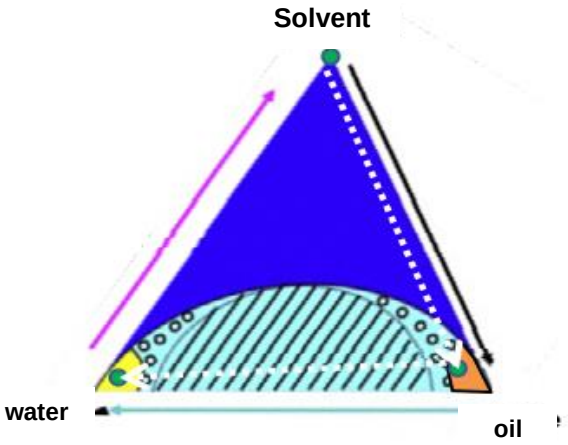
Encapsulation of Hydrophilic Solute by Spontaneous Emulsification

Encapsulation techniques have been widely investigated over the last decades as a way to protect from the surrounding medium, actives or reagents with a view to deliver these at precise locations and/or to release them in a controlled way. Many fields could benefit from such properties, e.g. pharmacology, cosmetics or agriculture. When the species to encapsulate is oily (albeit, water-insoluble), many papers have shown the feasibility of encapsulating a large variety of solutes into various micro- or nano-containers using different bottom-up techniques.[1] Arguably, there are as many water-soluble actives or reagents of importance, but these are trickier to encapsulate. To our knowledge, only a few, multi-scale systems have been described so far.[2] One strategy relies on trapping actives in water dispersions of water-filled polymer capsules. A quick, non-comprehensive literature survey showed that two processes have been recently designed to generate water-filled containers: (i) direct vesicle-like formation (cross-linked or solid liposomes,[3] polymersomes[4]…) in aqueous medium or (ii) a two-step formation, where preformed reverse micelles or W/O emulsions are evaporated or freeze dried, and then re-dispersed in water. The former is feasible only in rather dilute conditions, and generally does not permit high loading of hydrophilic solutes. The latter requires at least two types of surfactants/polymer dispersants, and is often solute-specific. One should remind also that, since the osmotic pressure is high inside the active-filled capsule, rupture often occurs in the course of capsules preparation if their polymer shell is too fragile.

Here, we aim to combine our expertise in chemistry and in physical-chemistry to generate, in the simplest manner, water dispersions of soft matter capsules loaded with hydrophilic actives. In the IMP lab, we have developed an emulsification technique, called the Ouzo effect[5] (a reference to the Greek aniseed aperitif), allowing generating nanocapsules in a very simple way.[6] So far, these were basically constituted of an oil core, possibly loaded with e.g. a fluorophore or a drug, surrounded by a crosslinked polymer shell, again feasibly functionalized with metal nanoparticles, biotin or antibodies. We likely showed that another domain of the phase diagram, called SFME (for surfactant-free microemulsion) was also exploitable to generate capsules. On the other hand, to our knowledge, encapsulation of water-soluble principles was not carried out so far using these spontaneous emulsification techniques that work independently of the solute considered. Theoretically, water-in-oil emulsions can be generated spontaneously in the inverse Ouzo or SFME domain. By using the right amphiphilic polymeric surfactant to precipitate at the water droplets' interface, capsules can be formed. Then, after shell crosslinking, post re-dispersion in water/solvent mixture will be carried out to reach the "direct" part of the phase diagram (see Figure below).



Over-simplified schematic procedure to generate water-dispersed, water-filled capsules by spontaneous emulsification. The first step consists in adding water in a highly-concentrated oil in solvent mixture (1st arrow, orange domain) and then to add extra water/solvent to come back to the direct emulsion zone (yellow zone). All steps will be studied independently to reach the final target.

There are several hurdles to jump through in this project. First, the design of amphiphilic molecules, either surfactants or polymers, that can be reversibly crosslinked according to different triggers, is a real challenge. The toolbox of IMP to polymerize specialty in a control manner, should allow generating new block co- or ter-polymers able to stabilize the interfaces. Besides, the physical chemistry of the inverse Ouzo (or inverse SFME) domain is unknown so far, and will require extensive phase diagrams establishment.

References

[1]. A recent book: Handbook of Encapsulation and Controlled Release, M. Mishra Ed., CRC press (2015).
[2]. e.g. D. J. MacClements, *Advances in Colloid and Interface Science*, **219**, 27–53 (2015).
[3]. R. H. Müller, K. Mäder, S. Gohla, *European Journal of Pharmaceutics and Biopharmaceutics*, **50**, 161–177 (2000).
[4]. B. M. Discher, Y.-Y. Won, D. S. Ege, J. C-M. Lee, F. S. Bates, D. E. Discher, D. A. Hammer *Science,* **284**, 1143–1146 (1999).
[5]. a) S. A. Vitale, J. L. Katz, *Langmuir*, **19**, 4105–4110 (2003); b) F. Ganachaud, J. L. Katz, *ChemPhysChem*, **6**, 209–216 (2005).
[6].a) X. Yan, M. Delgado, A. Fu, P. Alcouffe, S.G. Gouin, E. Fleury, J. L. Katz, F. Ganachaud, J. Bernard, *Angewandte Chemie, International Edition*, **53**, 6910–6913 (2014); b) X. Yan, A. Sivignon, P. Alcouffe, B. Burdin, S. Favre-Bonte, R. Bilyy, N.Barnich, E. Fleury, F. Ganachaud, J. Bernard, *Chemical Communications*, **51**, 13193–13196 (2015); c) X. Yan, P. Alcouffe, G. Sudre, L. David, E. Fleury, J. Bernard, F. Ganachaud, *Chemical Communications*, **53**, 1401–1404 (2017); d) X. Yan, R. Ramos, E. Hoibian, C. Soulage, P. Alcouffe, F. Ganachaud, J. Bernard, *ACS Macro Letters*, **6**, 447–451 (2017).