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Solid-state interaction of stearic acid with povidone and its effect on dissolution stability of capsules

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Abstract

Capsule formulations of two drugs under development showed slower dissolution upon storage; Drug A, after 2.5 weeks at 40 °C/23% RH and 4 weeks at 30 °C/60% RH, and Drug B, after 6 weeks at 50 °C and 40 °C/75% RH. The formulations of both drugs contained povidone as a binder and stearic acid as a lubricant. Replacement of stearic acid by magnesium stearate from the formulation of Drug B, which was selected for further studies, provided rapid dissolution profiles under similar storage conditions with no change occurring on storage. In order to investigate the role of stearic acid further, binary mixtures of stearic acid with the drugs and other excipients used in their respective formulations were prepared and stored at 40 °C/75% RH and 50 °C. After 1 week of storage, it was observed that povidone and stearic acid mixture formed a transparent, hard, glass-like insoluble substance. It is hypothesized that the substance formed by the interaction can reduce the porosity of the granules and thereby reduces the ingress of the dissolution medium leading to slower dissolution. The infrared (IR) spectra of the glass-like substance showed a slight broadening of the povidone carbonyl band at 1662 cm^{-1}. The powder X-ray diffraction of the stored mixture showed that the crystallinity of stearic acid was lost. Furthermore, repeated heating and cooling cycles of povidone and stearic acid mixtures in various proportions using differential scanning calorimetry (DSC) showed that recrystallization of stearic acid from its melt was strongly affected by the presence of increasing amounts of povidone. Based on the observed solid-state interaction, a combination of stearic and povidone should be avoided for immediate release formulations.

Keywords: Solid-state interaction; Povidone; Stearic acid; Solid solution; Capsule; Dissolution; Solid dispersion

1. Introduction

Povidone is a commonly used binder in wet granulation for capsule or tablet formulations. Its complexation behavior and other interactions have been widely reported in the literature (Plaizier-Vercammen and DeNeve, 1980, 1981; Horn and Ditter, 1982). Similarly, stearic acid is a commonly used lubricant, second only by preference, to magnesium stearate. However, the interaction between povidone and stearic acid has not been reported.

This paper describes formulation development experiences involving two drugs; an anti-hypertensive drug (Drug A) and an antiviral drug (Drug B). Capsule formulations of both drugs were made by aqueous wet granulations with povidone as a binder and crospovidone as a disintegrant, and stearic acid as a lubricant. The capsule formulations of both drugs showed a slower dissolution upon storage at various conditions. Studies were conducted to investigate the cause of dissolution slow down. Additional studies were conducted to understand the role of the physical interaction between povidone and stearic acid that was identified as the root cause for the dissolution slowdown. Results of these studies are reported.

2. Materials and methods

2.1. Materials

The following ingredients were used as received from the suppliers: lactose monohydrate (Foremost Whey, Baraboo, WI), microcrystalline cellulose (Avicel® PH 101) (FMC, Philadelphia, PA), povidone (Plasdone® K-30) and crospovidone (ISP, Wayne, NJ), silicon dioxide (Syloid® 244) (Grace Chemi-

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cals, Baltimore, MD), magnesium stearate, NF (Mallinkcrodt, St. Louis, MO), stearic acid, NF (Witco Chemicals, Newark, NJ), IR grade potassium bromide (Aldrich Chemicals, Milwaukee, WI), white opaque capsule shells size #2 and gray opaque capsule shells size # 1(Capsugel, Greenwood, SC), and Drugs A and B (Bristol-Myers Squibb Co., NJ).

2.2. Equipment

The following equipment were used in this study: Vanderkamp 600 six spindle dissolution tester (Vankel Industries, Edison, NJ), and HP 8451A diode array spectrophotometer (Hewlett-Packard Co., Palo Alto, CA), Mettler Toledo DSC, Type TC 11 (Mettler Instruments Corporation, Hightstown, NJ 08520), Rigaku Miniflex X-ray diffractometer (Rigaku Corporation, Danvers, MA 01923) with a CuKα radiation (wavelength 1.54 Å) tube output voltage and current of 30 kV and 15 mA, respectively and a scintillation counter with NaI as scintillator for the detector, infrared spectrophotometer (Mattson, Inc., Madison, WI), Hobart planetary mixer (Hobart Manufacturing Co., Troy, OH), tray oven (Shampaine Scientific Co., Roselle, NJ), oscillator (Erweka Instrument Co., Milford, CT) and Fielder (Aeromatic Fielder Division, Columbia, MD).

2.3. Formulations

The formulation compositions are given below.

Ingredients	Percent in formulation (w/w)	
	Drug A	Drug B
Active pharmaceutical ingredient	50.0	64.52
Microcrystalline cellulose, lactose hydrous, crospovidone	43.0	31.98 or 30.98
Povidone	2.5	2.5
Silicon dioxide	1.5	–
Magnesium stearate	1.0	1.0
Stearic acid	2.0	OR
Purified water[a]	q.s.	4.0
Capsule size and fill weight	#2 and 200 mg	#1 and 310 mg

[a] Not present in the final product, removed by drying.

3. Manufacturing of capsules

3.1. Capsules for Drug A

A commonly used wet granulation process was used to manufacture capsules. Drug A, half of the microcrystalline cellulose, and 80% of crospovidone were mixed in a five quart Hobart mixer for 5 min. The resulting blend was screened through a #20 mesh screen using an oscillator. Lactose monohydrate was also passed through a #20 mesh screen using an oscillator and was added into the blend and mixed for 5 min at a slow speed. The blend was granulated using a 25% (w/w) povidone solution in purified water. The granules were dried in the oven at 50–60 °C to less than 2.0% (w/w) residual moisture. The dried granules were passed through a #24 mesh screen using an oscillator. The remaining half of the microcrystalline cellulose, crospovidone, and silicon dioxide were added and mixed for 5 min in the Hobart mixer at the slow speed. Magnesium stearate and stearic acid were screened through a #30 mesh screen and added to the blend and mixed for 5 min. The final blend was filled manually into size #2 capsules with a 200-mg fill weight.

3.2. Capsules for Drug B

Drug B, microcrystalline cellulose, lactose, and crospovidone were mixed in a high shear mixer (Fielder) followed by granulation with a 15% (w/w) povidone solution in purified water. The granules were dried at 60 °C using a fluid bed dryer to residual moisture of less than 2% (w/w). The dried granules were passed through a screen and mixed with pre-screened magnesium stearate or stearic acid for 3 min. The final blend was filled manually into size #1 capsules with a 310 mg fill weight.

3.3. Dissolution stability studies

For dissolution stability evaluation, the capsules were packaged in HDPE bottles containing cotton and heat activated induction seal and stored at various conditions such as 30 °C/60% RH, 40 °C/23% RH, 40 °C/75% RH, and/or 50 °C. Samples were withdrawn at various time points and analyzed for dissolution using the methods described below.

4. Dissolution studies

4.1. Capsules of Drug A

Dissolution of capsules was conducted in 1000 mL of 33 mM pH 2 citrate buffer at 37 °C using paddles with an agitation speed of 75 rpm. Sinkers were used to prevent capsules from floating in the dissolution medium. The dissolution samples were taken at 5, 10, 20, 30, 45, and 60 min time points and the drug concentration was determined using a spectrophotometer at 272 nm.

4.2. Capsules of Drug B

Dissolution of capsules was conducted in 1000 mL of 50 mM pH 2 citrate buffer at 37 °C using paddles with an agitation speed of 50 rpm. The drug concentration was determined using a spectrophotometer at 256 nm. The rest of the procedure was same as described above.

4.3. Infrared spectroscopy studies

Samples were prepared as KBr pellets for infrared analysis. IR spectra were collected from 4000 to 400 cm^{-1} at 4 cm^{-1} resolution for 64 scans on a Mattson Polaris spectrometer with a DTGS detector.

4.4. DSC studies

The samples were weighed in the DSC aluminum pan and scanned from 25 to 100 °C at a rate of 10 °C per minute after sealing the pan.