Poster 1

Understanding Dibasic Calcium Phosphate impact on Chemical Stability - Trends in Immediate Release Tablet Formulations

Authors: Heather Fredricks Schmidt, Todd Zelesky, Marissa Puzan and Daniel Petock
Presenting Author: Heather Fredricks Schmidt
Affiliation: Pharmaceutical Sciences Small Molecule, Pfizer, Inc., Groton, CT
Corresponding Author's email: heather.frericksschmidt@pfizer.com

Purpose

Understanding the chemical and physical stability of an API under manufacturing and storage conditions is a key quality attribute impacting the performance and safety of a drug product. Immediate release (IR) tablet formulations with dibasic calcium phosphate (DCP) have historically been less chemically stable than similar formulations containing lactose. The poor chemical stability outcomes observed are not well understood as the impact of DCP on chemical stability has not been fully studied in a systematic way. In our research we examine API degradation mechanisms and DCP impurity levels, particle and surface properties that could lead to greater chemical instability of DCP formulations.

Methods

We completed a head-to-head comparison of four model APIs in DCP (A-Tab®) and lactose containing IR tablets formulations examining their chemical stability. These APIs were chosen as they were observed to degrade under major pharmaceutically relevant degradation pathways: acid hydrolysis, base hydrolysis, transition metal catalyzed oxidation, hydrogen peroxide and radical initiated oxidation. Tablets were staged under thermal stress (60°C and 60°C/75%RH for 5 weeks) and purity and potency assays were performed.

Impurity levels and particle and surface properties of DCP were explored to provide insight into the cause of API chemical instability. Innophos A-Tab® and JRS Pharma Emcompress were evaluated and compared to lactose monohydrate (Foremost Farms Fast Flo).

Results and Conclusion

For all the model APIs the DCP formulations had equal or higher total impurity levels than those containing lactose. Insight into degradation pathway in DCP tablets were evaluated for each model API using LC mass spectroscopy and HR-MS/MS. Initial findings suggest that DCP triggers degradation of reactive APIs through hydrolysis and oxidative degradation pathways.

DCP sources were found to contain higher levels of metals. We also found that the surface area of DCP was larger than lactose which leads to greater surface interaction with the APIs. Surface Energy Analysis was completed using an iGC-SEA method to characterize polar and non-polar surface properties, which showed that the DCP has a much higher polar surface free energy than the lactose. This could also impact surface interactions with the APIs and potentially cause acid or base catalyzed hydrolysis degradation.

Keywords: IR tablets, degradation, excipient, particle properties, surface analysis