COLLEGE ED BIOLOGIE DOCTORAL SANTE PAYS DE LA LOIRE

Year 2024/2025

THESIS TOPIC

Subject N° (to be completed by the ED):	**FUNDING:** ☒ **Requested** ☐ **Acquired**	**Funding origin:**
Thesis title: **Formulation of porous polymer microspheres by prilling coupled with temperature-induced phase separation for encapsulation and controlled delivery of proteins**		3 keywords: Drug Delivery System Prilling Porous microspheres
Unit / team: **Micro et Nanomédecines translationnelles (MiNt)**		
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Socio-economic and scientific context (approximately 10 lines):

Therapeutic drug delivery systems (DDS) for controlled and/or targeted release of active pharmaceutical ingredients (API) are now playing a major role in human medicine. However, in order to control this release, it is essential to develop DDS with controlled characteristics (size, structure, porosity, etc.). In particular, the controlled, gradual release of proteins is a major challenge for improving patient comfort. To date, one of the known options for achieving this is encapsulation in a biodegradable polymer, but this requires the use of solvents, and transferring processes developed in the laboratory to the industrial scale poses problems of controlling particle properties.

A prilling process has been developed by MINT to produce microparticles (30 to 100 µm) of controlled size and sphericity (theses by VT Tran, F. Violet and T. Nguyen-Pham). This process does not produce porous particles, but it can be transposed to industrial production according to good manufacturing practice. On the other hand, a process combining TIPS (Thermal Induced Phase Separation) and sc-CO_2 technologies has been developed by MINT (S. Gay's thesis) to produce porous, low-density, micro-cellular PLLA matrices with adjustable mechanical structural properties. A new sc-CO_2 drying technique has been developed, reducing environmental impact by an average factor of 4.

Working hypothesis and aims (approximately 8 lines):

The aim of this project is to develop an original process for formulating porous biodegradable polymer (PLLA or PLGA) microspheres (~100µm) for the controlled release of API. This process will combine the three technologies presented in the background and whose feasibility and interest have already been proven: prilling for shaping microspheres from organic solution, the TIPS process for phase separation between polymer and solvent, and sc-CO_2 extraction of residual solvent. The innovation will consist in coupling these three processes to formulate porous microspheres for controlled release of a model therapeutic protein (Fig. 1). In addition, in order to obtain injectable microspheres, a non-halogenated solvent already used in a pharmaceutical speciality, glycofurol, has been selected for this project. The challenge will be to optimize all the numerous operating parameters (shown in Fig. 1) to produce monodisperse microparticles, in particular by obtaining a regular droplet train (low size dispersity and constant spacing) and controlling the impact stage with the receiving medium.

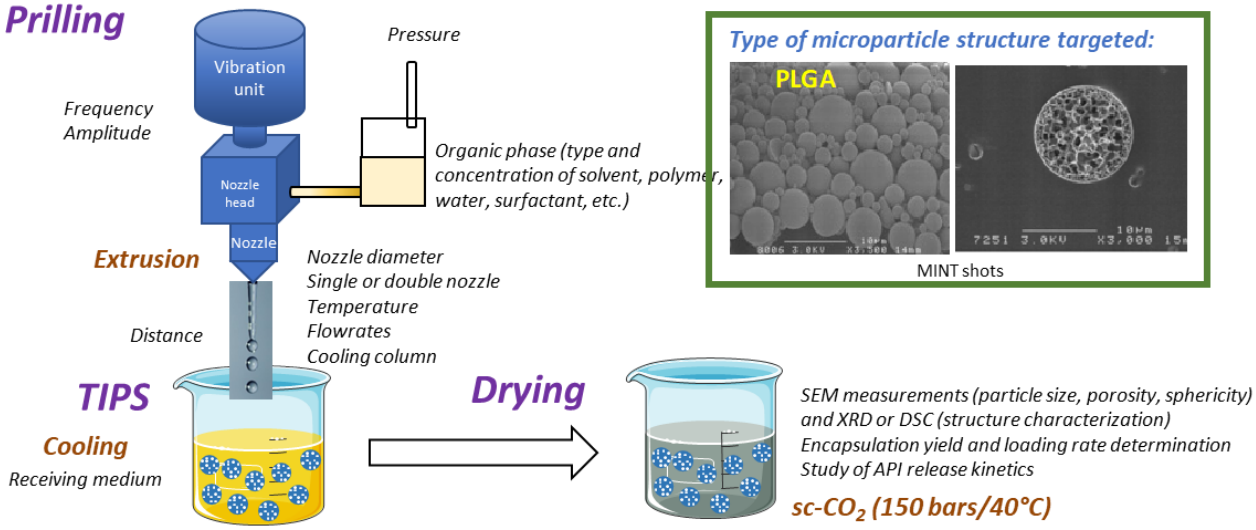

Figure 1 : Schematic diagram of the developed process and list of operating parameters studied.

Main milestones of the thesis (approximately 12 lines):

The thesis will focus on 3 main tasks.

Task 1: Characterization of the polymer/solvent/water/surfactant mixture and process phenomenology. This will involve characterizing the dynamic viscosity and density of different solutions, their cloud point temperature and surface tension, using a hanging drop tensiometer. The optimum operating conditions for jet formation (length, size and rupture) will be determined using a high-speed camera. Phase diagrams will be established for different polymer/solvent couples, and in the presence or absence of surfactants. Finally, the mixture/receiving medium properties will be characterized.

Task 2: Parametric study and statistical control of the Prilling/TIPS/sc-CO_2 process. This task will involve studying the impact of the formulation process operating parameters on the characteristics of the jet and the final properties of the polymer microspheres obtained (granulometry, porosity and sphericity characterized by scanning electron microscopy and structure characterized by X-ray or differential scanning calorimetry (DSC)). An optimization approach using design of experiments and principal component analysis will be implemented. Finally, predictive modeling of these properties will be carried out on the basis of the experimental data sets generated (in Task 1).

Task 3: Encapsulation of lysozyme and characterization of release kinetics. Proof of concept for encapsulation of a proteinaceous API will be established by correlating encapsulation rate and yield with operating parameters. API release kinetics will be studied in relation to microsphere properties. The results will be compared with those obtained for non-porous particles produced in previous theses.

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

The candidate should have a Master 2 or engineering degree in process engineering, a good level of English and be organized and rigorous. He/she should also have a strong interest in the healthcare field, and a specialization or double degree in pharmaceutical sciences would be a plus.

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

La thématique faisant l'objet de ce projet de thèse a du être mise de côté ces dernières années pour manque de financement et de personnel. Ainsi la troisième publication de l'équipe relative à ce domaine citée ici date d'il y a 6 ans.

T.-Q. Nguyen-Pham, L. Benyahia, G. Bastiat, J. Riou, M.-C. Venier-Julienne, Behavior of poly(d,l-lactic-co-glycolic acid) (PLGA)-based droplets falling into a complex extraction medium simulating the prilling process, 2020, Journal of Colloid and Interface Science , Vol. 561, p. 838-848

M.-Q. Le, J.-C. Gimel, X. Garric, T.-Q. Nguyen-Pham, C. Paniagua, J. Riou, M.-C. Venier-Julienne, Modulation of protein release from penta-block copolymer microspheres, 2020, European Journal of Pharmaceutics and Biopharmaceutics, Vol. 152, p. 175-182

M.-Q. Le, F. Violet, C. Paniagua, X. Garric, M.-C. Venier-Julienne, Penta-block copolymer microspheres: Impact of polymer characteristics and process parameters on protein release, 2018, International Journal of Pharmaceutics, Vol. 535, No. 1, p. 428-437

National and international collaborations:

The MINT and IBMM laboratories have been working together since 1999 on the synthesis and shaping of DDS in the form of polymer foams and microspheres derived from polylactic acid: this project will continue this collaboration. For the purposes of the project, IBMM will synthesize and characterize PLLA and PLGA of different molar masses and structures.