Step I (2018) Synthesis and characterization of PDMS-based copolymers

Activity 1.1: Synthesis of PDMS-based copolymers

1.1.1 Synthesis of PDMS-Br starting from the PDMS-OH

In order to obtain the functionalized PDMS with a Br-type terminal group, the following reaction was performed (Fig. 1):

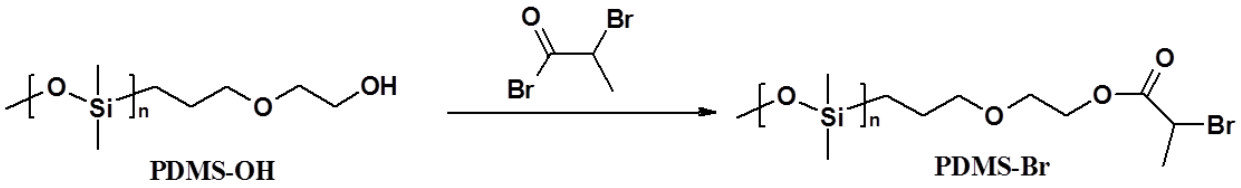

Fig.1 : Obtaining PDMS-Br starting from a PDMS-OH

1.1.1 Synthesis of PDMS-xanthate and PDMS-N_3 starting from the PDMS-Br

In order to obtain the functionalized PDMS with a terminal xanthate or N_3 type group, a previously prepared PDMS-Br was used. Figure 2 describes the reaction to obtain PDMS-xanthate macroradical.

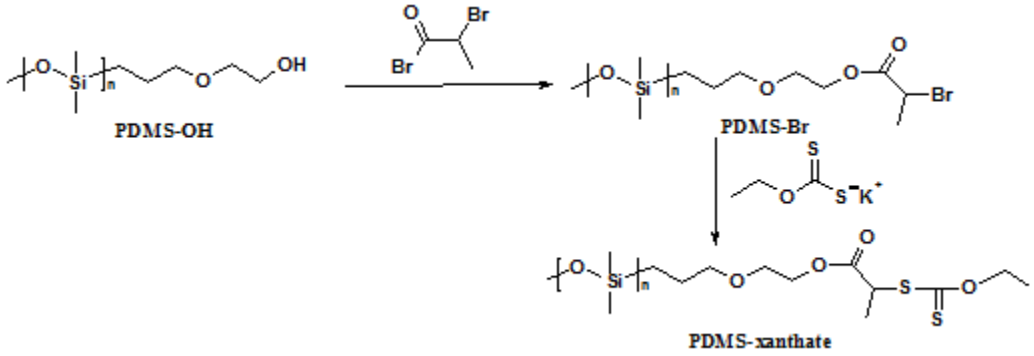

Fig. 2 : *Synthesis of PDMS-xanthate starting from the PDMS-Br*

1.1.2 Syntheis of PDMS-based copolymers

For the synthesis of PDMS-b-PCL copolymers, a "click-chemistry" reaction was used starting from a PDMS-N_3 and a PCL precursor functionalized at the end of the polymer chain with an alkyl group, as shown in Figure 3. Mn (^{1}H NMR) = 3400 g/mol. ^{1}H NMR ($CDCl_3$ at 25 °C): 2

ppm (1H, t, CH≡), 3.65 ppm (2H, t, OH-CH_2), 4.2 ppm (2H, t, CH_2O-), 4.08 ppm (2H, t, CH_2-O), 2.33 ppm (2H, t, C=O), 1.64 ppm (4H, m, CH_2-CH_2), 1.40 ppm (2H, m, CH_2).

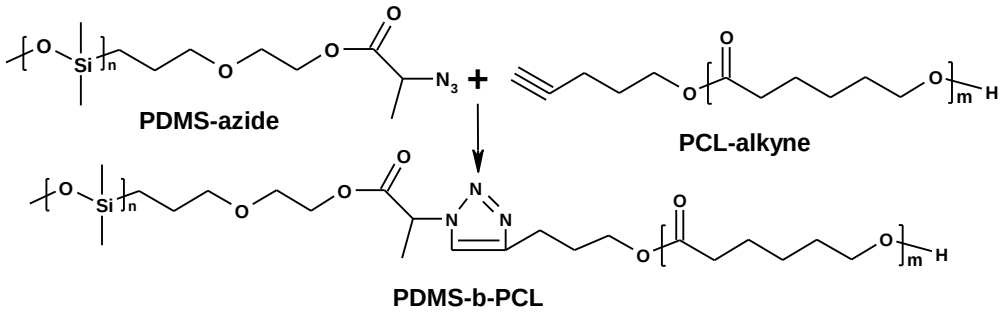

Fig. 3: *Synthesis route of PDMS-b-PCL copolymer*

Synthesis of the PDMS-b-PVP copolymer was accomplished by a RAFT-Madix controlled polymerization starting from a functionalized macroCTA PDMS with a xanthate group according to Figure 4:

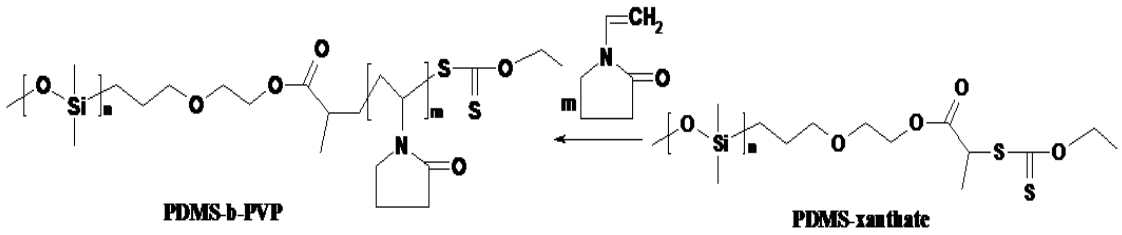

Fig. 4: *Synthesis route of PDMS-b-PVP copolymer*

Activity 1.2: ***Physico-chemical characterization of PDMS-based copolymers***

The physico-chemical characterization of the obtained products was performed by steric exclusion chromatography (SEC) and by nuclear magnetic resonance (NMR).

1.2.1 *Characterization of PDMS precursors*

The products PDMS-OH, PDMS-Br, PDMS-xanthate and PDMS-N_3 were characterized by NMR and SEC.

1.2.2 *Characterization of PDMS-based copolymers*

Similar to precursors, the obtained copolymers were characterized by the NMR and SEC techniques. The characteristic peaks for PDMS-PCL (ALI1) copolymer are the following: RMN

^{1}H ($CDCl_3$ 400MHz) δ (ppm) : 1. 3.63 (t, -C$\underline{H_2}$-OH), 2. 4.06 (t, -CH_2-C$\underline{H_2}$-O-), 3. 1.62 (m, -CH_2-C$\underline{H_2}$-CH_2-O-), 4. 1.42 (m, -CO-CH_2-CH_2-C$\underline{H_2}$-), 5. 1.62 (m, -CO-CH_2-C$\underline{H_2}$-), 6. 2.30 (t, -CO-C$\underline{H_2}$-), 7. 0.07 (m, -Si ($C\underline{H_3}$)$_2$-), 8. 0.53 (m, -CH_2-C$\underline{H_2}$-CH_2-), 9. 1.48 (m, CH_3-C$\underline{H_2}$-), 10. 0.88 (m, C$\underline{H_3}$-CH_2-), 11. 3.42 (m, -C$\underline{H_2}$-O-), 12. 1.62 (m, -Si-C$\underline{H_2}$-).

Table 1 presents the molecular characteristics of PDMS-b-PCL and PDMS-b-PVP copolymers.

Table 1: *Molecular characteristics of PDMS-b-PCL and PDMS-b-PVP copolymers*

Copolimer	M_n **PDMS**	M_n **PCL** (^{1}**H-RMN**)	M_n **PVP** (^{1}**H-RMN**)	M_n **copolimer** (^{1}**H-RMN**)	M_n **copolimer** (**SEC**)	**Đ**
ALI1	5680	3400	-	9100	9100	1.17
ALI2	5680	7100	-	12400	12600	1.14
ALI3	5480	-	2500	7150	7300	1.21
ALI4	5480	-	6500	11500	12000	1.31

1.2.3 *Self-assembly studies*

Increased interest in block copolymers in different areas of scientific research is related to their particular molecular structure, which gives them unique exploitable properties for industrial applications.

Self-assembling block copolymers in selective solvents is a well-known phenomenon and widely studied. For example, in an aqueous medium, micelisation is generally due to the presence of completely hydrophobic blocks.

At this stage, we examined through dynamic diffusion of light (DLS) self-assembly of these copolymers into an unfunctionalized silicone oil. For the PDMS-b-PCL and PDMS-b-PVP copolymers, formation of micelles systems with a hydrodynamic diameter of about 30 nanometers was observed.

Step II (2018) Preparation and characterization of non-aqueous emulsions based on PDMS (in the absence and in the presence of drugs)

Three more PDMS-based copolymers were synthesized in this step and the molecular characteristics of the copolymers obtained are given in Table 2:

Table 2: *Molecular characteristics of PDMS-based copolymers*

Copolymer	M_n PDMS	M_n PCL (^{1}H-RMN)	M_n copolymer (^{1}H-RMN)	M_n copolymer (SEC)	Đ
ALI5	3000	2000	5200	5100	1.20
ALI6	3000	4000	7400	7600	1.24
ALI7	10000	10000	21150	23000	1.35

2.1 ***Preparation and characterization of non-aqueous emulsions in the absence of drugs***

Three silicone oils having different viscosities as shown in Table 3 were tested. The viscosity was tested at 2 temperatures and 5 rotations ranging between 10 and 100 rpm.

Table 3: *Viscosity of silicone oils*

Silicon oil	Viscosity producer (cSt)	Experimental viscosity (cSt)*	
		25°C	**60°C**
SO3	3	4.5	3.4
SO50	50	116.2	30.7
SO350	350	386.3	230.0

* determined with the Brookfield viscometer by extrapolation at a zero rotation speed

In a first test, non-aqueous emulsions were prepared in the absence of copolymers. The total volume of an emulsion was fixed at 10 ml and the ratios of the two phases, 90/10, varied; 80/20 and 70/30 vol / vol. The continuous phase was represented by the silicone oils and the phase

dispersed by the VP and Ɛ-CL monomers. Emulsions were prepared by emulsification with a Ultraturrax 18 at a rate of 3000 rpm for 5 minutes at ambient temperature. The stability of these emulsions was visually verified by determining the time t25 representing the time at which 25% of the volume of the dispersed phase separated from the continuous phase. In the absence of copolymers, the emulsions stability was inferior to 10 minutes.

Activity 2.2: ***Preparation and characterization of non-aqueous emulsions in the presence of drugs***

The two drugs, cisplatin and paclitaxel, were solubilized in both monomers, VP and CL, up to a concentration of 20 mg/ml, and the stability of these solutions was studied as a function of time and temperature. No precipitation of drugs from monomer solutions was observed for one month (30 days). In addition, a temperature of 60 ° C did not produce adverse effects on drug solutions. In the next step, a drug concentration of between 10 and 20 mg / ml will be used.

Table 7 shows the stability of the emulsions depending on the type of copolymer used at a copolymer concentration of 5 wt% in the continuous phase. The total volume of an emulsion was fixed at 10 ml and an 80/20 vol / vol ratio for the two phases was used. The continuous phase was represented by the silicone oils and the phase dispersed by the VP and Ɛ-CL monomers. Emulsions were prepared by emulsification with a Ultraturrax 18 at a rate of 3000 rpm for 5 The most stable emulsions and therefore having the smallest diameter of dispersed droplets are the emulsions obtained with the copolymers AL5, AL6 and AL7.
In the dispersed phase of the EVP5, EVP6, EVP7, ECLL5, ECLL6 and ECLL7 emulsions the two drugs were solubilised at a concentration of 20 mg/ml and it was observed that the stability of the emulsions was not affected by the presence of the drugs.