

Impact of Excipient Compatibility Stability Storage Conditions on Low Melting Point Excipients

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Introduction

Excipient selection is based on a number of factors, including physicochemical properties of the API, formulator familiarity and preference, manufacturing method, and in rare cases by method of encapsulation or anticipated commercial batch size. Excipients function as fillers, release modifiers, binders, disintegrants, lubricants, glidants, surfactants, coloring agents, coating agents, anti-oxidants, and acidifiers. Some of the excipients are easy choice since they are only minimally influenced by the active. For that reason, formulators conduct API-excipient compatibility studies, where as the choice of excipient is dependent on excipient properties and stability storage conditions. This work is an evaluation of the ability of commercially available low melting point excipients by placing them at excipient compatibility storage conditions and analyzing the physical and chemical changes.

Objectives

To evaluate impact of stability storage conditions on low Melting Point (MP) excipients by visual observation, Differential Scanning Calorimetry (DSC), Thermo Gravimetric Analysis (TGA), and X-ray Powder Diffraction (XRPD).

Methods

Choice of Excipients

The commonly employed low MP excipients such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), Compritol 888 ATO, polyethylene glycol 3350 (PEG 3350), polyethylene glycol 8000 (PEG 8000), Polyox WSR 301, stearic acid, Sterotex K, and Xylisorb 90.

Stability Packaging and Storage

The chosen excipients were placed individually in a 40mL clear glass vial. The closed vials were placed in stability chamber/oven at 40°C/75% relative humidity (RH) and 80°C storage conditions.

Stability Pull Points and Visual Observation

A sample of the excipient was evaluated at initial, 2, 8, and 12 weeks. The samples were allowed to equilibrate to room temperature before sampling. At each time point the samples were visually examined before continuing with other tests.

Thermal Analysis

DSC – The thermal behavior was evaluated by TA Instruments Q100 Modulated DSC at a heating rate of 10°C/minute under a nitrogen purge.

TGA – The % weight loss analysis was evaluated by TA Instruments Q500 TGA run in a Hi-Res Dynamic Mode at a rate of 50°C/minute (sensitivity 1.0 resolution 4.0) under a nitrogen purge.

Diffraction Patterns

The Two-Theta plot was obtained by Rigaku MiniFlex II XRPD at a rate of 1 degree/minute (range of 3 to 40 degrees Two-Theta).

Results

Visual examination of the individual 80°C samples indicate change in color. Most noticeable color change was in BHA and BHT to dark brown and orange material, respectively.

DSC analysis showed noticeable changes in Compritol, stearic acid, BHA, BHT, Sterotex, & Polyox (Table 1) but was more pronounced in BHT at 80°C (figure 1).

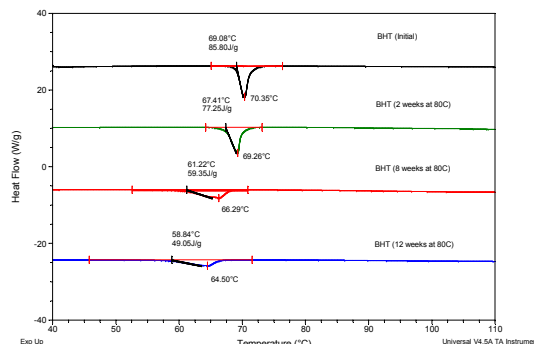


Figure 1: DSC thermal plot overlay of BHT at 80°C for various stability time points

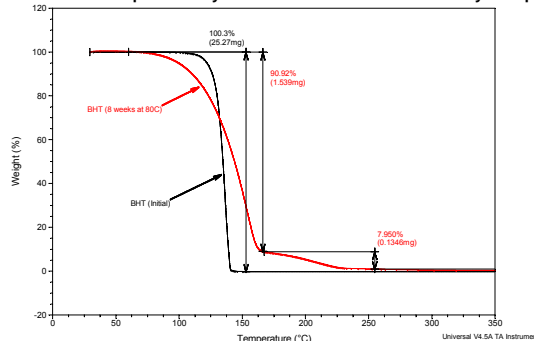


Figure 2: TGA thermal plot overlay of BHT at 80°C for two stability time points
The change in the thermal properties during the stability time points is more evident at 8 weeks and beyond as shown in figures 1 and 2. This change supports the above reported visual observation remark of BHT changing from white powder to orange crystals.

Table 1: DSC data of excipients at 80°C at various stability time points

Time point	DSC Results for Neat Excipients at Various Time Points											
	T=0			2 Weeks 80°C			8 Weeks at 80°C			12 Weeks at 80°C		
Name of Excipient	Onset Temp (°C)	Δ (J/g)	Peak Maxima (°C)	Onset Temp (°C)	Δ (J/g)	Peak Maxima (°C)	Onset Temp (°C)	Δ (J/g)	Peak Maxima (°C)	Onset Temp (°C)	Δ (J/g)	Peak Maxima (°C)
Compritol	68.37	112.00	71.36	67.93	118.40	71.94	62.85	69.64	67.88	60.95	44.64	65.16
Stearic Acid	55.21	181.70	56.92	53.91	162.60	56.21	49.39	136.10	53.64	47.30	132.60	52.45
BHA	61.93	27.21	63.33	54.98	84.21	58.54	45.12	17.31	52.50	Not tested		
BHT	69.08	85.80	70.35	67.41	77.25	69.26	61.22	59.35	66.29	58.84	49.05	64.50
Sterotex K	51.37	71.99	53.62	Not tested			56.81	105.00	60.91	55.92	106.80	60.23
Polyox	62.38	148.50	68.31	57.19	113.30	61.12	Not tested					

The data in figure 3 below supports the noticeable BHT change in structure as reported in the visual appearance, DSC, and TGA data on stability at 80°C.

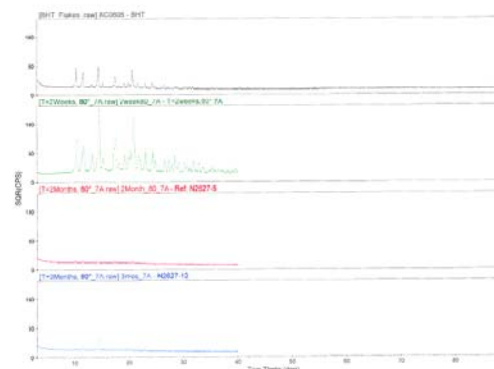


Figure 3: XRPD Two-Theta plot overlay of BHT at 80°C for various stability time points

Conclusions

Selection of appropriate elevated storage condition in an excipient compatibility study based on the MP of the excipient would lead to possible avoidance of "surprise" problems during long-term stability testing of drug products.

References

- Villa et al., "Drug-excipient compatibility studies by physico-chemical techniques; The case of Atenolol," Retrieved on July 02, 2009, from www.springerlink.com/content