Chitosan is a natural, biocompatible polymer. The aim of this work was to study the influence of drug solubility in 2% v/v acetic acid, formulation parameters, on mean hydrodynamic (MHD) diameters and drug entrapment efficiencies (% EE) into chitosan-TPP nanoparticles (NPs). Drugs of different aqueous solubilities with nearly similar molecular weights were chosen and admixed at several concentrations in 2% acetic acid at different chitosan concentrations and at fixed chitosan to TPP concentrations/volumes ratios. The NPs were freeze-dried, and the supernatants were utilized to determine % EE. Theophylline- and antipyrine-loaded NPs showed the best short-term physical stability in terms of MHD diameters. Antipyrine-loaded NPs possessed the larger MHD diameters, while vitamin C–loaded NPs showed the smallest ones. The relationships between the ratio of drug concentration relative to their solubilities in acetic acid were almost linear for antipyrine and vitamin C–loaded NPs when plotted against and the MHD diameters of NPs, and linear for antipyrine- and theophylline-loaded NPs when plotted against % EE with antipyrine NPs possessing the highest % EE. However, vitamin C– and propylthiouracil-loaded NPs exhibited curvilinear patterns with comparatively lower % EE. The concentration of chitosan, drug solubility in dispersion medium, and the ratio of the concentration of admixed drug relative to its solubility in dispersion medium were found critical in determining % EE and MHD diameters of NPs. It was evident that drugs with extremely low or high solubilities in dispersion medium resulted in low % EE when admixed at both low and high concentrations.