SUPPLEMENTARY MATERIAL TO

Development of a compounded propofol nanoemulsion using multiple non-invasive process analytical technologies

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Supplementary material

Eq. 2 is derived as follows. One starts with an IVLE with a number N of lipid droplets of size d_0, giving a total lipid volume:

$$V_{lip} = N \cdot \frac{\pi d_0^3}{6}$$

Eq. S1

When these droplets swell to a size d by absorption of a propofol volume V_p, volume conservation gives the following relation:

$$V_{lip} + V_p = N \cdot \frac{\pi d_0^3}{6} + V_p = N \cdot \frac{\pi d^3}{6} \rightarrow 1 + \frac{6V_p}{\pi N d_0^3} = \left(\frac{d}{d_0}\right)^3$$

Eq. S2

The propofol volume is linked to the total volume V_{tot} by $V_p = \phi_p \cdot V_{tot}$ with ϕ_p the propofol volume fraction. Further we have:

$$V_{tot} = V_{IVLE} + V_p = V_{IVLE} + \phi_p \cdot (V_{IVLE} + V_p) \simeq V_{IVLE}(1 + \phi_p)$$

Eq. S3

Where a small term $\phi_p V_p$ has been ignored. With these relations, and the definition for the initial lipid volume fraction $\phi_0 = V_{lip}/V_{IVLE}$, **Eq. S2** becomes:

$$\frac{d}{d_0} = \sqrt[3]{1 + \frac{\phi_P V_{tot}}{V_{lip}}} \simeq \sqrt[3]{1 + \frac{\phi_P(1 + \phi_p)}{\phi_0}} \simeq 1 + \frac{\phi_p}{3 \cdot \phi_0}$$

Eq. S4

In the last step Taylor expansion has been used, which is valid for small values of ϕ_p. To show that this last step from the cubic root to the approximation holds, both

equations were simulated. The results are shown in the **Figure S8**. As can be seen from the figure, the approximation holds well in the range used in this study.

Figure S1 Measurement configuration for simultaneous non-invasive DR-NIRS and SR-DLS measurements.

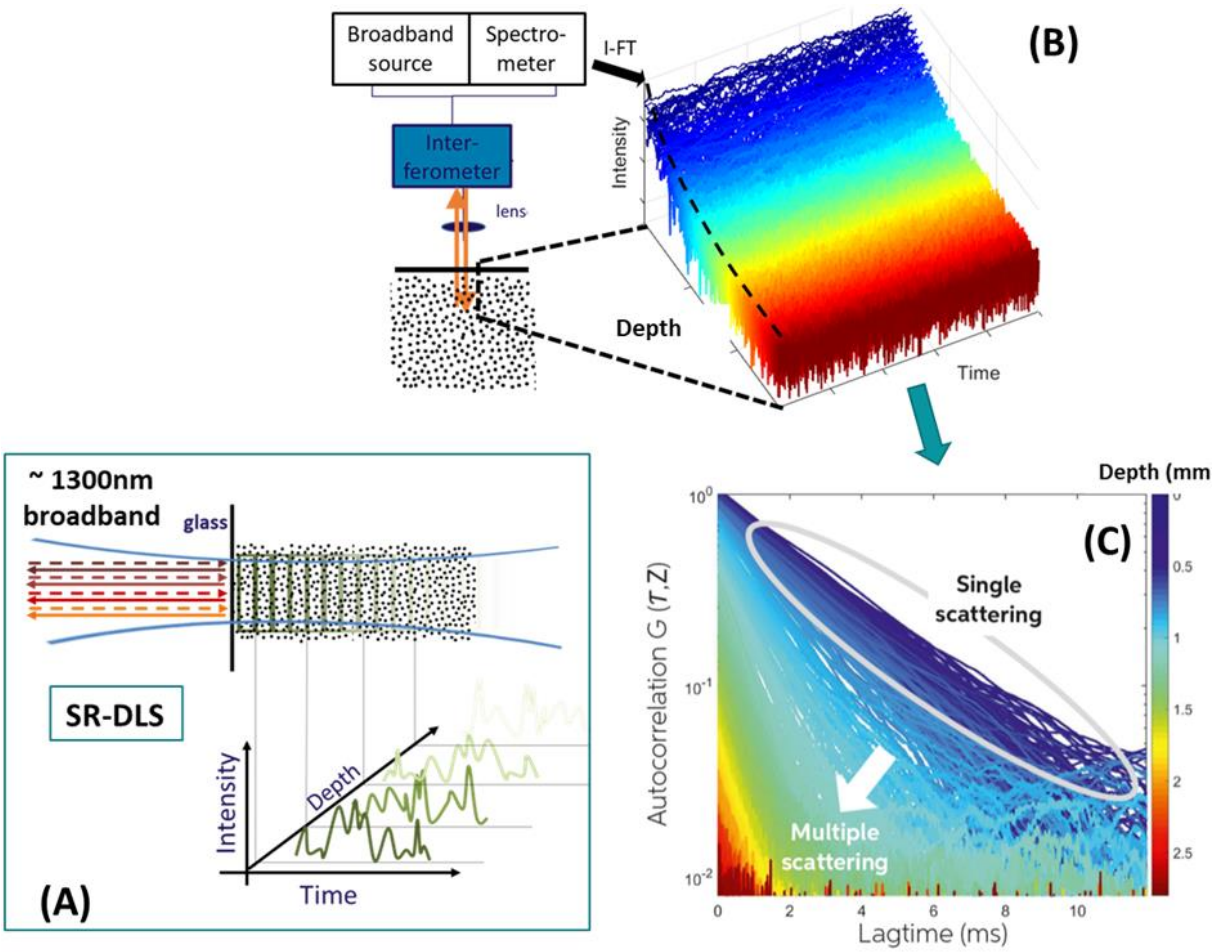
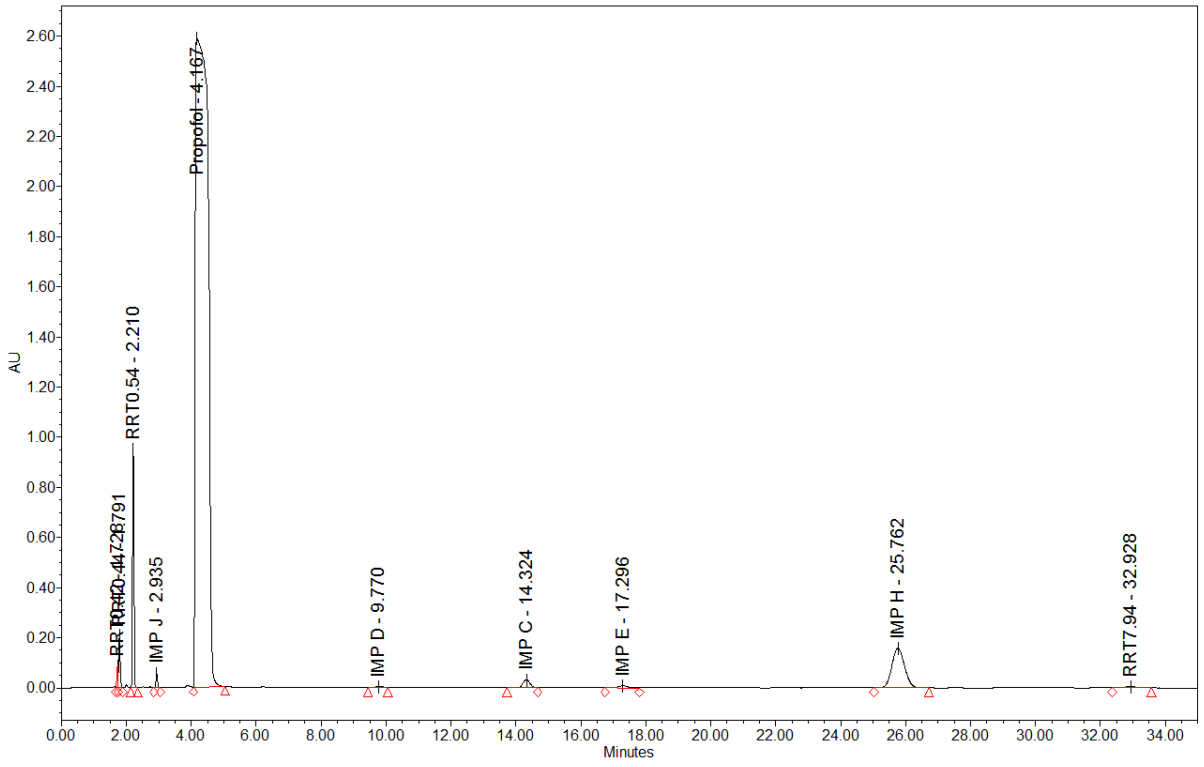


Figure S2 A) Basic sketch of SR-DLS. **B)** Spatial Resolution via Fourier Transformation of broadband interferograms. **C)** Depth resolved Correlation functions allow spatial filtering of multiple scattered light.



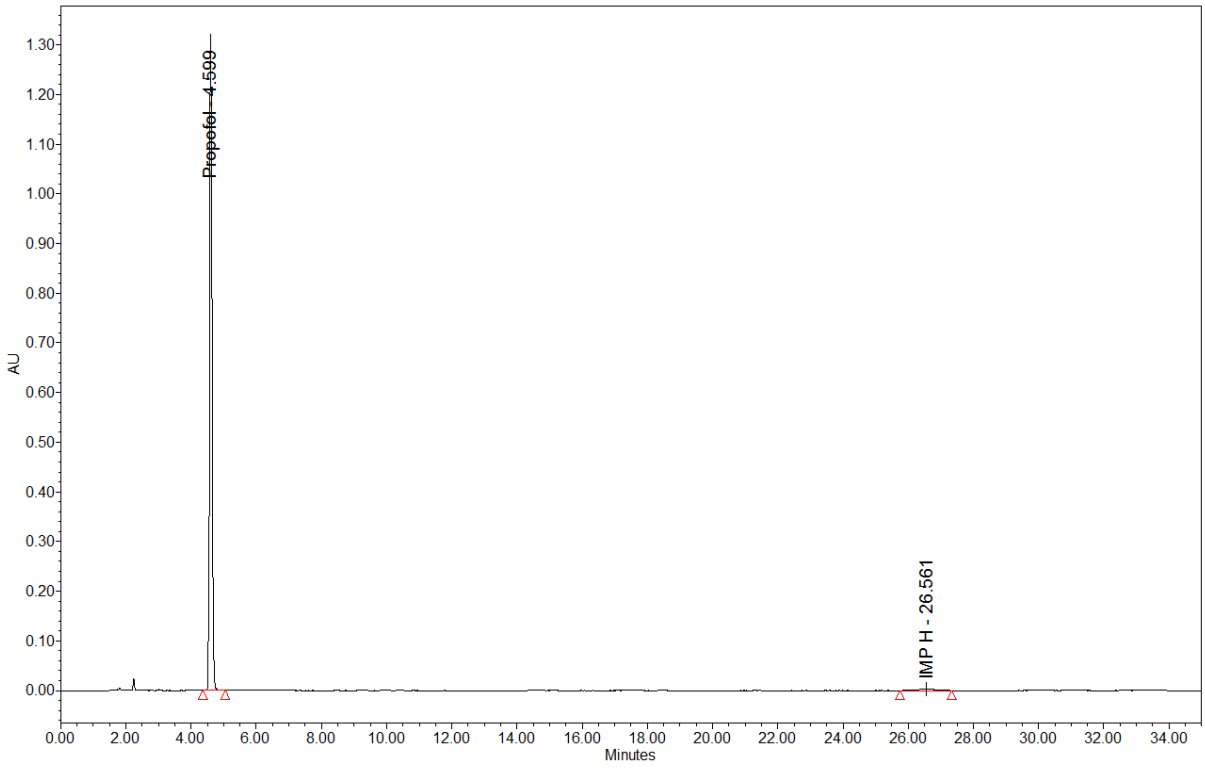


Figure S3 Typical HPLC chromatograms of the propofol drug substance obtained with the normal phase method for related substances (**upper panel**) and assay (**lower panel**). When known, specified impurities have been labelled, otherwise the relative retention time (RRT) is given.

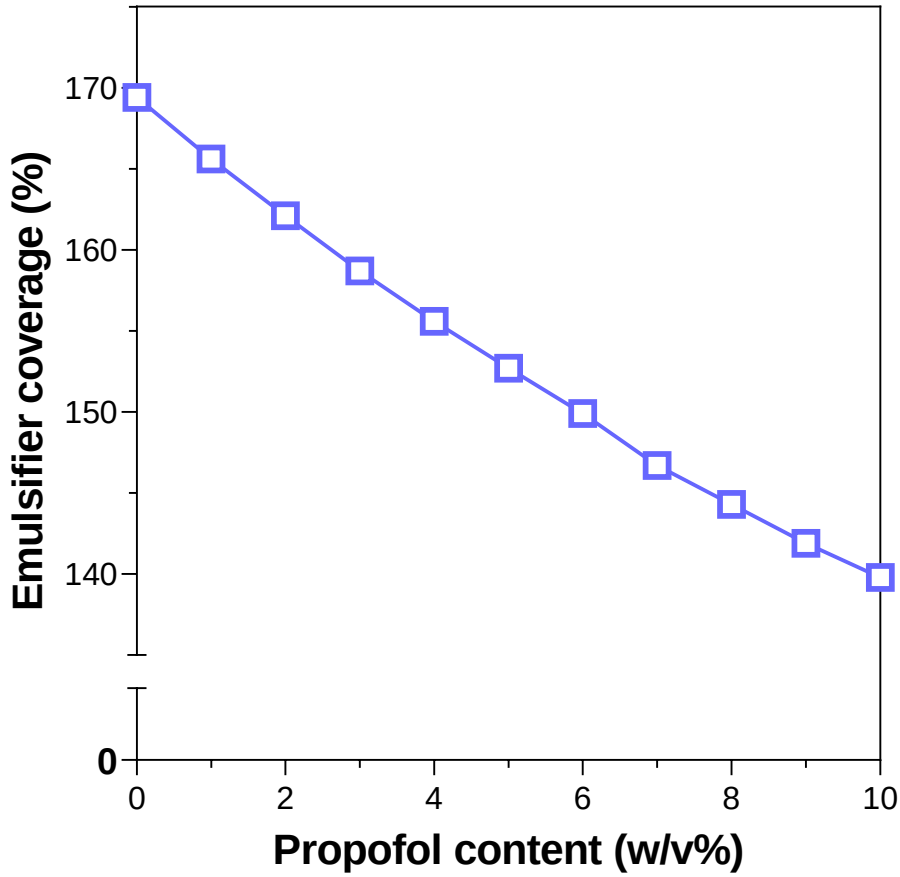


Figure S4 Theoretical lipid droplet total specific surface area covered by phosphatidylcholine.

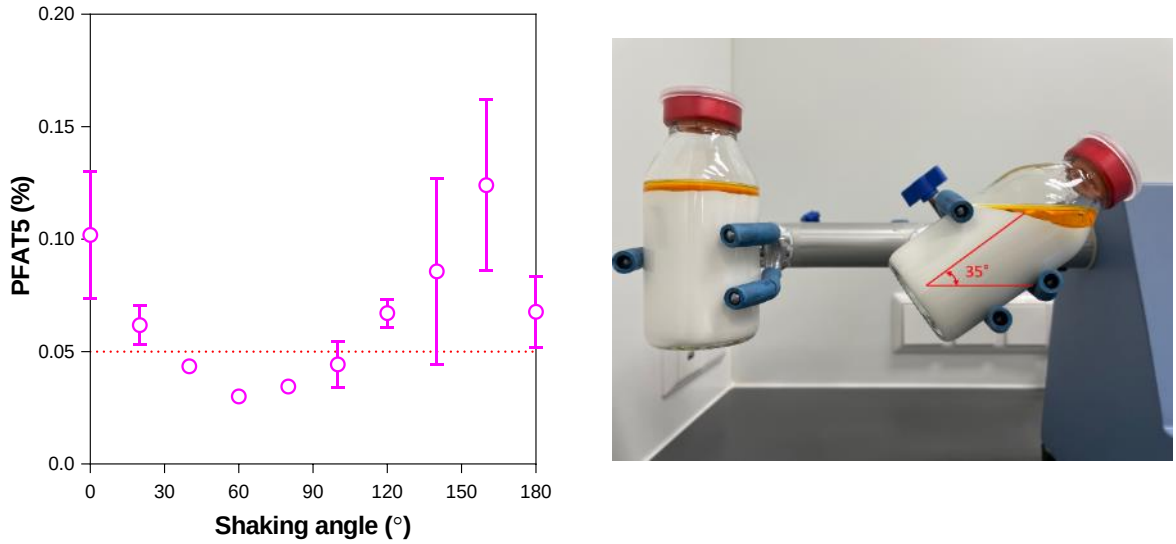


Figure S5 Effect of shaking angle (º) on the PFAT5 after 5 minutes for a 6% w/v remotely loaded propofol emulsion in IVLE. Symbols depict the mean and standard deviation (n=3), if no error bars are shown the value is smaller than the symbol value.

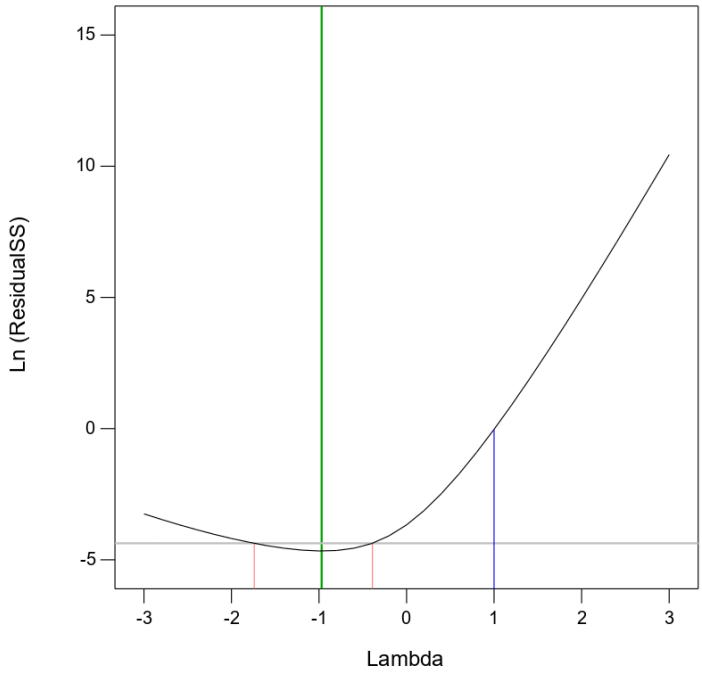


Figure S6 Box-Cox plot for transformations. The current power (no transformation) is indicated by the blue line (λ = 1) The minimum model residual is indicated by the green line and the 95%-confidence interval with both red lines.

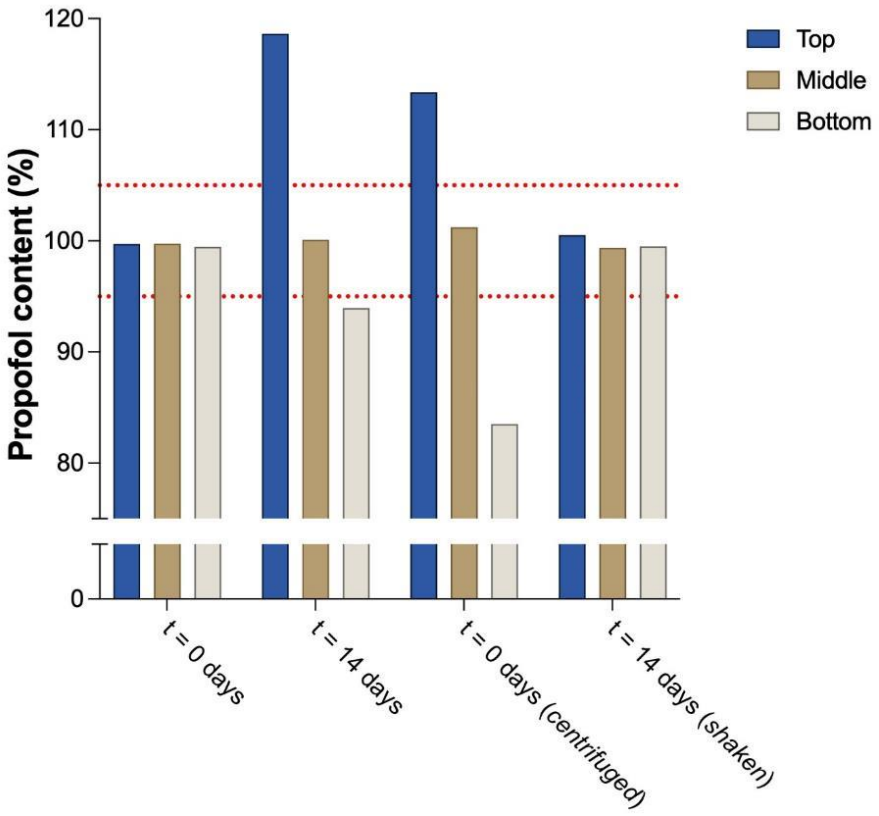


Figure S7 Propofol concentrations determined by HPLC withdrawn from three position within the glass container (top, middle and bottom). Centrifuged samples were exposed to 1450 x *g* for 30 minutes at room temperature. Results are expressed as the percentage of the theoretical concentration (4% w/v). Dashed lines at 105-95% indicated upper and lower specification limits as per Ph Eur.

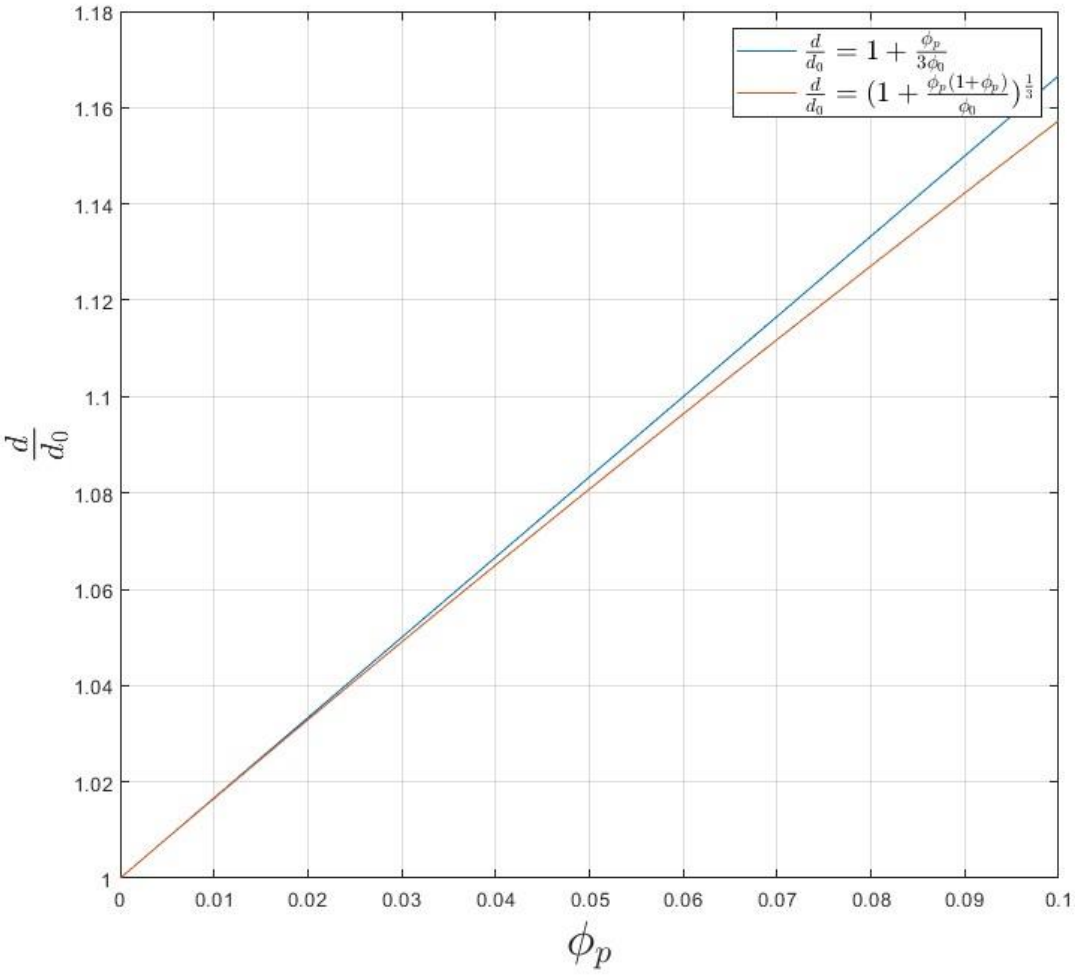


Figure S8 Simulation of the initial and final approximations of d/d_0 for ϕ_p ranging from 0 to 0.1.

Table S1 Overview of registered parenteral lipid emulsions in the Netherlands (anatomical therapeutic chemical code B05BA02).

Name	RVG	MAH	MA date (dd-mm-yyyy)	Presentation(s)	Oil phase (per 100 ml)	Excipients	Generation	Ref.
ClinOleic 20%	16863	Baxter	13-10-1997	Infusion bags (100, 250, 350, 500 and 1000 ml)	16 gram OO 4 gram SO	Phospholipids (egg), glycerol, sodium oleate, sodium hydroxide and purified water	3rd	CBG, 2023a
Intralipid 20%	02608	Fresenius Kabi	06-02-1974	Infusion bags (100, 250, and 500 ml)	20 gram SO	Phospholipids (egg), glycerol, sodium hydroxide and purified water	2nd	CBG, 2023b
Lipoplus 200 mg/ml	31376	B. Braun Melsungen	05-01-2006	Glass bottles (100, 250, 500 and 1000 ml)	10 gram MCT 8 gram SO 2 gram FO	Phospholipids (egg), glycerol, sodium oleate, ascorbyl palmitate, dl-α-tocopherol, sodium hydroxide and purified water	3rd	CBG, 2023c
Omegaven-Fresenius	23043	Fresenius Kabi	20-04-1999	Glass bottles (50 and 100 ml)	10 gram FO	Phospholipids (egg), glycerol, sodium oleate, dl-α-tocopherol, sodium hydroxide and purified water	3rd	CBG, 2023d
SMOFlipid 200 mg/ml	30787	Fresenius Kabi	17-01-2005	Glass bottles (100, 250 and 500 ml) and infusion bags (100, 250, 500 and 1000 ml)	6 gram SO 6 gram MCT 5 gram OO 3 gram FO	Phospholipids (egg), glycerol, sodium oleate, dl-α-tocopherol, sodium hydroxide and purified water	3rd	CBG, 2023e

Abbreviations: Ref. = reference; RVG = register verpakte geneesmiddelen (national authorisation number); MA(H) = marketing authorization (holder); OO = olive oil, SO = soybean oil; MCT = medium chain triglycerides and FO = fish oil.

References to Table S1

College ter Beoordeling van Geneesmiddelen (CBG), 2023a. Samenvatting van de productkenmerken. ClinOleic 20 %, emulsie voor infusie. [WWW Document]. URL https://www.geneesmiddeleninformatiebank.nl/smpc/h16863_smpc.pdf. (last accessed 25 February 2023).

College ter Beoordeling van Geneesmiddelen (CBG), 2023b. Samenvatting van de productkenmerken. Intralipid 20% emulsie voor infusie. [WWW Document]. URL https://www.geneesmiddeleninformatiebank.nl/smpc/h02608_smpc.pdf. (last accessed 25 February 2023).

College ter Beoordeling van Geneesmiddelen (CBG), 2023c. Samenvatting van de productkenmerken. Lipoplus 200 mg/ml, emulsie voor infusie. [WWW Document]. URL https://www.geneesmiddeleninformatiebank.nl/smpc/h31376_smpc.pdf. (last accessed 25 February 2023).

College ter Beoordeling van Geneesmiddelen (CBG), 2023d. Samenvatting van de productkenmerken. Omegaven-Fresenius, emulsie voor infusie. [WWW Document]. URL https://www.geneesmiddeleninformatiebank.nl/smpc/h23043_smpc.pdf. (last accessed 25 February 2023).

College ter Beoordeling van Geneesmiddelen (CBG), 2023e. Samenvatting van de productkenmerken. SMOFlipid 200 mg/ml, emulsie voor infusie. [WWW Document]. URL https://www.geneesmiddeleninformatiebank.nl/smpc/h30787_smpc.pdf. (last accessed 25 February 2023).

Table S2 Design table in actual units of each variable including the experimental results for the volume-weighted percentage of large-diameter droplets (PFAT5).

Run no.	Space type*	Concentration (%, w/v)	Angle (°)	Time (min.)	PFAT5 (%)
1	Axial	9.36	60	10	0.070
2	Axial	2.63	60	10	0.036
3	Axial	6	23.36	10	0.058
4	Factorial	8	40	5	1.704
5	Factorial	8	80	5	0.102
6	Axial	6	60	1.59	0.068
7	Center	6	60	10	0.052
8	Center	6	60	10	0.049
9	Axial	6	93.63	10	0.144
10	Factorial	4	40	5	0.061
11	Factorial	4	80	5	0.044
12	Factorial	8	80	15	0.131
13	Factorial	8	40	15	0.086
14	Center	6	60	10	0.044
15	Factorial	4	80	15	0.095
16	Center	6	60	10	0.053
17	Center	6	60	10	0.045
18	Factorial	4	40	15	0.030
19	Center	6	60	10	0.045
20	Axial	6	60	18.41	0.068

* Space type indicates the geometric location of each run within the design space.

Table S3 ANOVA table showing the statistical output of the final model used to describe the evolution of the PFAT5 as a function of the A) propofol concentration, B) shaking angle and C) time.

Source	Sum of Squares	Df	Mean Square	F-value	p-value	
Model	1057.64	8	132.20	19.88	< 0.0001	significant
A-Concentration	96.40	1	96.40	14.50	0.0026	
B-Angle	60.43	1	60.43	9.09	0.0118	
C-Time	13.98	1	13.98	2.10	0.1750	
AB	60.58	1	60.58	9.11	0.0117	
BC	226.17	1	226.17	34.01	0.0001	
B^2	170.59	1	170.59	25.65	0.0004	
C^2	92.23	1	92.23	13.87	0.0034	
AB^2	21.73	1	21.73	3.27	0.0981	
Residual	73.13	11	6.65			
Lack of Fit	61.17	6	10.20	4.25	0.0668	not significant
Pure Error	11.98	5	2.40			
Cor Total	1130.80	19				

Abbreviations: Df = degrees of freedom.