Novel Method of Bench-top ^{19}F NMR in Measuring API Phase Partition for Oil-in-Water Emulsion Drug Products

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Background

Generic drug products are expected to have the same active pharmaceutical ingredient (API) with the same strength as the innovator product. In addition, for complex drug products the same physiochemical properties need to be demonstrated between the generic and innovator products. One class of drugs where this is especially important is complex formulations such as oil-in-water emulsions. In these types of drugs, the hydrophobic API is formulated in oil droplets stabilized by surfactant and micelles composed of surfactant molecules. The way the API phase partitions into oil and water (mainly micelles) is a critical quality attribute (CQA) of emulsion products and bioequivalence of this property needs to be demonstrated for generic version of emulsion drugs. However, a robust analytical method is lacking to measure the partition. Here, using difluprednate (DFPN, Scheme 1) emulsion product Durezol® as a model, we developed a novel low-field benchtop NMR method to demonstrate its applicability in measuring DFPN phase partitioning for ophthalmic oil-in-water emulsion products. Low-field ^{19}F spectra were collected for DFPN in formulation, in water phase and the oil phase after separation by ultra-centrifugation. The analysis of NMR results demonstrated process difference affect API phase partition of oil emulsion products.

Figure 2: Schematic illustration of emulsion infrastructure showing the different structures and cyclosporine drug localization in various phases

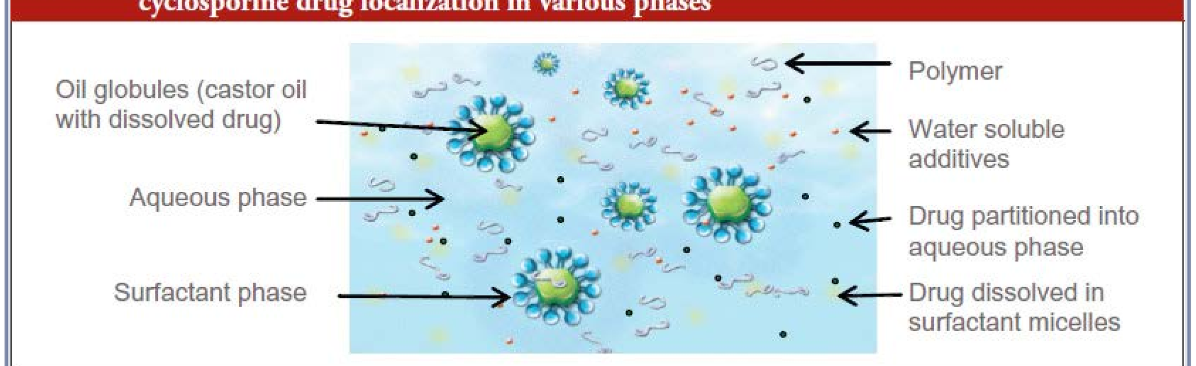


Figure 1. A schematic illustration of emulsion infrastructure showing the different structures and drug API localization in various phases. (adopted from the reference, Generics and Biosimilars Initiative Journal 2017;6(1):13-23.)

Materials

A total of 9 lots of DFPN oil emulsion products from the innovator Alcon and 2 samples from CDER/OPQ/OTR/DPQR home-made were analyzed (Table 1). Per label claim, each mL of Durezol® ophthalmic emulsion contains: difluprednate 0.5 mg (0.05%), castor oil, glycerin, polysorbate 80, *etc.* All of the drug products were analyzed in parallel. All of the emulsion products appeared as white opaque to slightly translucent homogeneous emulsions (Figure 2).

REFERENCES

[1] S. Patil and K. Chen, ^{19}F NMR selective analysis of API in difluprednate ophthalmic emulsion products, in: CDER/OPQ/OTR/DPA TR2017-31.

[2] A. Gore, C. Pujara, M. Attar and S. Neervannan, Ocular emulsions and dry eye: a case study of a non-biological complex drug product delivered to a complex organ to treat a complex disease. Generics and Biosimilars Initiative Journal 2017;6(1):13-23.

Table 1. Analyzed DFPN emulsion drug products.

Brand Name	Manufacturer	Lot#
Durezol®	Alcon	D1
		D2
		D3
		D4
		D5
		D6
		D7
		D8
		D9
Home-made	FDA/CDER	F1
		F2

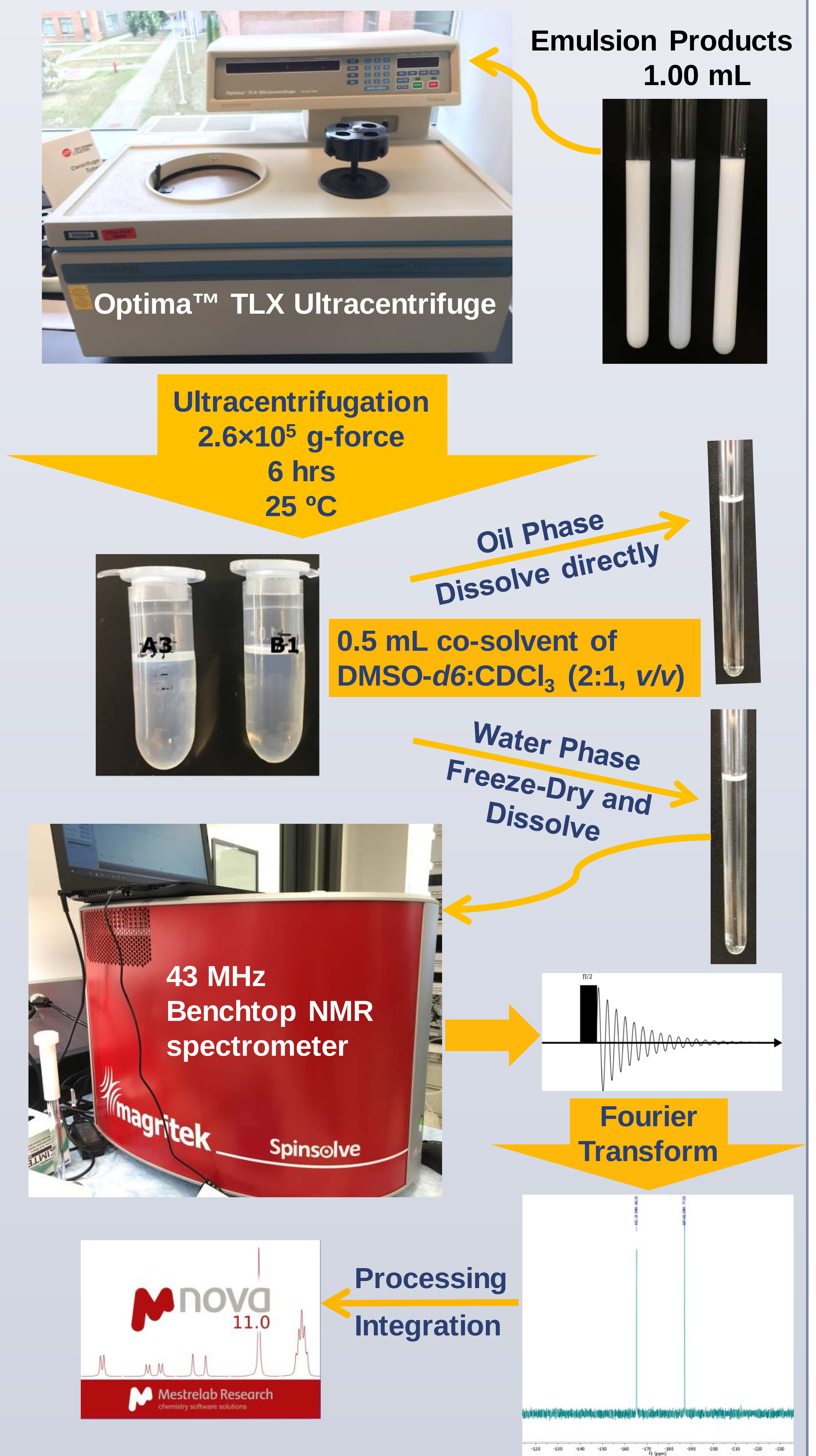
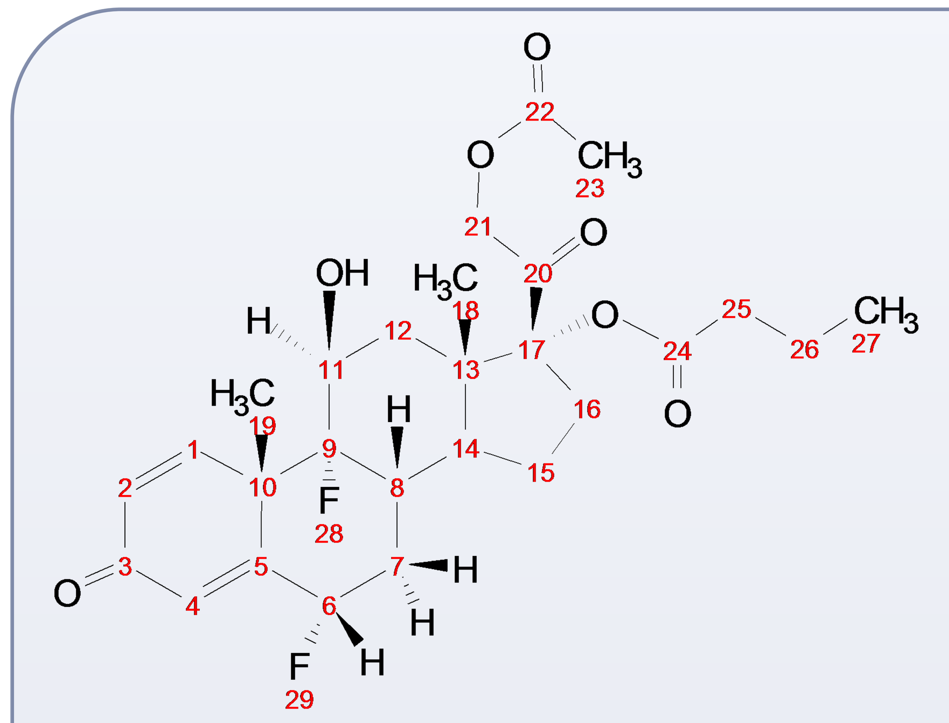


Figure 2. Flowchart of the centrifuge-NMR method.



Scheme 1. Molecular structure of difluprednate (DFPN).

Results

Table 2. The ^{19}F peak integration results showing mass balance after phase separation.

Sample		Volume (μL)	Peak F28 S/N	Peak F28 Peak Area (a.u.)	Peak F28 Peak Area × Volume	Peak F29 S/N	Peak F29 Peak Area (a.u.)	Peak F29 Peak Area × Volume
Durezol® D3	Oil Phase	5.20×10^2	66	69.3	3.60×10^4	78	68.2	3.55×10^4
	Water Phase	5.10×10^2	35	35.1	1.79×10^4	39	35.8	1.82×10^4
	Oil + Water Phase	—	—	—	5.39×10^4	—	—	5.37×10^4
	Emulsion	5.80×10^2	84	103.5	6.00×10^4	102	101.4	5.88×10^4
Home-made F1	Oil Phase	5.30×10^2	51	51.1	2.71×10^4	59	51.2	2.71×10^4
	Water Phase	5.50×10^2	46	51.0	2.81×10^4	50	51.2	2.82×10^4
	Oil + Water Phase	—	—	—	5.52×10^4	—	—	5.53×10^4
	Emulsion	6.20×10^2	75	97.1	6.02×10^4	90	94.4	5.85×10^4

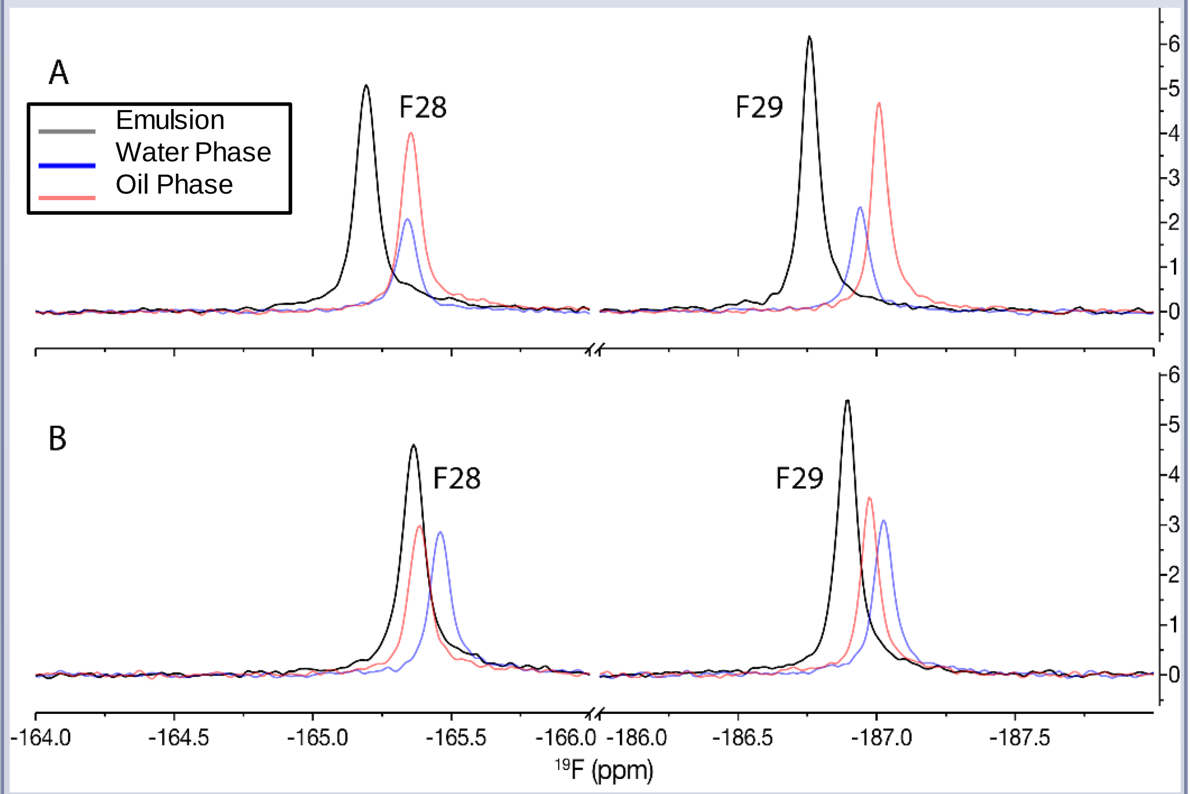


Figure 3. 1D ^{19}F NMR spectra of DFPN from emulsion drug product (black), water phase (blue) and oil phase (red). Spectra from Durezol® D3 (top) and home-made F1 (bottom) are shown.

Table 3. The method variation of the centrifuge-NMR method in measuring DFPN phase partition

Sample		Volume (μL)	Peak F29 S/N	Peak F29 Peak Area (a.u.)	Peak F29 Peak Area × Volume	Peak F29 Water Phase Percentage	Peak F29 Mean ± STD of Water Phase Percentage
Durezol® D3	Oil Phase 1	5.20×10^2	78	68.2	3.55×10^4	33.9%	35±1%
	Water Phase 1	5.10×10^2	39	35.8	1.82×10^4		
	Oil Phase 2	5.50×10^2	79	71.8	3.95×10^4	33.7%	
	Water Phase 2	5.30×10^2	36	37.9	2.01×10^4		
	Oil Phase 3	5.50×10^2	72	67.0	3.69×10^4	36.8%	
	Water Phase 3	5.30×10^2	37	40.5	2.14×10^4		
	Oil Phase 4	5.50×10^2	74	68.4	3.76×10^4	34.6%	
	Water Phase 4	5.30×10^2	37	37.6	1.99×10^4		
	Oil Phase 5	5.50×10^2	73	72.2	3.97×10^4	34.4%	
	Water Phase 5	5.30×10^2	35	39.3	2.08×10^4		
Home-made F1	Oil Phase 1	5.30×10^2	59	51.2	2.71×10^4	50.9%	51±1%
	Water Phase 1	5.50×10^2	50	51.2	2.82×10^4		
	Oil Phase 2	5.40×10^2	59	56.1	3.03×10^4	49.8%	
	Water Phase 2	5.50×10^2	54	54.6	3.00×10^4		
	Oil Phase 3	5.40×10^2	59	52.3	2.82×10^4	50.4%	
	Water Phase 3	5.50×10^2	49	52.1	2.86×10^4		
	Oil Phase 4	5.30×10^2	60	52.1	2.76×10^4	51.2%	
	Water Phase 4	5.50×10^2	55	52.6	2.89×10^4		
	Oil Phase 5	5.40×10^2	58	53.6	2.90×10^4	52.0%	
	Water Phase 5	5.50×10^2	56	57.1	3.14×10^4		

Table 4. Comparison of DFPN phase partition results within and across different manufactures.

Brand Name	Sample Number	Peak F29 Water Phase Percentage	Peak F29 Mean ± STD of Water Phase Percentage
Durezol®	D1	30.5%	32±3%
	D2	31.0%	
	D3	33.9%	
	D4	30.6%	
	D5	35.0%	
	D6	27.3%	
	D7	36.2%	
	D8	35.1%	
	D9	31.8%	
Home-made	F1	50.9%	52±2%
	F2	53.3%	

Conclusions

- The newly developed method of combining ultracentrifugation and low-field bench-top ^{19}F NMR has been demonstrated for mass balance and high reproducibility (1-3%), below lot-to-lot variations (3-5%).
- For the tested DFPN products, the different lots of innovator products have similar amount of water partition (including micelle), 32-35%. The home-made products have more water phase of 52%. The difference demonstrated manufacturing changes altered the API partitioning.

DISCLAIMER

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