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Effects of different types of lactose and disintegrant on dissolution stability of hydrochlorothiazide capsule formulations

D.S. Desai *, B.A. Rubitski, J.S. Bergum, S.A. Varia

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

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Abstract

Dissolution at the 20 min time point of hydrochlorothiazide (HCTZ) capsules containing Fast-Flo® lactose, hydrous lactose, or anhydrous lactose decreased by 45, 25, and 10%, respectively, after 6 months storage at 50°C. It was hypothesized that the decrease in dissolution was due to the formation of a trace amount of formaldehyde from the hydrolysis of HCTZ in the presence of moisture liberated from the excipients and the capsule shells, and the subsequent interactions of the formaldehyde with gelatin capsule shells and corn starch present in the formulation to form insoluble compounds. In a simulated storage environment of high temperature and moisture in Conway cells and using the diffusion method, it was demonstrated that the amount of formaldehyde formed depended on the type of lactose used in the blend and followed the rank order of Fast-Flo® > hydrous > anhydrous (pairwise p values ≤ 0.05). In the capsule formulation containing Fast-Flo® lactose as diluent, replacement of corn starch with a superdisintegrant such as sodium starch glycolate (Explotab®) or croscarmellose sodium (Ac-Di-Sol®) did not improve the dissolution stability. However, replacement of corn starch with crospovidone (Polyplasdone XL®) as a disintegrant resulted in a capsule formulation with satisfactory dissolution stability. It was observed that in formulations which exhibited poor dissolution, the dissolution of the capsule shells was more adversely affected by formaldehyde than that of the capsule contents. Moreover, in the presence of added water, significantly less formaldehyde was detected in blends containing corn starch, Explotab®, or Ac-Di-Sol® compared to blends containing Polyplasdone XL® or control (no disintegrant) probably because some of the formaldehyde generated was consumed in reactions with those disintegrants. Success of Polyplasdone XL® in improving dissolution stability of the HCTZ capsules was attributed mainly to its moisture scavenging ability, which prevented the formation of formaldehyde and, to some extent, its non-reactivity with formaldehyde.

Key words: Hydrochlorothiazide capsule; Dissolution stability; Formaldehyde; Superdisintegrant; Lactose; Polyplasdone XL®; Corn starch; Explotab®; Ac-Di-Sol®; Anhydrous lactose; Fast-Flo® lactose; Conway cell

1. Introduction

The effects of various formulation factors on dissolution stability of 50 mg potency aztreonam, hydrochlorothiazide (HCTZ), and sorivudine capsules were studied in HDPE bottles under various storage conditions (Desai et al., 1994). No large decreases in dissolution rates were observed for aztreonam and sorivudine capsules. However, hydrochlorothiazide (HCTZ) capsules containing Fast-Flo® lactose, hydrous lactose, or anhydrous

* Corresponding author.

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lactose demonstrated up to 45, 25, and 10% decrease in the amount of drug dissolved, respectively, compared to initial values at the 20 min dissolution time point after 6 months storage at 50°C (Desai et al., 1994). Given the excellent solid state stability of HCTZ (Deppeler, 1981), pronounced dissolution instability of HCTZ capsules under accelerated storage conditions was unexpected. A systematic study, therefore, was undertaken to investigate the reasons for the dissolution instability of HCTZ capsules.

2. Materials and methods

2.1. Materials

The following ingredients were used as received from the suppliers: 37% (w/w) formaldehyde and chromotropic acid disodium salt (Fisher Scientific, Springfield, NJ), sodium starch glycolate (Explotab®) (Edward Mendell Co., Carmel, NY), croscarmellose sodium (Ac-Di-Sol®) (FMC Corp., Newark, DE), and crospovidone (Polyplasdone XL®) (ISP, Wayne, NJ). Sources for other materials have been described in the preceding paper (Desai et al., 1994).

2.2. Equipment

Conway diffusion cells (Fisher Scientific, Springfield, NJ) were used in the study. Sources for the rest of the equipment used in this study have been detailed in the preceding paper (Desai et al., 1994).

2.3. Formulation

The composition (% w/w) of the HCTZ capsule formulation is as follows: HCTZ (assumes 100% chemical purity), 14.29%; lactose, 69.71%; corn starch or a superdisintegrant, 15.00%; magnesium stearate, 1.00%.

2 kg batch sizes of different powder blends, each containing a different type of lactose (Fast-Flo®, hydrous, or anhydrous), HCTZ, corn starch or a superdisintegrant, and 1% w/w magnesium stearate were prepared using the previously described procedure (Desai et al., 1994). Using the Zanasi AZ5 capsule filler, 350 mg blend was filled into size no. 2 white opaque hard gelatin capsule shells to obtain 50 mg potency capsules. For dissolution stability evaluation, the capsules were packaged in HDPE bottles containing cotton, desiccant, and glued filmaseal and placed at 50°C and 40°C/75% RH. Dissolution studies were performed in 1000 ml of 0.1 N hydrochloric acid at 37°C using USP Apparatus II at 75 rpm. The concentration of dissolved HCTZ was determined spectrometrically measuring absorbance at 272 nm. Sinkers were used to prevent capsules from floating in the dissolution medium.

In order to verify the reproducibility of the results, two batches of capsules containing corn starch as a disintegrant and Fast-Flo® lactose as a diluent were manufactured and used in the study.

2.4. Formaldehyde detection

Degradation of HCTZ in the environment of high temperature and presence of moisture was simulated using the Conway diffusion cell. 2 g of the powder blend containing different types of lactose were placed in the outer ring of a Conway diffusion cell and varying quantities of water (0.05, 0.1, 0.2, 0.4, or 0.6 ml) were added to the blend. For detection of formaldehyde formation in the HCTZ blends containing different disintegrants, 2 g of blend were placed in the outer ring of the Conway diffusion cell and 0.6 ml of water was added. 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 previously established that 2 h was sufficient time for the reaction to reach completion under the experimental conditions. The chromotropic acid solution was then removed, placed in a vial, sealed, and incubated in an 80°C water bath for 30 min. Vials were then cooled and the absorbance of the solution was measured at 570 nm (Manius et al., 1993). Comparison of the ab-

sorbance data with a standard curve allowed for quantitation of the formaldehyde formed. The presence of residual formaldehyde in the contents of the capsules exposed to various storage conditions was confirmed using the HPLC method reported by Benassi et al. (1989).

3. Results and discussion

The effect of various types of lactose on the dissolution stability of HCTZ capsules is shown in Fig. 1. Capsules containing Fast-Flo® lactose as a diluent exhibited the slowest dissolution at the 20 min sampling time point when tested after 2, 4, 12, and 24 weeks storage at 50°C. A similar trend, but to a lesser extent, was seen with capsules stored at 40°C/75% RH (Fig. 2). Capsules containing anhydrous lactose as a diluent exhibited the best dissolution stability (Fig. 1 and 2). Because of the inherently high dissolution variability at earlier sampling time points, the 20 min sampling time point was selected for comparison purposes.

In aqueous solutions, HCTZ has been reported to undergo hydrolysis to form formaldehyde and 5-chloro-2,4-disulfamoylaniline (Mollica et al., 1969, 1971). It was hypothesized that the

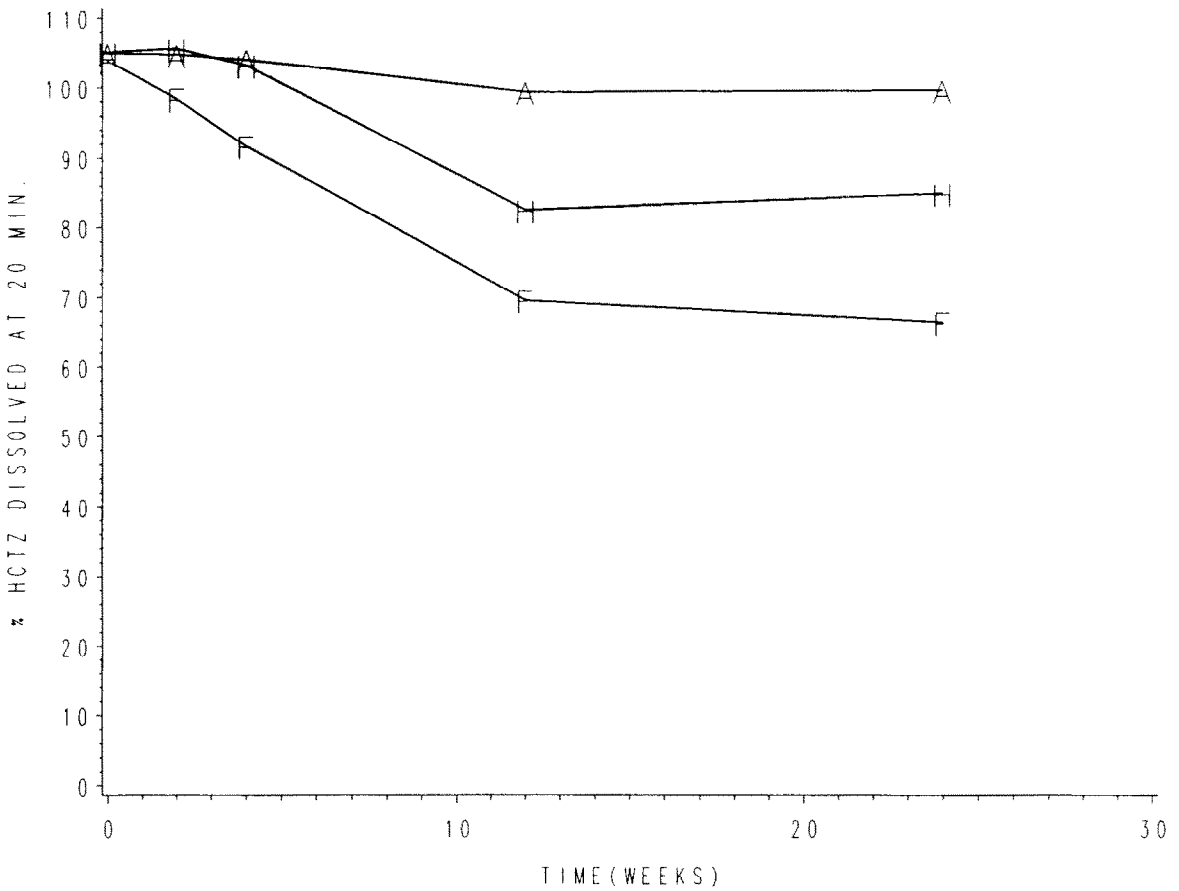

Fig. 1. Percent drug dissolved at the 20 min time point for HCTZ capsules containing Fast-Flo®, hydrous, or anhydrous lactose after 24 weeks storage at 50°C. (F) Fast-Flo®, (A) anhydrous, and (H) hydrous.

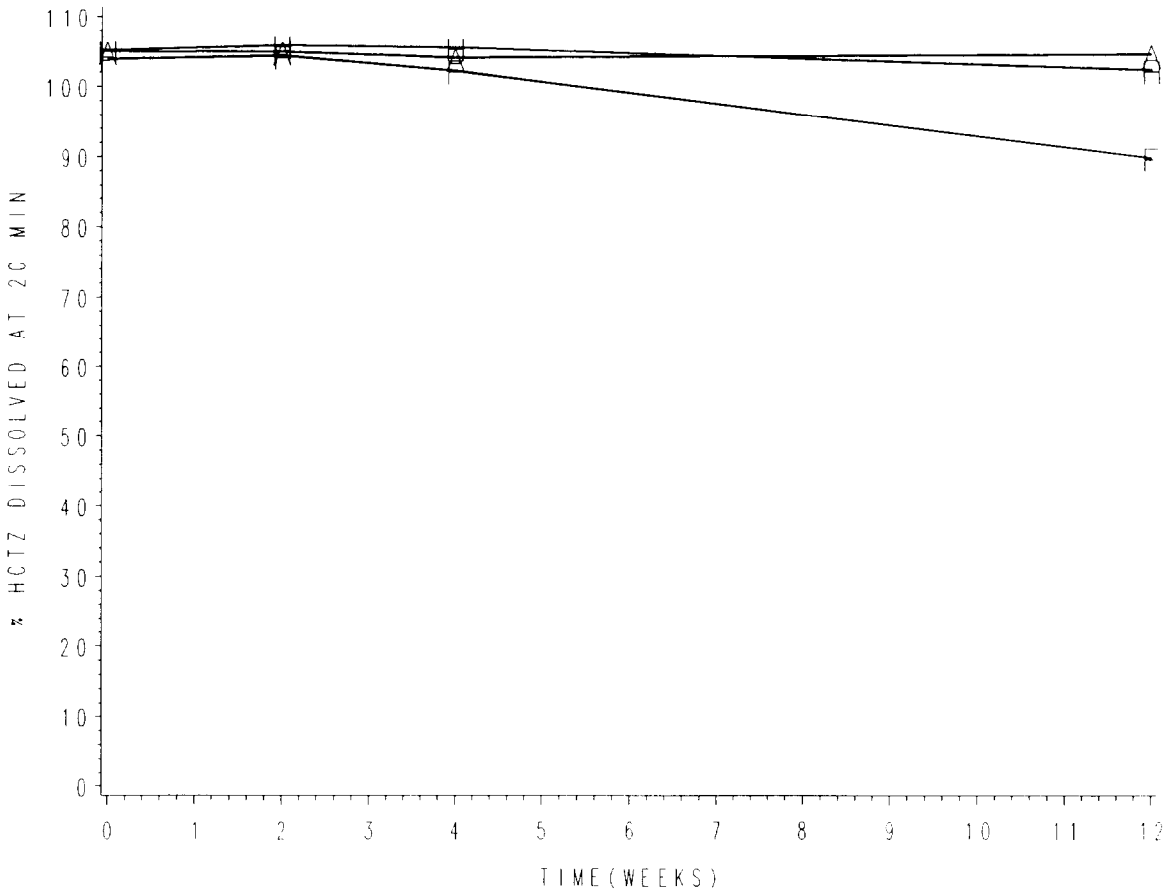

Fig. 2. Percent drug dissolved at the 20 min time point for HCTZ capsules containing Fast-Flo®, hydrous, or anhydrous lactose after 12 weeks storage at 40°C/75% RH. (F) Fast-Flo®, (A) anhydrous, and (H) hydrous.

decrease in dissolution rate was due to the formation of a trace amount of formaldehyde as a result of hydrolysis of HCTZ in the presence of moisture liberated from the excipient and/or the capsule shell, and the subsequent reaction of the released formaldehyde with gelatin capsule shells and corn starch to form insoluble compounds (Merck Index, 1976).

In a simulated storage environment of high temperature and added water in Conway cells and using the diffusion method (Hollander et al., 1951), the formaldehyde formed was detected and quantified in the HCTZ capsule blends. The amount of formaldehyde formed depended on the type of lactose used in the blend and followed the rank order of Fast-Flo® > hydrous > anhydrous (pairwise p values ≤ 0.05) (Fig. 3). This rank order of formaldehyde formation in the presence of equal amounts of added water can be explained by the fact that the Fast-Flo® lactose contains the greatest amount of surface moisture among the three types of lactose (Brittain et al., 1991). In placebo blends (blends without HCTZ) containing different types of lactose, no formaldehyde was detected.

The hypothesis that the slowdown in capsule dissolution was due to the formation of formaldehyde and its subsequent reaction with corn starch

was tested by replacing corn starch in the formulation containing Fast-Flo® as a diluent with an equal amount of a superdisintegrant such as Explotab®, Ac-Di-Sol®, or Polyplasdone XL®. The dissolution stability of the capsules containing superdisintegrants was monitored for up to 12 weeks under conditions of storage at 50°C and 40°C/75% RH. Under the 50°C storage condition, capsules containing Explotab® or Ac-Di-Sol® as a disintegrant exhibited dissolution stability no better than those containing corn starch (Fig. 4). In contrast, capsules containing Polyplasdone XL® as a disintegrant exhibited no slowdown in dissolution (Fig. 4). Under the 40°C/75% RH storage condition, capsules containing Polyplasdone XL® or Ac-Di-Sol® exhibited no slowdown in dissolution (Fig. 5). For other disintegrants, a slowdown in dissolution was observed, but to a lesser extent than under the 50°C storage condition (Fig. 5). This was probably due to release of more moisture at 50°C compared to 40°C/75% RH. Since capsules were packaged in HDPE bottles containing cotton, a 0.75 g silica gel desiccant, and glued filmaseal, the external humidity did not play significant role in the hydrolysis of HCTZ.

In a simulated storage environment of high temperature and added water in Conway cells

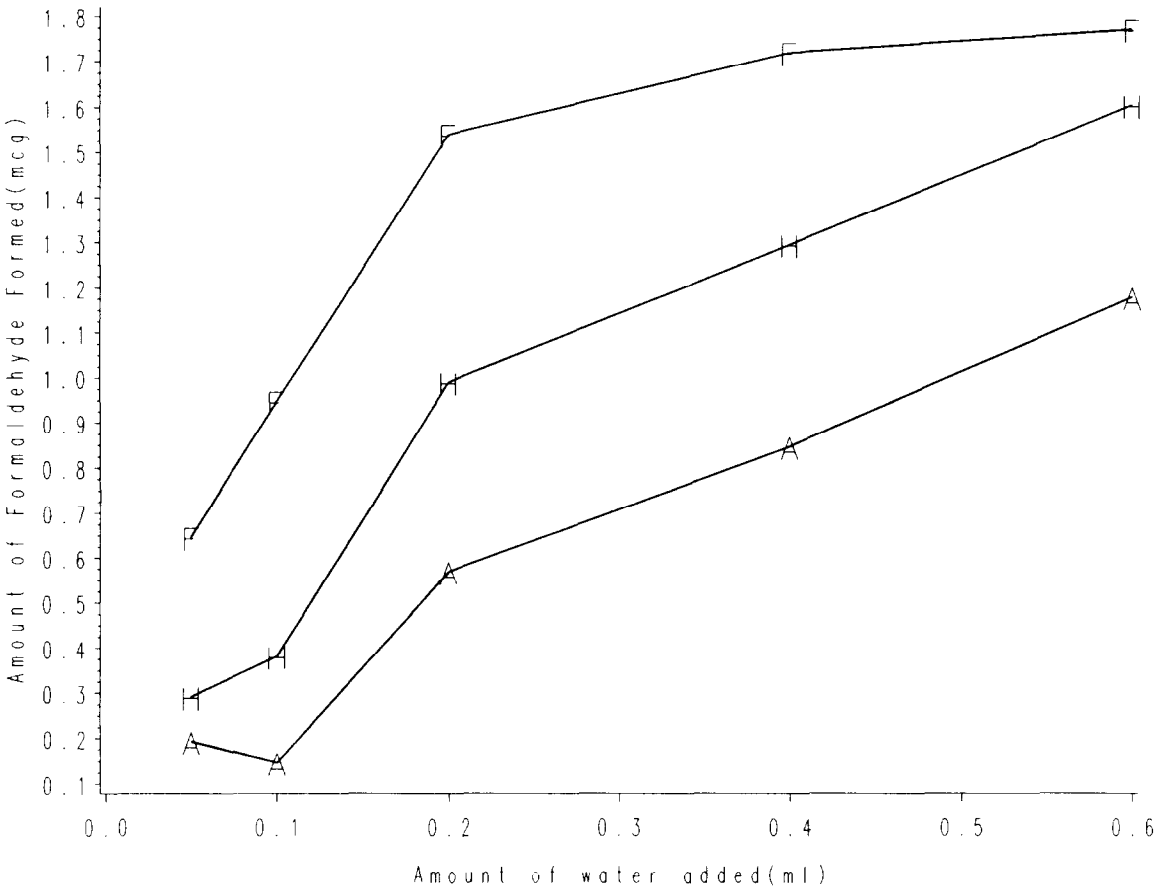

Fig. 3. Formation of formaldehyde in 2.0 g of powder blend containing different types of lactose in the presence of various amount of added water. (F) Fast-Flo®, (A) anhydrous, and (H) hydrous.

and using the diffusion method (Hollander et al., 1951), significantly less formaldehyde was detected for blends containing corn starch, Explotab®, or Ac-Di-Sol® compared to blends containing Polyplasdone XL® or control (no disintegrant) (Table 1) (p value < 0.05) probably because some of the formaldehyde generated was consumed in the interactions with those disintegrants. It has also been reported that upon reaction with formaldehyde, starch and cellulose lose their swelling capacity (Walker, 1953). On the other hand, Polyplasdone XL® did not react with formaldehyde.

Since formaldehyde can react with the starch and cellulose based disintegrants as well as the gelatin of the capsule shell, an evaluation was performed to identify the extent of the interaction of formaldehyde with these components on the dissolution stability. This was carried out by transferring the contents of capsules stored for 55 weeks at 50°C (aged contents) into new capsule shells and placing new blends (new contents) into the aged capsule shells (shells containing formulation exposed for 55 weeks at 50°C). Dissolution studies on these capsules indicated that for capsule formulations containing Fast-Flo® lactose as a diluent and Explotab®, corn starch, or Ac-Di-Sol® as disintegrants, the 'as is' aged capsules and capsules with new contents in the aged capsule shells both exhibited slower dissolution (Ta-

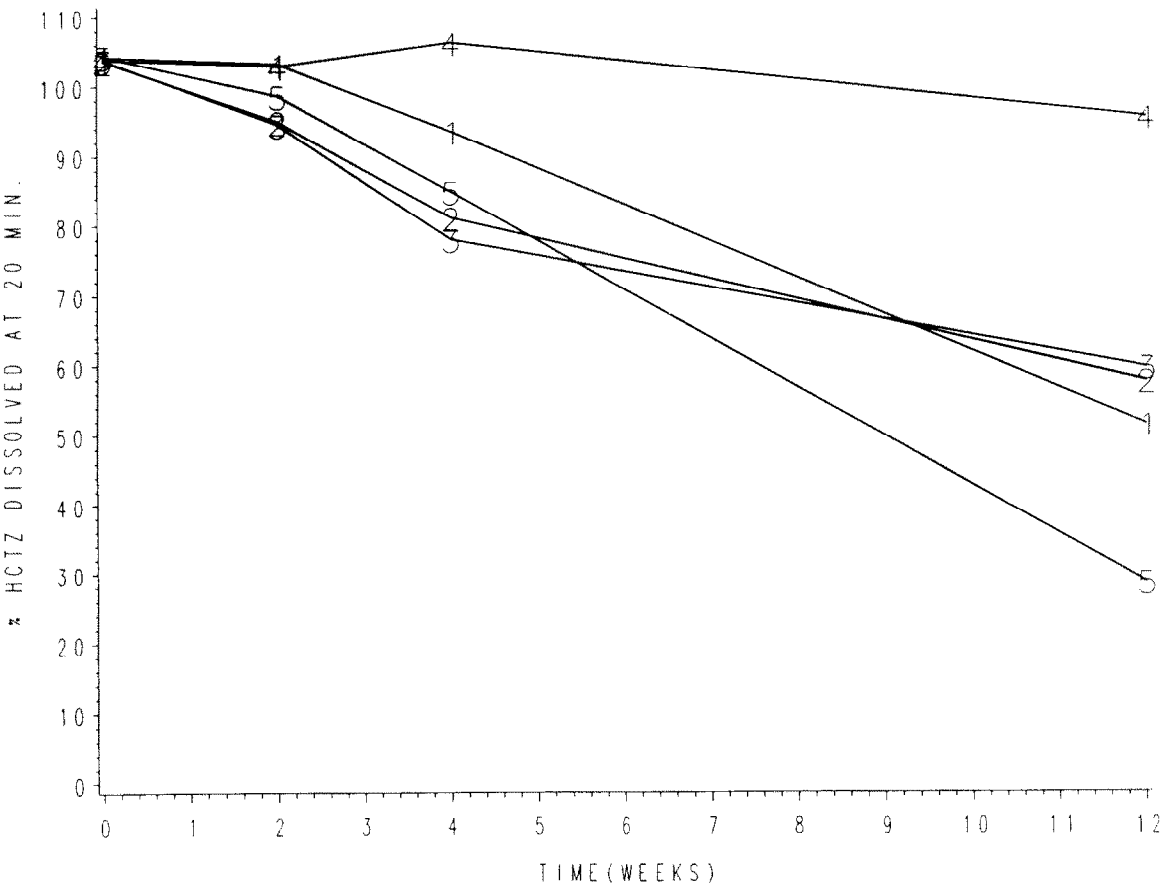

Fig. 4. Percent drug dissolved at 20 min time point for HCTZ capsules containing different disintegrants after 12 weeks storage at 50°C. (1) Ac-Di-Sol®, (2) corn starch batch 1, (3) corn starch batch 2, (4) Polyplasdone XL®, and (5) Explotab®.

Table 1
Detection of formaldehyde formed under stressed conditions (2 h at 50°C) using the diffusion method (0.6 ml water added to blend in diffusion cell)

Disintegrant	Mean amount of formaldehyde formed [a] (μg)	Standard deviation (μg)
None (control)	2.46	0.11
Explotab®	1.93	0.07
Corn Starch 1	1.87	0.06
Polyplasdone XL®	2.37	0.21
Ac-Di-Sol®	1.10	0.22
Corn Starch 2	1.79	0.07

[a] $n = 3$.

ble 2). However, capsules containing aged capsule contents and new capsule shells exhibited significantly better dissolution and the results were similar to initial dissolution values. This indicated that the capsule shells were more adversely affected by formaldehyde than were the capsule contents. In the case of capsules containing Polyplasdone XL® as a disintegrant, there was little difference in the dissolution between 'as is' aged capsules, capsules with aged contents in new capsule shell, and capsules with new contents in aged capsule shell, showing minimum effect of storage on the dissolution of the capsule shells. Polyplas-

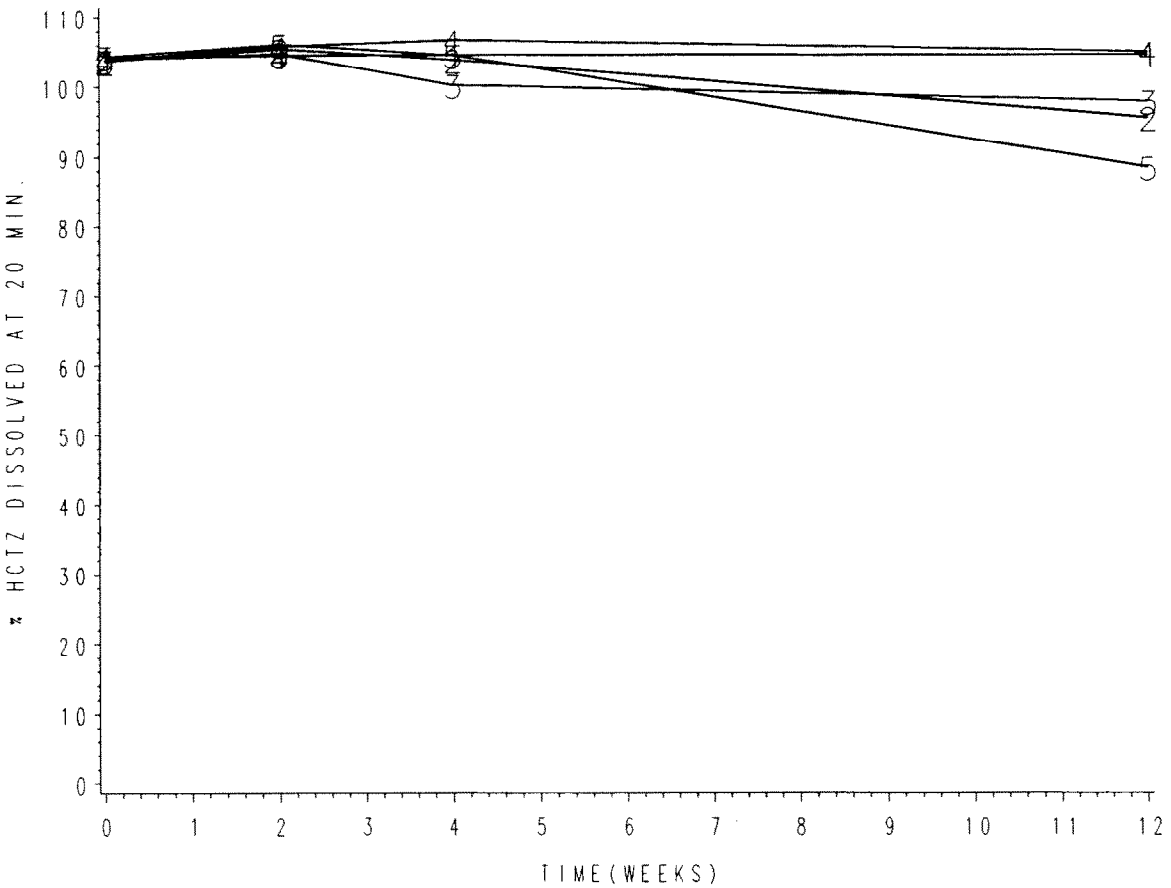

Fig. 5. Percent drug dissolved at 20 min time point for HCTZ capsules containing different disintegrants after 12 weeks storage at 40°C/75% RH. (1) Ac-Di-Sol®, (2) corn starch batch 1, (3) corn starch batch 2, (4) Polyplasdone XL®, and (5) Explotab®.

Table 2
Dissolution stability of HCTZ capsules stored at 50°C for 55 weeks

Disintegrant		Dissolution at 20 min (% HCTZ dissolved)			
		Initial capsules (as is)	Capsules stored at 50°C for 55 weeks		
			As is	(capsule combination) Aged contents, new shell	New contents, aged shell
Explotab®	Mean	104.33	4.42	97.70	16.02
	SD [a]	0.74	0.62	2.21	27.53
	p [b]			< 0.01	0.35
Corn Starch 1	Mean	103.65	39.02	98.40	24.53
	SD [a]	0.58	30.34	2.51	20.81
	p [b]			< 0.01	0.36
Polyplasdone XL®	Mean	103.85	83.83	96.93	89.77
	SD [a]	1.09	26.50	1.90	14.54
	p [b]			0.28	0.65
Ac-Di-Sol®	Mean	104.25	61.45	96.93	64.33
	SD [a]	0.43	37.47	2.84	24.09
	p [b]			0.07	0.88
Corn Starch 2	Mean	103.83	19.80	98.43	28.60
	SD [a]	0.50	11.64	1.24	22.49
	p [b]			< 0.01	0.42

[a] $n = 6$.
[b] p value is for the two-tailed test of whether or not there is a difference in the mean dissolution from that of the 'as is' capsules stored at 50°C for 55 weeks.

done XL® possesses maximum moisture sorption and hydration capacity compared to the other disintegrants evaluated (Kornblum and Stoopak, 1973). It is hypothesized that because of the moisture sorption capacity of Polyplasdone XL®, the amount of moisture available for the hydrolysis of HCTZ was limited, resulting in better dissolution stability.

4. Conclusions

The slowdown in the dissolution of HCTZ capsules at accelerated conditions was attributed to formation of a trace amount of formaldehyde from the hydrolysis of HCTZ in the presence of moisture liberated from capsule shells and excipients. The liberated formaldehyde reacted with the gelatin of capsule shell and corn starch present in the formulation to form insoluble compounds with a loss of disintegrating capacity of the latter. Even though formaldehyde can interact with gelatin as well as with disintegrants, the dissolution results showed that the interaction with the capsule shell was more deleterious to the dissolution stability. Among the capsule formulations containing different types of lactose, the maximum slowdown in dissolution was observed for HCTZ capsules containing Fast-Flo® lactose probably due to the high surface moisture content of Fast-Flo® lactose, which in turn, caused generation of more formaldehyde. Among the capsule formulations containing Fast-Flo® lactose and different disintegrants, capsules containing Polyplasdone XL® as a disintegrant showed the best dissolution stability probably because of the high moisture sorption capacity of Polyplasdone XL® limiting the amount of moisture available for the hydrolysis of HCTZ.

References

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

Brittain, H., Bogdanowich, S., Bugay, D., DeVincentis, J., Lewen, G. and Newman, A., Physical characterization of pharmaceutical solids. *Pharm. Res.*, 8 (1991) 963–973.

Desai, D., Rubitski, B., Bergum, J. and Varia, S., Effects of various factors on dissolution stability of aztreonam, hydrochlorothiazide, and sorivudine capsules. *Int. J. Pharm.*, (1994) in press.

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.

Kornblum, S. and Stoopak, S., A new tablet disintegrating agent: cross-linked polyvinylpyrrolidone. *J. Pharm. Sci.*, 62 (1973) 43–49.

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.

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.

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

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