Polymerization kinetics of a mixture of Lipiodol and Glubran 2 cyanoacrylate glue upon contact with a proteinaceous solution

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ABSTRACT

The Glubran 2 cyanoacrylate glue is a liquid embolic agent used to block blood vessels endovascularly. Typically mixed with an iodized oil (Lipiodol) for visualization under X-ray, it polymerizes when in contact with blood and tissues owing to the presence of ions and proteins. The objective of the study is to determine the influence of plasma proteins in the polymerization reaction. A triggering solution containing bovine serum albumin (BSA) and the main blood ions is used as a model of plasma. The polymerization kinetics of Glubran 2-Lipiodol mixtures is measured upon aspiration in a capillary tube and contact with the proteinaceous solution. Having varied the glue and protein concentrations, we show that glue-Lipiodol mixtures with concentrations larger or equal to 25% polymerize when put in contact with an ionic solution containing at least 4% of BSA. The reaction is decomposed into two phases: a fast zwitterionic polymerization induced by the BSA molecules followed by a slower polymerization phase. The reaction speed and extend of the solidification region mostly depend on the glue concentration. The time for the glue solution to polymerize over a 1 mm thickness varies from 5 s for pure glue to about 1 min for a 50% glue concentration, and 10 min for a 25% glue mixture. It is the first time that the kinetics of the two polymerization reactions is quantified for Glubran 2, which will provide the information needed by interventional radiologists to optimize the planning of endovascular glue injection.

1. Introduction

Vascular embolization is a minimally invasive treatment used to selectively reduce or stop the blood supply to specific parts of the body. It consists of introducing embolic agents into the circulation to occlude blood vessels. It is carried out under X-ray by navigating a guide wire and a catheter into the targeted blood vessel, through which the embolic agents are delivered. The technique has been widely used for the management of arteriovenous malformations (AVMs) (Rosen and Contractor, 2004; Gandini et al., 2008; Desal et al., 2005; Liu et al., 2000; Cognard et al., 2006), gastric varices (Sarin et al., 2002), tumors (Raffi et al., 2007; Lazzaro et al., 2011) or arteriovenous fistulas (Rosen and Contractor, 2004; Raffi et al., 2007), but new applications regularly appear in clinical practice. Cyanoacrylate glues are the main liquid adhesives used for vascular embolization, as they have a low viscosity, rapid polymerization and low tissue toxicity (Montanaro et al., 2001). The monomeric cyanoacrylate structure consists of a double-carbon ethylene group with two highly reactive electro-withdrawing functional groups (cyano − CN and ester − COOR). The polymerization may be initiated by different types of initiators leading to distinct mechanisms. The most usual one is the anionic polymerization, which is triggered by simple anions (acetate, hydroxide, cyanide,...). Upon reaction with anions a reactive carbanion forms, which reacts with further monomers to finally form a polymer as shown in Fig. 1a. However, amphiprotic amino acids can play the role of the anion and lead to zwitterionic polymerization, according to the reaction scheme shown in Fig. 1b (Donnelly et al., 1977; Limouzin et al., 2003; Nicolas and Couvreur, 2009; Levrier et al., 2003; Pepper, 1980).

A few previous studies have provided some results on the polymerization time of butyl cyanoacrylate glues using an empirical technique: it consists of dropping a small quantity of glue-oil mixture onto a plasma or citrated blood substrate and visualizing its change in opacity (whitening) (Brother et al., 1989; Takasawa et al., 2012). The change in opacity, however, depends on the volume of deposited mixture and the ending criteria of polymerization are not precisely defined. Consequently the technique is empirical and provides information on the initial stage of polymerization inside a thin sheet of glue mixture, only. To our knowledge, there are no published studies on the polymerization propagation kinetics inside a finite volume of glue-oil mixture.

In order to elucidate this question, we have recently proposed a...
novel experimental setup to monitor the polymerization kinetics of a volume of glue-oil mixture suddenly placed in contact with an ionic solution (Li et al., 2017). The technique consists of suddenly creating a sharp interface between the glue mixture and the ion reservoir. The propagation of the polymerization front in the glue volume is monitored through the change in opacity as measured by a high-speed camera. Upon contact with an ionic solution of similar ion contents and pH to blood plasma, we find that the glue mixture polymerizes quickly near the interface, but that the volume propagation takes time. For example, for a 1:1 glue in oil mixture, it takes 86 s to polymerize a 24-μm thick film, whereas it takes about 60 min for the polymerization front to progress by 0.5 mm inside the glue volume from the interface. The above results do not take into account the presence of proteins in the blood plasma.

In Europe, Glubran 2 (GEM, Viareggio, Italy) is a liquid adhesive that has the EC mark for endovascular use. It is composed of n-butyl cyanoacrylate (nBCA) mixed with a co-monomer: metacycloxyisulpholane (MS). The addition of MS allows to lower the polymerization temperature to about 45 °C and reduce its cytotoxicity (Cognard et al., 2006; Leonardi et al., 2002, 2003). To make the embolic agent radiopaque and enable its detection after injection in the vessels, cyanoacrylate glues are mixed with an iodized oil, such as Lipiodol (Laboratoire Guerbet, Aulnay-sous-Bois, France). The iodized oil has been shown to have a screening effect on the monomers and to increase the polymerization time (Brother et al., 1989; Gounis et al., 2002; Takasawa et al., 2012; Li et al., 2017). The volume ratio of cyanoacrylate glue to iodized oil is typically varied between 1:1 and 1:5 depending on the application and the practitioner’s empirical judgment and experience. No information can be found in the literature regarding the influence of plasma proteins on the polymerization kinetics of a Glubran 2-Lipiodol mixture.

In order to obtain the first results on the polymerization kinetics of mixtures of Glubran 2 and Lipiodol in contact with proteins, we have adapted our technique to investigate the influence of one of the main plasma proteins: albumin. We use a model solution made of an ionic solution (IS) that contains the main blood ions in the same proportion as plasma (see Table 1) and to which BSA (Sigma-Aldrich, France) is incorporated with different concentrations: 40 g/L (4%) and 80 g/L (8%). The resulting solutions are respectively denoted IS-BSA4 and IS-BSA8 in the following. Note that IS-BSA8 can be considered as a model of blood plasma where all the proteins are represented by BSA, whereas IS-BSA4 allows us to evaluate the role of albumin only.

<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<td>Composition of 1 L of ionic solution with BSA.</td>
</tr>
<tr>
<td><strong>Solute</strong></td>
</tr>
<tr>
<td>NaCl</td>
</tr>
<tr>
<td>KCl</td>
</tr>
<tr>
<td>KH2PO4</td>
</tr>
<tr>
<td>Na2HPO4·12H2O</td>
</tr>
<tr>
<td>Glucose</td>
</tr>
<tr>
<td>Deionized water</td>
</tr>
<tr>
<td>BSA</td>
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</tbody>
</table>
The pH of different solutions is measured with a pH meter (HI2210, HANNA, Germany) with an accuracy of ± 0.01 (Table 2).

### 2.2. Characterization of the polymerization process

Following the procedure described by Li et al. (2017), we use a glass capillary tube with internal diameter $D_r = 1.06 ± 0.01$ mm, to create a sharp well-defined interface between a glue-Lipiodol mixture and the solution containing the polymerization initiator. In Li et al. (2017), 8 μL of glue mixture (corresponding to a height of ~ 9 mm in the tube) and the IS are successively aspirated into the tube. When a proteinaceous solution is used, however, the polymerization is so fast, that we do not have time to perform the aspiration. We have thus slightly modified the procedure. First a volume of glue mixture is aspirated into the vertical tube from a small cup placed underneath, by means of a syringe connected to the tube upper end (Fig. 2a). The glue cup is removed and the lower glue meniscus is positioned at the bottom of the tube. Another cup containing the proteinaceous solution is then raised up to touch the lower tube tip and start up the polymerization reaction (Fig. 2b). As the polymerization proceeds, the glue mixture density increases, which leads to an increase of opacity. This change in opacity of the fluids is monitored with an imaging system consisting of a high-speed camera (SA3, Photron, USA) coupled to a back illumination source (Schott-Fostec, LLC, USA). The grey level $G_p$ of the recorded images is encoded in 16 bits which are converted to 8 bits in the measurement process, providing 256 possible shades of grey: 0 corresponding to black and 255 to white.

An upwards vertical z-axis is defined along the tube with origin $z = 0$ at the bottom of the capillary tube (Fig. 2b). The glue mixture is thus in the $z > 0$ region. The progression of the polymerization reaction is then evaluated from the change in image grey level $G_p(t, z)$ of the glue mixture for different values of $z$ and different instants $t$. Time $t = 0$ corresponds to the time when the proteinaceous solution is put in contact with the tube bottom. The $z$-distance between two successive measuring points is 0.5 $D_r$, where $D_r$ is the diameter of the liquid region as measured on the image ($D_r$ is slightly smaller than $D_r$ because of optical effects). Grey levels are averaged within boxes of width 0.7 $D_r$ and height 0.4 $D_r$ centered on each test point.

The progression of the polymerization reaction is monitored with two recording phases: a continuous recording to capture the beginning of the polymerization process at a frame rate of 50 fps, followed by a time-lapse mode to monitor the long-term polymerization process at a frame rate of 0.5 fps. The continuous recording time is set to either 217.8 s or 435.7 s. The duration of the time-lapse mode ranges from 60 min to 120 min in the different experiments. In both modes, the shutter time is 0.5 ms. All the experiments have been repeated 5 times.

Once the polymerization process is completed, the polymerized columns inside the tube are observed with a scanning electron microscope (QUANTA FEG 250, FEI, US). Images are taken of the bottom surface that is in contact with the BSA solution, and of a radial cross-section cut in the middle of the portion of the sample, where the slow volumetric polymerization takes place.

### 3. Results

In the following, we first present the results obtained with the 8% BSA ionic solution, which are considered as reference, and then consider the effect of the protein concentration of the ionic solution and of the concentration in glue of the glue/Lipiodol mixture. Interestingly, we find a similar polymerization kinetics in all cases, with the occurrence of two main phases: they will be denoted as fast and slow volumetric polymerization phases owing to their respective characteristic times.

#### 3.1. Fast volumetric polymerization

Typical results are shown for a glue mixture ($C_G = 50\%$) in contact with an 8% BSA ionic solution (IS-BSA8). As soon as the glue mixture is in contact with the proteinaceous solution, it darkens: this means that the glue becomes denser and thus that polymerization is occurring. The polymerization front propagates upwards within the glue mixture (Fig. 3a). When the front has travelled a certain distance (~ 2 mm in this case), the polymerization propagation stops and the boundary between the polymerized and liquid glue mixture remains stable. The time evolution of the grey level $G_p(z, t)$ within the darkening column is shown as a function of time at different locations $z \leq 2.4$ mm. At a given location $z$, the grey level $G_p(z, t)$ decreases from the initial value $G_p(z, 0)$ towards an asymptotic value $G_p(z, \infty)$ within one or two minutes. Note that the initial value of grey level $G_p(z, 0)$ varies with $z$, due to the shade cast by the cup.

The low value of $G_p(z, \infty)$, which corresponds to a dark grey level close to black, indicates that the glue column is dense. This is

![Fig. 2](image-url)
substantiated by scanning electron microscope (SEM) observations of the bottom surface (in contact with the BSA solution) of the polymerized glue mixture. The glue exhibits a complex network of connected polymerized structures (Fig. 4a), with interstices filled with oil (see insert in Fig. 4a). Qualitatively, the resulting structure is hard and resists compression.

For a given value of \( z \), the curve \( G_t(z, t) \) can be fitted with a sigmoid:

\[
G_t(z, t) = G_f(z, 0) - \frac{G_f(z, 0) - G_f(z, \infty)}{1 + \exp\left(-\frac{t - h(z)}{\tau}\right)},
\]

where \( h(z) \) is the half time, such that \( G_f(h(z)) = \frac{G_f(z, 0) + G_f(z, \infty)}{2} \). The progression of the polymerization front is thus characterized by \( h(z) \). The time \( \tau \) corresponds to a measure of the time that it takes the polymerization to be completed at position \( z \) (based on the grey level in the fluid). Indeed, it takes about \( 5.9\tau \) for the grey level at \( z \) to drop from \( G_f(z, 0) - 0.05[G_f(z, 0) - G_f(z, \infty)] \) to \( G_f(z, 0) - 0.95[G_f(z, 0) - G_f(z, \infty)] \).

We face the issue that the polymerization process is fast and occurs over a limited distance, which makes it very difficult to evaluate the propagation kinetics of the polymerization front. We have consequently studied the fast volumetric polymerization reaction by rather determining the height \( z_f \) of the front at the final time \( t_f \) of the fast polymerization phase. Before explaining how the height \( z_f \) is determined from the grey level evolution, one must first note that the final grey level has the same value \( G_f(z, \infty) \) at different \( z \) locations: for example, in Fig. 3b, \( G_f(z, \infty) \approx 42 \) for \( z \leq 1.8 \text{ mm} \). An increase of \( G_f(z, \infty) \) means that the glue is less dark (and thus less dense) in the measuring box about point \( z \). Starting from \( z = 0 \) and increasing \( z \), we look for the two successive measurement points \( z_1 \) and \( z_2 \) such that

\[
G_f(z_1, \infty) - G_f(z_2, \infty) \geq 0.1 G_f(z_1, \infty).
\]

We deduce that the boundary of the dark polymerized glue is located somewhere between \( z_1 \) and \( z_2 \), and take the position of the polymerized front to be \( z_f = (z_1 + z_2)/2 \). The position \( z_f \) is thus determined with an error \( \pm 0.25 \text{ mm} \). Correspondingly, the end of the fast polymerization is defined by

\[
t_f = [h(z_f) + 3r_f(z_f) + h(z_f) + 3r_f(z_f)]/2.
\]

The duration \( t_f \) of the fast polymerization is plotted as a function of the propagation distance \( z_f \) in Fig. 5. Not surprisingly, we note that \( t_f \) increases with \( z_f \) and that there is some dispersion of the results between two experiments, which may be attributed to the randomness of the propagation phenomenon. For the 8% BSA ionic solution, the polymerization altogether propagates over an average distance \( z_f = 2.1 \pm 0.4 \text{ mm} \) over an average time \( t_f = 132 \pm 73 \text{ s} \).

3.2. Slow volumetric polymerization

Tens of minutes after the fast polymerization has stopped, a new slow polymerization takes place and propagates upwards from \( z = z_f \); after about an hour from the beginning of the experiment, the front

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Fig. 3. Change in opacity observed in the glue mixture (C_G = 50%) in contact with IS-BSA8. (a) The darkening of the tube bottom indicates the polymerization of the G-L mixture. The polymerization front stops at \( z = z_f \) for time \( t = t_f \). (b) Time evolution of the relative grey levels at different vertical positions. The full line corresponds to the sigmoidal fit.

Fig. 4. Scanning electron micrography of the polymerized glue mixture (C_G = 50%) after contact with IS-BSA8: (a) fast polymerization; (b) slow polymerization. Inserts: zoom on the cross-section at a higher magnification.
reaches the top of the glue mixture column (Fig. 6a). The time evolution of
the grey level at different positions for \( z > z_f \) is shown in Fig. 6b. The
grey level decreases from the initial value \( G(z, 0) \sim 132 \) to the
asymptotic value \( G(z, \infty) \sim 105 \), which is much higher than the grey
level \( G(z, \infty) \sim 42 \) measured at the end of the fast volumetric poly-
merization \( (z \sim z_f) \). The new polymerized solid bulk is much less
opaque, which indicates that the polymerization reaction is different
from the fast one. The tube containing the slow polymerized column is
cut radially in its middle (approximately). The corresponding SEM
picture of a section of the polymerized column is shown in Fig. 4b. We
note that the structure is very different from the one observed for the
fast polymerization: micron size grains appear, which are micro
droplets encapsulated by polymerized glue. The same type of structures
had also been observed when the glue is undergoing pure anionic
polymerization upon contact with IS: encapsulated oil droplets had
been found in the glue that is in direct contact with the ionic solution
(Li et al., 2017) (see also Fig. 7a). Qualitatively, the column is still a
hard solid that resists compression, like in the bottom region where the
fast polymerization takes place.

For every value of \( z \), the curve \( G(z, t) \) can also be fitted with a
sigmoid. As the polymerization is slow, we have enough measurement
points to compute the propagation velocity \( V_p \) of the front from the half
time \( t_{1/2}(z) \):

\[
V_p = (z - z_f) / [t_{1/2}(z) - t_f].
\]  

We find that \( V_p \) increases slightly with \( z \), which may be due to the fact
that the reaction is exothermic (Fig. 8). The average velocity is of the
order of 0.05 mm/min, which is much smaller than the average velocity
in the fast polymerization phase \( (z_f/t_f \sim 0.95 \text{ mm/min}) \). The \( V_p \) values

3.3. Effect of the BSA concentration on the polymerization process

We now turn to the effect of protein concentration and study the
polymerization of a G-L mixture (\( C_G = 50\% \)) in contact with an ionic
solution containing only 4\% of BSA (IS-BSA4). We observe again a fast
polymerization (Fig. 9a), with a front which is not as sharply defined as
for IS-BSA8. The grey level evolution (Fig. 9b) allows us to determine
the position \( z_f \) of the front when the fast polymerization stops at time \( t_f \).
As shown in Fig. 5, there is no significant difference of the values of
\( t_f (z_f) \) for BSA concentrations of 8\% or 4\%. A slow polymerization phase
is also observed, which starts some 50 min later, with a front propaga-
tion velocity which is also of the same order as the one observed for a
pure ionic solution (Fig. 8). The SEM observation of the polymerized
glue corresponding to both the fast and slow polymerization phases are
very similar to the ones shown in Fig. 4, which would make it
redundant to show them. This indicates that an BSA concentration of
4\% is quite sufficient to induce the two steps of glue mixture
polymerization.

3.4. Effect of the glue-Lipiodol proportion on the polymerization process

We now consider the effect of the glue concentration on the
polymerization of a glue-oil mixture in contact with an IS-BSA8
solution. In the case of pure glue (\( C_G = 100\% \)), the fast polymerization
is very fast and extends over a short distance \( (z_f \sim 1 \text{ mm}, t_f \sim 5 \text{ s}) \).
It stops in the shadow of the cup and is thus difficult to measure with a
good precision. The resulting solid glue is organized as a compact
network of connected polymer bridges as it appears on SEM images
(Fig. 10a). A slow polymerization follows some 40 min later and
propagates fast within the glue column. The high velocity is difficult
to measure with precision, because there is little change in grey level
for the pure glue during the reaction. From the moment the second
polymerization reaction starts, it takes about \( 5 \sim 10 \text{ min} \) to poly-
merize the remaining 5 mm of glue column, which is of the same order as
what is measured for pure Glubran 2 in contact with an ionic solution
(Li et al., 2017). The resulting solid glue has a homogeneous structure
(Fig. 10b). It is very similar to what was observed for pure glue placed
in contact with an ionic solution containing no protein. Indeed, Fig. 7b
is one example of the SEM pictures that we have obtained cutting
different samples of pure glue after they polymerized upon contact with
IS. When analyzing the images, one must, however, keep in mind that
some regions of the cutting plane may experience large deformations.
during the breakup process, as the material has some ductility. This is what explains the presence of the small ridges at the bottom of Fig. 7b. Note that Fig. 14a published in Li et al. (2017) appears to be an effect of the breakup and may not represent an inherent structuring of the glue.

Conversely, when the glue concentration of the mixture is reduced to $C_G = 25\%$, the first stage of polymerization occurs over distances $z_f$ and times $t_f$ that are larger than for $C_G = 50\%$, as can be surmised from Figs. 11 and 5. The mean propagation velocity is $V_p \sim 0.11 \pm 0.02$ mm/min, which is an order of magnitude smaller than for $C_G = 50\%$. At the interface with the IS-BSA solution, the polymerized glue has a convoluted structure (Fig. 12a), which is similar, if less compact, to the ones observed for larger values of $C_G$ (Figs. 4a and 10a). However, in the middle of the column (Fig. 12b), the polymerized glue has a different aspect: there are some polymerized structures, immersed in an emulsion of encapsulated glue droplets in oil. For $z > z_f$ no change occurs in the glue mixture, which remains liquid for days. Note that a 25% G-L mixture does not polymerize at all when it is put in contact with IS (Li et al., 2017).

4. Discussion

The polymerization of cyanoacrylate glue in contact with an ionic solution containing albumin is obviously a complex process. Before proceeding with the discussion, we must first eliminate the possibility that the reactions are initiated by contact with the glass tube. We have thus conducted 7 experiments on a volume $9 \pm 1 \, \mu$L of pure glue (corresponding to a height of $10 \pm 1$ mm in the capillary glass tube) with the two menisci in contact with air. We find that it takes between 30 and 300 min to polymerize the glue volume (2 samples took between 30 and 60 min and 5 samples over 120 min). In our previous paper Li et al. (2017), we used the same technique as the one described here to...
study the polymerization of oil-glue mixtures when put in contact with an ionic solution with no BSA: we found that it takes less than 10 min to solidify 5 mm of glue upon contact with the ionic solution. In the present paper, it takes about 5 s to polymerize 1 mm of glue during the fast polymerization, and 5–10 min to polymerize ~4–5 mm during the slow polymerization. The chemical processes, when the glue is in contact with an ionic solution with or without BSA, have thus time scales which are quite shorter than the one observed when the glue polymerizes upon contact with glass or air. Furthermore, if the fast or slow polymerization were triggered by contact with the ambient air or with the glass tube, the polymerization would progress downwards from the top glue-air interface (in the first case), or radially inwards.

![Fig. 10. Scanning electron micrography of the polymerized pure glue ($C_G = 100\%$) after contact with IS-BSA8: (a) fast polymerization; (b) slow polymerization.](image)

![Fig. 11. Change in opacity observed in the glue mixture ($C_G = 25\%$) in contact with IS-BSA8. (a) Darkening of the tube bottom shows the polymerization of the G-L mixture. (b) Time evolution of the relative grey level at different vertical positions. Note that the time scale of the phenomenon is greatly increased.](image)

![Fig. 12. Scanning electron micrography of a polymerized glue mixture at low concentration ($C_G = 25\%$) on contact with IS-BSA8. (a) Interface between the glue mixture and ISBSA8; (b) cut of the polymerized column.](image)
from the tube wall (in the second case). In the latter case, the whole volume would also darken homogeneously. This is clearly not what we observe in Figs. 5a, 6a, 9a, 11a.

It is clear that two chain reactions occur. The fast polymerization is obviously triggered by the BSA molecules which have about 583 side chains of amino acids, and thus many possible sites for a zwitterionic polymerization as depicted in the chain reaction in Fig. 1b. It is fast because the concentration of BSA molecules is high and thus provides a large number of potential initiation sites. Note that polymerized cyanoacrylate nanoparticles can be obtained with BSA concentrations which are about ten times lower than the ones used here Kim et al. (2013). This very likely results in the formation of a star polymer, branching out from one BSA molecule (Kim et al., 2013), which would explain the compact structure of the fast reaction plug at the bottom of the tube. Furthermore, as there are also anions in the solution, linear polymer chains can also be formed. It seems that, with such processes, it is difficult to avoid chain coupling (Blencowe et al., 2009): a densely cross-linked polymer thus forms, in which the mobility of the monomers becomes increasingly reduced and the polymerization stops. This hypothesis is substantiated by the fact that the thickness of the fast reaction plug decreases when the glue concentration increases. The SEM images also show a denser convolution network as the concentration increases (Fig. 10a compared to Fig. 4a). In the case of CP < 100%, the oil may also limit the number of reacting monomers. Other phenomena could explain why the fast polymerization stops. The main one is the fact that nucleophilic carbainion killers are generated during the polymerization of cyanoacrylates notably in the presence of water (Eromosele et al., 1989). Furthermore, the increase in density of the medium during the reaction increases the likelihood of head collision, which may stop the growth of the two colliding chains.

The variation of the propagation time \( t_p(\zeta) \) (Fig. 5) may be attributed to the fact that the propagation/termination process includes some randomness. The values of \( t_p(\zeta) \) do not depend on the BSA concentration, which is high enough, but depend heavily on the glue/oil concentration \( C_p \), and thus on the availability of glue molecules. For pure glue, \( \zeta_p \) and \( t_p \) are small (1 mm and 5 s, respectively) and result in a dense polymerized network with pores of the order of 1 \( \mu \)m or less (Fig. 10). For \( C_p = 50\% \), \( t_p(\zeta) \) is about 20 times larger resulting in much wider network pores, of order of 10 – 20 \( \mu \)m, filled with oil. For \( C_p = 25\% \), we also observe a loose network of glue, together with encapsulated glue droplets.

When the fast polymerization stops, the liquid above the interface still contains glue monomers: this means that not all the monomers have been consumed by the fast polymerization. The second (slow) polymerization starts from the interface with the fast polymerization plug and takes a significant time to initiate (about 40 min for \( C_p \geq 50\% \)). The polymerization reaction is exothermic, so that the plug is at a higher temperature than the ambient air and the supernatant liquid. However, a simple cooling calculation of the plug (by conduction through air) shows that its temperature equilibrates to the ambient in about 30 s. This short duration being much smaller than the initiation time of the second polymerization, it follows that thermic effects can be neglected.

The slow polymerization must be either initiated by anions percolating/diffusing from the bottom of the plug or by the charged polymer chains at the interface between the plug and the oil-glue mixture. This process should thus lead to linear polymer chains, as shown in Fig. 1a. The reason why there is no slow polymerization for \( C_p = 25\% \) may be due to the fact that the large amount of oil shields the charges. It is interesting to note that the propagation velocity of the slow polymerization front is then of the same order of magnitude as the one measured for glue-oil mixtures in contact with a pure ionic solution (Li et al., 2017), a fact that substantiates the above hypothesis of formation of a chain polymer. Note that we do not observe any slow polymerization for \( C_p = 25\% \) (except maybe some mixed with the zwitterionic polymerization, from which it is impossible to distinguish), just as was the case when the glue was in contact with the ionic solution only (Li et al., 2017). The polymerization leads to phase separation between the oil and the glue: this results in a coherent convoluted glue structure immersed in oil after the fast polymerization (Fig. 4a) and to much smaller glue structures (Fig. 4b) probably encapsulating oil droplets.

5. Conclusion

We have designed an experimental set-up that allows us to measure the polymerization kinetics of Glubran-Lipiodol mixtures in contact with any triggering solution. This study shows that Glubran-Lipiodol mixtures with concentration larger or equal to 25% polymerize when they are put in contact with an ionic solution containing at least 4% of BSA. The time for the solution of glue to polymerize over a 1 mm thickness varies from 5 s for pure glue to 10 min for \( C_p = 25\% \). The final thickness of the polymer depends mostly on the glue concentration.

From a practical point of view and specifically for vascular embolization purposes where glue-oil mixture droplets are injected in a vessel, pure glue is never used, as it polymerizes too quickly for the injection process to be safely controlled. The common practice is to use either 50% or 25% Glubran-Lipiodol mixtures. The advantage of a 25% mixture is that the polymerization is slow to develop, which can be a disadvantage because the mixture droplets can be convected away from the injection site before they have started to solidify. Another disadvantage is the absence of polymerization (and thus solidification) beyond penetration distances of about 4 mm. This limits the amount of glue mixture that ought to be injected at once. Such restriction is especially true under static injection conditions, for which a large amount of glue mixture can be injected at a single location. Under dynamic conditions, the glue mixture will instead be ejected from the catheter in the form of drops, the radius of which is typically smaller than 4 mm (Sandulache et al., 2012). A 50% mixture may offer the good compromise between reaction time and injection control. Note though, that a droplet with a radius larger than 3 mm will take some time to solidify to the core.

Conflict of interest

The authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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