Asymmetrical-flow field flow fractionation to assess the impact of manufacturing process variables on the globule size distribution of cyclosporine emulsions

Haiou Qu[1], Deval Patel[1], Darby Kozak[2], Ross Walenga[2], Stephanie Choi[2], Muhammad Ashraf[1], Patrick J. Faustino[1], Celia N. Cruz[1] and Xiaoming Xu[1]

1. Division of Product Quality Research, Office of Testing and Research, Office of Pharmaceutical Quality, CDER, U.S. FDA
2. Office of Research and Standards, Office of Generic Drugs, CDER, U.S. FDA

Abstract

Cyclosporine ophthalmic emulsions are colloidal oil-in-water dispersions with physicochemical properties that are sensitive to the manufacturing process/conditions. As such, to ensure batch-to-batch product quality consistency and/or generic to reference product sameness it is critical that these properties, which include globule size distribution (GSD) and rheology, are adequately characterized using appropriate techniques. The measurement of GSD can be challenging for polydisperse drug products. In addition, the presence of carbomer as a stabilizing agent and viscosity enhancer in the formulation can also interfere with the size determination as reported. Our group previously developed an asymmetrical-flow field flow fractionation (AF4) method for determining the GSD of polydisperse emulsions [1]. The purpose of this study was twofold: 1) to further evaluate the developed AF4 method, and 2) to assess the interplay between GSD and formulation viscosity as well as how they were influenced by the manufacturing processes.

Method

Five formulations, that were qualitatively (Q1) and quantitatively (Q2) the same as the reference listed product (Restasis®), were manufactured in-house. Efforts were focused on obtaining formulations with different globule size distribution and viscosity. The globule size were varied by controlling the temperature and pressure during the microfluidization. The viscosities of the formulation were controlled by subjecting carbomer to different shear conditions using a homogenizer. The prepared formulations were directly analyzed by AF4 without further dilution or any other treatment.

Processing condition for in-house formulations

Formulation	Microfluidization T (°C)	Microfluidization pressure (kpsi)	Viscosity of carbomer solution
1	25-30	30	low
2	25-30	30	medium
3	25-30	30	high
4	35-40	30	medium
5	10-15	20	medium

Figure 1. Microfluidization system for globule size reduction (left); and high shear laboratory mixer for generating carbomer solutions of different viscosities (right).

AF4

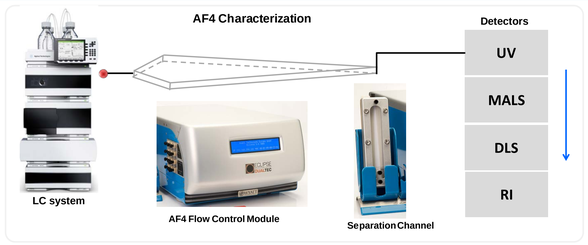

Figure 2. AF4 system setup (above) and conditions. AF4 Channel: short with 350 µm spacer; Mobile phase: 1 mM NaCl; Membrane: regenerated cellulose, 10 kDa; Focus flow: 1 mL/min; Detector flow: 1 mL/min. MALS: multi-angle light scattering. DLS: dynamic light scattering. RI: refractive index.

Results

Table 1. Particle size distribution characterization of cyclosporine emulsions by DLS (data shown as mean ± sd, n=6)

Sample*	Z-Ave (d.nm)	PdI	Dv(10) (nm)	Dv(50) (nm)	Dv(90) (nm)
Restasis	115.2 ± 4.9	0.339 ± 0.041	33.5 ± 11.5	49.3 ± 19.6	207.9 ± 124.0
F1	101.7 ± 1.9	0.278 ± 0.009	22.9 ± 14.2	37.8 ± 24.9	117.8 ± 61.6
F2	105.6 ± 0.7	0.289 ± 0.005	23.3 ± 13.4	39.2 ± 24.6	130.2 ± 69.1
F3	101.1 ± 0.8	0.273 ± 0.008	20.1 ± 14.8	32.5 ± 25.7	100.5 ± 56.0
F4	86.6 ± 0.7	0.270 ± 0.007	25.1 ± 13.5	40.7 ± 22.3	95.9 ± 43.6
F5	152.9 ± 3.0	0.263 ± 0.008	34.3 ± 21.4	69.7 ± 49.0	309.0 ± 97.6

*samples were diluted ten times with Milli-Q water prior to the analysis

- ❑ DLS results showed that manufacturing process conditions had a significant effect on the globule size of the formulations
- ❑ Higher microfluidization temperature and pressure were more effective in producing smaller oil globules
- ❑ Despite the change in formulation rheological properties, the hydrodynamic sizes of the oil globules were not affected

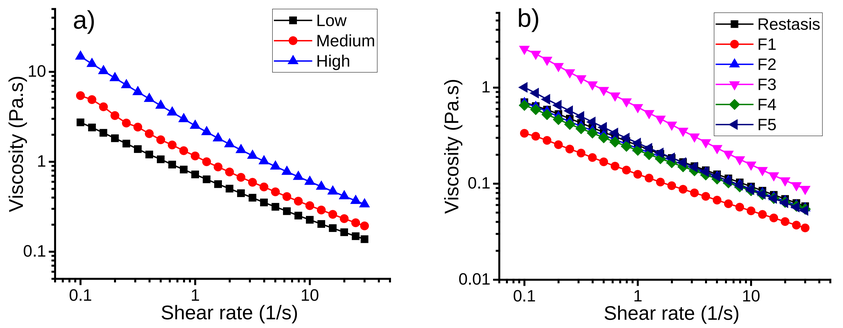

Figure 4. a) Rheological profiles of carbomer solutions subjected to different shear conditions. b) rheological profiles of the RLD and five in-house formulations.

- ❑ Carbomer was shear sensitive and its viscosity was reduced under increasing shearing force
- ❑ Carbomer largely determines the overall rheological profile of the formulation
- ❑ Formulations with carbomer of medium viscosity have similar rheological profiles as the RLD

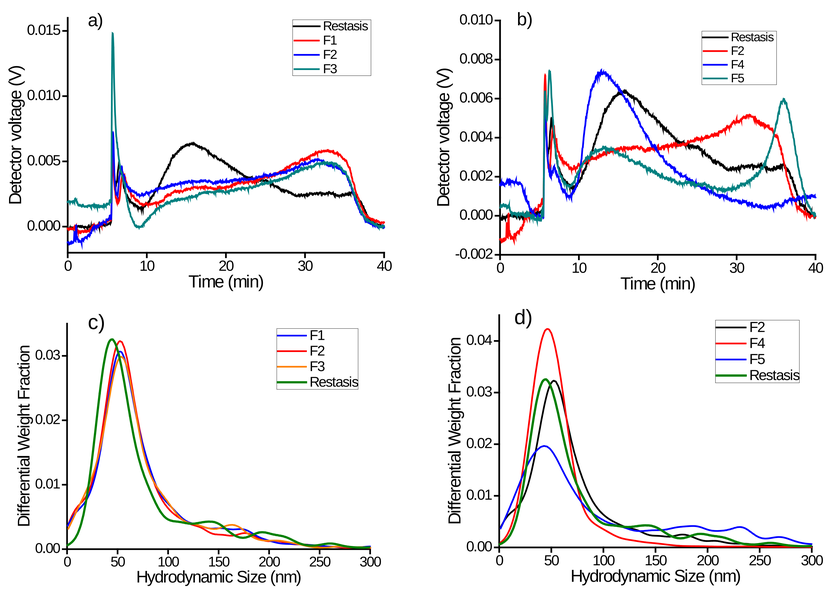

Figure 3. a) and b) AF4 fractograms of RLD and in-house formulations c) and d) globule size distribution from AF4 characterization based on refractive index (dRI) and online DLS results.

- ❑ AF4 has demonstrated discriminating ability in characterizing globule size distribution of cyclosporine emulsions manufactured under different conditions.
- ❑ AF4 is valuable in understanding the process variable and can assist to achieve better quality control.

Conclusions

- ❑ **Manufacturing conditions such as microfluidization pressure and operating temperature were found to affect globule size distributions of cyclosporine emulsion**
- ❑ **Under high shear condition, the viscosity of the formulation containing carbomer was found to decrease. It is noteworthy that carbomer is a shear sensitive excipient**
- ❑ **Viscosity changes in the formulation do not affect globule size distribution**
- ❑ **AF4 may become a valuable technique for evaluating the effect of process variables on the physicochemical properties of the complex formulations**

Reference

[1] H. Qu, J. Wang, Y. Wu, J. Zheng, Y.S.R. Krishnaiah, M. Absar, S. Choi, M. Ashraf, C.N. Cruz and X. Xu. Asymmetric Flow Field Flow Fractionation for the Characterization of Globule Size Distribution in Complex Formulations: A Cyclosporine Ophthalmic Emulsion Case. International Journal of Pharmaceutics. (2018). 538(1-2), 215-222.

Acknowledgements

Drs. Qu and Patel were supported in part by an appointment from Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and FDA.

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