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plasdone™ S630 ultra copovidone for oxidation-labile drugs

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introduction

Formulated pharmaceutical products containing oxidative-labile drug substances could have long-term chemical stability problems if the excipients used in the formulation contain even trace amounts of highly reactive impurities (peroxides, superoxides, hypochlorites, formic acid, etc.) and/or degradants of the excipients and/or its residues. A trace amount of impurities in an excipient can directly act as a reactive site, activating chain degradation reactions of the active pharmaceutical ingredients (APIs). Therefore, high-quality excipients with less impurities can play a pivotal role in the stabilization of oxidative-labile APIs. The purpose of this study was to evaluate the impact of copovidone (excipient) on the long-term chemical stability of an oxidation-susceptible model API, quetiapine fumarate. A comparison was conducted between standard copovidone and Plasdone™ S630 Ultra copovidone.

methods

In this study, Plasdone™ S630 Ultra copovidone was used to mitigate the stability problem of an oxidation-liable drug, quetiapine fumarate. This grade of copovidone was compared with standard copovidone. The stability study was carried out using binary dry blending mixtures of the drug and excipient at a ratio of 1:4. The dry blend mixtures were tableted to improve contact between drug and excipient. Then, tablets obtained were packed in loosely closed sample vials and stored at 40 ^{0}C/75 % RH for a period of six months. A peroxidation study was carried out and the main degradant was confirmed by HPLC and LC-MS/MS. Impurity assays of the stability samples were carried out using HPLC at predetermined time points.

results

1. Determination of Quetiapine Fumarate Degradation Mechanism

Piperazine structure is known to be susceptible to oxidative degradation and can form a corresponding N-oxide derivative when formulated with excipients that have radical impurities, such as peroxide. Oxidative degradation of quetiapine fumarate was investigated in formulations containing copovidone. The site of oxidation was proposed based on a correlation of the forced degradation results with peroxidation of quetiapine fumarate. The structure of the main degradant, quetiapine N-oxide derivative, and HPLC chromatograms of different samples, are illustrated in Figure 1.

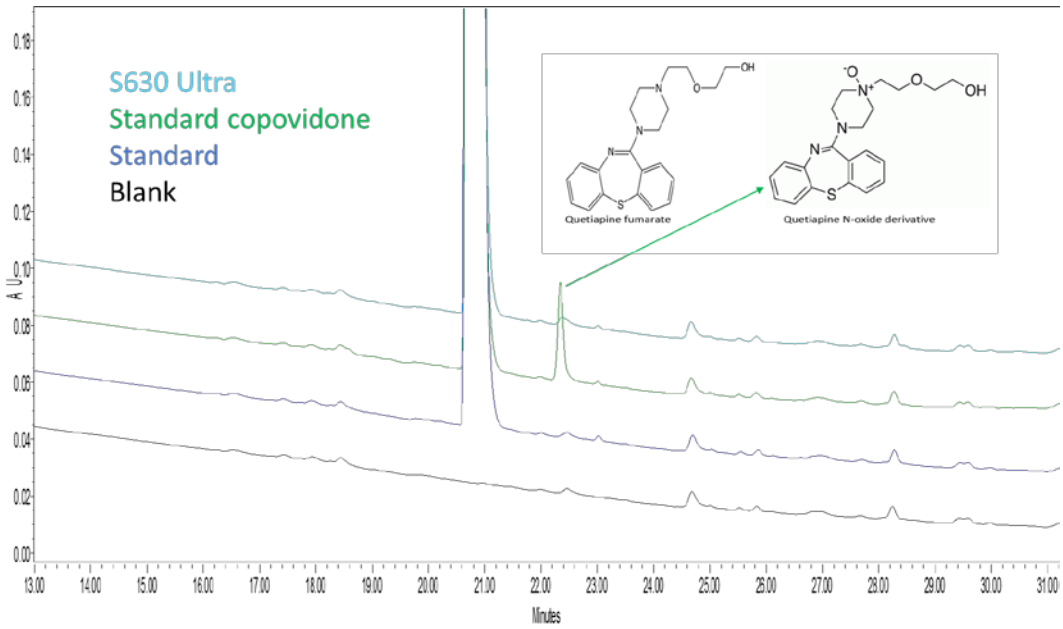

Figure 1. HPLC chromatograms of different samples

2. Peroxide Level and Growth Rate Control

Plasdone™ S630 Ultra copovidone exhibited a much lower initial peroxide level and slower growth rate than standard copovidone when stressed at 60°C (Figure 2), benefiting the chemical stability of oxidation-susceptible APIs. Further studies showed that Plasdone™ S630 Ultra copovidone had slower peroxide growth up to 24 months storage as compared with standard copovidone (data not shown).

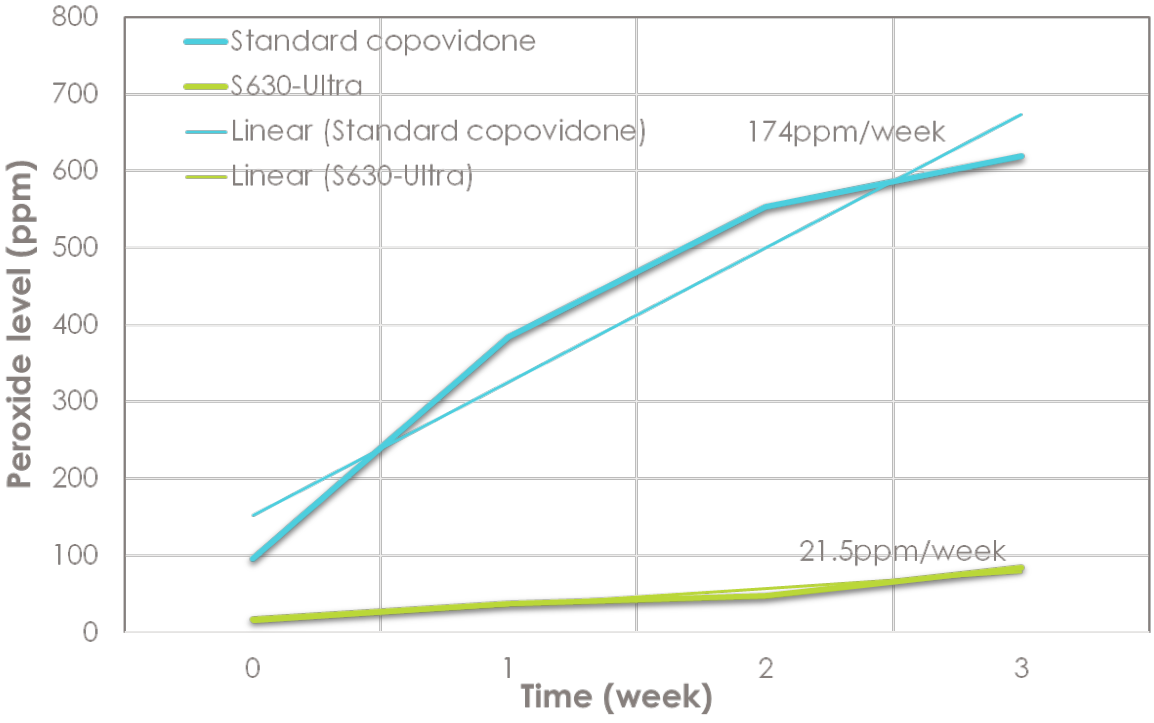

Figure 2. Peroxide level and growth rate of copovidone stressed at 60 °C

3. Stability Enhancement in Quetiapine Formulation

The percentage of N-oxide impurity increased during 6-month storage at 40°C /75% RH. Tablets made with Plasdone™ S630 Ultra copovidone showed only 0.16 % N-oxide impurity increase while tablets made with standard copovidone showed almost 2.06 % N-oxide impurity (~12.8 times more).

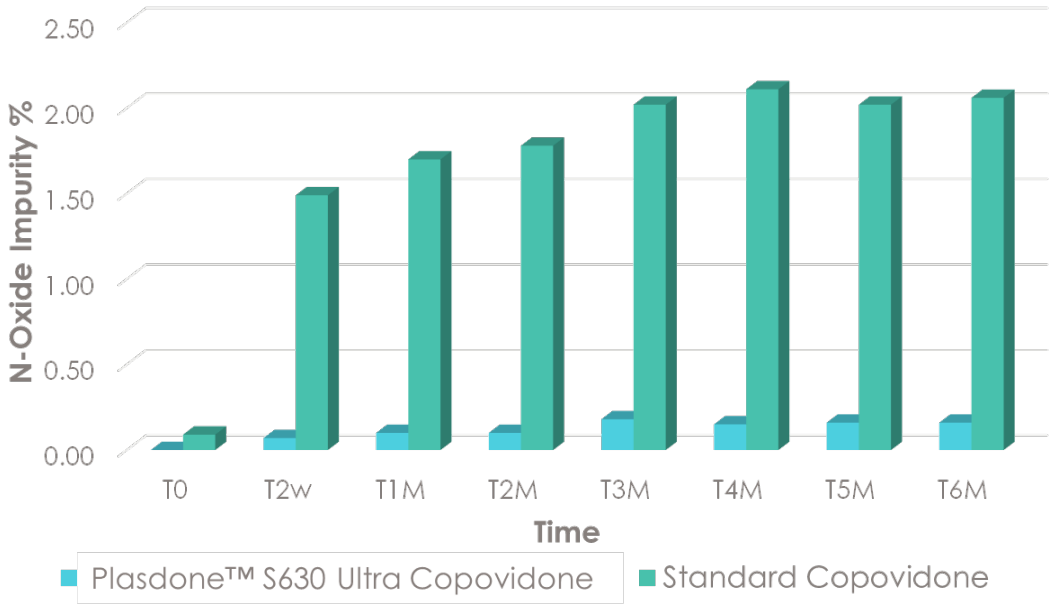

Figure 3. Histogram plot of N-Oxide impurity generated for the duration of 6 months at 40°C/75% RH

conclusion

This study demonstrated that the presence of a trace amount of peroxide in an excipient can play a pivotal role in the oxidative degradation of an oxidation-liable API. Under stressed storage conditions of 40°C /75% RH, quetiapine fumarate tablets formulated with Plasdone™ S630 Ultra copovidone yielded a lower amount of oxidative impurity compared with standard copovidone. Plasdone™ S630 Ultra copovidone with a very low peroxide level is a superior excipient candidate for oxidation-labile drugs.

Note: This work was presented at the 2019 AAPS PharmSci 360, Austin, Texas, USA