Development of Cyclosporine A Microemulsion for Parenteral Delivery
Y. Yuan 1, X. Che 1, M. Zhao 1, S. Li 1, Y. Wang 1, A. Schwendeman 2
1 Shenyang Pharmaceutical University of China, 2 University of Michigan

Purpose
The goal of this study was to develop a parenteral microemulsion formulation of cyclosporine A (CyA).

Methods
The CyA solubility in caprylic capric triglyceride (GTCC), ethyl oleate and soybean oil was determined by HPLC analysis. The pseudo-ternary diagrams of oil (GTCC), surfactant (Solutol® R HS-15), co-surfactant (ethanol/PEG400 mixture at 1:2, 1:1 and 2:1 v/v) and water were constructed to identify microemulsion existence boundaries. The CyA was added at 3, 6 and 9% w/v to the optimal microemulsion composition. Microemulsion particle size was determined by dynamic light scattering (DLS). Viscosity and conductivity of final CyA formulation were examined. Microemulsion particle size stability was determined upon 25-fold dilution in 5% dextrose solution for injection. The short-term stability of 25 mg/ml CyA microemulsion formulation was tested following a 3-month storage at 4 and 25°C by DLS and CyA HPLC purity analyses. The hemolytic potential of CyA microemulsion diluted with dextrose to 1 mg/mL was tested by incubation with rabbit erythrocytes for 3 hours at 37°C.

Results
The GTCC was selected as an oil phase for CyA microemulsion based on solubility results. The optimum CyA microemulsion formulation consisted of 2.5% CyA, 9% GTCC, 24% Solutol® HS 15, 8% PEG 400, 4% ethanol and 52.5% water based on weight percent. The average particle sizes of the optimized blank and drug-loaded microemulsions were 68.7 nm and 71.6 nm, respectively, and remained unchanged after 25-fold dilution with dextrose. The results of a 3-month stability study confirmed that microemulsion physical and CyA chemical stabilities at 4 and 25°C storage temperatures. In vitro hemolysis studies indicated that CyA microemulsions were well tolerated by erythrocytes.

Conclusion
The novel microemulsion formulation of CyA was developed that is suitable for parenteral administration. This new formulation could potentially have less vehicle-associated side effects that current commercial Cremophor E and ethanol based formulation of CyA.