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International Journal of Pharmaceutics 110 (1994) 249–255

international journal of pharmaceutics

Effects of various formulation factors on dissolution stability of aztreonam, hydrochlorothiazide, and sorivudine capsules

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Received 28 October 1993; modified version received 11 February 1994; accepted 1 April 1994

Abstract

A split-split-plot $3^2 \times 2^2$ factorial design was used to study the effects of capsule filling machine and formulation factors such as lactose type, lubricant concentration, and capsule shell size on the dissolution stability of 50 mg potency hydrochlorothiazide (HCTZ), sorivudine (BV-araU), and aztreonam capsules packaged in HDPE bottles and stored under different conditions. It was observed that neither magnesium stearate concentration nor the type of capsule machine used to fill the capsule shells had any effect on dissolution stability of capsules of all three drugs for up to 6 months of storage at 50°C. For aztreonam, neither capsule shell size nor the type of lactose had any effect on dissolution stability. On the other hand, HCTZ size no. 1 capsules demonstrated better dissolution stability than size no. 2 capsules. Moreover, dissolution stability of capsules of sorivudine and HCTZ on storage at 50°C, 40°C/75% RH, and 40°C was dependent on the type of lactose used. HCTZ capsules containing Fast-Flo® lactose, hydrous lactose, or anhydrous lactose showed up to 45, 25, and 10% decrease in dissolution, respectively, compared to initial values, at the 20 min dissolution time point after 6 months storage at 50°C. The extent of decrease in the dissolution rate was less under the conditions of storage at 40°C/75% RH and 40°C. Similar effects of decrease in the dissolution rate with the different types of lactose were observed with sorivudine, although to a much lesser degree compared to HCTZ capsules. No decrease in dissolution rate was observed for any drug after 20 months storage at 30°C. It was hypothesized that the slight decrease in dissolution rate of sorivudine capsules was due to significant caking of the capsule contents in the presence of the moisture liberated from the excipients and the capsule shells. For aztreonam capsules, the caking of their contents was without any discernable effect on dissolution because of the high aqueous solubility. In contrast, for HCTZ capsules, changes in dissolution rate were far too pronounced to be attributed to caking only.

Key words: Lactose; Aztreonam; Hydrochlorothiazide; Sorivudine (BV-araU); H&K 120; Zanasi AZ5; Magnesium stearate; Capsule size; Dissolution stability; Capsule formulation

1. Introduction

Changes in formulation components such as diluent, disintegrant, lubricant, or capsule shell induced by accelerated storage conditions can adversely affect the dissolution stability of capsules. Effects of lubricant concentration (Desai et al., 1993), capsule filling machine (Shah et al., 1987; Johansen et al., 1989), and scale-up factors (Ullah et al., 1992) on capsule dissolution have been reported in the literature. However, the

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SSDI 0378-5173(94)00108-H

effects of these factors on the long-term dissolution stability of capsules have not been investigated systematically in a statistically designed study. Also, no systematic study has been reported on the effects of various types of lactose, a commonly used diluent, on dissolution stability of capsules. For these reasons, a split-split-plot $3^2 \times 2^2$ factorial design was used to investigate the effects of capsule filling machine and formulation factors such as lactose type, lubricant concentration, and capsule size on dissolution stability of 50 mg potency hydrochlorothiazide (HCTZ), an experimental antiviral drug sorivudine, and aztreonam capsule formulations. The three drugs were selected so that a comparative evaluation could be made of factors affecting dissolution stability of active ingredients having different solubilities in the dissolution medium, 0.1 N hydrochloric acid. The solubilities of HCTZ, sorivudine, and aztreonam in 0.1 N hydrochloric acid are 0.6, 5.0, and 12 mg/ml, respectively (Desai et al., 1993).

2. Materials and methods

2.1. Materials

The following ingredients were used as received from the suppliers: HCTZ (Profarmaco, New York, NY), aztreonam (Bristol-Myers Squibb Co., New Brunswick, NJ), sorivudine (Yamasa Shoyu Co., Choshi, Japan), hydrous and Fast-Flo® (spray-dried) lactoses (Foremost Whey, Baraboo, WI), anhydrous lactose (Sheffield, Norwich, NY), corn starch (A.E. Staley, Decatur, IL), magnesium stearate (impalpable powder) (Mallinckrodt, St. Louis, MO), size no. 1 and 2 hard gelatin capsule shells (Capsugel, Greenwood, SC), and a 0.75 g silica gel desiccant (Dricap®) (Multiform Desiccants, Inc., Buffalo, NY).

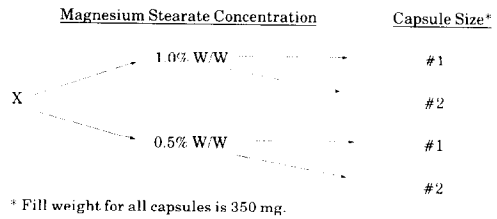
2.2. Equipment

The equipment used in the study included a Hobart planetary mixer (Hobart Manufacturing Co, Troy, OH), H&K 120 Capsule Filler (Bosch, South Plainfield, NJ), Zanasi AZ5 Capsule Filler (IMA North America, Fairfield, CT), Vanderkamp 600 six spindle dissolution tester (Vankel Industries, Edison, NJ), and 8451A diode array spectrophotometer (Hewlett-Packard Co., Palo Alto, CA).

2.3. Manufacture of capsules

Scheme 1 shows the experimental design used in this study. Nine 6 kg batches of powder blend, each containing a different type of lactose (Fast-Flo®, hydrous, or anhydrous) and drug (14.29% w/w HCTZ, sorivudine, or aztreonam) were prepared by mixing lactose, drug, and corn starch (15% w/w) in a Hobart mixer. Each batch was further divided into two sub-batches of equal size. These two sub-batches were mixed with 0.5 and 1.0% w/w magnesium stearate, respectively, for 1 min in a Hobart mixer. Each sub-batch was further divided into two equal size sub-sub-batches and filled into size no. 1 and 2 white opaque capsule shells, respectively, using the H&K 120 capsule filler. The fill weight was 350 mg for both size capsules providing 50 mg potency of each drug. In order to study the effects of capsule filling machine on dissolution stability of capsules, each sub-batch containing Fast-Flo® lactose as a diluent was also filled into capsule shells using the Zanasi AZ5 capsule filler. In order to

		LACTOSE TYPE		
		Fast-Flo	Hydrous	Anhydrous
DRUG	Sorivudine	X	X	X
	Hydrochlorothiazide	X	X	X
	Aztreonam	X	X	X



* Fill weight for all capsules is 350 mg.

Scheme 1. Experimental design: split-split-plot factorial $3^2 \times 2^2$.

reduce lot-to-lot variability of excipients and active ingredients, only one lot of each active ingredient, excipient, and capsule shell were used throughout the study.

2.4. Dissolution stability studies

For dissolution stability evaluation, the capsules were packaged in HDPE bottles containing cotton, desiccant, and glued filmaseal and placed at 50°C, 40°C/75% RH, 40°C, and 30°C. 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, sorivudine, and aztreonam was determined spectrophotometrically measuring absorbances at 272, 292, and 310 nm, respectively. Sinkers were used to prevent capsules from floating in the dissolution medium. Initial dissolution for each formulation composition was performed on 12 capsules. At subsequent time points, dissolution was performed on six capsules. 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.

3. Results and discussion

The split-split plot factorial design has been explained in many books (Cochran and Cox, 1957;

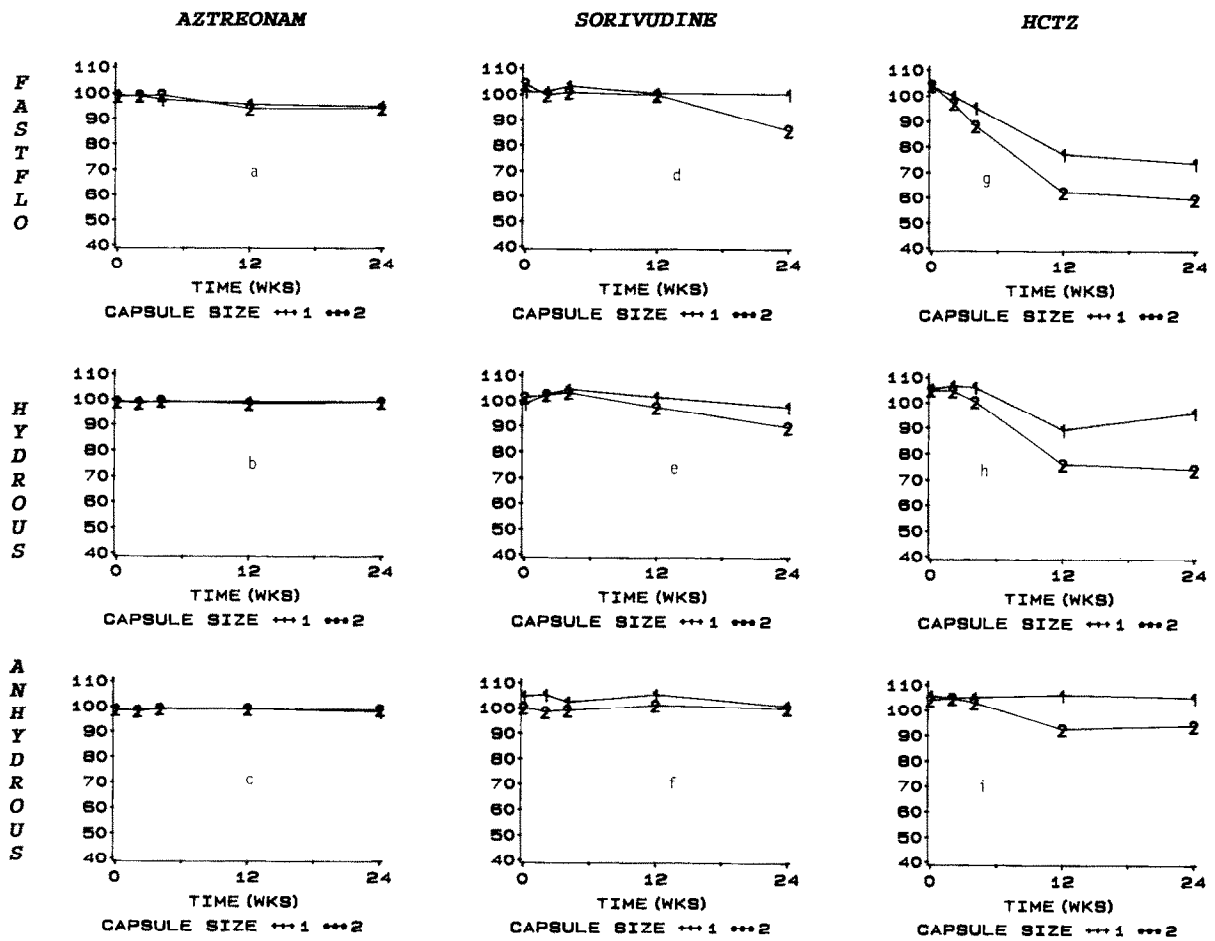


Fig. 1. Percent drug dissolved at 20 min time point for H&K filled aztreonam, sorivudine, and HCTZ capsules containing Fast-Flo®, hydrous, and anhydrous lactose after 6 months of storage at 50°C.

Milliken and Johnson, 1984; Peterson, 1985). The data generated for the present study were based on this design and were analyzed using the Statistical Analysis Software (SAS® 1985, 1989). The standard technique in analyzing factorials, which is to average over factors that have no effect, was followed in the data analysis. This technique of averaging resulted in presentation of the findings of the study with fewer plots. Also, because of the inherent variability associated with the 5 and 10 min dissolution time points, data obtained at the 20 min time point were selected for comparison purposes.

The effects of various types of lactose on dissolution stability of HCTZ, sorivudine, and aztreonam capsules, which were filled using the H&K 120 capsule filler and stored at 50°C, are shown in Fig. 1. For aztreonam capsules, the type of lactose and capsule size used had no effects on dissolution stability ($p = 0.65$) (Fig. 1a–c). For sorivudine, size no. 2 capsules containing Fast-Flo® (Fig. 1d) or hydrous lactose (Fig. 1e) exhibited slightly slower dissolution ($p = 0.20$) than size no. 1 capsules at the 24 week time point. On the other hand, no such dissolution stability dependence on capsule shell size was observed in sorivudine capsules containing anhydrous lactose (Fig. 1f).

More pronounced dissolution stability dependence on lactose type and capsule shell size ($p <$

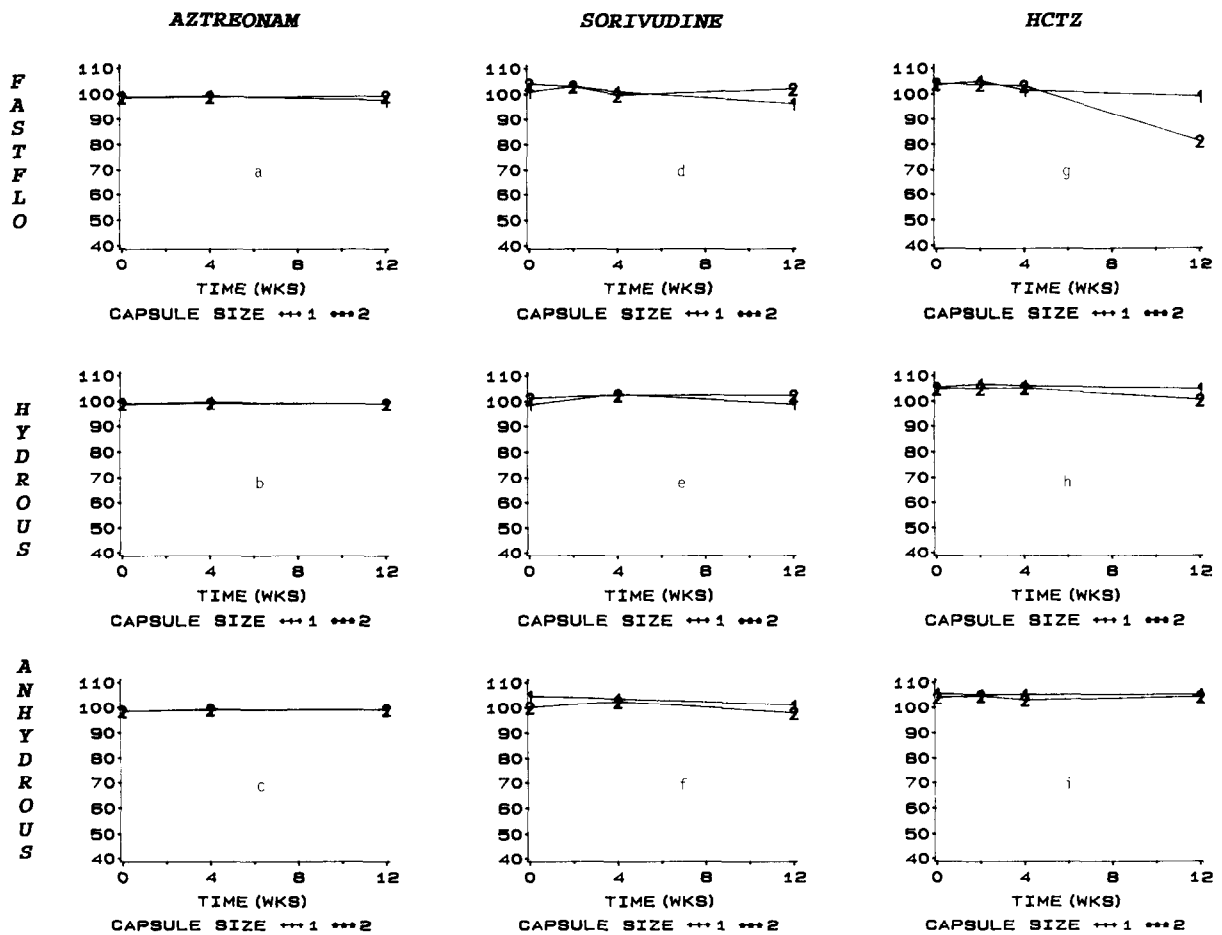


Fig. 2. Percent drug dissolved at 20 min time point for H&K filled aztreonam, sorivudine, and HCTZ capsules containing Fast-Flo®, hydrous, and anhydrous lactose after 6 months of storage at 40°C/75% RH.

0.0001) was observed for HCTZ capsules (Fig. 1g–i). Size no. 2 capsules filled with HCTZ formulation containing Fast-Flo®, hydrous, and anhydrous lactose demonstrated up to 45, 25, and 10% decrease in dissolution, respectively, compared to initial values, after 24 weeks storage at 50°C. However, size no. 1 capsules filled with HCTZ formulation containing anhydrous lactose exhibited no decrease in dissolution rate whereas those containing Fast-Flo® or hydrous lactose exhibited significant decrease in dissolution rate.

Under the 40°C/75% RH storage condition, of the three compounds, only HCTZ formulation containing Fast-Flo® or hydrous lactose in no. 2 capsules showed slowdown in dissolution at the 12 week time point (Fig. 2g and h). A smaller decrease in dissolution rate was observed, again only for HCTZ formulation containing Fast-Flo® or hydrous lactose in size no. 2 capsules, after 42 weeks storage at 40°C (Fig. 3). No decrease in dissolution rate was observed for capsules of any of the compounds evaluated in this study after storage for 20 months at 30°C.

Dissolution stability of aztreonam capsules was not affected by different types of lactose. For sorivudine and HCTZ, capsules with anhydrous lactose as a diluent exhibited the best dissolution stability whereas those containing Fast-Flo® lactose demonstrated the worst dissolution stability.

In this study, two types of capsule filling ma-

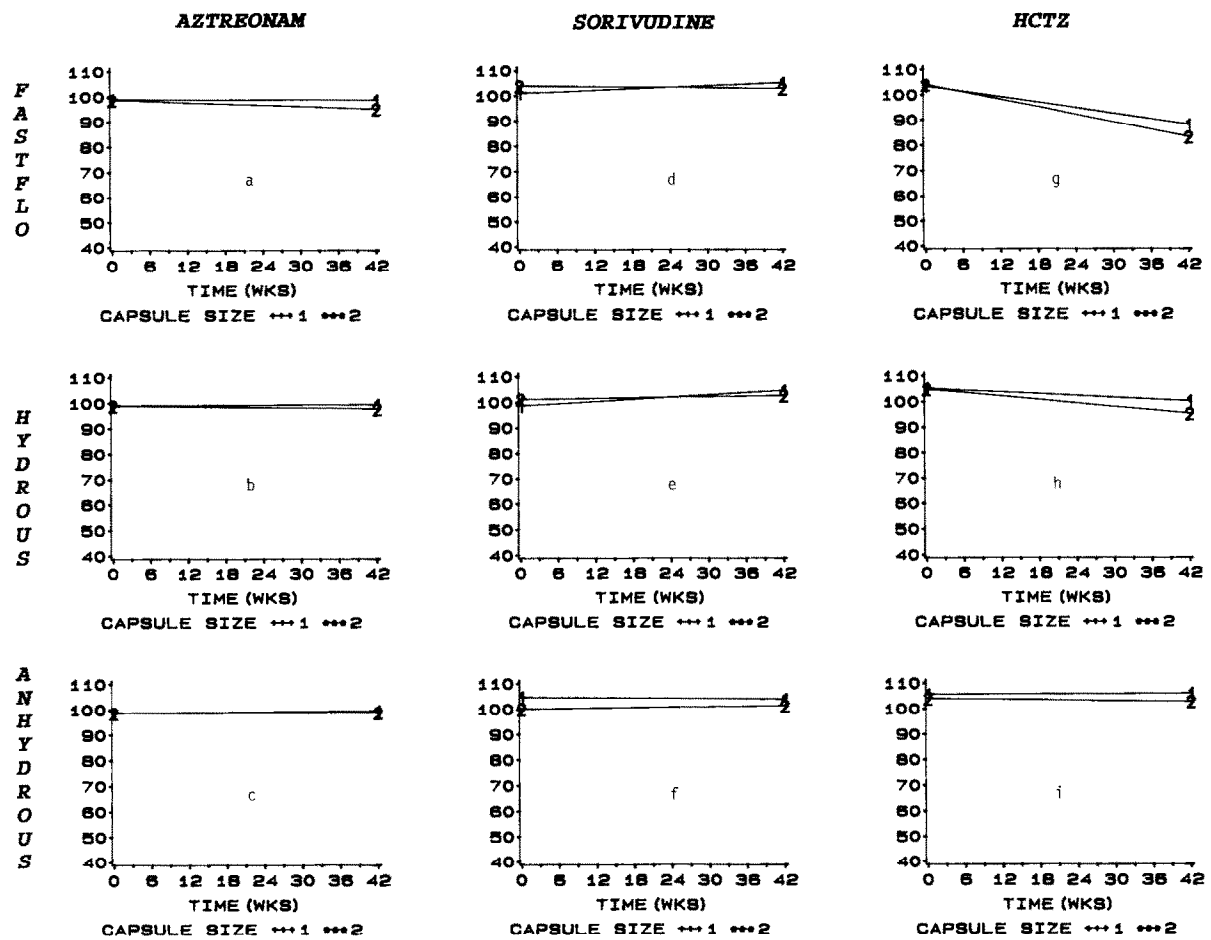


Fig. 3. Percent drug dissolved at 20 min time point for H&K filled aztreonam, sorivudine, and HCTZ capsules containing Fast-Flo®, hydrous, and anhydrous lactose after 42 weeks of storage at 40°C.

chines were used, dosing disk type H&K 120 and dosator type Zanasi AZ 5. Dissolution instability of aztreonam, sorivudine, and HCTZ capsules containing Fast-Flo® lactose was not linked to the filling mechanism of the capsule machine used. Upon storage at 50°C, trends in dissolution slowdown of the size no. 1 capsules filled using Zanasi AZ 5 were similar to those observed with size no. 1 capsules filled using the H&K 120 (Fig. 4). A similar trend was also observed for size no. 2 capsules ($p = 0.70$).

As expected, capsules of all three drugs with 1% magnesium stearate exhibited slightly slower dissolution initially than those with 0.5%. However, no effect of magnesium stearate concentration on dissolution stability of the capsules was observed for the three drugs irrespective of the type of lactose present or type of machine used during the filling operation ($p \geq 0.17$).

Changes in capsule dissolution are generally attributed to a physicochemical change in the basic structure of the capsule shell and/or a change in the properties of the capsule contents (Murthy and Ghebre-Sellassie, 1993). Since capsule shells used in the manufacture of aztreonam, sorivudine, and HCTZ capsules were from the same lot, storage-related changes (Kontny and Mulski, 1989) in the capsule shells must be similar for the capsules of all three drugs and should have equally adverse effects on their dissolution. Therefore, the changes in dissolution reported above were probably due to physical changes taking place in capsule contents under the accelerated storage conditions or due to drug-capsule shell interactions. Chemical stability of the active ingredients in the formulations was not an issue since after 90 min all capsules showed 100% dissolution.

Although the different types of lactose are similar chemically, their morphology differs significantly (Brittain et al., 1991)). Fast-Flo® and hydrous lactose have higher moisture contents than anhydrous lactose. Visual observations of capsule contents revealed formation of large lumps in sorivudine capsule contents and small lumps in aztreonam and HCTZ capsules. It is hypothesized that water liberated from Fast-Flo® or hydrous lactose tends to bind the capsule contents, resulting in lumps or caking. These lumps are not easily penetrated by the dissolution medium. Corn starch used in the present formulation has poor swelling efficiency (Botzolakis and Augsburger, 1988; Sarisuta and Parroot, 1988) and was not effective in promoting penetration, resulting in dissolution slowdown. In size no. 2 capsules, the capsule contents are more tightly filled, resulting in a higher degree of caking and slower dissolution than found in size no. 1 capsules. An active ingredient such as aztreonam can overcome this effect to some extent because of its relatively greater aqueous solubility. No caking was observed in capsules of any drug in which anhydrous lactose was used as diluent, probably because it has very little surface moisture (Brittain et al., 1991), and can also absorb a significant amount of liberated moisture from capsule shells and other excipients. Moreover, anhydrous lactose dissolves more rapidly than hydrous or Fast-

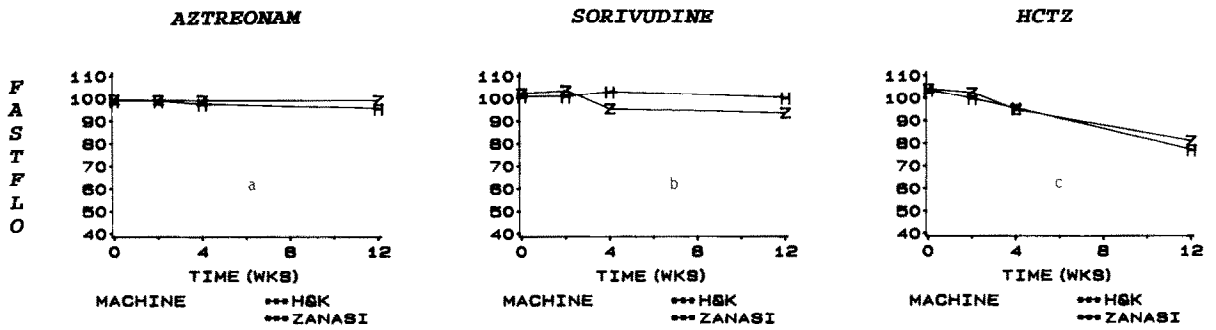


Fig. 4. Percent drug dissolved at 20 min time point for H&K or Zanasi filled size no. 1 capsules of aztreonam, sorivudine, and HCTZ capsules containing Fast-Flo® after 12 weeks of storage at 50°C.

Flo® lactose (Handbook of Excipients, 1986). Therefore, capsules containing anhydrous lactose demonstrated excellent dissolution stability.

The decrease in dissolution rate of HCTZ was too pronounced to be attributed to caking only. It was possible that there was some interaction between HCTZ and capsule shells upon storage which led to a pronounced decrease in dissolution of the HCTZ capsules. This possibility is the subject of a separate investigation and a follow-up article.

4. Conclusions

Capsules containing anhydrous lactose exhibited the best dissolution stability followed by those containing hydrous and Fast-Flo® lactoses. Adverse effects on dissolution stability caused by hydrous and Fast-Flo® lactoses were probably due to the liberation of their surface moisture on storage at high temperatures causing agglomeration and caking of the capsule contents. In general, for the same fill weight, a higher degree of caking was observed in size no. 2 capsules compared to size no. 1, resulting in slower dissolution for the former. These trends were more pronounced in HCTZ capsules, and were present to a much lesser degree in sorivudine capsules. With aztreonam, whose aqueous solubility is greater than that of sorivudine or HCTZ, in spite of slight caking, no decrease in dissolution rate upon storage was observed. The decrease in dissolution rate of HCTZ capsules was too pronounced to be attributed to caking only. Neither the level of magnesium stearate used nor filling mechanisms of the capsule machines had any effect on dissolution stability.

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