Amisulpride is practically insoluble in water and suffers from irregular and low bioavailability (48%). It is metabolized in liver to a minor degree. Accordingly, this irregular and low bioavailability could be due to low solubility and P-glycoprotein efflux which also affect its penetration through blood brain barrier. In the current study, in an attempt to solve these problems, Amisulpride self-nanoemulsifying drug delivery systems (SNEDDS) were prepared. Preliminary screening was carried out to determine Amisulpride solubility in various oils and surfactants. The formulations were prepared using oil (Caproyl-90), two surfactants (Cremophor EL and Labrasol, “Smix”) and cosurfactant (Transcutol HP). Response surface methodology based on central composite design was applied for formulation optimization. Oil percentage, Smix: cosurfactant ratio and Cremophor EL: Labrasol ratio in Smix were selected as independent variables while mean droplet sizes at pH 1.2, 4.5 and 6.8, drug loading and absorbance of diluted SNEDDS at pH 1.2, 4.5 and 6.8 as dependent variables. A second-order polynomial equations were fitted to data. Optimized formulation, containing 10% oil, 1.31 Smix: cosurfactant ratio and 2 ratio of Cremophor EL: Labrasol was prepared according to software determined levels using desirability function and overlay plot. It provided a drug loading of 50.2 mg/ml and mean droplet sizes of 28, 120 and 95 nm in pH 1.2, 4.5 and 6.8 respectively. Also, it released Amisulpride completely within 15 min irrespective of the type or pH of dissolution medium. Bearing in mind that optimized SNEDDS incorporates bioactive ingredients, it could be potential for improving Amisulpride oral bioavailability.