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International Journal of Pharmaceutics 354 (2008) 77–81
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

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

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Received 19 July 2007; received in revised form 2 November 2007; accepted 6 November 2007
Available online 14 January 2008

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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doi:10.1016/j.ijpharm.2007.11.042

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.

Table 1
Dissolution of 50 mg potency Drug A capsules

Storage conditions	Mean % Drug A dissolved (±S.D.) at								
	5 min	10 min	20 min	30 min	45 min	60 min	90 min[a]	120 min	150 min
Initial	26 (7)	55 (11)	79 (7)	87 (3)	92 (2)	95 (2)	97 (2)	99 (2)	100 (1)
4 weeks at 30 °C/60% RH	16 (1)	40 (8)	63 (9)	71 (9)	83 (8)	85 (6)	91 (6)	95 (6)	99 (4)
2.5 weeks at 40 °C/23% RH	18 (3)	36 (6)	55 (8)	66 (5)	74 (4)	80 (3)	84 (3)	90 (3)	93 (2)

[a] Paddle speed was increased to 250 rpm after 90 min ($n = 6$).

4.5. Powder X-rays

Approximately 20 mg samples were placed on aluminum sample holders for the scans. The scans were performed at 5°2θ per minute.

5. Results and discussion

Dissolution data on the Drug A capsule formulation are shown in Table 1. Dissolution slowdown was observed at 30 °C/60% RH and 40 °C/23% RH storage conditions. Even at the 30 °C/60% RH storage condition, the slowdown in dissolution was observed only after 4 weeks. The slowdown in dissolution occurred after 2.5 weeks at 40 °C storage condition. Dissolution data on the Drug B capsule formulation are shown in Table 2. The formulation containing 1% (w/w) magnesium stearate did not show significant slowdown in dissolution at 40 °C/75% RH and 50 °C storage conditions up to 4 weeks. However, the formulation containing 2% stearic acid started showing significant slowdown in dissolution at 50 °C at the 4-week time point. At the 6-week time point, the slowdown in dissolution was very pronounced at 40 °C/75% RH and at 50 °C storage condition; practically no drug was released for 30 min (Table 2). It was also observed that gelatin from capsule shells was completely dissolved leaving behind an insoluble mass. With the exception of 40 °C/75% RH and at 50 °C storage condition, for both drugs, almost all the drug was released at the later time points indicating that there was no drug degradation. Since there was no slowdown in the formulation containing magnesium stearate as a lubricant, the slowdown in dissolution was not due to possible cross-linking of gelatin in the capsule shell at these conditions. From the dissolution data of Drug B, it was evident that stearic acid was responsible for the dissolution slow down of the samples stored under the accelerated stability conditions. No significant slowdown in dissolution was observed at the room temperature (RT) storage for 6 months.

To investigate this further, binary mixtures of stearic acid were prepared with drugs and other excipients from the formulation and stored at 40 °C/75% and 50 °C. After 1 week of storage, it was observed that povidone and stearic acid mixture formed a hard, transparent and glass-like substance. This interaction was seen visually only in the binary mixtures stored at 40 °C/23% RH and above. Such interaction was not observed between povidone and magnesium stearate.

To further investigate the interaction between povidone and stearic acid, mixtures of the two were prepared in varying ratios. The DSC scans for "as is" materials as well as mixtures, are shown in Fig. 1. It can be seen from Fig. 1 that the melting point of stearic acid (curve 1) remains unchanged up to two successive melting-recrystallization cycles. Thus, stearic acid has the ability to recrystallize back to its original crystalline form after melting and cooling. Curve 2 is that of povidone with no distinct features on the scan, except for the huge drop in heat conducted between 50 and 100 °C in the initial cycle, which indicates moisture removal. Curve 3 in Fig. 1 is that of a 10:90% (w/w) mixture of povidone and stearic acid. It can be observed that there is a slight reduction in the heat of recrystallization for stearic acid that is also reflected in its re-melting endotherm. However, the pattern of melting-recrystallization is retained for two successive heating and cooling cycles. For a 20:80% mixture of povidone and stearic acid as in curve 4, it can be seen that there is a negative shift in the recrystallization temperature for stearic acid, as

Table 2
Dissolution[a] of 200 mg potency Drug B capsules

Formulations	Storage temperature	Storage duration	Mean % Drug B dissolved at (±S.D.) at			
			10 min	20 min	30 min	60 min
1% (w/w) magnesium stearate	Initial	–	79 (2)	96 (1)	98 (1)	98 (1)
	40 °C/75% RH	4 weeks	70 (4)	90 (5)	96 (2)	99 (1)
	50 °C	4 weeks	65 (4)	88 (2)	97 (2)	100 (1)
	RT	24 weeks	69 (2)	87 (1)	93 (1)	98 (1)
2% (w/w) stearic acid	Initial	–	70 (3)	92 (3)	96 (1)	97 (1)
	40 °C/75% RH	4 weeks	55 (8)	87 (3)	95 (1)	97 (1)
		6 weeks	10 (35)	42 (23)	75 (16)	96 (2)
	50 °C	4 weeks	8 (3)	40 (7)	76 (13)	98 (1)
		6 weeks	0	0	2 (1)	20 (4)
	RT	24 weeks	63 (4)	86 (5)	95 (3)	98 (1)

[a] $n = 6$ except samples stored at room temperature where $n = 3$.

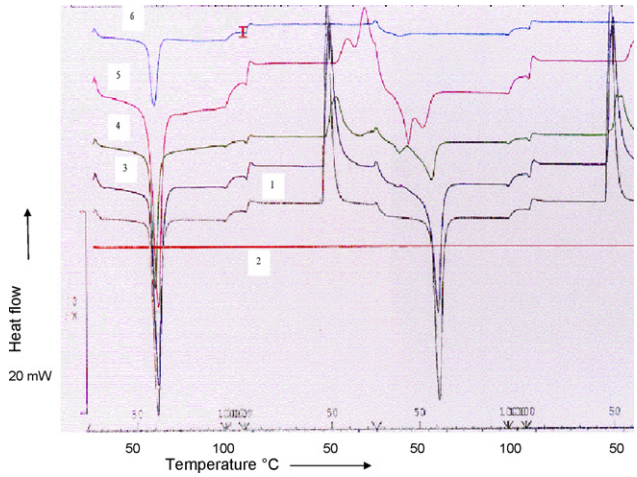

Fig. 1. The DSC scans: (1) stearic acid, (2) povidone, (3) 90% stearic acid:10% povidone mixture, (4) 80% stearic acid:20% povidone mixture, (5) 70% stearic acid:30% povidone mixture, (6) 50% stearic acid:50% povidone mixture.

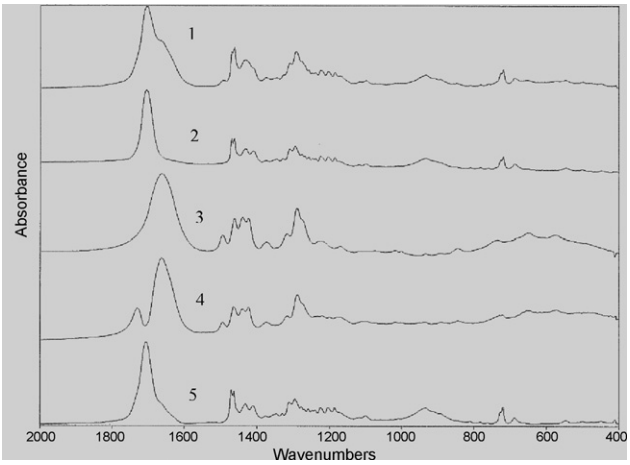

Fig. 2. The IR spectra: (1) 1:1 mixture of stearic acid and povidone after exposure to 50 °C, (2) stearic acid, (3) povidone, (4) difference spectrum by subtracting spectrum 2 from 1, (5) difference spectrum by subtracting spectrum 1 from spectrum 3.

well as, peak broadening. In the re-melting curve, two distinct melting endotherms are observed (37 and 55 °C), which indicate the possibility of the presence of two forms of stearic acid that may have crystallized out in the presence of 20% (w/w) povidone (Garti et al., 2006; Sato et al., 1988). Also, the endothermic peak at 55 °C (in the second DSC cycle) is significantly lower than that of the first endothermic peak (in the first DSC cycle) for the same mixture. Similarly, curve 5 for a 30:70% mixture of povidone and stearic acid shows two distinct recrystallization exotherms (42 and 33 °C) and two distinct melting endotherms (41 and 51 °C). Based on these results, it could be postulated that, with varying amounts of povidone in a mixture of povidone and stearic acid, different crystal forms of stearic acid may be formed during a DSC heating-cooling event, that show different melting endotherms. Curve 6 is that for a 50:50% (w/w) mixture of povidone and stearic acid. In this system, no crystallization exotherm is observed, thus indicating the complete inhibition of recrystallization of stearic acid by 50% (w/w) povidone in the mixture. A small endotherm is observed in the second cycle of heating on the DSC indicating the presence of negligible amount of one of the crystalline forms of stearic acid. The same trend is observed with a complete disappearance of the exotherm and endotherm peaks representing recrystallization and re-melting of stearic acid in mixtures containing more than 50% (w/w) of povidone. In summary, the DSC investigation suggests that povidone acts as a crystallization inhibitor for stearic acid. This is similar to inhibition of indomethacin crystallization by povidone reported by Yoshioka et al. (1995).

5.1. Infrared spectra

The possibility of a complex formation between povidone and stearic acid was investigated using IR spectroscopy. The IR scans were performed on the individual component and a physical mixture of the two that was stored at 50 °C for 2 days (Fig. 2). As described earlier, this mixture formed a transparent, hard, glass-like insoluble substance on storage at 50 °C. There were changes observed in carbonyl region (1600–1800 wavenumbers) of 1:1 mixture (Fig. 2, spectrum 1) compared to its individual component (Fig. 2, spectrum 4 compared to spectrum 3 and spectrum 5 compared spectrum 2), suggesting the disruption of hydrogen bonding in stearic acid and the possibility of hydrogen-bonding formation between the acid functional group of stearic acid and the lactam nitrogen of the povidone. This may influence the crystallization kinetics by preventing the self-association of stearic acid molecules. Similar povidone influence was reported on crystallization kinetics of indomethacin (Taylor and Zografi, 1997).

5.2. Powder X-ray diffraction

Fig. 3 shows the XRD patterns for individual stearic acid, povidone and a 50:50 (w/w) mixture of the two stored for 2 days at 50 °C and RT, respectively. The diffractogram for the mixture stored at 50 °C shows the disappearance of the sharp crystalline pattern of stearic acid that is evident in the diffractograms of "as is" material as well as the physical mixture (of povidone and stearic acid) stored at room temperature.

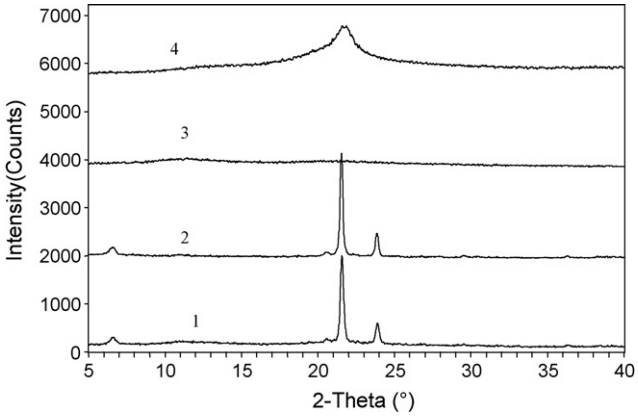

Fig. 3. The powder X-rays: (1) (1:1) physical mixture of stearic acid and povidone at room temperature, (2) stearic acid, (3) povidone, (4) (1:1) mixture of stearic acid and povidone after exposure to 50 °C.

The IR spectra, DSC scans, and powder X-ray patterns suggested the possibility of a physical interaction between povidone and stearic acid. A similar interaction has been reported by Hops and Mueller (1999) between povidone and ibuprofen (contains carboxylic group), which was characterized as a solid dispersion.

The interaction between povidone and stearic acid forming a solid dispersion could be responsible for slow down in dissolution of capsules of Drugs A and B. Based on the physical characterization results, the slowdown in dissolution can be related to the coating or embedding of the granulation within this solid dispersion or solution reducing its porosity and hence ingress of the dissolution medium. For Drug A, dissolution slowdown was seen as early as 4 weeks at 30°/65% RH storage, but for Drug B, the slowdown was observed only at accelerated conditions in 4–6 weeks. This difference can be attributed to the solubility difference of these drugs in pH 2 citrate buffer, the dissolution medium. Drug B is ten times more soluble than Drug A in pH 2 citrate buffer.

6. Conclusions

A solid-state interaction leading to the formation of solid dispersion was observed between povidone and stearic acid at the storage temperature of 40 °C/23% RH and above. Capsule formulations containing both povidone and stearic acid exhibited a slower dissolution upon storage probably because of such an interaction. Therefore, it is recommended that they should not be used together in an immediate release capsule formulation.

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