Formulation, Characterization and Pharmacokinetic Evaluation of Tacrolimus Proliposomes
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Purpose
The objective of our study was to develop a proliposomal formulation to enhance oral bioavailability of a poorly water soluble drug, tacrolimus.

Methods
Proliposomes were prepared by thin film hydration method using different lipids such as soy phosphatidylcholine (SPC), hydrogenated egg phosphatidylcholine (HEPC), distearyl phosphatidylcholine (DSPC), dimyristoylphosphatidylcholine (DMPC) and dimyristyl phosphatidyl glycerol sodium (DMPG) and cholesterol in various ratios (1:1:0.25, 1:2:0.25 and 1:2:0.5). The prepared proliposomal formulations were evaluated for particle size (following hydration), encapsulation efficiency, solid state properties, in vitro drug release, and in vivo pharmacokinetics. The solid state characterization of proliposomes was performed by differential scanning calorimetry (DSC). In vitro drug release studies were carried out in distilled water using USP type-II dissolution apparatus. The samples were analyzed in triplicate using a gradient HPLC method. In vivo pharmacokinetic studies were conducted in male Sprague-Dawley rats following oral administration of 5mg/kg dose. Pharmacokinetic parameters were estimated by analyzing the plasma samples using an LC/MS/MS technique.

Results
Among the proliposomal formulations, the formulation containing drug: DSPC: cholesterol in the ratio of 1:2:0.5 exhibited highest encapsulation efficiency (98.89±1.1%) with a particle size in the range of 1070±63.7 nm following sonication for 5 minutes. The dissolution study demonstrated that there was an increase in the dissolution of tacrolimus when incorporated in proliposomal form (91.82±3.8%) as compared to pure drug (19.87±2.1%) after 60 minutes. Following oral administration in male Sprague-Dawley rats, the T_{max} of proliposomal formulation was 3 h as compared to pure drug, which is 2 h. While the C_{max} of proliposomal formulation was 154.75±9.1 ng/ml indicating higher plasma levels as compared to pure drug, which was 57.39±6.3 ng/ml. The systemic exposure (AUC_{0-24}) of pure tacrolimus suspension and proliposomal formulation was 601.63±50.2 ng.h/ml and 1163.14±28.7 ng.h/ml respectively, showing nearly a two fold increase for proliposomal formulation in comparison to pure drug.

Conclusion
Proliposomal formulation of poorly water soluble drug tacrolimus was successfully prepared using phospholipids. The rate and extent of drug dissolution was significantly enhanced by developing proliposomal formulation for tacrolimus. The in vivo pharmacokinetic studies resulted in an increase in systemic exposure demonstrating the utility of proliposomal formulations for improved oral delivery of tacrolimus.