Producing an optimal balance between engine performance and exhaust emissions has always been one of the main challenges in automotive technology. This paper examines the use of RSM (response surface methodology) to optimize the engine performance, and exhaust emissions of a spark-ignition (SI) engine which operates with 2-butanol–gasoline blends of 5%, 10%, and 15% called GBu5, GBu10, and GBu15. In the experiments, the engine ran at various speeds for each test fuel and 13 different conditions were constructed. The optimization of the independent variables was performed by means of a statistical tool known as DoE (design of experiments). The desirability approach by RSM was employed with the aim of minimizing emissions and maximizing of performance parameters. Based on the RSM model, performance characteristics revealed that increments of 2-butanol in the blended fuels lead to increasing trends of brake power, brake mean effective pressure and brake thermal efficiency. Nonetheless, marginal higher brake specific fuel consumption was observed. Furthermore, the RSM model suggests that the presence of 2-butanol exhibits a decreasing trend of nitrogen oxides, carbon monoxides, and unburnt hydrocarbon, however, a higher trend was observed for carbon dioxides exhaust emissions. It was established from the study that the GBu15 blend with an engine speed of 3205 rpm was found to be optimal to provide the best performance and emissions characteristics as compared to the other tested blends.