ECOLE DOCTORALE DE CHIMIE DE LYON

Projet : Stabilisation d'émulsions de Pickering par association de particules polymériques biodégradables et biocompatibles
Stabilization of Pickering emulsions by association of biodegradable and biocompatible polymer particles

Laboratoires : Laboratoire d'Automatique, de Génie des Procédés et de Génie Pharmaceutique (LAGEPP, UMR CNRS 5007)

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Context and general objectives of the PhD project:

An emulsion is a mixture of two immiscible or partially miscible liquids. One of the two phases is dispersed in the other as fine droplets by using mechanical stirring. The resulting system is usually stabilized by the addition of surfactants. Emulsion-based formulations are widely used in industry, particularly for pharmaceutical and cosmetic applications. However, the presence of surfactants in these formulations can cause undesirable effects due to their irritant nature and haemolytic behaviour.
Another type of emulsion, made without surfactants, has come into increasing use: **Pickering emulsions**. Pickering emulsions are stabilized by solid particles. Depending on the wettability and size of the particles used, oil/water or water/oil emulsions can be prepared with average drop sizes ranging from a few micrometers to a few millimeters. **The absence of surfactants and the high resistance to coalescence** of these emulsions make them particularly interesting for pharmaceutical and cosmetic applications [1].

LAGEPP is recognized for its research activities in the development of these emulsions and their applications, particularly for the cutaneous administration of pharmaceutical or cosmetic active ingredients [2-6]. Very recently, we studied **Pickering emulsions stabilized with a mixture of two types of biocompatible PMMA-based microparticles with different surface charges** (neutral/anionic, neutral/cationic and anionic/cationic). We have disclosed the influence of particle adsorption rate on the size, coverage, morphology and stability of the emulsion droplets [6]. We have also shown the benefits of combining these microparticles to co-encapsulate two different active ingredients (one in the oil phase and the other in the polymer particles) and to deliver them topically. Topical drug administration is particularly interesting. For dermatological pathologies, the active ingredient is applied locally onto the site of the disease, thus optimizing its dermatological efficacy. In addition, its locally restricted diffusion limits side effects on nearby tissues. The topical route can also be used for systemic delivery, which avoids the first hepatic passage of metabolization of the active ingredient and therefore improves its bioavailability [7].

To go farther in this project, we want to investigate **neutral, anionic and cationic biodegradable and biocompatible polymer nanoparticles and microparticles**. Once again, **two types of polymer particles** will be used to stabilize the emulsion and to encapsulate two different active ingredients. The aim is to examine **the differences of behaviour between emulsions prepared using nanoparticles and those obtained using microparticles**, and to propose **a biodegradable and biocompatible vector for the simultaneous and controlled topical delivery of two active ingredients**.

Detailed description of the project:

T**hree types of biodegradable and biocompatible polymer nanoparticles and microparticles** (neutral, anionic and cationic) will first be developed. Their size and surface charges will have to be controlled. Secondly, and following on from the work carried out at LAGEPP [6], the approach will involve using microparticles alone or in a binary mixture to stabilize emulsions. **Fluorescent microparticles** will be prepared to be observed by confocal fluorescence microscopy. Adsorption at the interfaces of the microparticles will be related to the stability of the emulsions. The results will be compared with those previously obtained with biocompatible microparticles (Figure 1). The characteristics (size, stability) of

emulsions stabilized with nanoparticles (alone or in a binary mixture) will then be studied in order to compare their behaviour with that of microparticles as stabilizers.

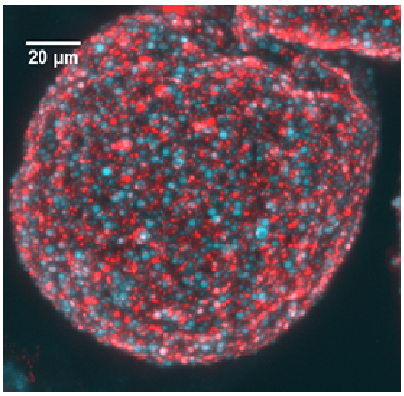

Figure 1: Image of a o/w Pickering emulsion droplet (20% isononyl isononanoate oil) stabilized by microparticles made of cationic (red) or anionic (green) PMMA copolymer [6].

Another fundamental aspect is **the experimental study of the transfer of active ingredients within the emulsion**. In a final step, we will use two active ingredients which will be co-encapsulated in the emulsion (the stabilizing systems used will be defined according to the results obtained previously). The aim is the mastery over the various mass transfers from the core of the microparticles into the oil phase in emulsion droplets or into the continuous phase. These transfer phenomena would modify the location of the active ingredients within the emulsion and could therefore have an impact on the bioavailability of the active ingredient. This stage of the study aims at making it **possible the delivery of several active ingredients in a differentiated way** to different biological targets.

Finally, the **optimal emulsions** will be tested for **cutaneous administration of two active ingredients**. Their penetration will be determined experimentally *in vitro* in metabolically inactive pig skin explants using Franz diffusion cells. Penetration will be monitored in the different layers of the skin: the epidermis, whose surface layer is the *stratum corneum*, the dermis and the hypodermis. The aim is to validate **the possibility of targeting the active ingredients to a specific skin layer**.

This study will provide knowledge on the stabilization mechanisms of Pickering emulsions and develop formulations of interest capable of delivering several active ingredients in a targeted manner.

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