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Povidone- and poloxamer-mediated degradation of hydrochlorothiazide in an antihypertensive combination tablet product

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Abstract

Although hydrochlorothiazide (HCTZ) drug substance is known for its excellent solid-state stability, it can undergo hydrolysis with the formation of formaldehyde and 4-amino-6-chloro-1,3 benzenedisulfonamide (free amine). The degradation of HCTZ in a dosage form is undesirable due to the tight limits that need to be set for the free amine content. In a combination wet granulated tablet formulation of an antihypertensive drug A and HCTZ containing povidone K-30 NF (PVP) as a binder and poloxamer 188 NF (Pluronic® F68) as a wetting agent, a progressive increase in the free amine level was seen after only 2 months storage at various conditions. Binary mixtures of HCTZ with PVP, pregelatinized starch (Starch® 1500), and lactose (control) were incubated at elevated temperatures after adding an amount of water to simulate wet granulation conditions. Analysis of these mixtures showed more free amine formation in the HCTZ:PVP binary mixtures than the HCTZ:Starch® 1500 or HCTZ:lactose binary mixtures. Replacement of PVP with Starch® 1500 in the tablet formulation resulted in comparatively lower free amine levels on storage. The free amine formation in tablets was further reduced and dissolution of both drugs was not significantly affected when Pluronic® F68 was removed from the formulation. It was hypothesized that the mechanism of degradation of HCTZ in the presence of PVP and/or Pluronic® F68 was due to solubilization of the HCTZ by these excipients in the moisture present in tablets, followed by its hydrolysis.

Keywords: Hydrochlorothiazide; Poloxamer 188 NF; Povidone; Degradation

1. Introduction

Combination products of various antihypertensive drugs with hydrochlorothiazide (HCTZ) are routinely formulated to augment their pharmacological effects or to provide step-up therapy. Al-

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though HCTZ drug substance is known for its excellent solid-state stability (Deppeler, 1981), it can undergo hydrolysis with the formation of formaldehyde and 4-amino-6-chloro-1,3-benzenedisulfonamide (free amine) (Mollica et al., 1969, 1971). Recently, degradation of HCTZ in bead formulations (Desai et al., 1994a) and capsule formulations (Desai et al., 1994b,c) has been reported. The degradation of HCTZ in a dosage form is undesirable since the US Pharmacopeia (USP) sets a tight limit for the free amine content of not more than 1% of the HCTZ potency due to toxicological reasons. Additionally, formaldehyde can cross-link starch-derived disintegrants which can then have an untoward effect on tablet disintegration and dissolution. During the development of a combination tablet of HCTZ and an antihypertensive drug, an increase in free amine level in the tablets was noted after 2 weeks of storage at 40°C/75% relative humidity (RH) (open HDPE bottle) and 60°C (closed HDPE bottle). This study was conducted to determine the cause of the increased free amine formation.

2. Experimental section

2.1. Materials

The following ingredients were used as received from the suppliers: antihypertensive drug A (Bristol-Myers Squibb, New Brunswick, NJ), HCTZ (Profarmaco, New York), hydrous lactose (Foremost Whey, Baraboo, WI), microcrystalline cellulose (Avicel® PH 102) and croscarmellose sodium (Ac-Di-Sol®) (FMC, Philadelphia, PA), pregelatinized starch (Starch® 1500) (Colorcon, Indianapolis, IN), povidone (Plasdone® K-30)(ISP, Wayne, NJ), poloxamer 188 NF (Pluronic® F68) (BASF, Parsippany, NJ), iron oxids (Crompton and Knowles, Fairlawn, NJ), magnesium stearate (Mallinckrodt, St. Louis, MO), and silicon dioxide (Syloid® 244) (Grace Chemicals, Baltimore, MD).

2.2. Equipment

The following equipment was used: Beta tablet press (Manesty, UK, distributed in US by Thomas Engineering, Chicago, IL); Fuji vertical granulator (Fuji Sangyo, distributed in US by Aeromatic, Towaco, NJ); GPCG-5 Fluid Bed Granulator/Dryer (Glatt Air Techniques, Ramsey, NJ); Oscillator (Erweka Instrument, Milford, CT); and Computrac Max 50 Moisture Analyzer (Arizona Instrument, Tempe, AZ).

2.3. Manufacture of tablets

The tablet formulation contained drug A (25% w/w), HCTZ (2.08% w/w) and excipients (72.92% w/w) which included lactose, povidone, Ac-Di-Sol®, Pluronic® F68, Avicel® PH 102, Syloid® 244, red and yellow ferric oxides and magnesium stearate. Drug A, HCTZ, lactose and 80% of total Ac-Di-Sol® were screened through the oscillator with a # 20 mesh screen and mixed in the Fuji mixer for 1 min. About 50% w/w water was added to the blend with continuous mixing to granulate the blend. The total mixing time was about 3 min. The granules were dried to less than 2% LOD using the GPCG-5 fluid bed dryer. The dried granules were passed through an oscillator with a # 20 mesh screen. To the milled granules, Avicel® PH 102, Ac-Di-Sol®, Syloid® 244, and red and yellow ferric oxides were added and mixed for 2 min in the Fuji mixer. To this mix, # 30 mesh screened magnesium stearate was added and mixed for an additional 1.5 min. The resulting final mix was compressed into 600-mg-weight tablets on the Beta press using appropriate tooling. The 600-mg tablets contained 12.5 mg of HCTZ and 150 mg of Drug A.

2.4. Stability studies

For stability evaluation, tablets were packaged in HDPE bottles with cotton and induction seal closure. These bottles were placed at 30°C, 40°C/75% RH (open and closed bottle), and 50°C. Samples were withdrawn at regular time intervals and analyzed for HCTZ and the free amine, Drug A and its degradants. Both drugs were extracted from the tablets using the high performance liquid chromatography (HPLC) mobile phase (composition given below) and analyzed using HPLC (method given below).

Table 1
HCTZ potency/degradants on Drug A/HCTZ tablets containing PVP and Pluronic® F68 as excipients, stored in high density polyethlyene (HDPE) bottles with cotton and induction sealed cap

Time point (days)	Storage condition	HCTZ potency (mg/tablet)	HCTZ degradant free amine (mg/tablet)
Initial	—	12.6	0.02
30	40°C/75% RH (open)	12.2	0.13
	40°C/75% RH (closed)	12.4	0.1
	50°C	12.1	0.27
60	30°C	12.4	0.05
	40°C/75% RH (closed)	12.2	0.17
	50°C	11.8	0.35

$n = 5$

2.5. Solubility studies

To determine the saturation solubility of HCTZ in aqueous solutions of PVP and Pluronic® F68, excess HCTZ was added to the different known concentrated aqueous solutions of these ingredients. These solutions were agitated for 48 h at room temperature (24 ± 3°C) using a shaker. At the end of 48 h, the solutions were filtered through a 0.45-μm filter and analyzed using HPLC. The pH of hydrochlorothiazide solution containing 150 mg/ml PVP and 7% w/v (70 mg/ml) Pluronic® F68 were 3.9 and 6.8, respectively. The pH of the hydrochlorothiazide solution without any additive was 7.0. Over the pH range observed in this study, the hydrochlorothiazide solubility (Deppeler, 1981) and the rate of hydrolysis (Mollica et al., 1971) are constant.

2.6. Binary mixtures

PVP:HCTZ binary mixtures in ratios of 0.2:1.0, 0.6:1.0, 1.2:1.0, and 3:1.0 were prepared and 3 g of each mixture was placed in a glass vial and spiked with 2.0 ml of water. After spiking with water, the blends were mixed thoroughly using a

Table 2
Amount of free amine formed in PVP:HCTZ, Starch® 1500:HCTZ, and lactose:HCTZ blends spiked with 2 ml water and placed at 60°C

Condition	Amount of water added	Amount of free amine formed (% of total HCTZ and free amine peak area)			
		PVP:HCTZ (0.2:1.0)	PVP:HCTZ (0.6:1.0)	PVP:HCTZ (1.2:1.0)	PVP:HCTZ (3.0:1.0)
87 h at 60°C	2 ml/3 g blend	0.61 0.57 Mean = 0.59	1.27 1.11 Mean = 1.19	1.83 2.12 Mean = 1.98	2.87 2.59 Mean = 2.73
Condition	Amount of water added	Starch® 1500:HCTZ (1.5:1.0)	Starch® 1500:HCTZ (2.5:1.0)	Starch® 1500:HCTZ (4.0:1.0)	Lactose:HCTZ (1.2:1.0)
87 h at 60°C	2 ml/3 g blend	0.09 0.12 Mean = 0.11	0.09 0.12 Mean = 0.11	0.16 0.16 Mean = 0.16	0.06 0.06 Mean = 0.06

$n = 2$

Table 3
HCTZ potency/degradants in Drug A/HCTZ tablets containing Starch 1500 and Pluronic F68 as excipients stored in HDPE bottles with cotton and induction sealed cap

Time point (days)	Storage condition	HCTZ potency (mg/tablet)	HCTZ degradant free amine (mg/tablet)
Initial	—	12.7	0.03
160	40°C/75% RH	12.2	0.25
	50°C	11.9	0.31

$n = 5$

spatula and the open vials were placed at 60°C for 87 h. Similarly, Starch® 1500:HCTZ binary mixtures in ratios of 1.5:1.0, 2.5:1.0, and 4:1.0, were also prepared. A lactose:HCTZ binary mixture in a ratio of 1.2:1.0 was prepared as a control. For control, lactose was added to HCTZ such that the ratio of added water to HCTZ remained similar to that present in the PVP:HCTZ and Starch® 1500:HCTZ binary mixtures. After 87 h of storage at 60°C, the dried material was mixed thoroughly. From the dried material, a quantity of the mixture containing approximately 12.5 mg of HCTZ was weighed and placed in a calibrated flask. HCTZ and the free amine were extracted using the mobile phase and assayed using HPLC.

2.7. HPLC analysis

HPLC analysis was performed using a 10-μm 300 × 4 mm i.d. octadecylsilane column (Column Resolution, Palo Alto, CA). Mobile phase composition was 0.1 M phosphate buffer and acetonitrile (9:1). The pH of the buffer was adjusted to 3.0 using 85% phosphoric acid. HCTZ, free amine, Drug A and its degradants were monitored using an UV detector at a wavelength of 272 nm.

3. Results and discussion

Stability data on the tablet formulation collected at the 30- and 60-day time points are summarized in Table 1. No change in dissolution was observed for both Drug A and HCTZ compared to their initial values (data not shown). However, there was a loss in HCTZ potency and increase in the free amine levels in the samples stored in open and closed bottles at 40°C/75% RH and 50°C for 30 and 60 days. The potency loss and free amine formation were greater at the 50°C storage condition compared to the 40°C/75% RH storage condition. The loss in potency and free amine formation for samples stored at 40°C/75% RH were slightly less in the closed bottles compared with the open bottles. At the 60-day time point, increased levels of free amine were also detected in tablets stored at the 30°C storage condition. The free amine level was very low in the

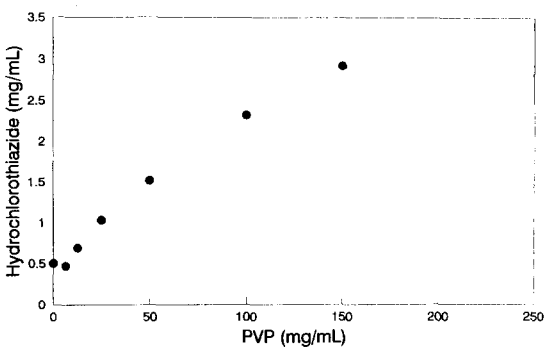

Fig. 1. Effect of PVP on saturation solubility of hydrochlorothiazide in water at room temperature.

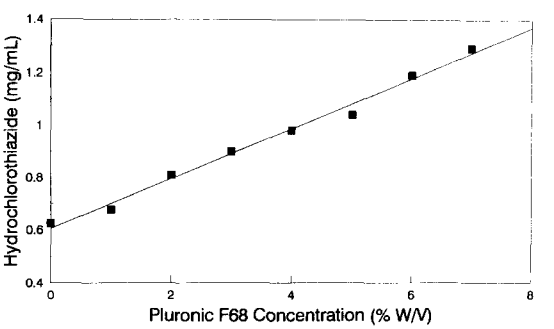

Fig. 2. Effect of Pluronic® F68 on saturation solubility of hydrochlorothiazide in water at room temperature.

Table 4
HCTZ potency/degradants in Drug A/HCTZ tablets with Starch® 1500 (no PVP and no Pluronic), stored in HDPE bottle with cotton and induction sealed cap

Time point (days)	Storage condition	HCTZ potency (mg/tablet)	HCTZ degradant free amine (mg/tablet)
Initial	—	12.9	<0.02
31	40°C/75% RH	12.8	0.04
	50°C	12.8	0.04
91	30°C/60% RH	12.6	0.03
	40°C/75% RH	12.8	0.04
	50°C	12.8	0.06
168	25°C/60% RH (open)	13.0	0.02
	30°C/60% RH	13.1	<0.02
	40°C/75% RH	13.1	<0.02
	50°C	12.8	0.02

$n = 5$

initial samples, indicating that the drug was not hydrolyzed during the granulation process. In contrast to HCTZ, there was neither loss in potency of Drug A nor any increase in its degradant level.

Based on the previous work in our laboratory (Desai et al., 1994a,b,c), compatibility of HCTZ with most of the other formulation ingredients except PVP and Pluronic® F68 was found to be satisfactory. In order to determine compatibility of PVP with HCTZ, HCTZ stability in presence of PVP and added water was studied at 60°C. In PVP:HCTZ binary mixtures, percentages of free amine of the total peak area are shown in Table 2. As PVP fraction in the binary mixture increased, there was an increase in the amount of free amine formed. However, a similar trend was not observed in Starch® 1500:HCTZ mixtures. The free amine levels detected in Starch® 1500:HCTZ mixtures were similar to that detected in lactose:HCTZ blend, which was used as a control. These results indicate that PVP was responsible for the increased amount of free amine formed in the tablet formulation while Starch® 1500 and lactose had little effect. As shown in Fig. 1, PVP at 150 mg/ml concentration was found to increase HCTZ saturation solubility in water at room temperature by a factor of six. Based on these observations, it was decided to replace PVP with Starch® 1500 as a binder to improve stability.

Stability data on the tablets containing Starch® 1500 and Pluronic® F68 are shown in Table 3. These tablets showed a slower rate of free amine formation compared with that seen in tablets containing PVP as the binder (Table 1). However, the amount of free amine formed in these tablets was still unacceptable. Additionally, as shown in Fig. 2, Pluronic® F68 at 7% (w/v) concentration was also found to increase HCTZ saturation solubility by 2-fold. Therefore, it was decided to remove Pluronic® F68 from the formulation. The tablets made without Pluronic showed excellent stability at various storage conditions (Table 4). In absence of Pluronic® F68, dissolution of both drugs was not significantly affected. Stability of the antihypertensive Drug A was not affected by the presence or absence of PVP or Pluronic® F68 (data not shown).

Since free amine is formed as a result of HCTZ hydrolysis, it is hypothesized that HCTZ was solubilized by PVP and/or Pluronic® F68 in the surface moisture present in the tablets followed by HCTZ hydrolysis, resulting in increased levels of free amine. The hydrolysis was accelerated in high temperature and/or moisture environments, therefore higher free amine levels were observed at these conditions compared to 30°C storage conditions. Removal of both PVP and Pluronic® F68 resulted in a stable tablet formulation.

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