Poor bioavailability of drugs via oral route is the greatest challenge facing drug formulation. To overcome this obstacle, transdermal route was commonly used as an alternative route to improve bioavailability. Lercanidipine HCL (LER) is a vasoselective calcium-channel blocker that has a poor oral bioavailability of 10% due to its hepatic metabolism and low aqueous solubility. The main objective of this study was to develop nanoethosomal LER gel for transdermal delivery to increase its skin permeation and promote bioavailability. Nanoethosomes were prepared and optimized using a Box–Behnken design employing ethanol injection method. The design studied the influence of Phospholipon 90G(PL90G), LER and ethanol concentrations on entrapment efficiency (EE%); vesicle size; % cumulative LER release (CLERR) and cumulative LER permeated per unit area at 24 h Q24 (μg/cm2). The pharmacokinetic parameters of the optimized formulation were determined in rats. Nanoethosomes showed a mean vesicle size between 210.87 and 400.57 nm and EE% ranging from 49.26 to 97.22%. The developed Nanoethosomes enhanced % CLERR and Q24 values compared to drug suspension. The experimental parameters of optimized formulation were very close to those calculated by software. The pharmacokinetics study showed three times statistically significant (p < 0.05) enhancement in LER bioavailability following nanoethosoml LER gel transdermal application compared to that of oral LER suspension. Nanoethosomes can be considered as a promising carrier for LER transdermal delivery, thus will be fruitful therapy in hypertension management.