PROPOSITION SUJETS DE THESES

CONTRATS DOCTORAUX 2021-2024

**Appel ciblé**(merci de cocher la case correspondante) :

**□ Contrat doctoral ministériel ED 536**

**□ Contrat doctoral ministériel ED 537**

**X Contrat doctoral EUR Implanteus**

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**Directeur de thèse** : Christine CONTINO-PEPIN (CBSA team, Avignon University)

**Co-directeur éventuel :** Patrick BOREL (C2VN team, AMU)

**Co-encadrant éventuel :** Charles DESMARCHELIER (C2VN team, AMU)

**Titre en français** : Eco-extraction et encapsulation de xanthophylles issus de matrices végétales dans des extraits-émulsions permettant d’accroitre leur stabilité et leur biodisponibilité.

**Titre en anglais** : One-pot solvent-free extraction and encapsulation of xanthophylls from plant matrices to improve their stability and bioavailability.

**Mots-clés** : Nano/micro-émulsions, eco-extraction, formulation, amphiphiles, phytomicronutriments, caroténoïdes, biodisponibilité, digestion.

Key-Words : Nano/microemulsions, eco-extraction, formulation, amphiphiles, phytomicronutrients, carotenoids, bioavailability, gastro-intestinal digestion.

**Co tutelle** : ~~Oui~~ - Non **Pays :**

**Opportunités de mobilité à l’international du doctorant dans le cadre de sa thèse :** ~~oui~~ - non

**Profil du candidat :**

* The candidate should have a master degree (or equivalent) in chemistry.
* The candidate wants to work in a multidisciplinary subject from extraction and formulation of natural products to the characterization of resulting colloidal solutions through a large set of analytical techniques (HPLC, Dynamic Light Scattering…) followed by the study of their stability, bioaccessibility and uptake by intestinal cells.
* The candidate should demonstrate a good experience in bioorganic and green chemistry. Knowledge in biology/physiology of digestion would be appreciated as well.
* A good knowledge in English (spoken and written) is required.

**Présentation détaillée du sujet :**

The CBSA team recently developed an innovative process allowing a dual extraction and formulation of lipophilic bioactive molecules in a solvent-free middle mainly consisting of water, therefore meeting the expectations and requirements of green chemistry. The resulting extract-emulsions, so-called “extremulsions”, are nano- or microemulsions whose properties (droplet size, polydispersity, loading in bioactive molecule, stability) can be fine-tuned playing on several parameters including the nature and concentration of the surfactant constituting the droplet shell, the nature of dispersed phase and the level of energy delivered during the extraction process. Extremulsions appear to be of particular interest for applications in the field of food fortification and supplementation. Moreover, the freeze-drying of the achieved extremulsions provide stable dry formulations easy to store and to reconstitute identically by simple addition of water.1 A recent work carried out in collaboration with P. Borel's team at C2VN has demonstrated the interest of extremulsions derived from Curcuma longa in improving the bioaccessibility and enterocyte uptake of curcumin. Following this proof of concept, we now aim to explore the potential of this technology for the design of extremulsions enriched with lutein and zeaxanthin, two lipophilic molecules that belong to the carotenoid family and that have been shown to be involved in visual function. We hypothetize that lutein- and zeaxanthin-loaded extremulsions could be of high interest to prevent and delay the progression of age-related macular degeneration (AMD)2 and neurocognitive disorders.

**Domaine / Thématique :** Green chemistry, natural products, extraction/formulation, nutrition, bioavailability.

**Objectif :**

The main aim of this PhD project is to prepare stable lutein- and zeaxanthin-rich formulations and to explore their bioaccessibility and absorbtion by intestinal cells in an in vitro gastro-intestinal digestion model.

**Contexte et enjeux :**

The search for alternatives to the use of organic solvents, which can result in the denaturation of bioactive molecules, and/or energy-consuming extraction processes is a major ecological, economic and scientific issue for the EUR IMPLANTEUS. Despite the ubiquity of water in plants, many plant-derived bioactive molecules (carotenoids, phytosterols, phylloquinone, etc.) exhibit poor solubility in water, which hampers their efficient extraction in a solvent-free middle.3 In this context, the CBSA team recently developed an innovative process for the extraction of lipophilic bioactive molecules in an oil in water solution (mainly composed of water), with the addition of natural or synthetic “GRAS” (generally recognized as safe) surfactants. The latter process provides, in a limited number of steps, nano- or microemulsion type plant extracts enriched with liposoluble molecules of interest. These extract-emulsions, patented under the name “extremulsions”,1 undergo a final freeze-drying step resulting in dry formulations, which can be stored for several months in the form of powders, easy to exchange within a consortium and to reconstitute by simple addition of water without noticeable change in their characteristics (nanometric size of the droplets, composition of the emulsion).

This process has been implemented during the PhD project of Alice Dall'Armellina (final year PhD student at ED 536 of Avignon University), which aimed to prepare optimized curcumin-loaded extremulsions from Curcuma longa (publication submitted to Green Chemistry Journal). Thanks to the SFR Tersys network, the C2VN team has emerged as a partner of choice to demonstrate the ability of these extremulsions to improve the bioavailability of curcumin, a molecule with very poor bioavailability. Indeed, Patrick Borel's team at C2VN routinely uses an in vitro digestion model to measure the stability and distribution of nutrients in the phases co-existing during the digestion of different foods.4 This model allows the calculation of the bioaccessibility of these molecules, i.e. the relative quantity available for absorption by intestinal cells, which is considered to be a good estimate of their bioavailability. In addition, the team uses a model of enterocyte cells, namely Caco-2 cells, to study the uptake and absorption of molecules incorporated in formulations or obtained from in vitro digestion fluids (mixed micelles). Recent work has thus shown that curcumin from extremulsions is significantly more bioaccessible than curcumin in commercial formulations (curcumin adsorbed on silica), regardless of the food used (publication in preparation).

Building on the complementarity and know-how of our teams, we now propose to jointly explore the potential of this innovative technology for the development of dry formulations of xanthophylls that could be used as food supplements or for the fortification of foods commonly consumed, e.g. yogurts, flours. These pigments are present in many vegetables and fruits (broccoli, corn, spinach, etc.) but their bioavailability is relatively low and very variable, in particular because of the interactions with the plant matrix in which they are present.5,6 The consumption of their main food sources remains low in a large part of the French population, thereby providing a rationale for an increase of their consumption via food supplements or via the fortification of other foods more commonly consumed (dairy products, flour or others) for people at risk of developing eye or neurodegenerative pathologies (family history, low consumers of fruits and vegetables, smokers, etc.). In addition to improving their bioavailability, the incorporation of these antioxidant molecules into extremulsions should also protect them from oxidative degradation, therefore increasing their health benefits.7 The green extraction and powder preparation conditions will be optimized to maximize the stability and bioaccessibility of xanthophylls (design of experiments approach). Finally, this work could find applications beyond the field of the food industry and could notably lead to the development of food supplements, given the demonstrated potential of these two xanthophylls to prevent AMD and neurocognitive disorders.

**Références bibliographiques :**

**1-** C. Contino-Pépin et al, 2020, WO 2020/109418A1.

**2**- J. Mares, “Lutein and Zeaxanthin Isomers in Eye Health and Disease”, Annual Review of Nutrition, 36 (2016) 571-602.

**3**- F. Chemat, M. A. Vian, A.-S. Fabiano-Tixier, M. Nutrizio, A. R. Jambrak, P. E. S. Munekata, J. M. Lorenzo, F. J. Barba, A. Binello and G. Cravotto, Green Chemistry, 2020, 22, 2325–2353.

**4**- C. Desmarchelier, F. Tourniaire, D.P. Preveraud, C. Samson-Kremser, I. Crenon, V. Rosilio, P. Borel. “The distribution and relative hydrolysis of tocopheryl acetate in the different matrices coexisting in the lumen of the small intestine during digestion could explain its low bioavailability.” Molecular Nutrition & Food Research, 57 (2013) 1237-1245.

**5-** P. Borel, « Les matrices végétales : leurs effets sur la biodisponibilité des caroténoïdes », Cahiers de Nutrition et Diététique, 53 (2018) 114-122.

**6-** C. Desmarchelier, « Effets de la matrice alimentaire sur la biodisponibilité des micronutriments et phytomicronutriments lipidiques », Cahiers de Nutrition et Diététique, 55 (2020) 240-248.

**7-** D. J. McClements, L. Saliva-Trujillo, R. Zhang, Z. Zhang, L. Zou, M. Yao, H. Xiao, « Boosting the bioavailability of hydrophobic nutrients, vitamins, and nutraceuticals in natural products using excipient emulsions », Food Research International, 88 (2016) 140–152.

**Les sujets devront être adressés à**

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**avant le 6 avril 2020**