COLLEGE ED BIOLOGIE DOCTORAL SANTE PAYS DE LA LOIRE

Year 2022 /2023

THESIS TOPIC

Subject N° (to be completed by the ED):	**FUNDING:** ☒ **Requested** ☐ **Acquired**	**Funding origin:**
Thesis title: **Drug delivery system for oral peptide administration**		3 keywords: Drug delivery system Oral delivery Peptide
Unit / team: **INSERM UMR_S 1066/CNRS 6021 – MINT Micro et Nanomedécines Translationnelles**		
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Socio-economic and scientific context (approximately 10 lines):

For decades, the **oral route** (*p.o*) is the most common route for drug delivery. It provides treatment acceptability for patients and facilitates the administration with non-invasive and ambulatory treatments. Accordingly, it constitutes the first investigated administration route during the pharmaceutical development of a new drug. Unfortunately, this oral administration route is most of the time not suitable for the emerging therapeutic peptides despites their great potential. More than 100 peptides are already approved and more than 200 are under clinical trials reflecting the great interest for their high efficiency at low dose and their important pharmacological specificity and selectivity. However, as the gastro-intestinal (GI) degradation and the low permeability lead to an oral peptide bioavailability below 1-2%, peptides are mainly administered by parenteral route.

To knock down the locks of peptide administration by oral route, **Drug Delivery Systems (DDS)** are an alternative solution to protect the peptide and enhance its permeability and oral bioavailability. In this context, a drug delivery system based on lipid and polymer composition and without class 1 or 2 solvents (according to ICH standards) was developed in the MINT laboratory (pending patent).

Working hypothesis and aims (approximately 8 lines):

This project proposes a rational approach to design a novel drug delivery system to encapsulate peptides, and to be compatible with oral administration. Nanomedicine's approach will allow peptide oral administration, to prevent their degradation in gastrointestinal settings and to allow their absorption through the intestinal barrier. This DDS will have to possess a size of less than 200 nm, a polydispersity index of less than 0.2, a potential zeta optimal, an encapsulation rate, and an encapsulation efficiency are optimal. Moreover, this DDS will be able to keep full integrity in the gastrointestinal tract, diffuse through the mucus without mucoadhesion, and improve the transport profiles of peptides across the epithelial barrier, by avoiding drug efflux or metabolism. In the literature, both lipid and polymer nanoparticles are studied by oral administration, but to date, no nanoparticles are able to be absorbed while keeping their integrity, and thus able to behave as circulating nanocarriers. Thus, the purpose of this project is to optimize oral DDS to encapsulate peptide (nisin) and to maintain full integrity until liver after oral administration.

Main milestones of the thesis (approximately 12 lines):

1. Optimization of DDS formulation: The use of new lipids and different polymers will be studied. Nanoparticles will be formulated in 2 steps without solvent (patent under review).

2. Incorporation of peptide in DDS: A model peptide (nisin) will be encapsulated. Different methods of encapsulation will be tested passive or active encapsulation. Moreover, in order to study the fate of nanoparticles, two dyes will be encapsulated to obtain FRET signal.

3. Physicochemical Characterizations: Size, morphology and zeta potential will be determined by Dynamic Light scattering (DLS) and microscopy (TEM, Cyro-EM). The encapsulation efficiency and drug loading will be carried by appropriate analytical method that should be developed such as HPLC-UV, LC-MS/MS.

4. Biopharmaceutics Characterizations of DDS: In vitro stability in different artificial gastro-intestinal fluids (FaSSGF-V2, FeSSGF, FaSSIF-V2, FeSSIF-V2) will be performed. Interaction between DDS and the intestinal barrier will be determined on in vitro cellular models (Caco-2 cells ± /endothelial cells model developed in the MINT laboratory) in order to predict the ability of peptide and/or DDS to reach the blood compartment. Peptide and DDS itself will be studied with appropriate analytical method or a combine method (FRET/NTA).

5. In vivo studies: In vivo efficacy and pharmacokinetic of peptide and DDS will be tested on rats.

Scientific and technical skills required by the candidate (2 lines):

The selected phD student should have scientific and technical skills in drug delivery system, more especially in formulation, physicochemical characterization and in *in vitro* and *in vivo* characterizations.

3 publications from the team related to the topic (last 5 years):

1. KAEOKHAMLOED N., **ROGER E.,** BÉJAUD J., LAUTRAM N., MANERO F., PERROT R., ABBARA C., BRIET M. AND LEGEAY S. "New In Vitro Coculture Model for Evaluating Intestinal Absorption of Different Lipid Nanocapsules" Pharmaceutics **2021**, 13, 595. https://doi.org/10.3390/pharmaceutics13050595
2. DESHAYES C., ARAFATH N., APAIRE-MARCHAIS V. AND **ROGER E.,** "Drug Delivery Systems for the Oral Administration of Antimicrobial Peptides: Promising Tools to Treat Infectious Diseases", Frontiers in Medical Technology, **2022.** http://dx.doi.org/10.3389/fmedt.2021.778645
3. LEBRETON V., KAEOKHAMLOED N., VASYALAKI A., HILAIRET G., MELLINGER A., BEJAUD J., SAULNIER P., LAGARCE F., GATTACCECA F., LEGEAY S. AND **ROGER E., "**Pharmacokinetics of intact lipid nanocapsules using new quantitative FRET technique" Journal of Controlled Release. **2022**, November 2022, vol. 351, pages 681-691. https://doi.org/10.1016/j.jconrel.2022.09.057

National and international collaborations:

- Professeur Thierry BENVEGNU,Ecole Nationale Supérieure de Chimie de Rennes, UMR CNRS 6226 Sciences Chimiques de Rennes, Equipe Chimie Organique et Supramoléculaire
- Dr Florence Gattacceca, Inria – Inserm team COMPO, Pharmacy Faculty, Aix-Marseille University