Journal of Pharmaceutical Sciences xxx (2016) 1-5

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Rapid Communication

Use of Activated Carbon in Packaging to Attenuate Formaldehyde-Induced and Formic Acid—Induced Degradation and Reduce Gelatin Cross-Linking in Solid Dosage Forms

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ARTICLE INFO

Article history:
Received 11 January 2016
Revised 7 April 2016
Accepted 13 April 2016

Keywords:
stability
chemical stability
physical stability
dissolution
solid dosage form

ABSTRACT

Formaldehyde and formic acid are reactive impurities found in commonly used excipients and can be responsible for limiting drug product shelf-life. Described here is the use of activated carbon in drug product packaging to attenuate formaldehyde-induced and formic acid—induced drug degradation in tablets and cross-linking in hard gelatin capsules. Several pharmaceutical products with known or potential vulnerabilities to formaldehyde-induced or formic acid—induced degradation or gelatin cross-linking were subjected to accelerated stability challenges in the presence and absence of activated carbon. The effects of time and storage conditions were determined. For all of the products studied, activated carbon attenuated drug degradation or gelatin cross-linking. This novel use of activated carbon in pharmaceutical packaging may be useful for enhancing the chemical stability of drug products or the dissolution stability of gelatin-containing dosage forms and may allow for the 1) extension of a drug product's shelf-life when the limiting attribute is a degradation product induced by a reactive impurity, 2) marketing of a drug product in hotter and more humid climatic zones than currently supported without the use of activated carbon, and 3) enhanced dissolution stability of products that are vulnerable to gelatin cross-linking.

Introduction

Active pharmaceutical ingredients (APIs) with either a primary or secondary amine may be vulnerable to reactions with formaldehyde, formic acid, or both.[1-4] These reactive compounds are ubiquitous as impurities or degradation products in many common excipients (e.g., polyethylene glycol, croscarmellose sodium, lactose, microcrystalline cellulose, etc.).[1,2] For example, varenicline is known to react with formaldehyde and formic acid via the Eschweiler-Clarke reaction to form an N-methyl degradation product.[5] Varenicline also reacts with formic acid to form an N-formyl degradation product, which limits the drug product's shelf-life.[5]

Gelatin-containing products such as gelatin capsules are vulnerable to cross-linking, and formaldehyde is known to be a cross-linking agent.[6-8] This can slow or prevent drug release resulting in highly variable and out-of-specification dissolution results.[6,8] Although enzymes (i.e., pepsin or pancreatin) can be added to the dissolution medium to mitigate the effects of cross-linking, surfactants and the pH of the dissolution medium can affect the activity of these enzymes.[8] Furthermore, some regulatory authorities do not allow the use of enzymes during dissolution testing.[9,10] Therefore, cross-linking complicates the dissolution testing of these products and may limit their shelf-life.

Although activated carbon is known to adsorb water and many volatile organic compounds including formaldehyde and formic acid,[11,12] its use in pharmaceutical packaging has focused on removal of odor from some formulations.[13] It has not been used as part of the packaging strategy to purposefully protect drug products from drug degradation caused by formaldehyde or formic acid

This article contains supplementary material available from the authors by request or via the Internet at http://dx.doi.org/10.1016/j.xphs.2016.04.016.

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http://dx.doi.org/10.1016/j.xphs.2016.04.016
0022-3549/

or to prevent gelatin cross-linking. It is hypothesized here that by adsorbing headspace formaldehyde or formic acid, activated carbon can mitigate the reactions of these species with formulated drugs or gelatin capsules.

Experimental Section

Two tableted products with known vulnerabilities to formaldehyde-induced and formic acid–induced drug degradation were subjected to accelerated stability challenges in the presence and absence of activated carbon. Appearance and purity were measured, and degradation levels in the presence and absence of activated carbon were compared. Formic acid levels were measured in varenicline tartrate tablets stored in the presence of and in the absence of activated carbon. Two gelatin-encapsulated products were packaged with and without activated carbon and stored at 50°C/75% relative humidity for 3 months. The samples were evaluated for appearance, pliability, and dissolution performance. Details of the analytical methods used for these studies can be found in the Supplementary Information section.

Materials

The following dosage forms were studied:

- Commercially available varenicline tartrate tablets containing 0.5 mg of varenicline, microcrystalline cellulose, dibasic calcium phosphate anhydrous, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The film coat contained Opadry® white and Opadry® clear.
- Compound A tablets containing 40 mg of compound A, microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate.
- Commercially available hard gelatin capsules containing 500 mg of acetaminophen, corn starch, croscarmellose sodium, sodium lauryl sulfate, magnesium stearate, gelatin, titanium dioxide, indigo carmine, and erythrosine. The capsules were packaged in PVC and aluminum foil blisters enclosed in an outer carton.
- Commercially available hard gelatin capsules containing 25 mg of diphenhydramine HCl, anhydrous lactose, benzyl alcohol, butylparaben, D&C red no. 28, edetate calcium disodium, edible ink, FD&C blue no. 1, FD&C red no. 40, gelatin, magnesium stearate, methylparaben, polysorbate 80, propylparaben, sodium lauryl sulfate, and sodium propionate. The capsules were packaged in 100-count high density polyethylene (HDPE) bottles with induction seals and caps.

Polyethylene canisters containing 1 g of activated carbon (Getter Can®, Material No. 27325427698) were purchased from Clariant Corporation (Belen, NM). Tyvek sachets (22 × 48 mm) containing 1 g of activated carbon were custom made by Texas Technologies, Inc. (Cedar Park, TX).

Results and Discussion

Attenuation of Formaldehyde-Induced and Formic Acid–Induced Degradation

Initial feasibility studies were conducted in 20-mL crimp-top glass serum vials. Test vials contained 5-10 mg of API (varenicline tartrate, a secondary amine, or compound A, which contains both primary and secondary amine moieties) spiked (on the inside wall of the vial) with 1 μL of formaldehyde or formic acid and either a 1-g activated carbon sachet or nothing (the control). Samples were stored at 40°C for 4 days and analyzed by HPLC. In all cases, the activated carbon significantly attenuated degradation:

- Area percent of varenicline in sample spiked with formaldehyde with activated carbon = 100.0 versus 98.79 without activated carbon (N-methyl adduct = 0.99; N-formyl adduct = 0.22)
- Area percent of varenicline in sample spiked with formic acid with activated carbon = 100.0 versus 98.83 without activated carbon (N-methyl adduct = not detected; N-formyl adduct = 1.17)
- Area percent of compound A in sample spiked with formaldehyde with activated carbon = 97.40 versus 22.94 without activated carbon. The initial area percent for compound A was 98.01.

For these experiments, the spiked levels of formaldehyde or formic acid represent a significant excess of what would be present if these reactive compounds were present as impurities or degradants in the excipients or the film coat of the formulated drug products.

Although the spiked API results were encouraging and noting that this methodology could be used to study the vulnerability of APIs to formaldehyde and formic acid degradation as part of a forced degradation protocol, the idea of using activated carbon to attenuate degradation will be most useful if it works on formulated drug products. As such, short-term high temperature and high-humidity stability studies of varenicline tablets were prosecuted. The tablets used for these studies were not spiked with formaldehyde or formic acid, and the tablets were stored with and without a 1-g activated carbon canister. (The other packaging and storage details can be found in the legends for Figs. 1 and 2.)

The appearance of the accelerated stability samples packaged without activated carbon was not significantly different from tablets stored with activated carbon. These results in Figures 1 and 2 illustrate that activated carbon effectively attenuated

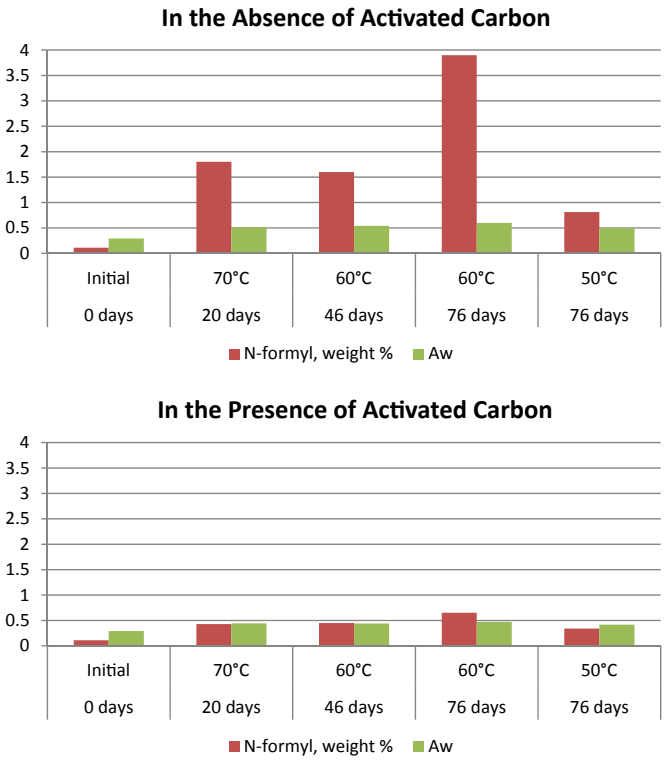

Figure 1. Levels of the N-formyl adduct and water activity in stability samples of varenicline tablets after storage in the absence of and in the presence of activated carbon at various temperatures and 75% RH. Tablets were packaged in 60-mL HDPE bottles with induction seal closures, 56 count.