Thesis offer

BIOSOURCED GELS BASED ON CEREAL CO-PRODUCTS FOR THE CONTROLLED RELEASE OF BIOACTIVE MOLECULES IN THE COLON

Etablissement **Université de Montpellier**
École doctorale **GAIA - Biodiversité, Agriculture, Alimentation, Environnement, Terre, Eau**
Spécialité **APAB - Agroressources, Procédés, Aliments, Bioproduits**
Unité de recherche **IATE - Ingénierie des Agropolymères et Technologies Emergentes**
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Keywords

feruloylated arabinoxylans, encapsulation matrix, therapeutic molecules, covalent hydrogels, in vitro digestion, colon

Context

Cereal processing generates several tones of bran containing bioactive molecules (antioxidants, anti-diabetics, prebiotics) and polysaccharides with interesting rheological properties (thickener, gelling agent), making it possible to exploit this technological fraction. In addition to their biocompatible and renewable nature, the extensive structural biodiversity of these polysaccharides suggests that they have multiple functionalities, making them highly attractive candidates for replacing fossil-based polymers in a variety of fields (health, materials). Among the parietal polysaccharides, feruloylated arabinoxylans are of great interest as a matrix for encapsulating bioactive molecules in the pharmaceutical field. The fact that they are non-digestible by humans but fermentable by intestinal bacterial flora means that therapeutic molecules (probiotics, antioxidants, anti-carcinogens) can be released in the colon in a controlled manner when administered orally. The colon is a target organ which, because of its high vascularity, allows rapid diffusion of therapeutic molecules into the bloodstream. In addition, inflammatory diseases of the colon, which are widespread and can lead to the development of cancer, can be prevented (antioxidants) or treated (anti-carcinogenic peptides and proteins) locally by controlled release of these bioactive molecules.
In this application context, previous work has shown that oral administration of an AX excipient is safe and that xyloglucans, another family of polysaccharides, are not toxic to tissues. Finally, AX gels effectively protect the structure of the encapsulated molecules. In vitro hydrolysis of insulin by trypsin is reduced by 30-60% when encapsulated in a gel.
In order to promote the use of AX gels as vectors for therapeutic molecules administered orally to reach the colon, this project aims to further study the influence of AX molecular structure on the stability/bioaccessibility of molecules encapsulated in AX gels and to characterize the stability of gels and bioactive molecules under in vitro digestion.

Project description

Arabinoxylans (AX), the main non-starch polysaccharides found in cereal walls, are biosourced and biodegradable arabinose and xylose polymers that can form covalent hydrogels by cross-linking the ferulic acids on their side chains. They can replace synthetic polymers whose biodegradability and biocompatibility may be questionable. In addition, AX gels can be formed using green solvent-free processes, i.e. by enzymatic or physical oxidation of ferulic acids. The covalent nature of AX gels gives them a high water absorption capacity as well as great stability to pH, temperature and ionic strength. Their swelling properties and macroporous structure (pore size ranging from around ten nm to 400 nm) make them excellent encapsulation matrices. In addition, the non-digestible but fermentable nature of AXs enables the controlled release of therapeutic molecules in the colon. While the relationship between the structure of AXs and the

properties of gels has been extensively studied, the impact of the molecular structure of AXs on the encapsulation capacity of gels and on the release of encapsulated molecules has only been partially addressed.
The aim of the thesis project will therefore be to (i) construct and characterise AX gels with contrasting molecular structures, (ii) produce and characterise gel spheres using millifluidics and electrospray and (iii) study the evolution of their properties when they are subjected to physico-chemical conditions mimicking human digestion. The second part will aim to (i) construct and characterise gels from the various AXs loaded with a therapeutic molecule and to study its release during in vitro digestion. The encapsulation of two model therapeutic molecules, CLA (conjugated linoleic acid, anticarcinogenic; 250 Da) and HAMELET (Human Alpha-lactalbumin Made LEthal to tumor cells, tumorigenic milk lipid protein complex; 14.2 kDa) will be studied with the aim of developing a local oral treatment for colon cancer.
The first part of the thesis project will therefore aim to (i) construct and characterize AX gels with contrasting molecular structures, (ii) produce gel spheres by millifluidics and atomisation and characterize them, and finally (iii) study the evolution of their properties when they are subjected to physico-chemical conditions mimicking human digestion. The second part will aim to (i) construct and characterize gels from the various AX mixed with a therapeutic molecule and to study its release during in vitro digestion. The encapsulation of two model therapeutic molecules, CLA (conjugated linoleic acid, anticarcinogenic; 250 Da) and HAMELET (Human Alpha-lactalbumin Made LEthal to tumor cells, tumorigenic milk lipid protein complex; 14.2 kDa) will be studied with the aim of developing a local treatment for the colon by the oral delivery.

Scientific topics/ fields

valorization, food co-products; biopolymers, health
biochemistry, rheology, biopolymers; encapsulation, diffusion

Objective

The aim of the thesis will be to elucidate the relationships between the molecular structure of feruloylated arabinoxylans, the encapsulation capacity of the gels and the release of encapsulated therapeutic molecules during in vitro digestion.

Methods

- biochemical characterization of the various AX extracts (HPLC, CPG, etc.)
- monitoring the gelling of arabinoxylans and characterizing the viscoelastic properties of gels using rheology
- structural characterization of the gels (estimation of the degree of covalent cross-linking by measuring the ferulic acid dimers and trimers formed after gelation using HPLC, determination of the theoretical average pore size and the theoretical average molecular distance between covalent bonds from equilibrium swelling measurements; morphology of the aerogels by observation using a scanning electron microscope)
- characterization of the maximum swelling capacity of gels
- construction of spheres using milli-fluidics and atomisation (Ecole des mines d'Albi; CIA, Mexico)
- in vitro digestive behaviour (swelling and mechanical resistance)
- characterization of the oxidative stability of gels during in vitro digestion
- effect of a drying/hydration cycle on the properties of gels and the stability of therapeutic molecules
- encapsulation of therapeutic molecules: quantification of encapsulated molecules and homogeneity of their distribution within the gels
- Diffusion of therapeutic molecules in in vitro digestion using NMR mixed imaging and assays

Expected results

-understanding the 'structure/health functionality' continuum of different biopolymer gels derived from different cereal co-products
-comparison with synthetic polymer and alginate controls
-loading capacity with different types of bioactive molecules (of varying polarities, sizes and loads) in the gels
-identification of the most promising matrices in terms of protection and controlled release of bioactive compounds at the level of the fixed digestive target

Bibliography

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Scientific, material and financial conditions of the research project

The thesis will be carried out within the IATE joint research unit (INRAE, Montpellier University, Institut Agro). This joint research unit is developing a multidisciplinary scientific approach to the characterisation, processing and valorisation of renewable agri-resources from the agricultural, forestry and agri-food sectors. The IATE lecturers and researchers involved in supervising the thesis are members of the GRAINES team, whose activities cover the processing of seeds and food matrices with optimised nutritional properties from plant-derived resources.

International

A three-month stay will be funded in the Biopolymers CTAOA laboratory under the supervision of Professor Elizabeth Carvajal-Millan (Biopolymers CTAOA, Carretera Gustavo Enrique Astiazaran Rosas 46, Hermosillo 83304, Sonora, Mexico) to manufacture spheres of AX gels by atomisation.

Objectives for promoting the doctoral student's research work: dissemination, publication and confidentiality, intellectual property rights, etc...

The doctoral student will publish his/her results in peer-reviewed journals and present results at conferences (at least one international and one national conference during his/her thesis).
To date, the objectives in terms of publications are :
- 1 journal article on the state of the art in the field
- 3 research articles.

These targets will of course be adjusted as the project progresses.

Planned collaborations

- L2C, université Montpellier
- UMR OPAALE, RMN
- Equipe Nano, BIA, Nantes
-TBI, Toulouse
- GDR SLAMM

Profile and skills required

M2 or engineering degree in biochemistry, physical chemistry or materials science. Plus: an interest or skills in nutrition and health.
Skills in enzymology and physical chemistry.
Interpersonal skills for teamwork. Good laboratory practice.
Good writing skills, written and spoken scientific English.
Autonomy, curiosity, rigour and dynamism.
Experience in a research laboratory may be an asset but is not required to apply.

Application

Send a letter of application, curriculum vitae and transcripts of your undergraduate, Master 1 and Master 2 degrees. Contact : carole.assor@inrae.fr.