Development, Characterization and In Vivo Evaluation of Self Micro Emulsifying Formulation of Tacrolimus
V. Nekkanti, Z. Wang, G. V. Betageri
Western University of Health Sciences

Purpose
To develop and characterize a self micro emulsifying drug delivery system of tacrolimus for improving in-vitro dissolution and oral bioavailability.

Methods
Preliminary solubility studies were carried out using blends of oil (Capmul MCM), surfactants (Labrasol, Labrafil M2125) and co-surfactant (Tween 80). Pseudo-ternary phase diagrams were constructed to identify the self micro emulsification region. The self-micro-emulsification properties, droplet size and zeta potential of the developed formulations were studied upon dilution with water. Formulation screening was conducted based on results obtained from phase diagrams and characteristics of the resultant micro emulsions. The dissolution characteristics of SMEDDS filled into hard gelatin capsules was investigated and compared with pure drug substance to ascertain the impact on self-emulsifying properties in USP type-II dissolution apparatus at 50 rpm using distilled water as a medium. The drug content in samples was analyzed using a HPLC method. In vivo pharmacokinetic studies were conducted in male Sprague-Dawley rats following oral administration of 5 mg/kg dose. Pharmacokinetic parameters were calculated by analyzing the plasma samples using an LC/MS/MS technique.

Results
The optimized formulation containing Capmul MCM (12% w/w), Labrasol (32% w/w), Labrafil M 2125 (32% w/w) and Tween 80 (16% w/w) showed rapid self-micro emulsification in aqueous media. The size of the oil globules in the emulsion was 121.2±1.9 nm and the zeta potential was –12.9 mV. The SMEDDS filled in hard gelatin capsules showed faster rate of drug release (98.34±3.9%) compared to pure tacrolimus (19.87±2.1%) after 60 minutes indicating the self-emulsifying properties of SMEDDS. Following oral administration in male Sprague-Dawley rats, the T\text{max} of proliposomal formulation was 3 h as compared to pure drug, which was 2 h. While the C\text{max} of proliposomal was 122.72±10.4 ng/ml indicating higher plasma levels as compared to pure drug, which was 57.39±6.3 ng/ml. The systemic exposure (AUC\text{0-24}) was significantly higher for proliposomal formulation (1399.44±41.2 ng.h/ml) in comparison to pure drug suspension (601.63±50.2 ng.h/ml).

Conclusion
An optimized SMEDDS formulation was successfully developed with an increased dissolution rate and oral bioavailability of a poorly soluble drug, tacrolimus. The study indicated that SMEDDS formulation can be used as a possible alternative to conventional oral formulations of tacrolimus to improve its oral bioavailability.