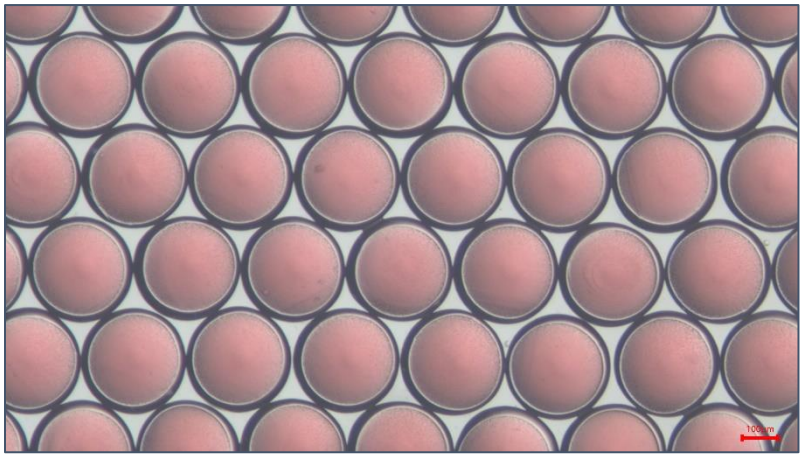
POLYMETHACRYLATE MICROCAPSULES WITH AN OILY CORE GENERATION



Application note

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I) Introduction

Over the past few decades, core-shell microcapsules (see Figure 1) have been extensively used for the delivery and release of materials in the pharmaceutical, cosmetic, and food industries. The encapsulation of Active Pharmaceutical Compounds in core-shell microcapsule is of great interest for several purposes: taste and odor masking, controlled release of drugs… In pharmaceutics the possibility to encapsulate drugs, nutrients, and living cells that can be protected by a solid biocompatible shell in order to target a specific site is an intense field of research.

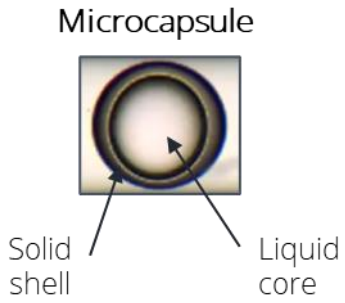


Figure 1: Definition of a solid core-shell microcapsule

However, classical methods of microencapsulation, like coacervation, spray drying, solvent evaporation, etc, require complex process and equipment and make difficult to control the size and load of the microcapsules.

In contrast, microfluidics allows to produce monodisperse double emulsions which lead to monodispersed microcapsules with a high control over both the size and the structure. Microfluidics tools are also used to create capsules of varying compositions. With this technology, it is possible to encapsulate aqueous or oily solutions. The encapsulation of aqueous solutions allows the capsule to contain proteins or active pharmaceutical ingredients (APIs). On the other hand, oily solutions containing lipophilic or poorly water-soluble drugs can also be encapsulated. Moreover, capsules can be used for drug delivery thanks to programmable active release mechanism. [1]

This Application Note is complementary to the application note entitled *Polymethacrylate resin microcapsules synthesis*, available on the website of Secoya Technologies (https://secoya-tech.com/documents/application-note-polymethacrylate-resin-microcapsules-synthesis/). The main difference is the composition of the core phase. In this document, the capsules contain an oily core, which is essential to encapsulate oily-soluble molecules. The capsule formation is, here again, made by the cross-linking of the polymeric shell of the double emulsion. This reaction consolidates the shell phase and makes it solid. [2] Thus, the oil is encapsulated in polymeric microcapsules (PMCs) with tunable sizes [3].

II) Materials and methods

1) Materials

Core phase:

- Soybean oil (Sigma-Aldrich) with a 0.07% of red dye Sudan IV (Sigma-Aldrich)

The red dye creates a contrast between the polymeric shell and the oily core of the double emulsions. The observation is thus facilitated.

Shell phase:

- Commercial Allnex methacrylate-based resin containing 20% of ethyl acetate (EtOAc, Merck) and 0.1% wt of photoinitiator Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide (TPO, Sigma-Aldrich)

It is important to notice that the photoinitiator reacts with light, so to avoid solidification of the solution, the solution must be protected from light by using a smoked glass container for example.

Continuous phase:

- Water containing 2% Poly(vinyl alcohol) (PVA, Sigma-Aldrich)

Priming and cleaning phase:

- Ethyl acetate (EtOAc, Merck)

2) Platform device

The production of droplets is performed with the Raydrop® Platform, presented in Figure 3. The Raydrop Platform is a lab equipment integrating all the components needed to produce simple and double emulsions using the Raydrop® device. This platform is divided into three parts: mechanics, fluidics and optics. More information about this platform cand be found on the platform webpage available on the Secoya website at https://secoya-tech.com/technologies/emulsifications/. In Figure 2, a schematic representation is shown of the setup used for this work.

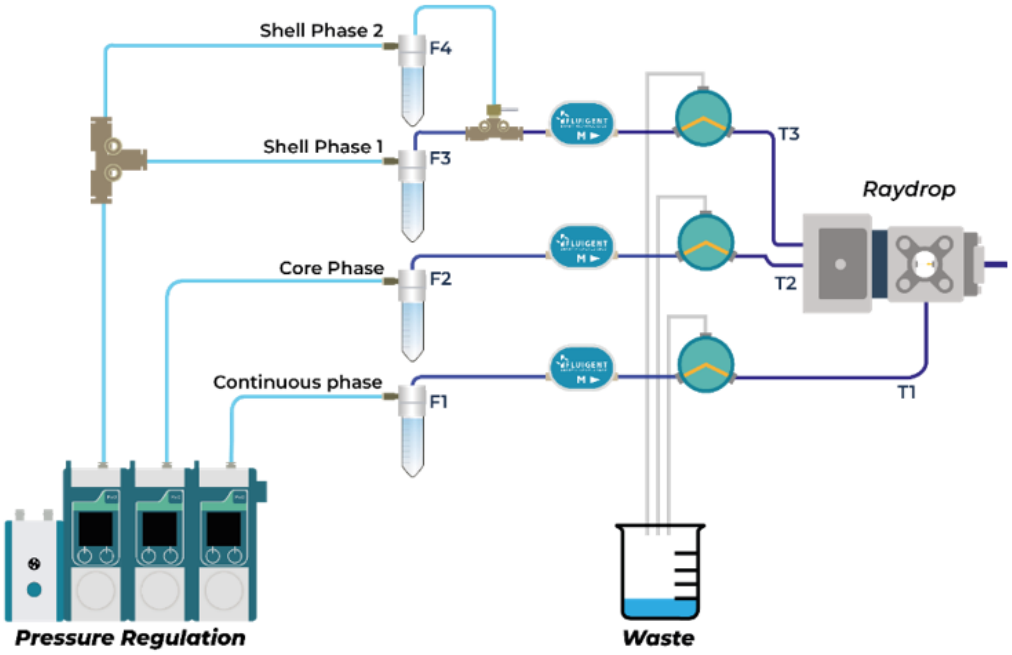


Figure 2: Experimental set-up to produce double emulsion. This flow scheme can be slightly different from the one corresponding to the commercialized version of the platform, where two reservoirs for the core phase are included.

Fluid reservoirs

Falcon identification	F1	F2	F3	F4
Volume (mL)	50	50	50	15

Phase[1]	Continuous	Core	Shell (priming and cleaning)	Shell
Composition	Water + 2% PVA	Soybean oil + Sudan IV	EtOAc	Allnex methacrylate-based resin + 20% EtOAc + 0.1% wt TPO

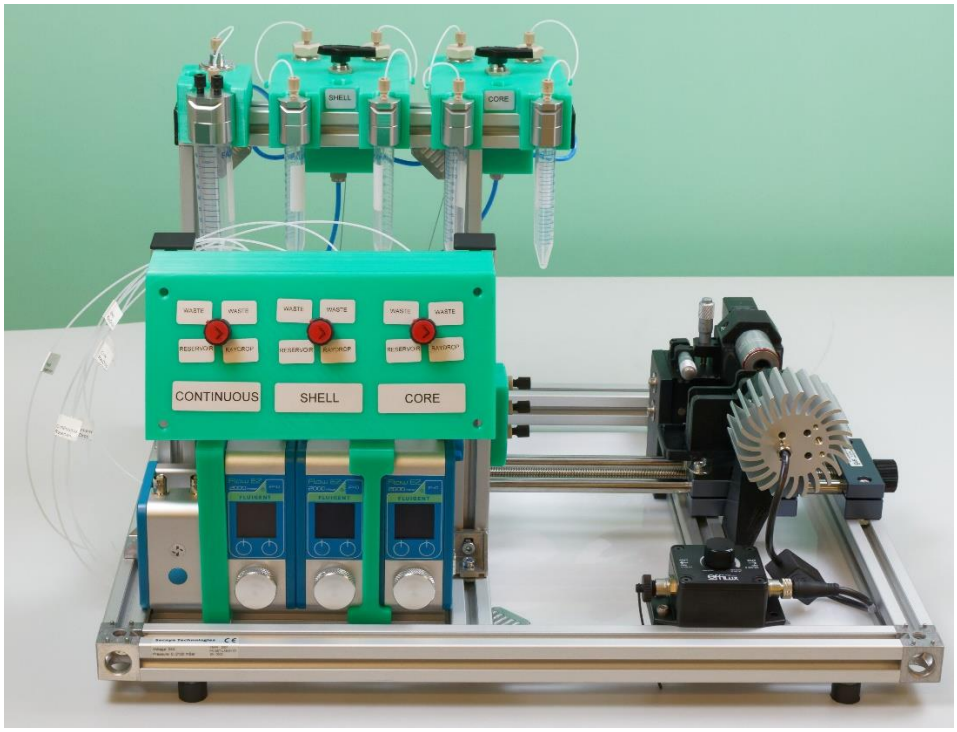


Figure 3: Raydrop Platform

- **Mechanics:** The mechanical part includes x-y-z displacement plates that allow to adjust the focus and the observation window in the Raydrop®.
- **Fluidics:** The fluidic part consists of flowrate controllers along with the required tubing and valves, allowing for automated fluidic injection. A pressure is set on each reservoir, and fluids are injected into the microfluidic chip. It also includes Falcon reservoirs and the Raydrop®, in which double emulsions are

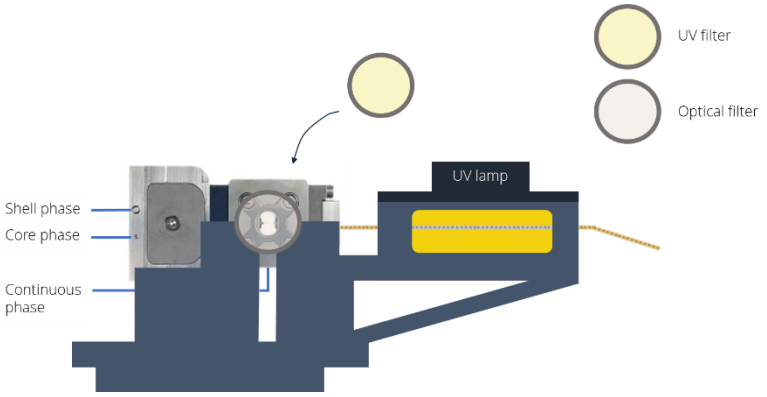
[1] *Each phase is filtered to avoid contaminating the tubing or the nozzle of the Raydrop®. Therefore, there is an integrated filter after each Falcon on the platform. In this case, the continuous phase filter has a 10 µm filter pore size and the shell and core filters have a 2 µm filter pore size.*

generated. After each reservoir, a filter is included that eliminates impurities that could plug the Raydrop®.

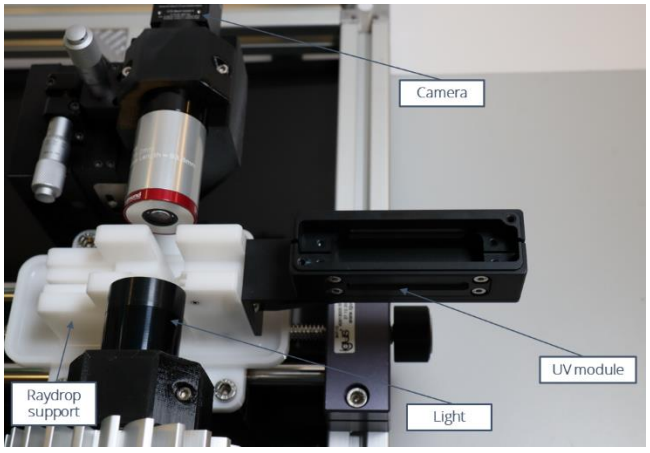
- **Optics:** The optical part of the platform contains a LED light source and a color USB 3.0 camera. This camera is connected to a computer to observe the droplet formation in live, control the stability of the emulsion and measure the size of interest (core, shell).

Double emulsions are formed by pumping the three fluids through the Raydrop® using a pressure controller. The flowrates are monitored using flowmeters. This time, as a polymeric double emulsion is formed, the platform configuration changes a bit.

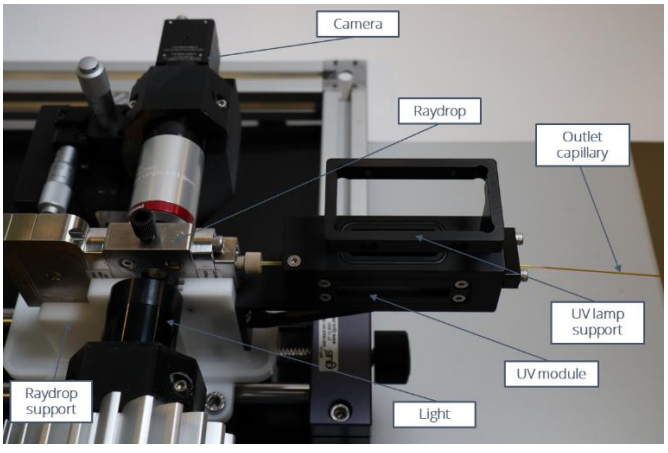
A module integrating a UV-lamp is added to the platform to precisely control the cross-linking of the resin shell, as shown in Figure 4.



Scheme of the module



Module integrated to the platform



Raydrop and outlet tubing placed in the module. An UV lamp has to be fixed in the lamp holder.

Figure 4: The module integrated to the Raydrop Platform

This module is movable using a displacement plate, which allows to observe not only the formation of the emulsion in the Raydrop® but also to check at the exit of the Raydrop® that the emulsion remains stable (essential step during the formation of double emulsion) in the outlet tubing. The observation is made with the camera of the platform, by moving the module (see Figure 5) so that the camera can follow the emulsion progression in the outlet tubing.

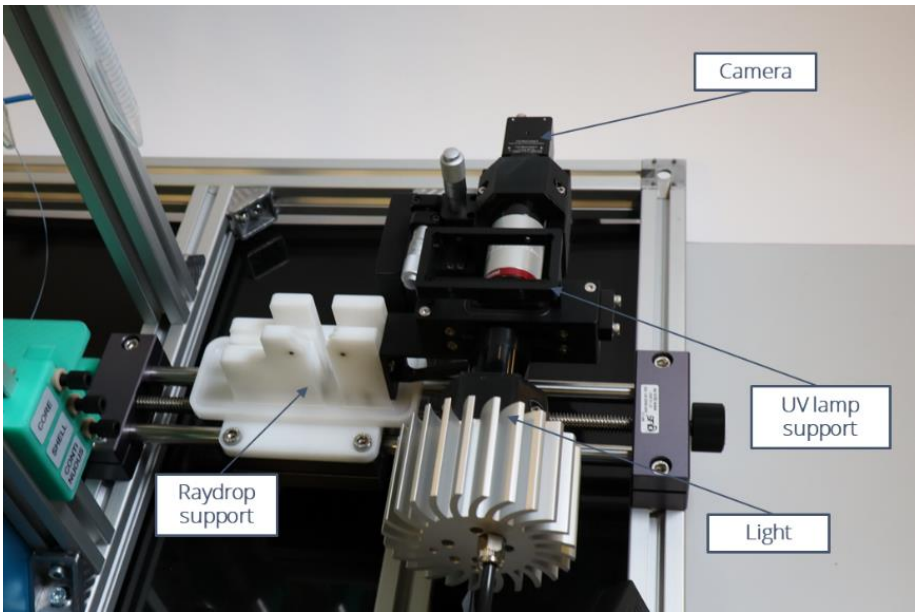


Figure 5: Module in observation position in the outlet tubing

Two windows with an anti-UV glass filter guarantee a safe observation for the user.

A UV light source irradiates the tubing to initiate the cross-linking of the resin. Hard shell capsules come out at the end of the tubing, which can be more or less inclined to simplify the collection in a vial.

The in-situ cross-linking of the emulsion (see Figure 6) is useful: it avoids coalescence and deformation of the droplets that can arise in an ex-situ process where the droplets are cross-linked after collection.

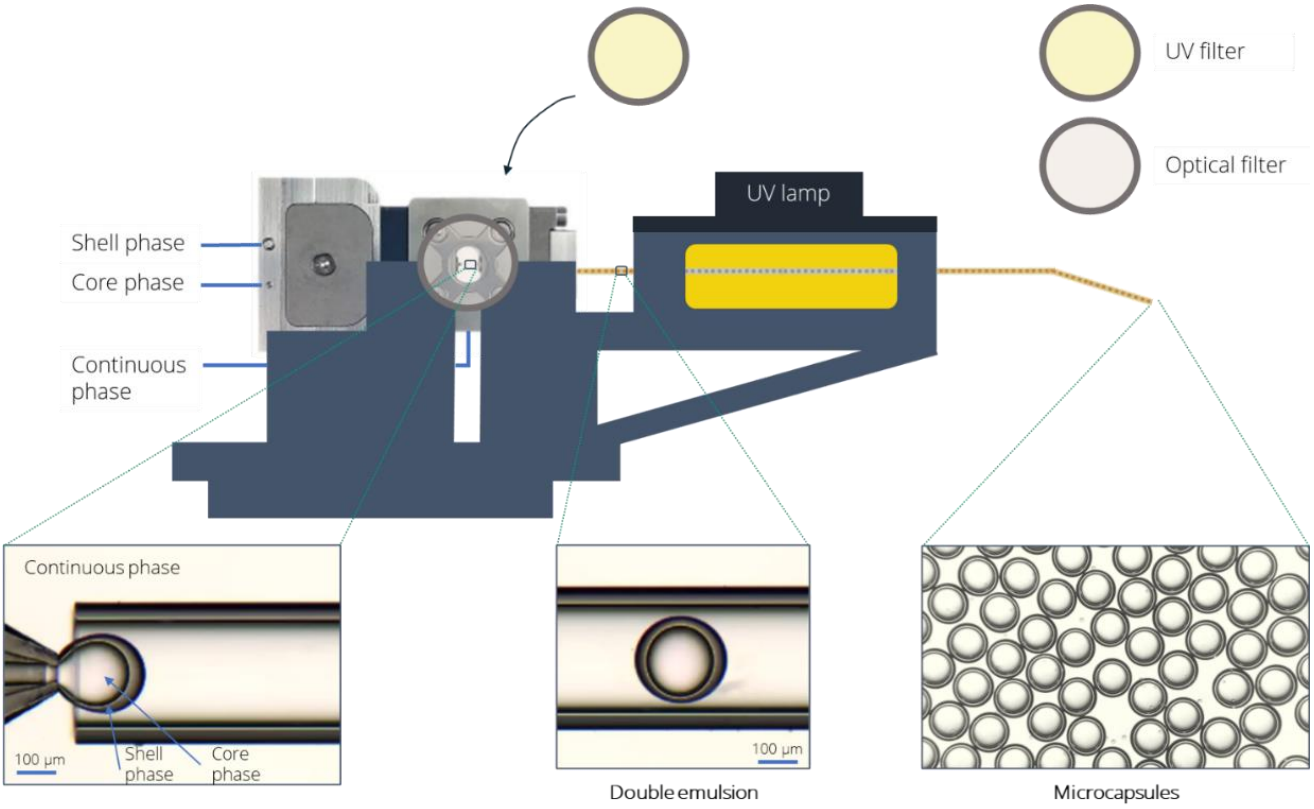
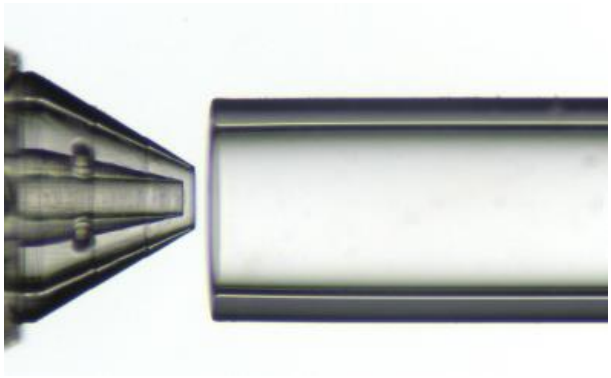


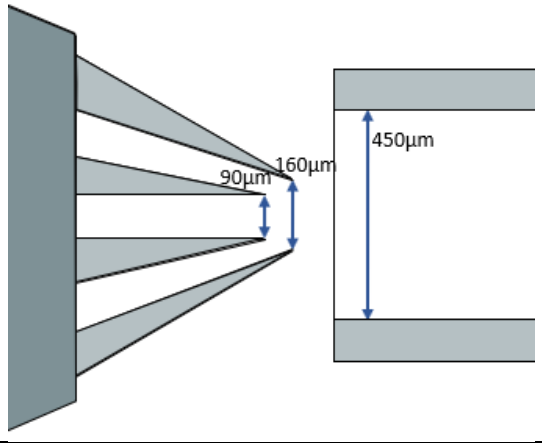
Figure 6: In-situ cross-linking process leads to the formation of monodispersed microcapsules

3) Raydrop® configuration

The Raydrop® is Secoya's microfluidic droplet generator. This emulsification technology produces controlled simple emulsions. By changing an insert (see Figure 7) of the Raydrop®, stable double emulsions can be produced without coating of oily and water phases; for stability reasons usually surfactants are added to the different phases.



Picture of the Raydrop®



Scheme of the Raydrop®

Figure 7: Insert and extraction capillary

Nozzle information

Part	Core nozzle	Size-shell nozzle	Size-extraction capillary
Inside diameter (µm)	90	160	450

4) Emulsion generation

To generate droplets, the system must first be primed with pure solvent in the shell phase. Once droplet formation is stable, the shell phase is switched to the polymethacrylate-based solution. This permits to avoid clogging issues during the transient phase. The user should follow the steps below:

1. Set the valve on the Falcon F3 (priming solution)
2. Fill the Raydrop® with the continuous phase
3. Set the continuous phase (F1) to the desired flow rate
4. Set the shell phase (F3) to the desired flow rate. At this point, a co-flow of ethyl acetate and water is generated
5. Set the core phase (F2) to the desired flow rate to generate double emulsions

6. Once the double emulsion production is stabilized – which can be observed with the camera images – switch the valve to the methacrylate-based shell solution (F4)
7. Wait[2] until the polymethacrylate solution crosses the tubing and reaches the Raydrop® to form a double emulsion with a polymethacrylate solution shell and an oily core in the continuous phase, in the same way as in Figure 8

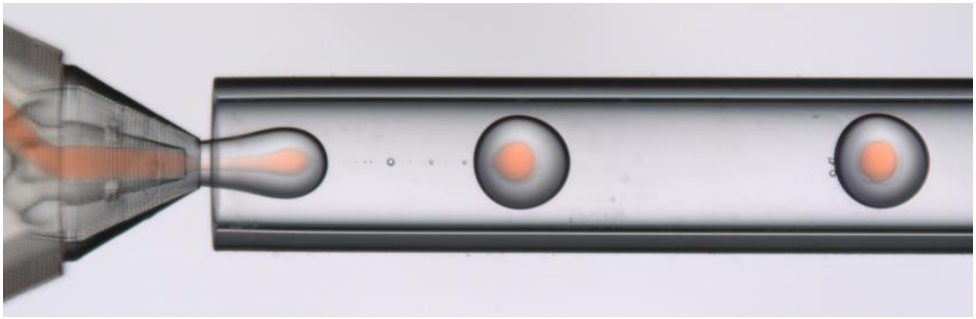


Figure 8: Generation of droplets in the Raydrop®

8. If necessary, stabilize the double emulsion by varying the flow rates
9. Adjust the flow rates to obtain the desired droplet diameter and shell thickness, as highlighted in Figure 9

[2] *This can take 3 to 5 minutes, depending on the flow rate of the polymethacrylate phase and the diameters and length of the tubing.*

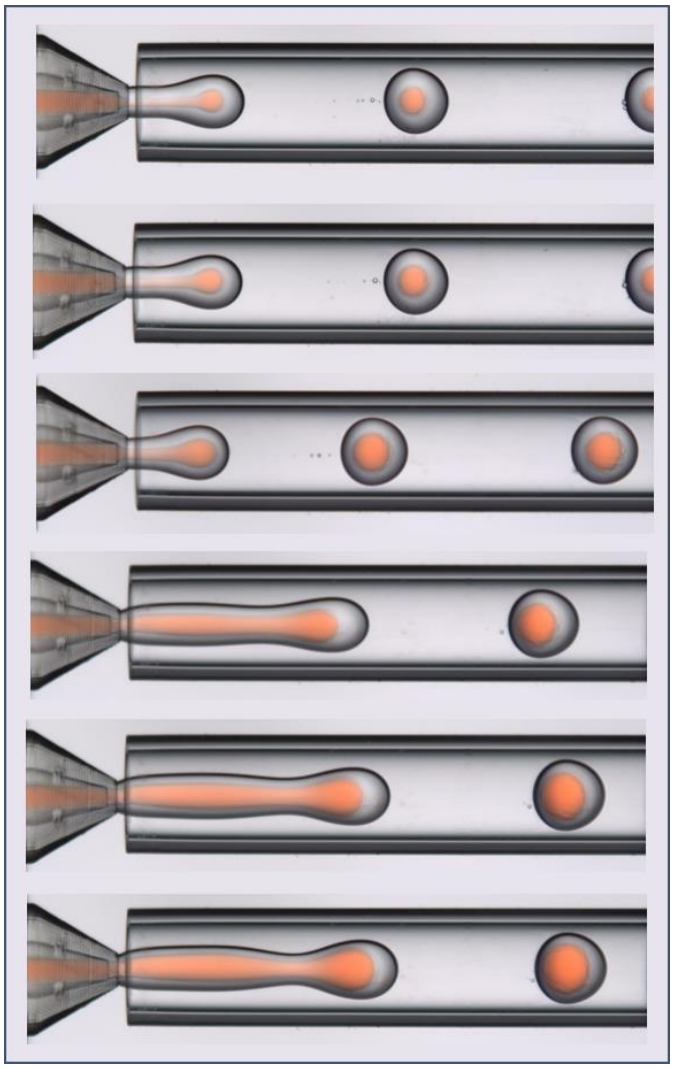


Figure 9: Generation of double emulsions at various core flowrates (from 1,6 to 6 µL/min)

1) Capsule formation

Now that the double emulsion is produced with the adapted flow rates, the in-situ cross-linking take place. Figure 10 describes the cross-linking phenomena thanks to the UV radiation action.

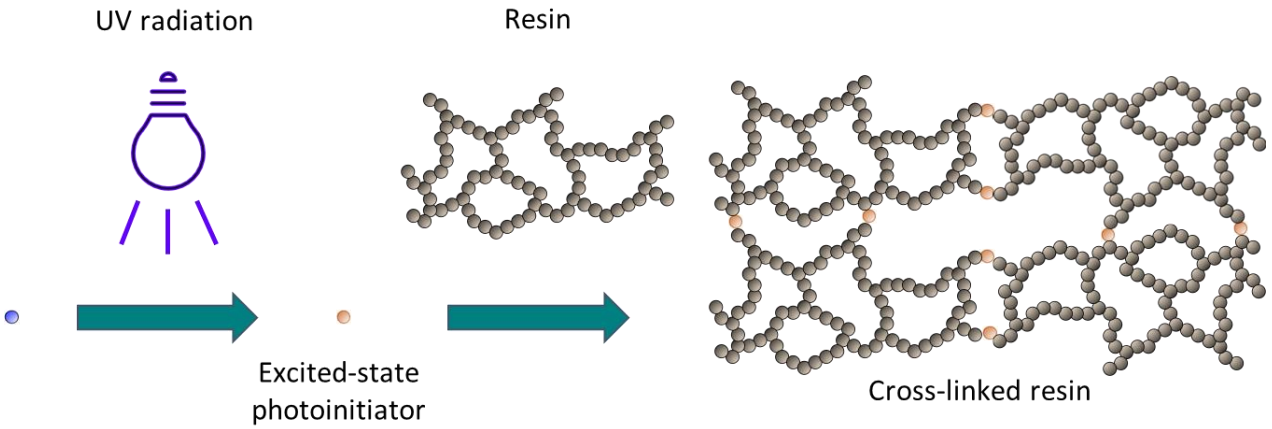


Figure 10: Principle of the cross-linking process of a resin

10. Translate the module so that the camera shows the double emulsion in the outlet tubing
11. Check that all droplets are of the same size and that the droplet train is regular with a constant space between each drop. If the droplet train is not regular, modify the flow rates to stabilize the production
12. Once the drop train is stable, switch on the UV light
13. Collect the capsules at the outlet of the tubing. A result similar to the picture on the left in Figure 11 is obtained.

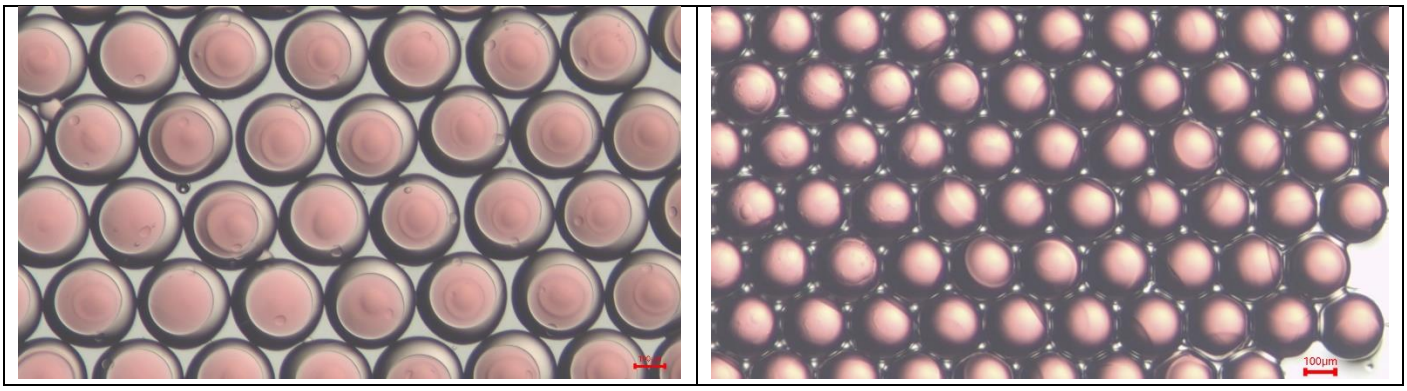


Figure 11: Polymethacrylate capsules containing colored oil, observed under the microscope. On the left, capsules collected in water. On the right, dried capsules.

14. Once that enough capsules have been produced, switch off the UV lamp.

Before stopping the experiment, it is important to flush the shell tubing (T3) and the nozzle of the Raydrop® with the priming solution (F3). This priming and cleaning solution allows the evacuation of the polymethacrylate resin. In this way, the tubing stays clean and clogging is avoided.

15. First, translate the module so that the camera shows the nozzle of the Raydrop
16. To flush the polymethacrylate resin out of tubing and Raydrop®, switch the valve on the priming solution (F3)
17. Wait[2] until the cleaning solution crosses the tubing and reaches the Raydrop® to form a double emulsion with an ethyl acetate shell and an oily core in the continuous phase.
18. Cut the flow of the core phase
19. Then, cut the flow of the shell phase
20. Finally, cut the flow of the continuous phase

III) Results

Evolution of droplet diameters by varying the core flowrate

The outer diameter of the emulsions and thus the capsule size can be varied within a broad range by changing the size of the collector capillary and the nozzle tip dimensions. This is easily achieved by a change of the two inserts.

For a configuration with the nozzle and output capillaries (respectively 90µm and 450µm), as presented in this application note, adjusting the flowrates of the fluids allows for fine control of the capsule dimensions (see Figure 12). With this setup, capsules from 200µm to 400µm can be easily produced.

The shell thickness of microcapsules can also be varied by changing the ratio of flowrates of the core phase, as underlined in Table 1. In Figure 13, the shell thickness varies from 181µm to 216µm.

	Continuous phase	Shell	Core
Composition	Water + 2% PVA	Allnex methacrylate-based resin + 20% EtOAc + 0.1% wt TPO	Soybean oil + Sudan IV
Flow rate (µL/min)	100	30	various

Table 1: Flowrates used to produce numerous samples with different capsules sizes

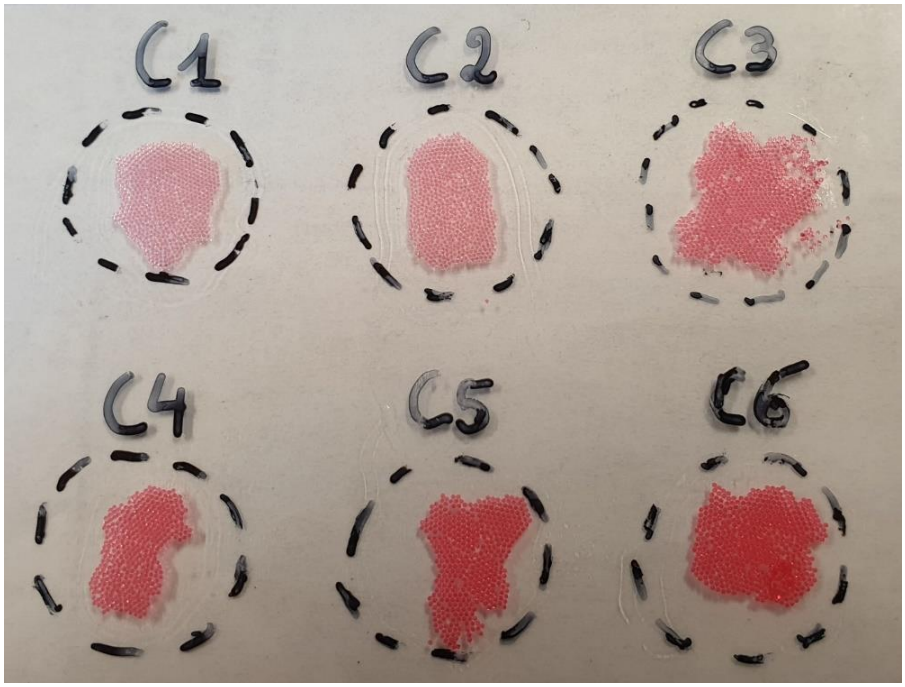


Figure 12: Overview of the samples, with a visible color difference depending on the core size

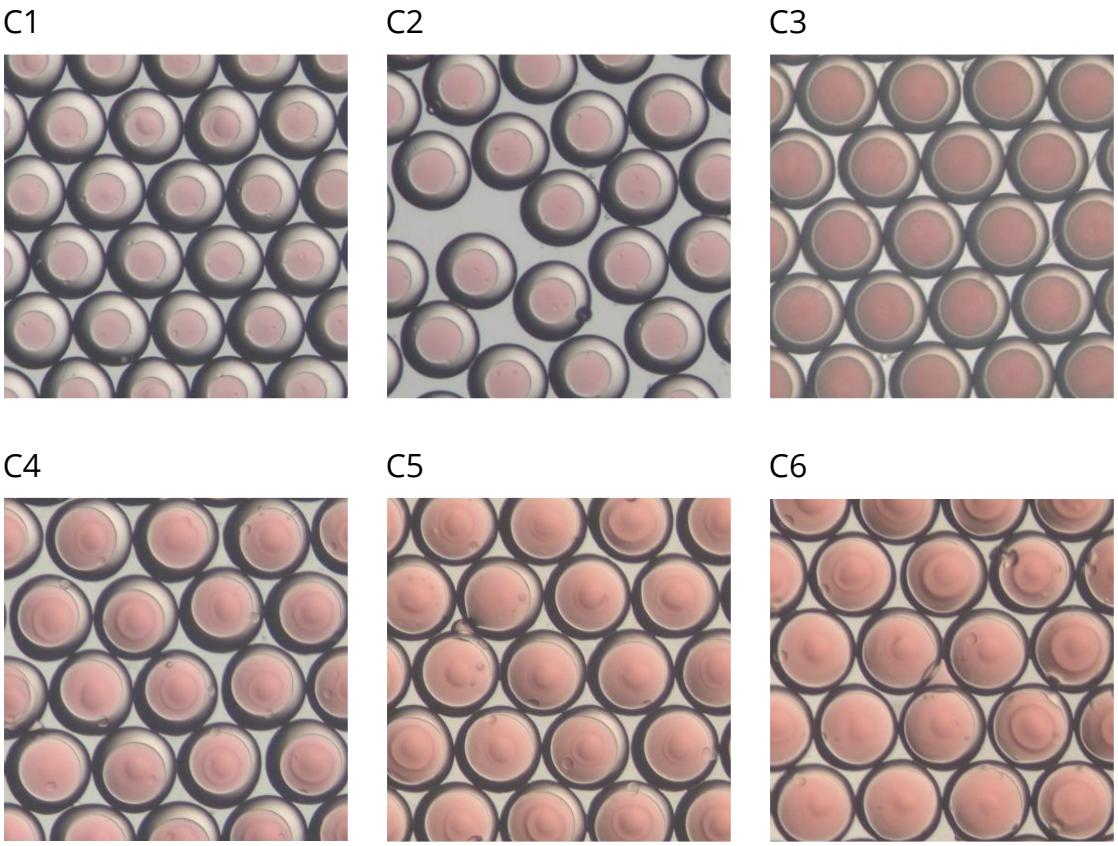


Figure 13: Microcapsules with shell thickness adjustment between 181µm to 216µm, under the microscope

Measurements of internal and external diameters (ID and ED) on a large number of capsules lead to Figure 14 and Figure 15. In Figure 14, we notice that the increase of the core flow increases the internal diameter and thus the external diameter. Moreover, as the shell flowrate is kept constant, the shell thickness decreases as the core flowrate is increased, as shown in Figure 15.

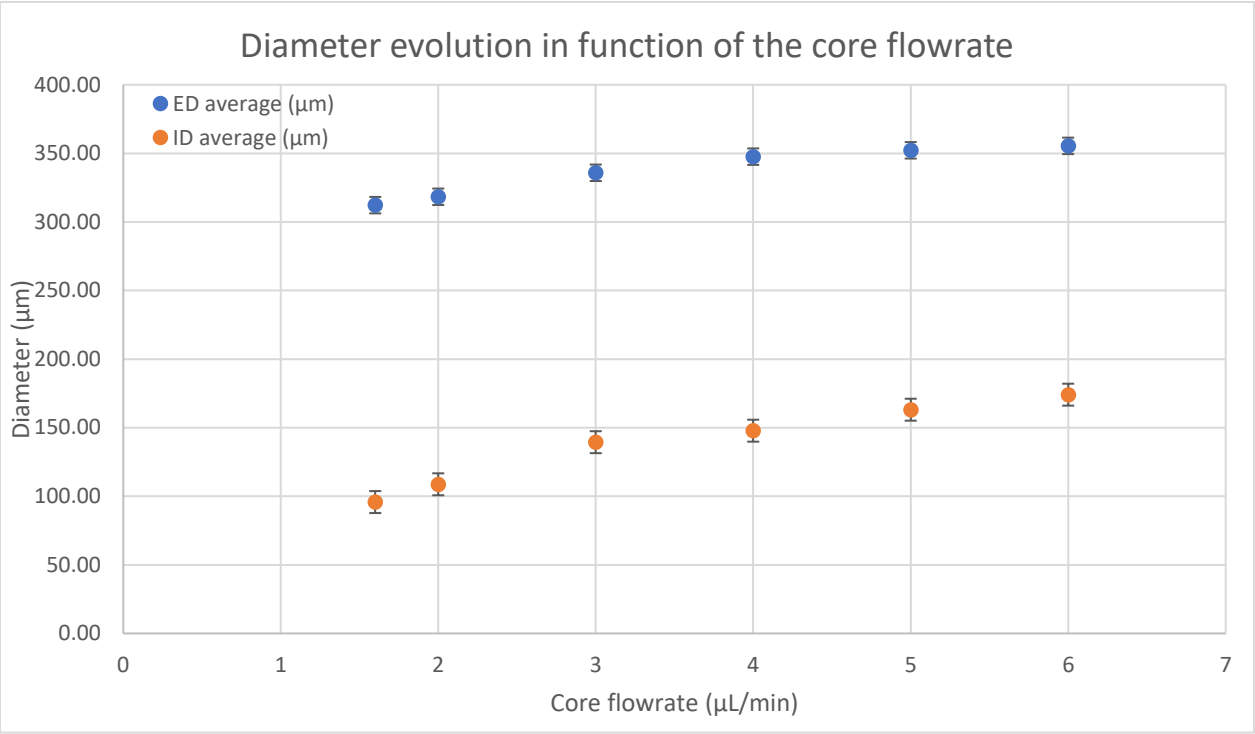


Figure 14: Internal and external diameters evolution depending on the core flowrate

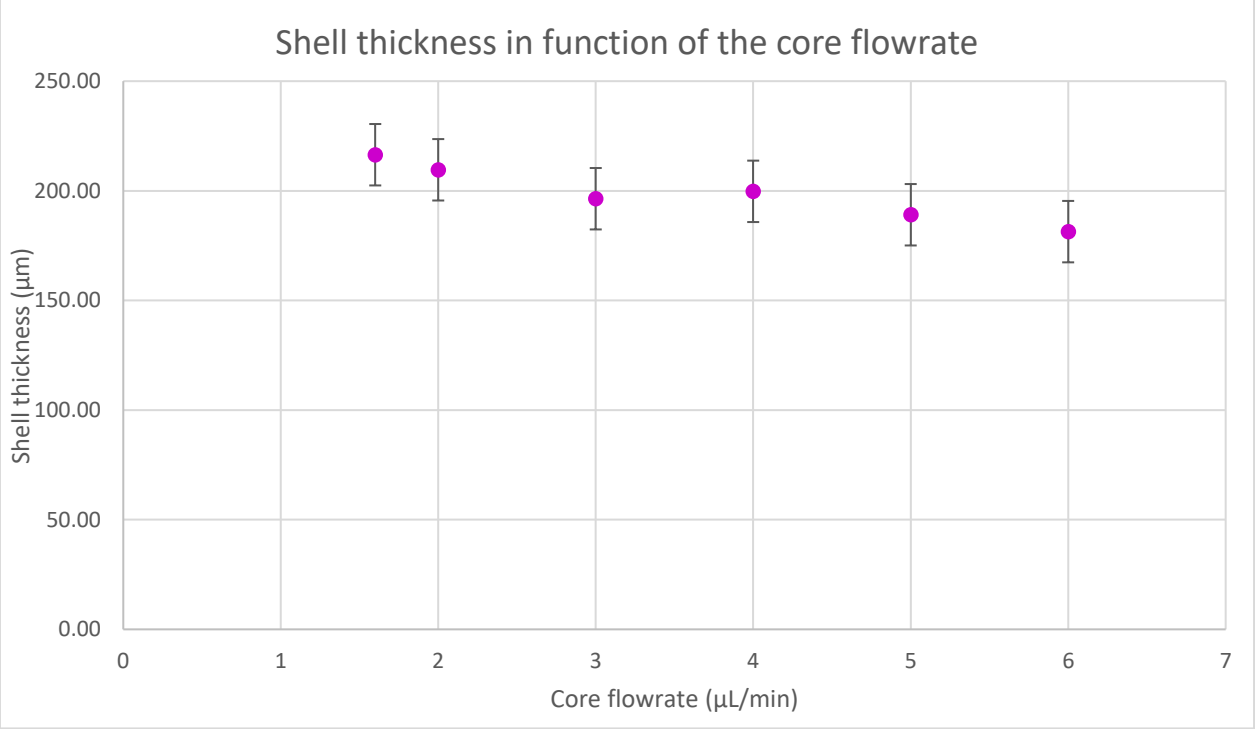


Figure 15: Shell thickness evolution

IV) Conclusion

The formation of the double emulsion oil/resin/water allows to produce solid capsules containing an oily phase. The oily core enables the encapsulation of oily compounds, which is useful for liposoluble active ingredients. With the Raydrop®, the variation of the shell thickness is easily feasible, and in the same way the volume of material to be encapsulated can also be easily adjusted.

As a supplement to the application note entitled *Polymethacrylate resin microcapsules synthesis*, this document highlights the versatility of the Raydrop platform. With the same continuous phase and resin as a shell, the production of oily core capsules and aqueous core capsules is also possible.

V) References

[1] ABBASPOURRAD, Alireza, CARROLL, Nick J., KIM, Shin-Hyun et WEITZ, David A., 2013. Polymer Microcapsules with Programmable Active Release. Journal of the American Chemical Society [en ligne]. 22 mai 2013. Vol. 135, n° 20, pp. 7744-7750. [Consulté le 20 mai 2022]. DOI 10.1021/ja401960f.

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[3] SEEKELL, Raymond P., PENG, Yifeng, LOCK, Andrew T., KHEIR, John N. et POLIZZOTTI, Brian D., 2018. Tunable Polymer Microcapsules for Controlled Release of Therapeutic Gases. Langmuir [en ligne]. 7 août 2018. Vol. 34, n° 31, pp. 9175-9183. [Consulté le 20 mai 2022]. DOI 10.1021/acs.langmuir.8b01328.