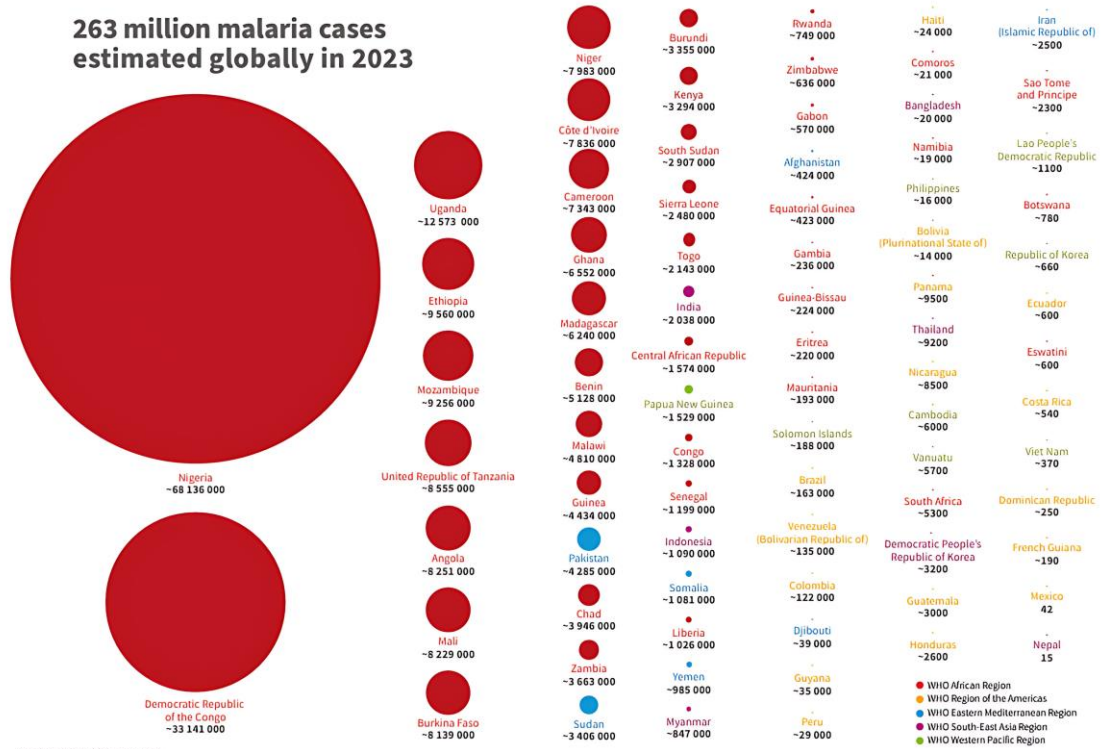
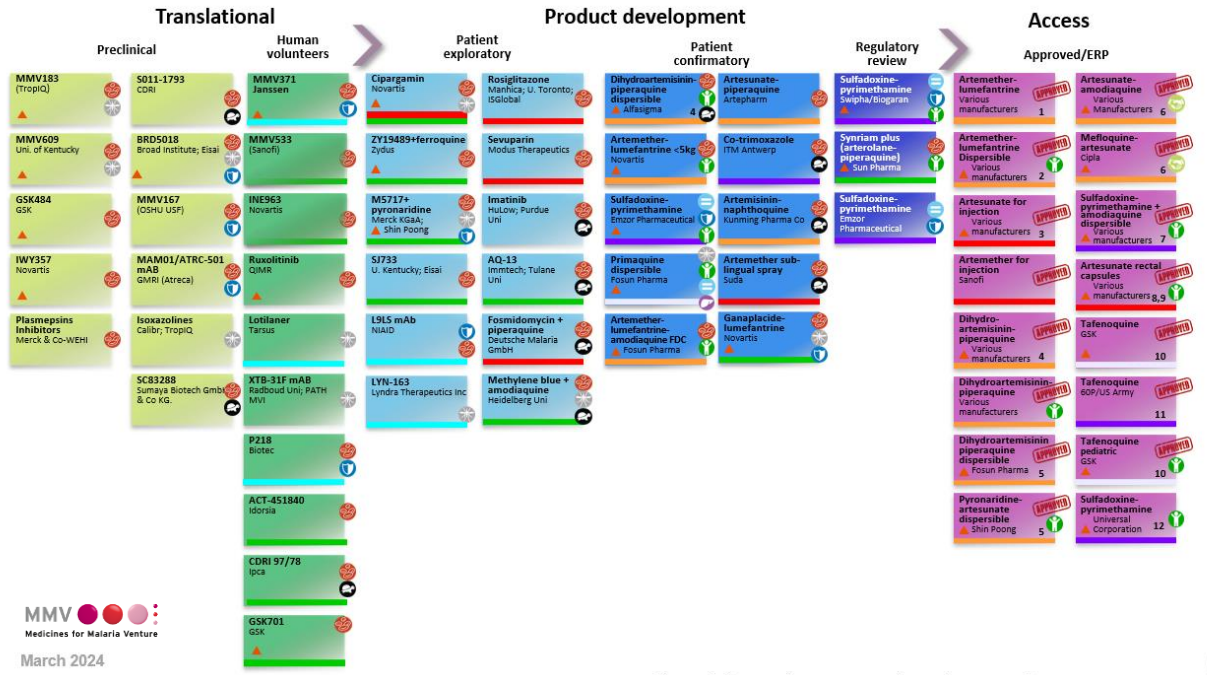


Most of the global malaria burden is concentrated in **sub-Saharan Africa**, where malaria transmission is moderate to high

*World malaria report 2024

Antimalarial Medicines

- Treatments include common antimalarial drugs, as **artemisinin-based combination therapies** (ACTs)



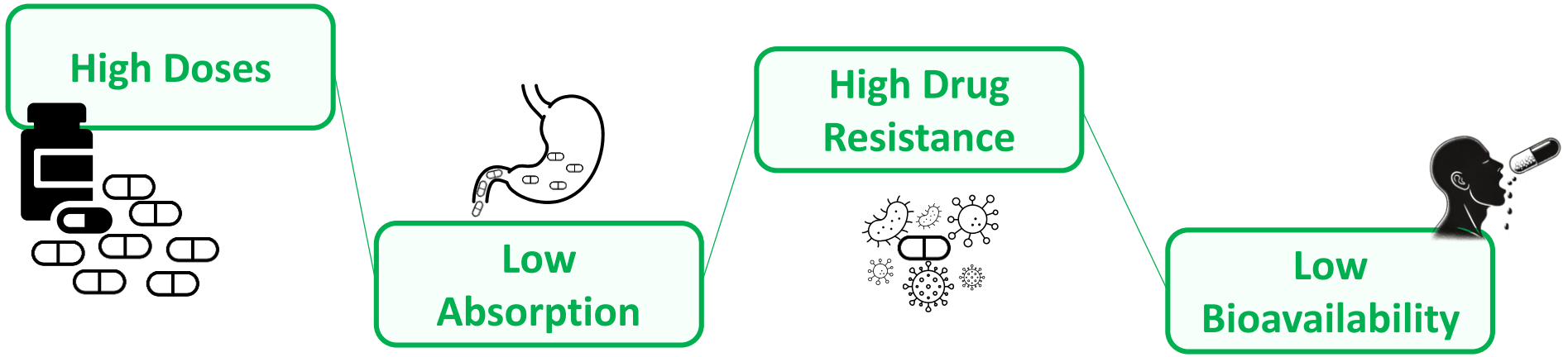
Fast-acting artemisinin derivative

+

Second long-acting drug

Antimalarial Medicines

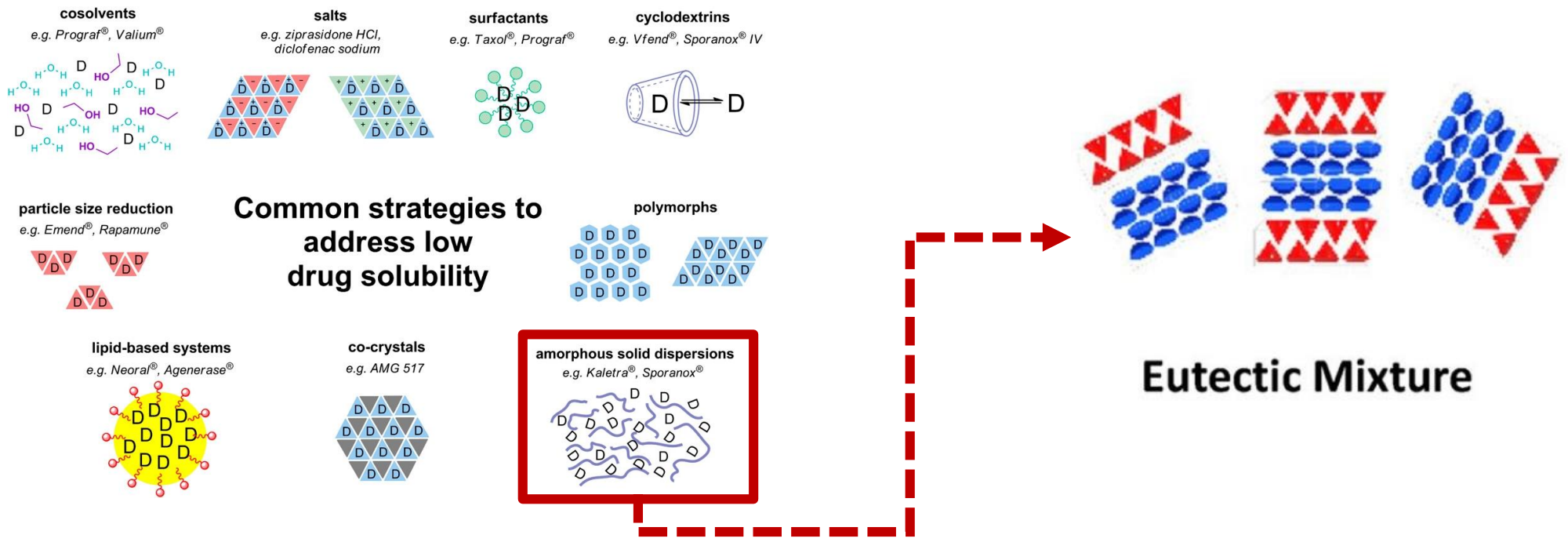
- Most ACT-related drugs are very **low soluble in water** what compromises bioavailability and therapeutic efficiency



Main challenges in treatment

Low solubility of APIs in water

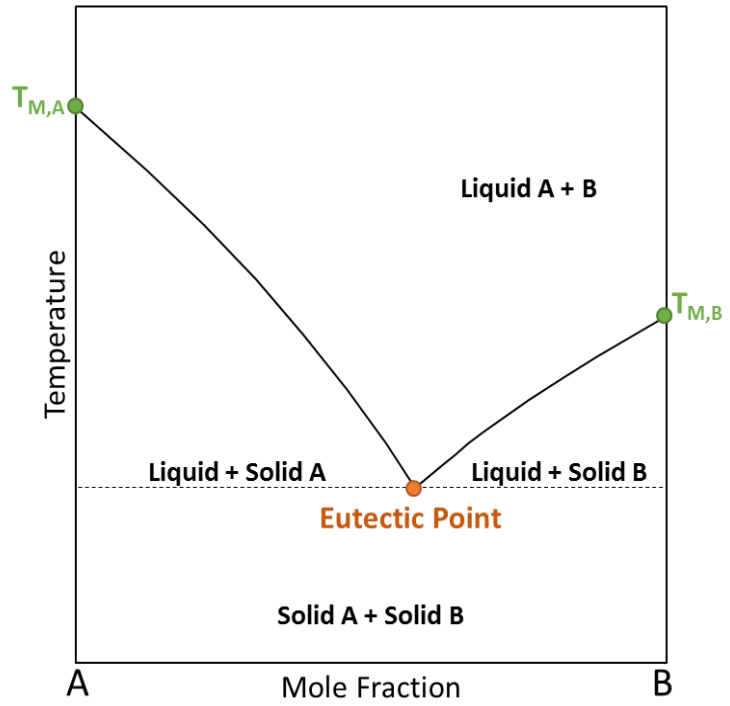
- The **low solubility of APIs** in water represents one of the main challenges in the development and commercialization of many drugs
- It is estimated that **40% of marketed drugs** and **70-90% of molecules** in the research phase have **low solubility**, which limits their effectiveness



Eutectic Mixtures

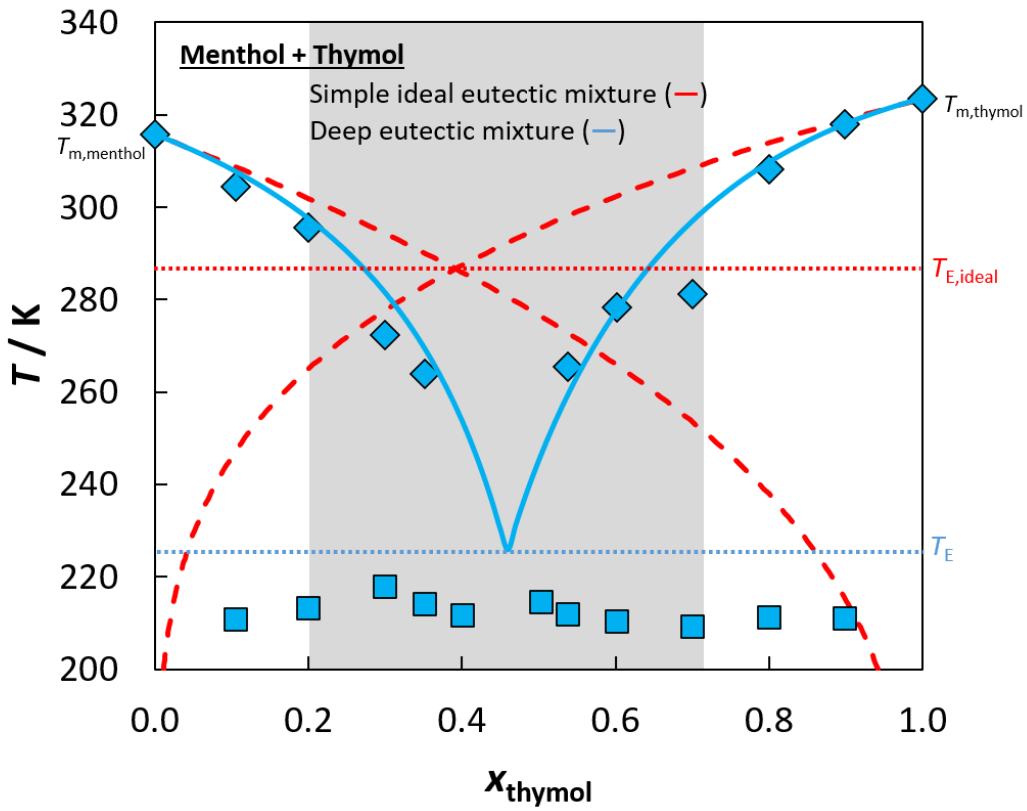
- … *eutectic* (1884) «a lower temperature of liquefaction than that given by any other proportion» by Frederick Guthrie, LII. On Eutexia

Properties	Applications
☐ Easy to prepare	☐ Catalysis
☐ Availability of precursors	☐ Organic synthesis
☐ Versatile	☐ Dissolution processes
☐ Economic	☐ Extraction processes
☐ Renewability	☐ Electrochemistry
☐ Biodegradability	☐ Material chemistry
☐ Greener alternative to ionic liquids	



Deep Eutectic Solvents

- Mixture of pure compounds for which the $T_{Eutectic}$ is below that of an ideal liquid mixture $T_{Eutectic,\ ideal}$
- Present significant **negative deviations** from ideality
- The mixture is **liquid** at the operating temperature



Solid-liquid equilibria equation

$$ln(x_i\gamma_i) = \frac{\Delta_m H}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) + \frac{\Delta_m C_p}{R}\left(\frac{T_m}{T} - ln\frac{T_m}{T} - 1\right)$$

0

When the temperature range of the system is not far from the melting temperature of the pure compound

Deep Eutectic Solvents

Deviations to thermodynamic ideality

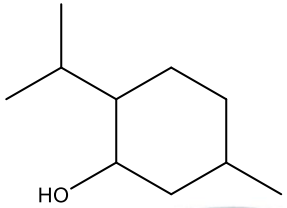
None/Positive: The molecular interactions between the components of the mixture are similar or weaker than those found in the liquid phases of pure substances

$\gamma \geq 1$ → **Eutectic System**

Negative: The molecular interactions between the components of the mixture are stronger than those found in the liquid phases of pure substances

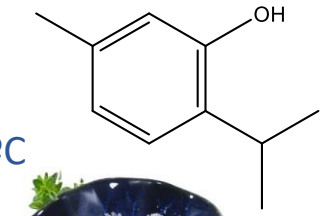
$\gamma < 1$ → **Deep Eutectic System**

Deep Eutectic Solvents



Menthol
mp = 42 ºC

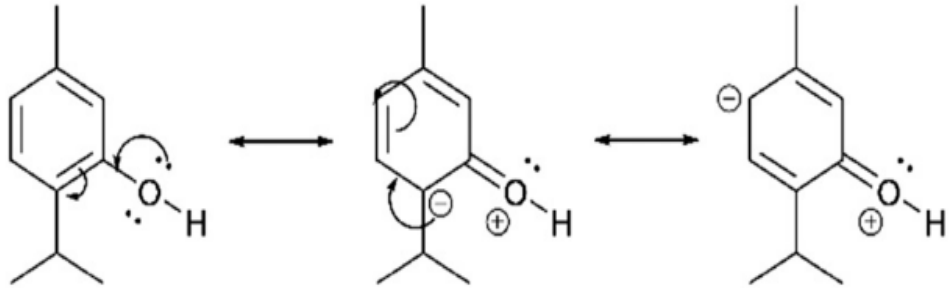
Thymol
mp = 51 ºC



~30 min
No stirring
No heating

Strong Interactions

The **hydrogen of thymol** (a better than usual hydrogen bond donor) interacts favorably with the **oxygen of menthol**, forming a hydrogen bond that is stronger than any present in the pure liquid components



Resonance structures of thymol

How to draw a *D*ES for a specific application?

1. **Structural evaluation of the molecules**

   Identification of families of compounds with suitable properties for the desired application

2. ***D*ES selection and preparation**

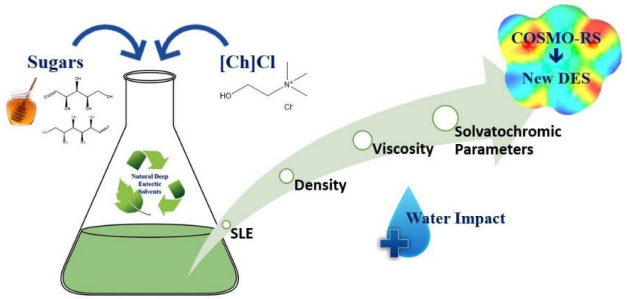
   Selection tools (COSMO-RS, Hansen Solubility Parameters), Preparation depends on the hydrophobicity/hydrophilicity of the precursors

3. **Solid-Liquid Equilibria (SLE) phase diagrams measurement**

   Provides information on the range of compositions and temperatures for operating these systems

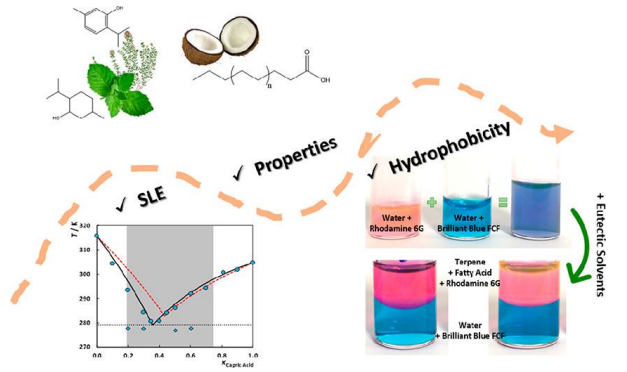
4. **Fundamental properties evaluation (viscosity, density, solvatochromic parameters, hydrophobicity, TGA, …)**

   *D*ES properties can be adjusted by selecting the right combination of precursors, further tailoring their phase behavior and physical properties → **Designer Solvent Character**



ACS Sustainable Chem. Eng. 6, 10724-10734 (2018)

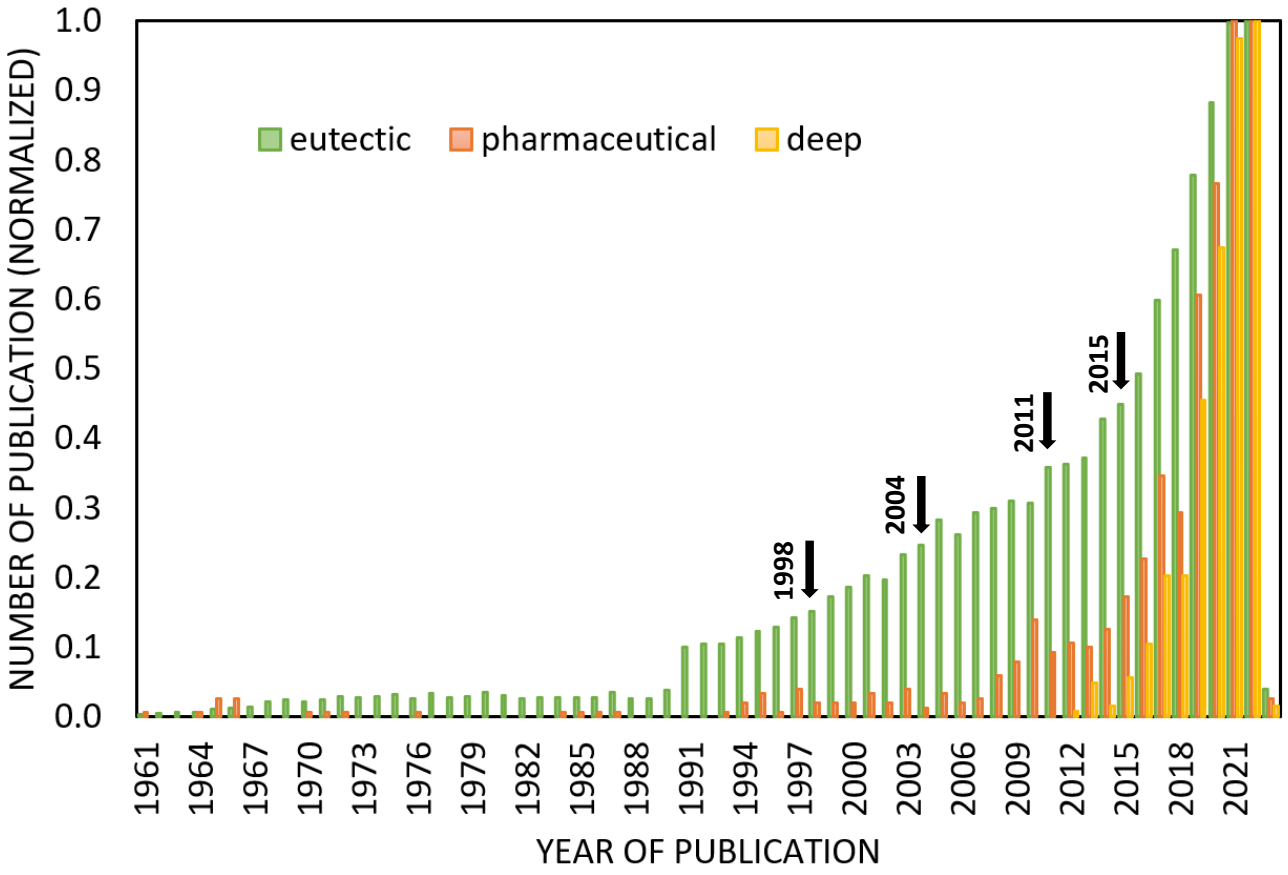
Terpenes + Fatty Acids

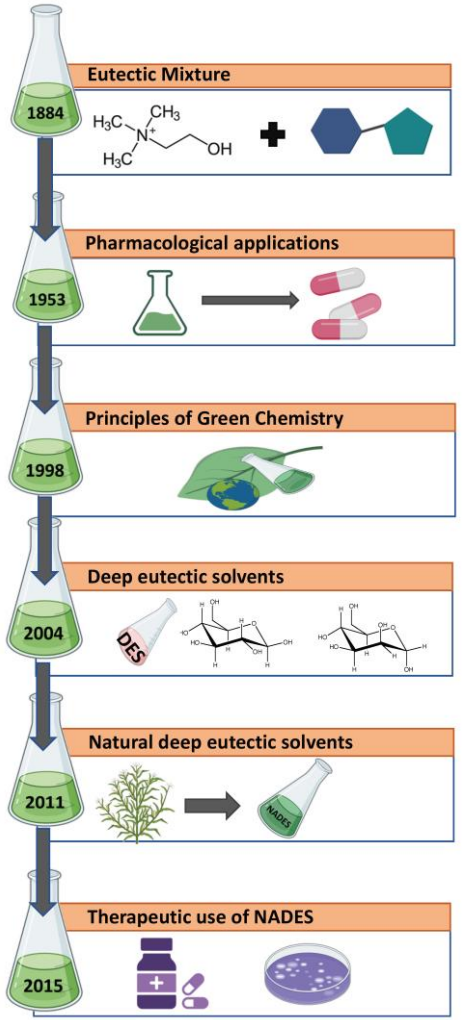


ACS Sustainable Chem. Eng. 6, 8836-8846 (2018)

*D*ES in the pharmaceutical industry

Evolution of DESs over time and their relationship with pharmaceutical applications

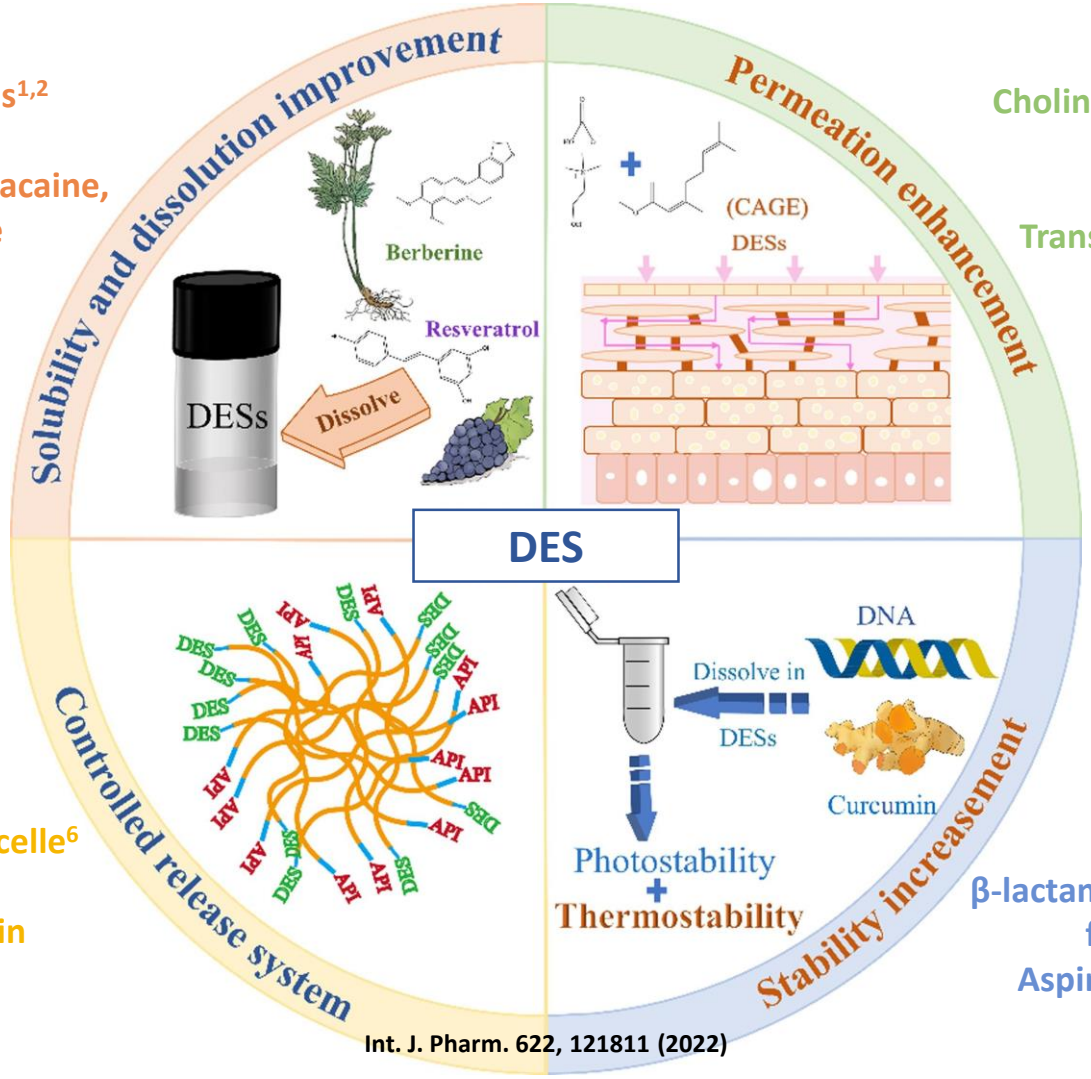




Appl. Sci. 11, 10156 (2021)

*D*ES in the pharmaceutical industry

Arginine + organic acids[1,2]
↓
Water dissolution of bupivacaine, prilocaine, procaine



Int. J. Pharm. 622, 121811 (2022)

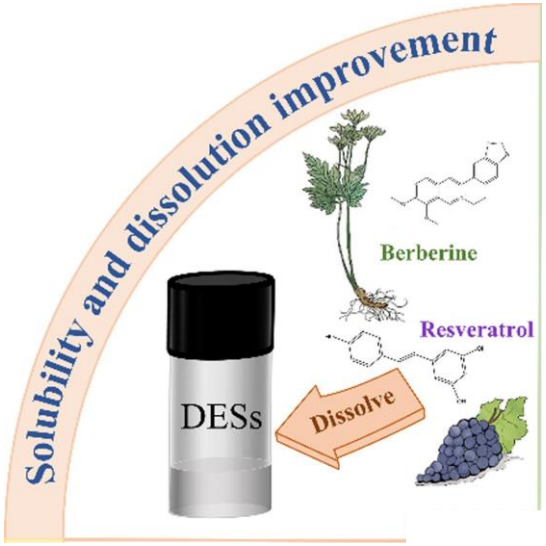
Choline bicarbonate + geranic acid (CAGE)[3]
↓
Transdermal delivery of insulin

DES-based polymeric micelle[6]
↓
release of doxorubicin

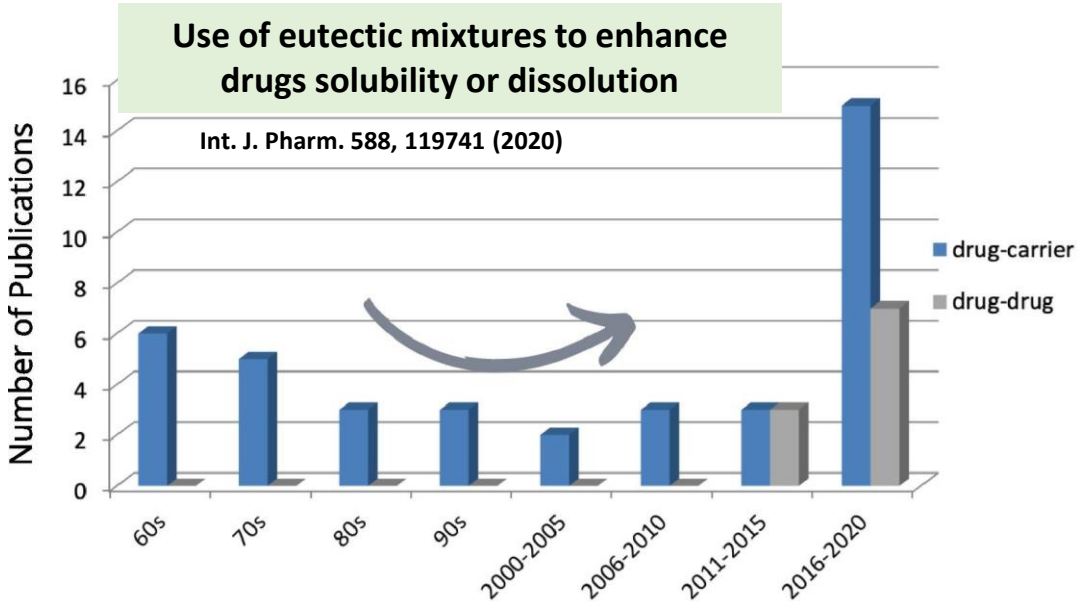
NADES[4,5]
↓
β-lactam antibiotics stability improved from 2.5 folds to 7 folds
Aspirin stability against cleavage improved 8.2-fold

[1]Phys. Chem. Chem. Phys. 21, 10621-10634 (2019); [2]J. Phys. Chem. B 124, 1794 - 18055 (2020); [3]J. Control. Release 286, 137 – 134 (2018); [4]Sci. Rep. 8, 14900 (2018); [5]Med. Chem. Commun., 7, 955-959 (2016); [6]ACS Appl. Bio Mater. 1, 2094–2109 (2018)

*D*ES in the pharmaceutical industry

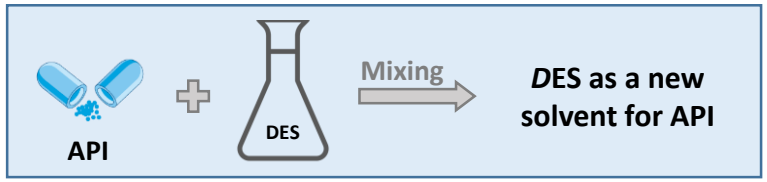


Int. J. Pharm. 622, 121811 (2022)



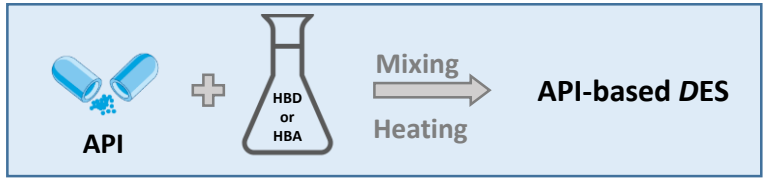
- **Dissolve the API in a eutectic system**

  Dissolution enhancers of APIs



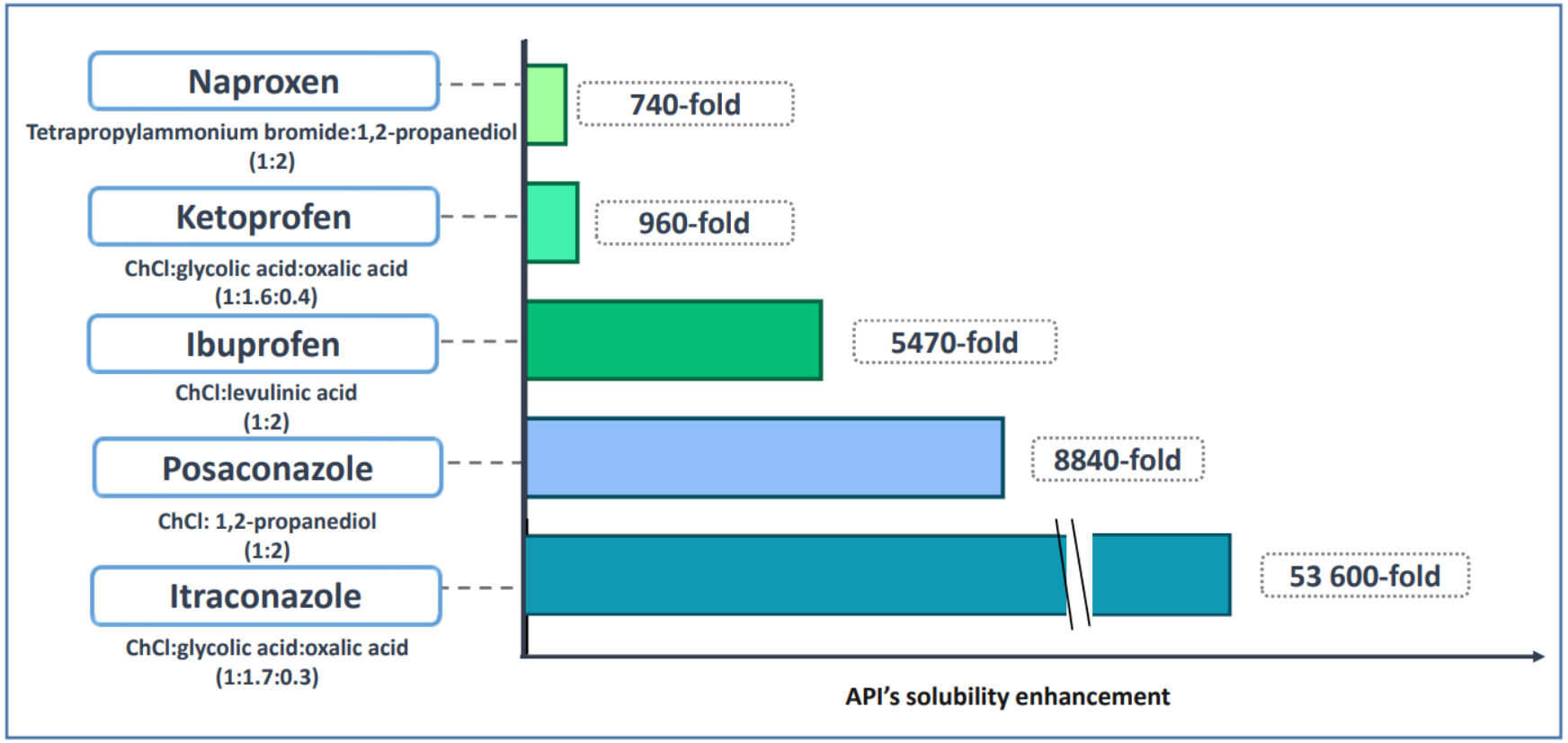
- **Use the API as component of the *D*ES**

  API-based deep eutectic system



*D*ES in the pharmaceutical industry

Experimental **solubility enhancements** achieved for anti-inflammatory and antifungal APIs using *D*ES as alternative solvents **in comparison with their solubility in water**



PhosAgro/UNESCO/IUPAC Partnership in Green Chemistry for Life

IUPAC

UNESCO
United Nations Educational, Scientific and Cultural Organization

PHOSAGRO®

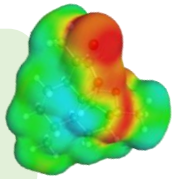
Green Chemistry for Life

Artemisinin bioavailability enhancement through eutectic formation with natural excipients
project financed by PhosAgro/UNESCO/IUPAC Partnership in Green Chemistry for Life (Agreement n° 8087).

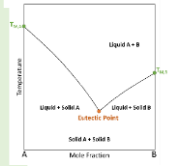
Objectives

Explore non-conventional **green solvents** to **improve the solubility** and, thus, the **bioavailability** and **absorption** of antimalarial drugs

Identify **green excipients** that interact favorably with antimalarial drugs



Measurement of the **phase behavior** and **physicochemical properties** of the selected mixtures



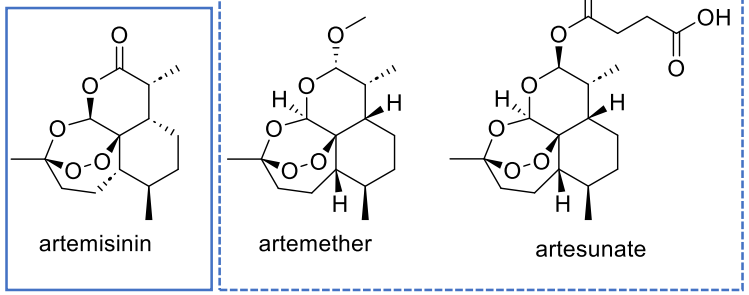
Extract **antimalarial compounds** from *Artemisia annua L.*

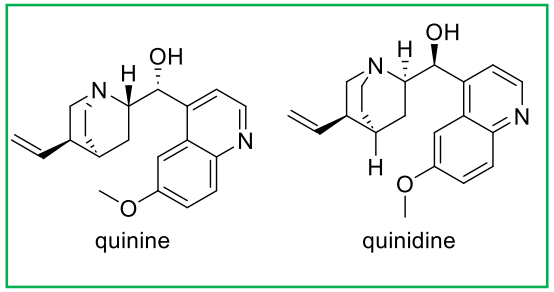
Test the **antimalarial potential** of the extracts using a bioassay

Antimalarial drugs

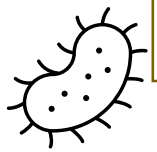
Artemisia Annua L.

Semi-synthetic derivative of artemisinin

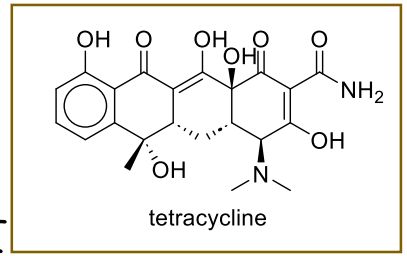


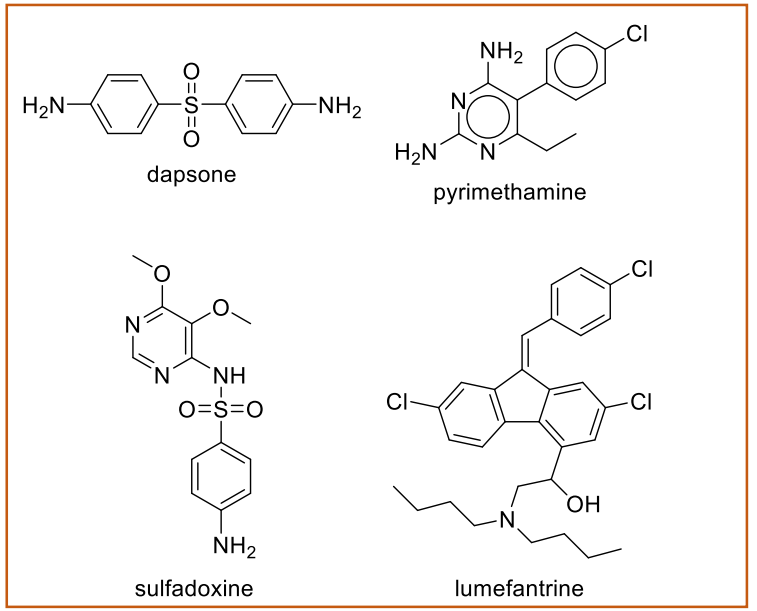


Cinchona pubescens



Streptomyces aureofaciens

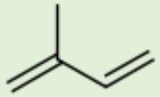


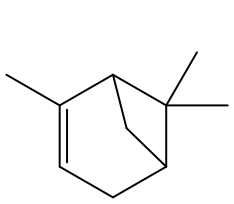


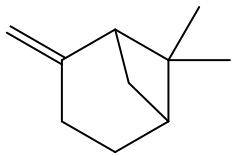
Synthetic antimalarial drugs

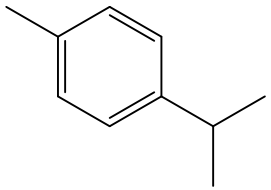
Natural Excipients

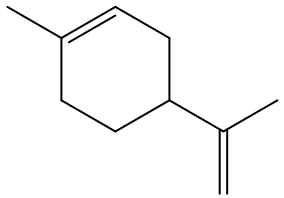
TERPENES

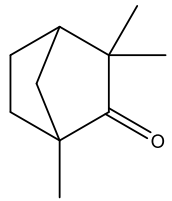
- **>55.000** different structures
- Majority found only in **plants**
- Derived from **isoprene** 
- Complex unsaturated **hydrocarbons**
- Oxygenated functional groups → **terpenoids**


α-pinene

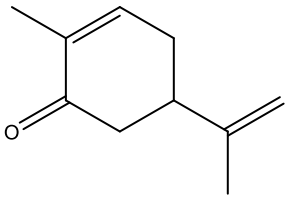

β-pinene


p-cymene


Limonene



Fenchone

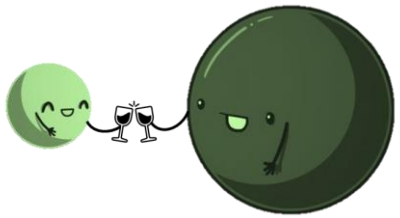


Carvone

- Food
- Agriculture
- Fine Chemicals
- Pharmaceutical
- Cosmetics & Perfumery

Experimental - COSMO-RS

- COnductor-like Screening MOdel for Realistic Solvents calculates **thermodynamic properties** of fluids and solutions based on **quantum mechanical data**



Indirect methodology for screening purposes

Drug – Excipient Interactions

$$\gamma^{\infty}$$

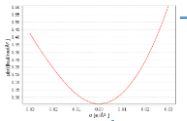
TURBOMOLE

Chemical Structure Optimization

COSMOconfX

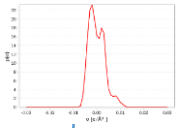
Sigma Surface

COSMOthermX



Sigma Potential

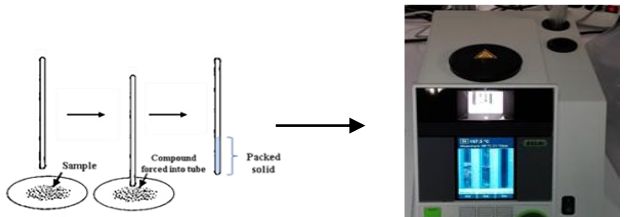
Sigma Profile



Activity coefficients at infinite dilution

Experimental – SLE measurements

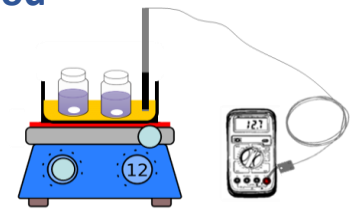
Melting Points Device



***Solid samples at RT**

The solid mixtures are milled (hydrophilic - glove-box) and the resulting powder filled into a capillary

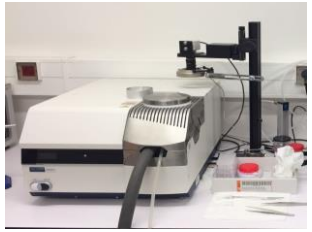
Visual Method



***Paste-like consistency samples**

The melting point is determined with a thermocouple connected to a multimeter

DSC



***Monitor the changes of phase transitions**

Hydrophilic samples are prepared and sealed inside the glove box

Experimental – Extraction

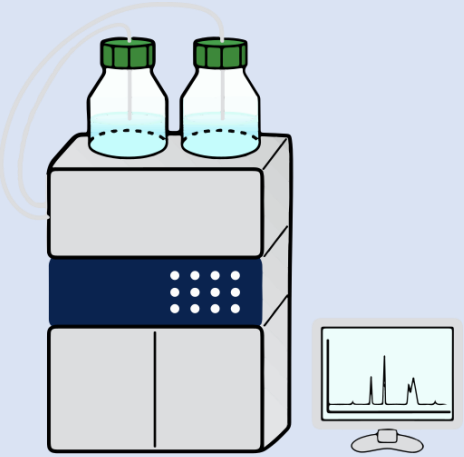
Artemisia Annua L.

Natural excipient

S/L ratio

Mixing (*T*, *t*)

Sampling

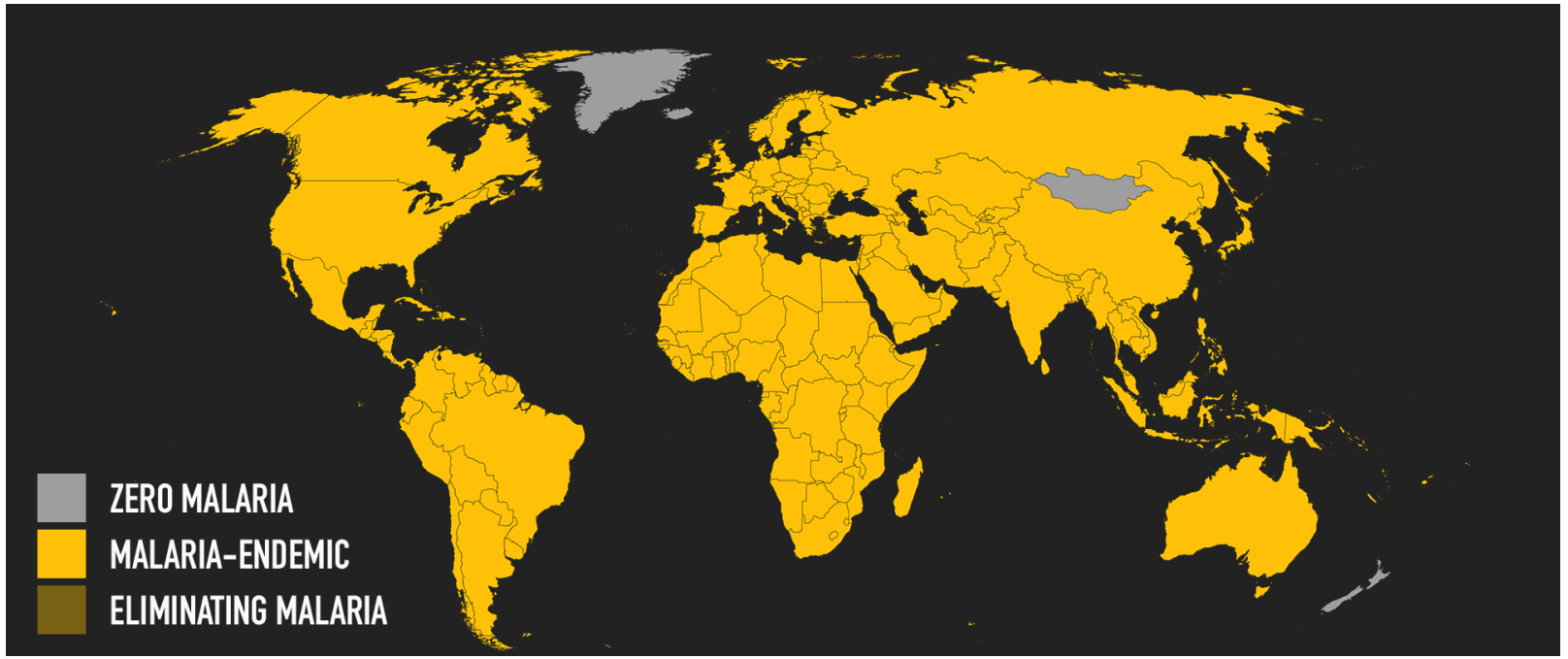


Artemisinin quantification - HPLC

Plants extracts

Antimalarial activity

Final Remarks



This study investigated drug-excipient mixtures, aiming to address the challenge of low water solubility in many active pharmaceutical ingredients

Enhancing antimalarial drug bioavailability via eutectic synergy with natural excipients

PRO AGRO
LECTORIUM

PRO AGRO
LECTORIUM

Thank you!