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Screening of process parameters for the formulation of alginate microparticles with efficient encapsulation of fragile molecules using a Plackett-Burman design.

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A.R.S. MACKIN-MOHAMOUR¹, T. BASTOGNE^{3,4,5}, L. HASSLER⁵, J. BUDZINSKI⁵, T. ROQUES-CARMES², V. SADTLER², M. LEBRUN², P. MARCHAL², A. SAPIN-MINET¹, M. PARENT¹

¹Université de Lorraine, CITHEFOR, F-54000, Nancy, France ; ²Laboratoire Réactions et Génie des Procédés (LRGP), UMR CNRS, 7274, Université de Lorraine, 54001, Nancy, France, ³Université de Lorraine, CNRS, CRAN, F-54000 Nancy, France, ⁴INRIA BIGS, Nancy, France, ⁵CYBERNANO, Nancy, France

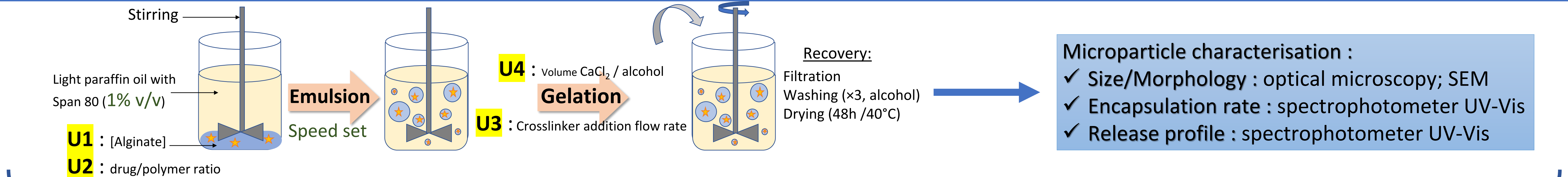
Introduction

Peptide drugs efficacy and safety are often limited by instability, short half-life, immunogenicity and their hydrophilic nature which compromises their transport across biological membranes. These limitations could be addressed by polymeric formulations produced with processes adapted to these hydrophilic and labile drugs. For example, **S-nitrosoglutathione (GSNO)** is a **tripeptide, highly hydrophilic, and physiological** form of storage of nitric oxide (NO). NO is involved in several physiological processes, particularly in the cardiovascular system. It inhibits platelet aggregation, prevents endothelial dysfunction and promotes vasodilation but **NO bioavailability is decreased both by ageing and various diseases** [1]. GSNO has been shown to be safe in clinical trials and effective in various preclinical models [2]. However, GSNO needs to be presented in an adapted galenic form for using as a prodrug for **oral administration**. Consequently, we have developed several **polymeric particles** based on **alginate** obtained by **emulsion/gelation process** [3] that target the following specifications: **efficient encapsulation** of hydrophilic molecules, with a **particle size control, release control**.

An optimization of the formulation is currently proposed. A model compound (FCF sun yellow) with similar physicochemical properties to GSNO is used during particle development, to facilitate the analytical steps. A 4-factor Plackett-Burman **experimental design** was carried out to optimize the formulation process using the **Quality by Design** development paradigm, including one critical material attribute and three process parameters. The physico-chemical characterization of particles was performed to identify the optimized process and formulation parameters.

[1] Moncada S., et al. *Pharmacol. Rev* 43, 109-42 (1991), [2] Gaucher C., et al. *Curr Pharm Des* 19, 458-72 (2013), [3] Rastogi R., et al. *Int Pharm* 334, 71-77 (2007)

Materials and Methods



Level of experimental variables:

- U1: 2% and 5%
- U2: (0.1:1) and (0.5:1)
- U3: Low and High
- U4: 5mL and 10mL

Experimental design

4-factor 2-level plan

8 duplicate randomized trials (16 batches)

Statistical analysis

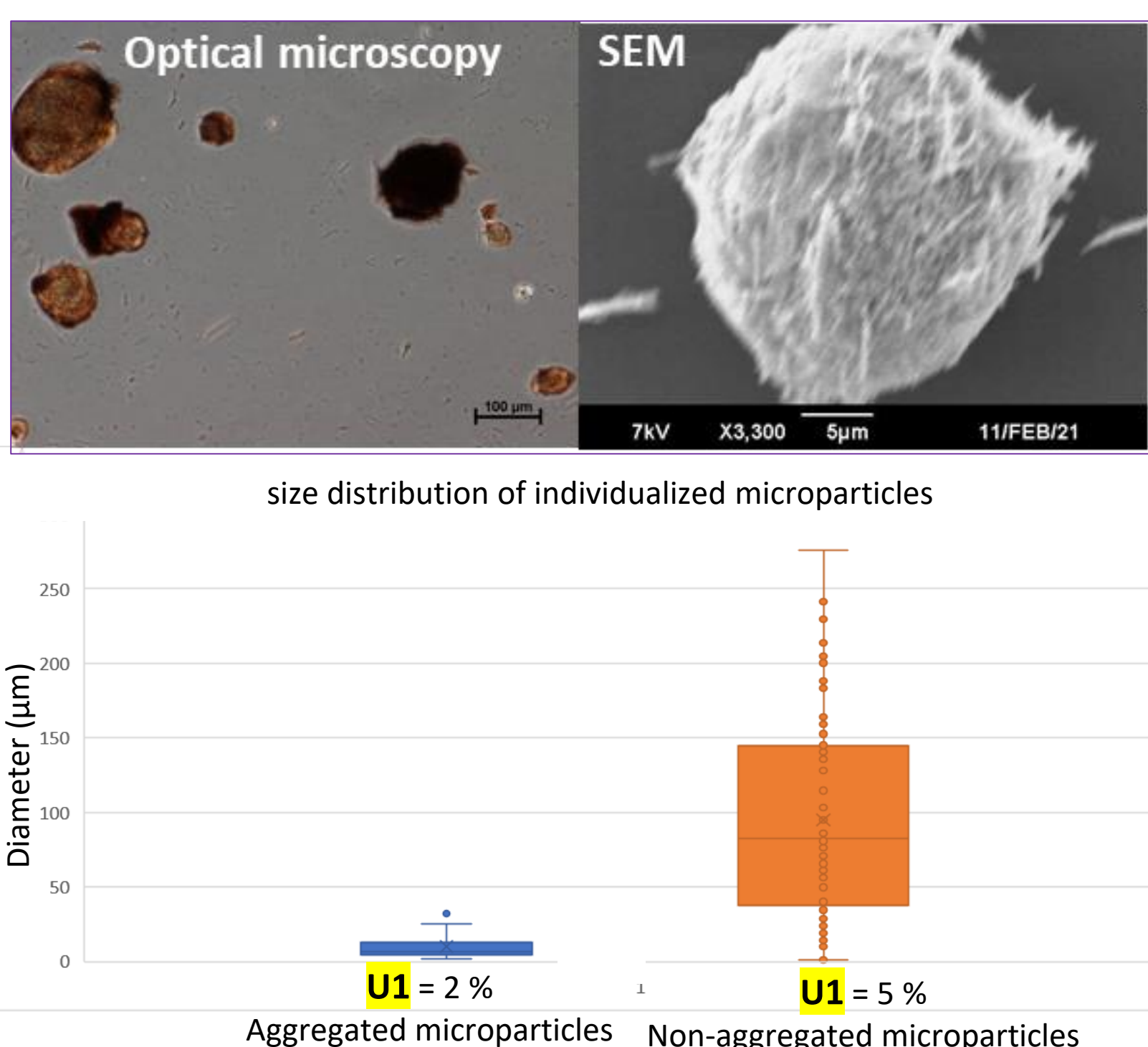
Linear regression model

Response variables:

- ✓ Size distribution
- ✓ Particle size
- ✓ aggregation
- ✓ Encapsulation efficiency
- ✓ Drug loading
- ✓ Release profile

Results

Morphology and particle size



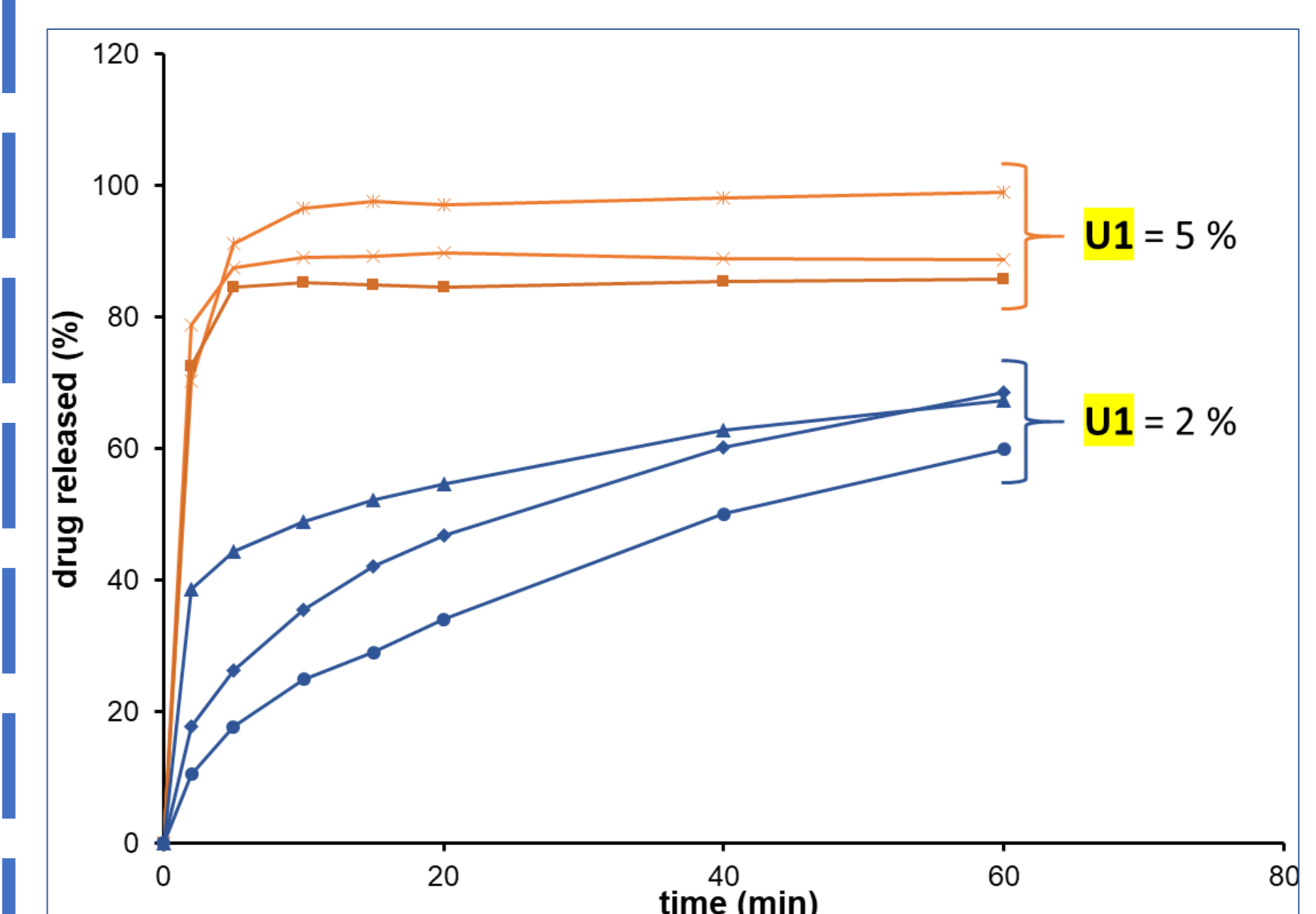
Encapsulation Efficiency > 80 %; Drug loading > 20 mg

Statistical analysis : Qualitative regression
 $Y1 \sim u1 + u2 + u3$

Variable	Limits	Estimate	p
Polymer concentration (% w/w) : U1	2 5	EE ↑ 19 %	<0.001
Active ingredient/polymer ratio : U2	0.1 0.5	EE ↑ 36 %	<0.001
Crosslinker flow rate : U3	Low High	EE ↓ 12 %	0.01
Crosslinker volume (mL) : U4	5 10	EE ↑ 5 %	0.25

Significant impact of U1, U2, U3 on the Encapsulation responses

Fast release profile : 50% in 1 h



Responses	Factors	U1 : increase from 2 % to 5 %	U2 : increase from (0,1 : 1) to (0,5 : 1)	U3 : increase from low to fast	U4 : increase from 5 mL or 10 mL
1) Polydispersity > 0.5		No significant impact : p value > 0.05			
2) Particle size < 100 μm		↗	↗		
3) Presence or absence of aggregation		↗			
4) Encapsulation efficiency > 80%		↗	↗	↘	
5) Drug Loading > 20 mg		↗	↗		
6) Release profile > 50% in 1 h		↘			

Discussions / perspectives

The results show that, depending on the different formulation conditions, particles are extremely polydisperse (polydispersity index (PDI) over 0.5). **Microfluidic technology** could help to control size distribution and will be next tested.

The encapsulation efficiency reached 80 % (w/w) in specific conditions with more than 20 % (w/w) drug loading. However, the release profile still needs to be optimized, for example by using a **coating with an hydrophobic polymer**.

Alginate concentration (U1) and drug/polymer ratio (U2) are the two main critical parameters conditioning the physicochemical properties of particles. **A Sequential composite central plan will be performed in the future to define design space for U1 & U2, with the final aim to develop of a polymeric platform adapted to hydrophilic drug encapsulation and delivery**

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