Propranolol hydrochloride `is widely used in the treatment of hypertension and other cardiac conditions. However, the drug is extensively metabolized in the liver. The purpose of this research was to formulate and optimize a nanoethosomal buccal gel of propranolol hydrochloride in an attempt to improve its bioavailability. The ethosomes were prepared using cold method whereas a 2^3 full-factorial design was employed to investigate the effect of phosphatidylcholine (PC), propylene glycol (PG), and ethanol concentration on entrapment efficiency, particle size and % drug released. The adjusted and predicted coefficients of determination as well as the CV% were used to assess the fitness of the experimental model. The optimized formulation F5 containing (1% PC, 10% PG and 50% ethanol) was incorporated in 1% Carbopol 934 gel base. The buccal gel was evaluated by assessment of the ex-vivo drug permeation and in vivo bioavailability. It was noted from regression equations, contour plots and 3D-respnse surface plots that the three dependent variables had a direct relationship with PC concentration and an inverse relationship with PG and ethanol concentrations. The viscosity of both the ethosomal and control gel which contains the free drug powder was 20745cp and 12411cp respectively. Both gel preparations were homogenous with a pH value of 6.8. The ethosomal gel exhibited a high flux across a freshly dissected chicken buccal mucosa with an enhancement ratio of 1.314. The mean AUC_{0-24} for oral tablets, control gel and ethosomal gel were 426.17±51.78 ng.hr/mL, 579.102±66.19 ng.hr/mL and 810.39±92.33 ng.hr/mL respectively. The relative bioavailability was dramatically enhanced from 135.885% after using the control gel to 190.157% with the ethosomal system when compared to the marketed product Inderal ® tablet (40mg). The choice of the buccal route together with the use of ethosomes was an appropriate approach to improve the propranolol bioavailability.