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In Vitro Characteristics of a Cyanoacrylate/Water-Soluble Contrast Emulsion: Preliminary Data from Light Microscopy Approach

Kévin Guillen^{1,2} · Anne-Virginie Salsac³ · Pierre-Olivier Comby^{2,4} ·
Ludwig Serge Aho-Glele⁵ · Olivier Chevallier^{1,2} · Romaric Loffroy^{1,2} 

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Letter to the Editor

The last 50 years have produced phenomenal advances in the development of embolic agents, of which a broad array is now available for transcatheter endovascular embolization of vascular lesions. Liquid embolic agents, including N-butyl cyanoacrylate (NBCA), are now used in highly prevalent conditions. Glubran®2 (GEM, Viareggio, Italy) was the first cyanoacrylate glue to receive the CE mark for endovascular use [1]. NBCA is typically diluted with Lipiodol Ultra Fluid® (LUF; Guerbet, Aulnay-sous-Bois, France) to enable fluoroscopic guidance and modulate polymerization kinetics. Both are lipophilic compounds and therefore may destroy some catheter hubs and stop-cocks [2]. In contrast, water soluble contrast agents are less corrosive for catheter and common

interventional devices and can hypothetically enable fluoroscopic guidance. Considering studies of LUF and chemoembolization, we used light-microscopy to assess the emulsions obtained with Glubran®2 and either of two last-generation nonionic water-soluble iodinated contrast agents, namely, iodixanol (Visipaque®, GE Healthcare, Chicago, IL) and iopamidol (Iopamiron®, Bracco Imaging, Princeton, NJ) [3].

We chose both iopamidol and iodixanol because we wanted to assess the reproducibility of the results with several water-soluble contrast agents, considering the osmolality variation and also their ionic properties. The ratio was empirically defined as one part NBCA for three parts contrast agent because it is a cyanoacrylate/Lipiodol often used ratio in clinical practice. We mixed the two components at three different speeds: dropwise using a single syringe that was gently turned: one flip over per second, at conventional mixing speed, that is to say 30 back and forth per minute between two syringes through a Luer connector, and at a high speed of over 100 back-and-forth movements in one minute between two syringes through a Luer connector (Fig. 1). For each of the two mixtures and three speeds, we prepared five smears, using three drops for each. To quantify the emulsion characteristics, each smear was examined by light microscopy from $\times 100$ to $\times 400$ magnification up to 3 min after mixture emulsion. We counted the number of micelles per field and categorized the results as low if less than ten, intermediate if 10 to 200, and high if over 200. Polymerization was linked to the opacity of the mixture and can so be qualitatively analyzed [2]. We also assess the distribution of the lipophilic NBCA and of the water-soluble contrast by adding blue stain (E133 food colorant, Vahiné, Avignon, France) to the latter at a conventional mixing speed. Regarding statistical

✉ Romaric Loffroy
romaric.loffroy@chu-dijon.fr

¹ Department of Vascular and Interventional Radiology, Image-Guided Therapy Center, François-Mitterrand University Hospital, 14 Rue Paul Gaffarel, BP 77908, 21079 Dijon, France

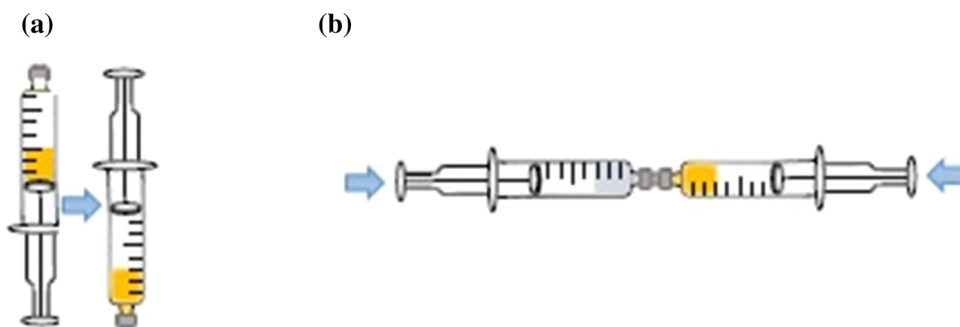
² ICMUB Laboratory, UMR CNRS 6302, University of Burgundy, 9 Avenue Alain Savary, 21000 Dijon, France

³ Biomechanics and Bioengineering Laboratory, UMR CNRS 7338, Université de Technologie de Compiègne, 60203 Compiègne, France

⁴ Department of Neuroradiology and Emergency Radiology, Image-Guided Therapy Center, François-Mitterrand University Hospital, 14 Rue Paul Gaffarel, BP 77908, 21079 Dijon, France

⁵ Department of Epidemiology, Statistics and Clinical Research, François-Mitterrand University Hospital, 14 Rue Paul Gaffarel, BP 77908, 21079 Dijon, France

Fig. 1 Diagram of the experiment. **a** Drop mixing method. **b** The two other mixing methods, which differed in the speed of piston depression



approach, clusters of five iterations were considered for each test. Micelle diameter was handled as a continuous variable and described as mean \pm SD. To look for associations, we performed multivariate linear regression analysis with a robust estimator. Micelle number, categorized as low, intermediate, or high, was an ordinal categorical variable and was described as median [interquartile range, IQR]. Ordinal regression including a robust variance estimator was used for the multivariate analysis. P values of 0.05 or less were considered significant. Qualitative approach displayed that the polymerization kinetics increased with the mixing speed. Increasing the mixing speed was associated with the production of a more granular emulsion composed of a larger number of smaller micelles more uniform in size (Fig. 2). Examination by light microscopy of the mixtures prepared after adding blue stain to the water-soluble contrast agents demonstrated that the mixtures were water-in-oil emulsions, with aqueous micelles in a continuous oil phase in 1:3 ratio emulsion. Table 1 reports the data on micelle number and diameter.

We see with higher mixing speed that number of micelles increased drastically, and size of micelles was divided by 30 to 100. Table 2 shows the results of the multivariate analyses done to determine whether the nature of the contrast agent and/or mixing speed were associated with the number and diameter of the micelles: higher mixing speed was linearly associated with larger numbers of smaller micelles ($p < 0.001$). In contrast, the nature of the contrast agent (iopamidol vs. iodixanol) was not significantly associated with the number or size of the micelles.

We demonstrated that mixing NBCA with water-soluble iodinated contrast agents produced water-in-oil emulsions. This preliminary work allowed to assess water-soluble agents as the only contrast added to NBCA [4, 5]. Both iopamidol and iodixanol are widely used for computed tomography and angiography, whereas iopamidol is a low-osmolar agent, iodixanol is iso-osmolar and might therefore be expected to cause a greater delay of polymerization but both agents produced similar emulsions in our work.

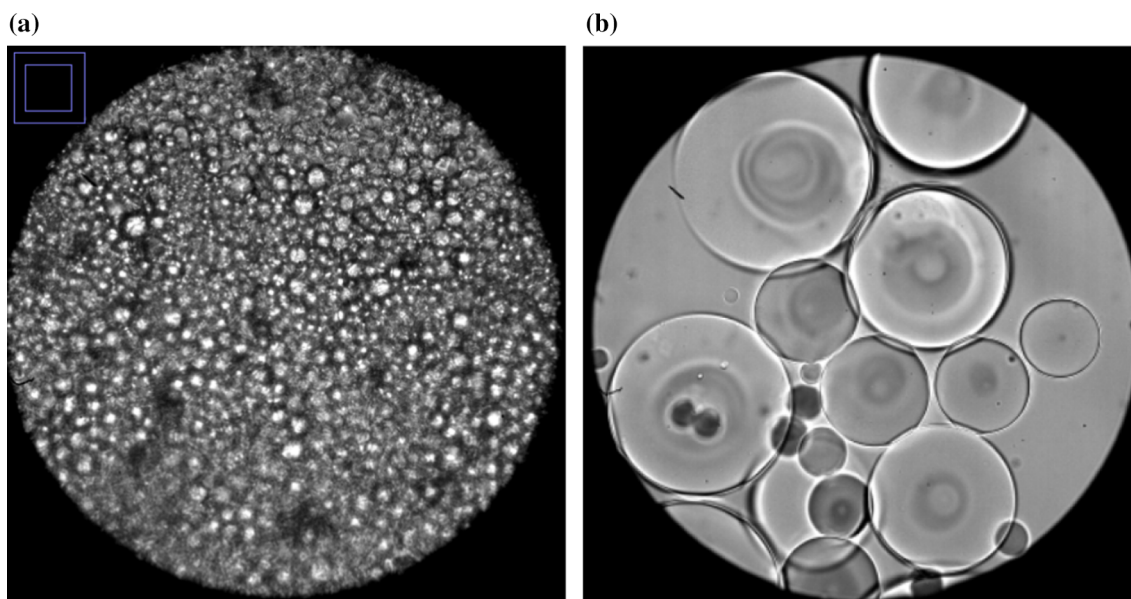


Fig. 2 Light microscopy images of the emulsion obtained with Glubran®2 (NBCA) and iodixanol; width of the analysis window was 470. **a** Highest mixing speed: large number of small micelles. **b** Intermediate mixing speed: the micelles are larger and less numerous

Table 1 Number and size of the micelles

Mixing speed	Contrast media	Micelle size as mean (μm) \pm SD	Number of micelles as median [IQR]
Slow	Iodixanol	1105 \pm 862	1 [1–1]
Standard	Iodixanol	441 \pm 320	2 [1, 2]
Rapid	Iodixanol	15 \pm 8	3 [3–3]
Slow	Iopamidol	1146 \pm 822	1 [1–1]
Standard	Iopamidol	422 \pm 218	2 [2–2]
Rapid	Iopamidol	30 \pm 34	3 [3–3]

SD, standard deviation; IQR, interquartile range

Table 2 Multivariate analysis to identify factors associated with the number and diameter of the micelles

	Coefficient	SE	Pr > z	95%CI
Micelle diameter				
Mixing speed	−544.35	102.26	0.000	−744.78 to −343.93
Contrast agent	17.84	141.69	0.900	−259.86 to 295.54
Micelle number				
Mixing speed	7.12	2.05	0.001	3.10 to 11.15
Contrast agent	1.68	1.18	0.155	−0.64 to 3.99

SE, standard error; 95%CI, 95% confidence interval

Considering fundamental physical properties of emulsion, water soluble contrast agent could result in an oil-in-water emulsion [3]. Polymerization kinetics should therefore be different in a blood vessel with the close contact with ions and we can suppose that the polymerization should be instantaneous. Li et al. proved that NBCA/LUF mixture can be kept at room temperature for 30 min before use. Qualitative assessment of emulsion displayed a spontaneous polymerization of the emulsion and so a less stable condition that can be a limitation for clinical use [2].

Some limitations need to be highlighted. Our aim with this work was to provide preliminary data and establish the groundwork for future studies. Indeed, viscosity, polymerization kinetics and emulsion stability were not quantitatively studied here. Further in vitro studies are needed to precisely assess the polymerization kinetics of NBCA mixed with nonionic water-soluble iodinated contrast agents when mixed with ionic solution.

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Declarations

Conflict of interest None.

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