ELSEVIER

International Journal of Pharmaceutics 107 (1994) 141–147

international journal of pharmaceutics

Effect of formaldehyde formation on dissolution stability of hydrochlorothiazide bead formulations

D.S. Desai *, B.A. Rubitski, S.A. Varia, M.H. Huang

Bristol-Myers Squibb Co., P.O. Box 191, New Brunswick, NJ 08903-0191, USA

(Received 4 October 1993; Modified version received 23 November 1993; Accepted 27 December 1993)

Abstract

An immediate release hydrochlorothiazide (HCTZ) bead formulation (formulation A) containing drug, lactose hydrous, sodium starch glycolate (Primojel®) and microcrystalline cellulose (Avicel® PH 101), and a control formulation (formulation B), without Primojel®, were exposed to 22°C/80% RH, RT/ambient RH, 40°C/75% RH, and 40°C/ambient RH in open petri dishes for 4 weeks. After the exposure, formulation A exhibited a significant decrease in dissolution rate under all conditions except 40°C/ambient RH. In contrast, no change in dissolution rate was observed for formulation B. It is possible that the decrease in dissolution rate of formulation A was due to the formation of a trace amount of formaldehyde due to hydrolysis of HCTZ in the humid environment and its subsequent reaction with Primojel®, which resulted in formation of an insoluble product and a reduction in disintegrating power of the Primojel®. In a simulated storage environment of high humidity in Conway cells and using the diffusion method, significantly less formaldehyde was detected in the formulation A beads compared to the formulation B beads ($P = 0.03$). This may indicate that formaldehyde present in the formulation A was partially consumed through a reaction with Primojel®. In both formulations, a significantly greater amount of formaldehyde was detected in beads containing smaller particles of HCTZ ($P = 0.02$). The formation of formaldehyde and its reaction with Primojel® seemed to be confined to the exposed surfaces of the beads since compression of the exposed beads into tablets resulted in faster dissolution of HCTZ.

Key words: Dissolution; Stability; Hydrochlorothiazide; Formaldehyde; Bead formulation; Primojel®; Conway cell

1. Introduction

Hydrochlorothiazide (HCTZ) is a popular diuretic and antihypertensive agent, used alone or in combination with other antihypertensive drugs. Most of the gastrointestinal absorption of HCTZ takes place in the duodenum and upper jejunum (Beermann et al., 1976). Rapid disintegration and dissolution of an oral HCTZ dosage form is, therefore, important for its bioavailability. In spite of widespread use of HCTZ, there are very few instances reported in the literature about its interaction with other ingredients in the solid state (Bornstein and Lach, 1966). However, in aqueous solutions, HCTZ is known to undergo hydrolysis to give formaldehyde and 5-chloro-2,4-disulfa-

* Corresponding author. Tel. (908)-519-3053.

SSDI 0378-5173(94)00005-P

moylaniline (Mollica et al., 1969, 1971). Formaldehyde, which is a highly reactive substance, can cross-link with starch (Merck Index, 1976) resulting in a loss of swelling capacity of starch (Walker, 1953).

In spite of the reported good solid state stability of HCTZ (Deppeler, 1981), a bead formulation containing HCTZ, lactose (hydrous), microcrystalline cellulose, and sodium starch glycolate (Primojel®) exhibited poor dissolution stability upon storage. In order to understand the causes of poor dissolution stability, an investigation was initiated. The results of this study are reported herein.

2. Materials and methods

2.1. Materials

The following ingredients were used as received from the suppliers: HCTZ (Vinchem Inc., Chatham, NJ, and Profarmaco Nobel, Sweden), lactose hydrous (Foremost Whey, Baraboo, WI), sodium starch glycolate (Primojel®) (Generichem Corp., Little Falls, NJ), microcrystalline cellulose (Avicel® PH 101) (FMC Corp., Newark, DE), size no. 1 hard gelatin capsule shells (Capsugel, Greenwood, SC), 37% (w/w) formaldehyde and chromotropic acid disodium salt (Fisher Scientific, Springfield, NJ), and IR grade potassium bromide (Aldrich Chemicals, Milwaukee, WI).

2.2. Equipment

The following equipment were used during the course of this study: Hobart planetary mixer (Hobart Manufacturing Co., Troy, OH), Nica extruder (Aeromatics, Towaco, NJ), Caleva spheronizer model 15 (Caleva, U.K.), Versaglatt (Glatt Air Technique, Ramsey, NJ), Carver laboratory press – model C (Fred S. Carver Inc., Menomonee, WI), Conway diffusion cells (Fisher Scientific, Springfield, NJ), Vanderkamp 600 six spindle dissolution tester (Vankel Industries, Edison, NJ), disintegration test apparatus (Hansen Research, Northridge, CA), 8451A diode array spectrophotometer (Hewlett-Packard Co., Palo Alto, CA), Perkin Elmer SEC-4 pump (Perkin Elmer, Norwalk, CT), Waters 712 WISP injector (Waters, Morristown, NJ), ABI 783A UV detector (Applied Biosystems, Foster City, CA), infrared spectrophotometer (Mattson, Inc., Madison, WI), and PSA-32 laser light scattering system (Munhall & Co., Worthington, OH).

2.3. Formulations

Formulation compositions for formulations A and B are given below.

Ingredient	Formulation A	Formulation B
Hydrochlorothiazide [a] (HCTZ)	20.0%	20.0%
Lactose, hydrous	67.5%	77.5%
Microcrystalline cellulose (Avicel® PH 101)	2.5%	2.5%
Sodium starch glycolate (Primojel®)	10.0%	
Purified water [b]	q.s.	q.s.
Total	100.0%	100.0%

[a] Amount of HCTZ shown assumes 100% chemical purity.
[b] Not present in the final product. Removed by drying.

2.4. Manufacture of beads

Beads for formulations A and B were prepared using conventional techniques (O'Connor and Schwartz, 1989). Three different lots of HCTZ were used to prepare three batches each of formulations A and B. The Hobart mixer was used for mixing and granulating the ingredients, the Nica extruder (speed setting of 4) for extruding the wet mass, and the Caleva spheronizer (370 rpm) for making the beads from the spaghetti-like extrudate. The residence time of the extrudate in the spheronizer was 1 min. Beads were dried to less than 2.0% w/w residual moisture at 50°C using the Versaglatt. The dried beads were then separated into different sizes using different mesh sieves and those retained on no. 16, 18, and 20 mesh screens were used in this study.

2.5. Dissolution

For dissolution studies, 125 mg of beads representing 25 mg HCTZ potency were placed into

size no. 1 white opaque capsule shells. The dissolution of these capsules was monitored, using a spectrophotometer at 272 nm, in 900 ml 0.1 N hydrochloric acid at 37°C using baskets at an agitation speed of 50 rpm. The HP 89026A dissolution testing system, in conjunction with the HP 8451A diode array spectrophotometer, automated the sampling, analyzing, data processing and report generating tasks.

For dissolution stability evaluation, beads were exposed to 22°C/80% RH, RT/ambient RH, 40°C/75% RH, and 40°C/ambient RH in open petri dishes for 4 weeks. Subsequently, the exposed beads were filled into capsule shells and dissolution was performed. For compression of beads into 125 mg weight tablets, a Carver press equipped with flat-faced 1/4 inch tooling was used. Dissolution of these tablets was monitored using the above-described conditions.

2.6. Disintegration tests

Primojel® was compressed into 200 mg pellets using a Carver press equipped with flat-faced 11/32 inch tooling. These pellets of Primojel® were exposed for 24 h to formaldehyde vapor (using 37% (w/w) formaldehyde solution) in a Conway diffusion cell. Disintegration test (with disks) was performed on the pellets according to the procedure described in the USP XXII. The medium for the disintegration test was 0.1 N hydrochloric acid. As a control, Primojel® pellets exposed to 100% humidity using the Conway diffusion cell and water were evaluated.

2.7. Formaldehyde detection

2 g of HCTZ beads were placed in the outer ring of the Conway diffusion cell (Hollander et al., 1951) and 0.4 ml of water was added to the beads. In the inner ring of the cell, 3 ml of chromotropic acid reagent was placed. The cells were sealed and placed in a 50°C oven for 2 h. It was established that the 2 h time period was enough for the reaction to reach completion under the experimental conditions. The chromotropic acid solution was then removed, placed in vial, sealed, and incubated in an 80°C water bath for 30 min. After cooling, the absorbances of the solutions were measured at 570 nm (Manius et al., 1993). Comparison of the absorbance data with a standard curve allowed for quantitation of formaldehyde formed. The presence of residual formaldehyde in the exposed beads was confirmed using an HPLC method (Benassi et al., 1989).

2.8. Particle size determination

HCTZ particle size was measured using the laser light scattering technique. A saturated solution of HCTZ was prepared in saline (0.9% sodium chloride in water). This solution was used as a dispersion medium. Using a spatula, 5–10 mg of the test sample was added into a test tube containing the dispersion medium. The test tube was vortexed for 15 s, ultrasonicated for 60 s, and then vortexed for an additional 15 s. The particle size distribution of the sample was then determined using a Munhall PSA-32 sizer instrument.

Table 1
Dissolution stability of HCTZ bead formulation A

Exposure time	Exposure condition	Mean % HCTZ dissolved (SD [a])							
		10 min	15 min	20 min	30 min	45 min	60 min	90 min	120 min
Initial	–	72.6 (9.5)	85.7 (5.2)	92.4 (3.4)	98.5 (1.4)	101.6 (1.0)	102.9 (0.9)	104.1 (0.8)	104.8 (0.8)
4 weeks	22°C/80% RH	21.7 (8.2)	28.9 (4.3)	34.7 (3.4)	43.7 (2.6)	54.1 (2.7)	62.8 (2.8)	74.9 (2.4)	83.9 (2.2)
	RT/ambient RH	30.9 (13.8)	41.9 (11.1)	50.8 (11.0)	63.0 (10.8)	77.0 (9.4)	84.5 (7.5)	94.6 (4.7)	99.4 (2.9)
	40°C/75% RH	19.8 (11.0)	27.1 (6.8)	32.1 (4.8)	39.7 (3.9)	50.5 (3.4)	58.0 (3.1)	ND	78.6 (2.8)
	40°C/ambient RH	72.3 (6.5)	85.4 (3.9)	92.3 (2.1)	98.2 (1.1)	101.4 (0.8)	102.8 (0.6)	103.9 (0.6)	ND

[a] $n = 6$.
ND, not determined.

Table 2
Dissolution stability of HCTZ bead formulation B

Exposure time	Exposure condition	Mean % HCTZ dissolved (SD [a])							
		10 min	15 min	20 min	30 min	45 min	60 min	90 min	120 min
Initial	–	68.5 (8.2)	ND	80.1 (4.9)	85.2 (4.5)	89.6 (3.9)	ND	97.6 (3.2)	100.4 (2.7)
4 weeks	22°C/80% RH	53.3 (6.8)	63.4 (2.8)	69.0 (2.4)	76.2 (2.0)	84.1 (1.7)	90.0 (2.0)	96.7 (2.4)	100.1 (1.6)
	RT/ambient RH	58.0 (15.1)	66.7 (6.5)	72.3 (3.2)	79.4 (3.0)	85.7 (3.4)	90.2 (3.4)	96.2 (2.8)	100.5 (2.2)
	40°C/75% RH	58.9 (4.6)	68.4 (2.4)	75.0 (1.3)	83.3 (1.9)	90.6 (2.3)	95.5 (2.2)	101.7 (2.4)	105.3 (1.8)
	40°C/ambient RH	65.7 (5.2)	74.4 (4.8)	79.6 (4.8)	84.3 (4.2)	88.8 (3.5)	91.4 (3.4)	ND	97.3 (2.9)

[a] $n = 6$.
ND, not determined.

2.9. Infrared spectra

1 mg of Primojel®, either exposed to 100% humidity or to formaldehyde vapors for 24 h was mixed with 300 mg of IR grade potassium bromide (KBr) and pressed into a 13 mm KBr pellet under vacuum and a pressure of 8 ton. Infrared absorption spectra were measured with a Mattson Polaris Fourier transform infrared spectrophotometer equipped with a mercury-cadmium-telluride detector. Each spectrum was collected under 4 cm^{-1} resolution and 1024 scans from 4000 to 400 cm^{-1}. The spectrophotometer was under constant nitrogen purge to eliminate water vapor and carbon dioxide absorption.

3. Results and discussion

The beads of formulation A exhibited significantly slower dissolution compared to initial results after their exposure in open petri dishes to

Table 3
Dissolution of three batches of HCTZ beads containing Primojel (initial and 1 week exposed to 40°C/75% RH in open petri dishes) and dissolution of tablets compressed from 1 week 40°C/75% RH exposed beads

Hydrochlorothiazide lot no.	Material and exposure condition	Mean % HCTZ dissolved (SD [a])							
		10 min	15 min	20 min	30 min	45 min	60 min	90 min	120 min
473739	beads – initial	74.6 (1.5)	85.5 (0.8)	92.4 (1.0)	98.4 (0.8)	102.1 (0.8)	103.0 (0.6)	103.6 (0.5)	104.0 (0.5)
	beads – exposed to 40°C/75% RH for 1 week	26.6 (1.1)	33.3 (1.1)	39.1 (1.8)	47.9 (2.2)	58.2 (3.0)	66.9 (2.6)	77.6 (2.6)	86.1 (1.9)
	tablets – compressed from exposed beads	47.3 (4.1)	58.6 (3.7)	66.1 (3.1)	76.4 (2.0)	85.3 (1.2)	90.8 (0.7)	96.2 (0.2)	98.6 (0.2)
48232	beads – initial	91.8 (3.1)	99.8 (1.2)	102.5 (1.2)	104.5 (1.0)	105.5 (0.8)	105.8 (0.7)	106.3 (0.6)	106.8 (0.7)
	beads – exposed to 40°C/75% RH for 1 week	30.2 (1.6)	37.9 (0.8)	44.0 (0.9)	53.6 (1.4)	64.2 (1.6)	72.0 (1.8)	83.2 (1.7)	90.5 (1.4)
	tablets – compressed from exposed beads	59.6 (5.6)	68.7 (4.1)	74.7 (3.1)	82.6 (2.0)	89.3 (1.4)	93.2 (1.3)	97.5 (1.1)	99.9 (1.0)
44801	beads – initial	91.4 (1.5)	98.9 (0.3)	101.6 (0.6)	104.2 (0.8)	105.3 (0.8)	105.9 (0.8)	106.6 (0.8)	106.4 (0.8)
	beads – exposed to 40°C/75% RH for 1 week	29.6 (3.2)	37.3 (1.8)	43.0 (1.2)	52.1 (1.4)	62.1 (1.5)	70.5 (0.8)	81.3 (1.7)	89.4 (1.6)
	tablets – compressed from exposed beads	57.8 (3.2)	68.5 (2.8)	75.1 (2.5)	84.2 (2.0)	92.0 (1.2)	96.2 (1.0)	100.1 (0.5)	101.7 (0.6)

[a] $n = 3$.

22°C/80% RH, RT/ambient RH, and 40°C/75% RH environment in for 4 weeks (Table 1). In contrast, no significant slowdown in dissolution was observed for formulation B when stored under the same conditions (Table 2). In order to confirm that the incomplete recovery of HCTZ from the beads stored at 22°C/80% RH and 40°C/75% RH was not due to degradation of HCTZ, beads were assayed for HCTZ content. The assay results showed no significant loss in HCTZ potency of the beads stored under these high humidity conditions. Further, for both formulations A and B, exposure to 40°C/ambient RH had no adverse effect on their dissolution. Based on these results, it was apparent that formulation A beads were very sensitive to environmental humidity at a low storage temperature.

In order to confirm these observations regarding the dissolution stability of beads of formulations A and B, three additional batches of each formulation were made using three different lots of HCTZ. Beads of these three different batches of formulations A and B were exposed to 40°C/75% RH in open petri dishes for 1 week. After only 1 week of exposure, a slowdown in dissolution of HCTZ from formulation A was observed as compared to the initial dissolution (Table 3). In the case of formulation B, as observed earlier, no slowdown in dissolution was observed in all three lots exposed to 40°C/75% RH. Upon compression of the formulation A beads exposed to 40°C/75% RH for 1 week into tablets, faster and complete dissolution of HCTZ from these tablets was observed (Table 3). Based on these observations, it was believed that during the exposure to the humid environment some changes occurred on the beads' surfaces retarding their dissolution.

In aqueous solutions, HCTZ is known to undergo hydrolysis to give formaldehyde and 5-chloro-2,4-disulfamoylaniline (Mollica et al., 1969, 1971). In order to explore the possibility of hydrolysis of HCTZ taking place in these beads, a simulated storage environment of high humidity was created in the Conway diffusion cells as described in section 2. Under these simulated conditions, formation of formaldehyde from both of these bead formulations was detected by color formation of the chromotropic acid. The formation of formaldehyde in the beads was also confirmed using a reverse-phase HPLC method (Benassi et al., 1989). Significantly less formaldehyde was formed in the formulation A beads compared to formulation B beads ($P = 0.03$) (Table 4). Further, in both formulations, a significantly greater amount of formaldehyde was detected in beads containing smaller particles of HCTZ ($P = 0.02$) (Table 4). The smaller HCTZ particles provided a larger surface area for the reaction. It is also possible that at 40°C/ambient RH, there was not enough moisture available for HCTZ hydrolysis, therefore, dissolution of beads stored under this condition remained unaffected (Table 1).

Formaldehyde is a very reactive substance,

Table 4
Determination of formaldehyde formed under stressed conditions using the diffusion method in 2 g of HCTZ beads containing different HCTZ particle sizes and with Primojel (formulation A) and without Primojel (formulation B)

HCTZ lot no. present in beads	HCTZ particle size (μm)			Formulation	Mean amount of formaldehyde formed (μm) in 2 g beads	SD [a]
	< 6	< 20	< 40			
473739	12.1%	62.1%	83.5%	B	1.59	0.21
				A	1.37	0.05
48232	7.7%	44.3%	73.9%	B	1.57	0.24
				A	1.25	0.07
44801	4%	31%	66%	B	1.17	0.01
				A	1.01	0.11

[a] $n = 2$.

which can cross-link with starch or starch derived disintegrants such as Primojel® to form an insoluble compound (Merck Index, 1976). In this case, it is hypothesized that this insoluble compound was formed on the surfaces of beads. This probably prevented penetration of the disintegrating medium into the beads, resulting in slower disintegration and dissolution. Also, as a result of cross-linking, Primojel® loses its swelling capacity (Walker, 1953). The disintegrating time of pellets of Primojel® made on the Carver press increased from 2.3 (±0.1) min to 6.2 (±0.4) min upon exposure to formaldehyde vapor for 24 h. These results show that formation of formaldehyde in the beads could have possibly contributed significantly toward their slowdown in dissolution. The larger surface area of the beads, compared to the pellets, could explain the more pronounced effects on the disintegration and dissolution of the beads.

When the IR spectra of Primojel® exposed to humidity were compared with the IR spectra of Primojel® exposed to formaldehyde vapor for 24 h, there was a 50% increase in band intensity at 1020 cm^{-1} for the formaldehyde exposed Primojel® samples (Fig. 1). The bands at 1610 cm^{-1} (from the asymmetric COO^- stretch of carboxyl salt, COONa) were used as an internal standard to determine relative peak heights. The band at 1020 cm^{-1} is in the region of C-O stretch frequencies. It is also very close in frequency to one of the strong C-O stretching modes of dialkoxymethanes; for example, dimethoxymethane (CH_3-O-CH_2-O-CH_3), absorbs strongly at 1139 and 1043 cm^{-1}. Thus, the increase in intensity of the 1020 cm^{-1} band in formaldehyde exposed Primojel® supports the mechanism that formaldehyde attacks the hydroxyl groups in Primojel® (Handbook of Pharmaceutical Excipients, 1986) forming acetal (C-O-CH_2-O-C) cross-linkage.

Since the amount of HCTZ was the same in both formulations, the same amount of formaldehyde should have formed in beads of formulations A and B. It is hypothesized that the smaller amount of formaldehyde detected in the formulation A beads was due to a reaction of some of the liberated formaldehyde with the Primojel® (Table 4). The formation of a trace amount of formaldehyde in the humid environment and its reaction with Primojel® seems to be confined to the exposed surfaces of the beads. Compression of the exposed beads into tablets probably resulted in the disruption of these surface layers of the insoluble product of the Primojel®-formaldehyde reaction, improving its dissolution (Table 3).

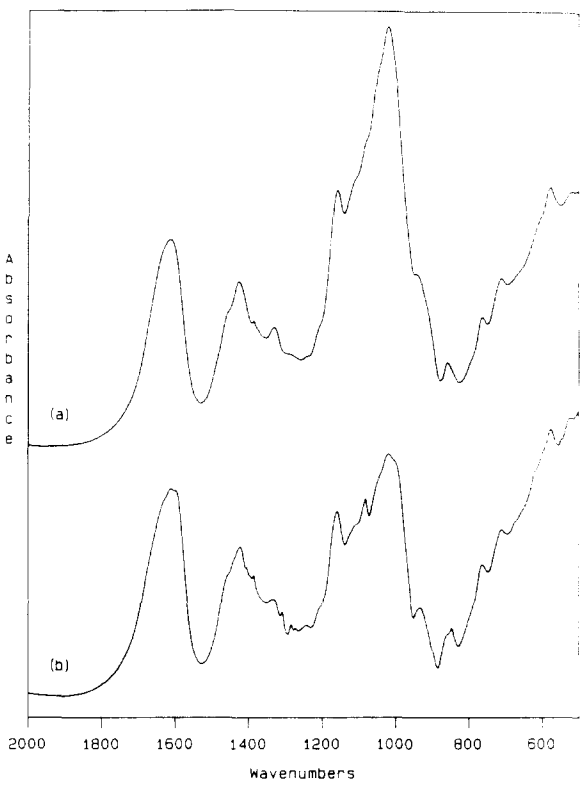

Fig. 1. IR spectrum of (a) Primojel® exposed to formaldehyde vapor for 24 h, and (b) Primojel® 'as is'.

The results reported here have importance, since most failures in dissolution result in decreased oral bioavailability. This is more probable for HCTZ because its absorption mainly occurs in the duodenum and upper jejunum which requires rapid liberation and dissolution of drug for absorption to occur.

4. Conclusions

In the environment of high humidity, it is possible that degradation of HCTZ in the bead surfaces produced a trace amount of formaldehyde. The latter possibly reacted with the disintegrant Primojel®, resulting in formation of an insoluble product and loss of swelling capacity of Primojel®. This insoluble compound on the bead surfaces prevented penetration of disintegration medium into the HCTZ beads, leading to a slowdown in disintegration and dissolution.

Acknowledgments

The contributions to this study by Dr Ajit Thakur and Mr Joseph DeVincentis are gratefully acknowledged.

References

Beermann, B., Groschinsky, M. and Rosen, A., Absorption, metabolism, and excretion of hydrochlorothiazide. *Clin. Pharmacol. Ther.*, 19 (1976) 531–537.

Benassi, C., Semenzato, A. and Bettero, A., High-performance liquid chromatographic determination of free formaldehyde in cosmetics. *J. Chromatogr.*, 464 (1989) 387–393.

Bornstein, M. and Lach, J., Diffuse reflectance studies of solid-solid interactions: II. Interaction of metallic and nonmetallic adjuvants with anthracene, prednisone, and hydrochlorothiazide. *J. Pharm. Sci.*, 55 (1966) 1033–1040.

Deppeler, H., Hydrochlorothiazide. In Florey, K. (Ed.), *Analytical Profiles of Drug Substances*, Academic Press, New York, Vol. 10, 1981, pp. 405–441.

Hollander, V., Dimauro, S. and Pearson, O. A diffusion method for the estimation of formaldehydogenic steroid. *Endocrinology*, 49 (1951) 617–623.

Manius, G., Wen, L. and Palling, D., Three approaches to the analysis of trace formaldehyde in bulk and dosage form pharmaceuticals. *Pharm. Res.*, 10 (1993) 449–453.

Merck Index, Merck & Co., Rahway, NJ, 9th Edn, 1976, p. 545.

Mollica, J., Rehm, C. and Smith, J., Hydrolysis of hydrochlorothiazide. *J. Pharm. Sci.*, 58 (1969) 635–636.

Mollica, J., Rehm, C. and Smith, J., Hydrolysis of benzothiadiazines. *J. Pharm. Sci.*, 60 (1971) 1380–1384.

O'Connor, R. and Schwartz, J., Extrusion and spheronization technology. In Ghebre-Sellassie, I. (Ed.), *Pharmaceutical Pelletization Technology*, Dekker, New York, 1989, pp. 187–216.

Walker, J., Reaction of formaldehyde with aliphatic hydroxy compounds and mercaptans. In *Formaldehyde*, Reinhold, New York, 1953, pp. 209–211.