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AN IN VITRO COMPARATIVE EVALUATION OF PANCREATIC ENZYME PREPARATIONS

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An in vitro evaluation of various commercial pancreatic enzyme preparations was undertaken to compare three main types of dosage forms, namely uncoated tablets and powder filled capsules, enteric coated tablets and encapsulated enteric coated microspheres. Each product was analyzed for its amylase, lipase and protease contents. All preparations were subjected to a pH-dependent dissolution method to evaluate the release pattern of enzymes. The measured enzyme contents of most preparations were proportionate to their declared values. Acid resistance and dissolution profiles varied among different and similar types of preparations. The enteric coated preparations showed more resistant to acid and displayed rapid rate of enzyme release once the pH threshold was attained. Of the three enteric coated microspheres tested, Creon® contained the highest lipase content per capsule, was most resistant to acid and afforded greater release of enzyme activity in pH-dependent dissolution tests.

INTRODUCTION

The pancreas is a vital organ having exocrine and endocrine functions. The exocrine secretion of the pancreas into the gut is composed of sodium bicarbonate and three main groups of digestive enzymes, namely, amylases, lipases and proteases. These enzymes break down carbohydrates, dietary fats and proteins and are, therefore, essential for normal digestion and absorption of

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nutrients. The pancreatic enzyme preparatiions are often used in the management of pancreatic exocrine insufficiency associated with conditions such as cystic fibrosis and chronic pancreatitis (1-5).

The pancreatic enzyme of most significance in exocrine insufficiency is lipase. Lipase deficiency usually results in failure to absorb adequate amounts of essential fatty acids causing steatorrhea (6) and deficiency of fat soluble vitamins.

The management of pancreatic exocrine insufficiency, through administration of pancreatic enzyme preparations, is known to be inadequate in three main areas. Firstly, an estimated 30,000 units of lipase activity are required with each meal to control steatorrhea (5,7). A large number of pancreatic enzyme dosage units is needed to achieve this and therefore, patient compliance may be very poor. Secondly, lipase is intolerant to gastric secretions of low pH values (4,7,8), therefore, non-enteric coated enzyme preparations are subject to loss of potency in the gut. Thirdly, enzyme preparations such as uncoated tablets may not attain adequate dispersion in the chyme to produce sufficient enzyme levels in the duodenum (9).

There are three types of pancreatic enzyme preparations currently available in the United States: simple pancreatic enzyme preparations in the form of uncoated tablets, powders and powder filled capsules; enteric coated tablets and enteric coated encapsulated microspheres.

These preparations have differing enzyme contents and ability to resist gastric secretions. Thus they may have differing availability of enzymes in the proximal small intestine. An effective enzyme preparation should contain high lipase activity, be able to resist gastric secretions and be adequately dispersed in the chyme. This study was undertaken to evaluate the in vitro properties of currently available preparations since in vitro enzyme activity has been shown to correlate with in vivo activity (9).

MATERIALS AND METHODS

The following products, representing each of the three types of enzyme preparations, were obtained from commercial sources and tested:

(1) Simple Pancreatic Enzyme Preparations

Viokase Tablets, Uncoated - (AH Robins) and Kuzyme-HP, Powder Filled Capsules - (Kremers-Urban)

(2) Enteric-Coated Tablets

Festal II Tablets - (Hoechst-Roussel)

(3) Enteric-Coated Microspheres

Cotazym-S Capsules - (Organon), Pancrease Capsules - (McNeil) and Creon Capsules - (Reid-Rowell)

Enzyme Activities

The activities of the enzymes amylase, lipase and protease were measured by the compendial method described in USP XXI (10) under the Pancrelipase Capsules monograph.

Acid Resistance

Six units of each product were agitated in simulated gastric fluid (0.1N HCl, pH 1.2) at 37°C for 2 hours in a disintegration apparatus. The contents were filtered and dried on a filter paper. The residue was tested for lipase activity according to USP XXI method of analysis.

Dissolution Characteristics

The dissolution profile of enteric coated product was generated using 900 mL dissolution medium prepared from monobasic potassium phosphate buffer adjusted to desired pH with 0.1N HCl. The experiments were performed with media having pH 4.0, pH 5.0, pH 5.3, pH 5.5, pH 5.6 and pH 6.0. USP apparatus I (baskets at 100 rpm) was used. The temperature of the dissolution medium was maintained at 37°C $\pm$ 0.5°C.

Each experiment was run for 2 hours. The samples were withdrawn at 15 minute intervals and immediately analyzed for lipase activity according to USP XXI method of analysis.

TABLE – 1

COMPARISON OF ENZYME ACTIVITIES

(The values shown are the mean of three measurements for each product.)

PRODUCT	EXPIRATION DATE	LIPASE		AMYLASE		PROTEASE	
		DECLARED ACTIVITY	MEASURED ACTIVITY	DECLARED ACTIVITY	MEASURED ACTIVITY	DECLARED ACTIVITY	MEASURED ACTIVITY
Viokase (86292)	08/87	8,000	8,088	30,000	33,166	30,000	27,565
Festal-II (720036)	12/87	6,000	6,699	30,000	40,487	20,000	25,679
Kuzyme-HP (11001L1033)	12/87	8,000	7,728	30,000	32,185	30,000	26,089
Cotazym-S (L651585388)	10/87	5,000	4,620	20,000	28,801	20,000	20,559
Pancrease (BA1379)	02/88	4,000	5,979	20,000	35,283	25,000	27,640
Creon (011186)	11/88	8,000	10,359	30,000	42,216	13,000	28,933

RESULTS AND DISCUSSION

The results in Table 1 show that there are notable differences among the types of preparations available and the preparations within similar categories. Although the measured enzyme activities for most products are equal to or greater than their declared values, Viokase tablets and Kuzyme-HP capsules showed lower measured values of protease activity. Kuzyme-HP capsules and Cotazym-S capsules showed slightly lower measured activity of lipase than their declared values. These findings may indicate that simple pancreatic enzyme preparations and those with less

TABLE-2

COMPARATIVE ACID RESISTANCE (0.1N HCl)

[Remaining Lipase Activity is Expressed as Residual and Percent of Measured Lipase Activity in USP Units]

PRODUCT	DECLARED LIPASE ACTIVITY	MEASURED LIPASE ACTIVITY	RESIDUAL* LIPASE ACTIVITY	% OF MEASURED LIPASE ACTIVITY
Viokase	8,000	8,088	0	0
Kuzyme	8,000	7,728	0	0
Festal-II	6,000	6,699	6,759	100%
Cotazym-S	5,000	4,620	2,499	54%
Pancrease	4,000	5,979	5,424	90.7%
Creon	8,000	10,359	10,348	99.9%

* The values shown are the mean of three measurements (n=3) for each product.

efficient enteric coating, may lack adequate stability over the periods of declared expiration dating.

Simple preparations, Viokase tablets and Kuzyme HP powder filled capsules showed no resistance to acid and their enzyme activities were completely destroyed in the gastric medium. The resistance to acid of the enteric coated preparations was confirmed, but the degree of resistance varied. Of the three enteric coated microsphere preparations, Creon showed more resistance to acid than Pancrease and Cotazym-S, as indicated by the results in Table 2 and Figure 1. As it is generally recognized that some form of acid protection is desirable for these preparations, it is important to note that the degree of acid resistance does vary to some extent among enteric coated microsphere preparations. This may directly affect the efficacy and dosage of the product for adequate patient treatment.

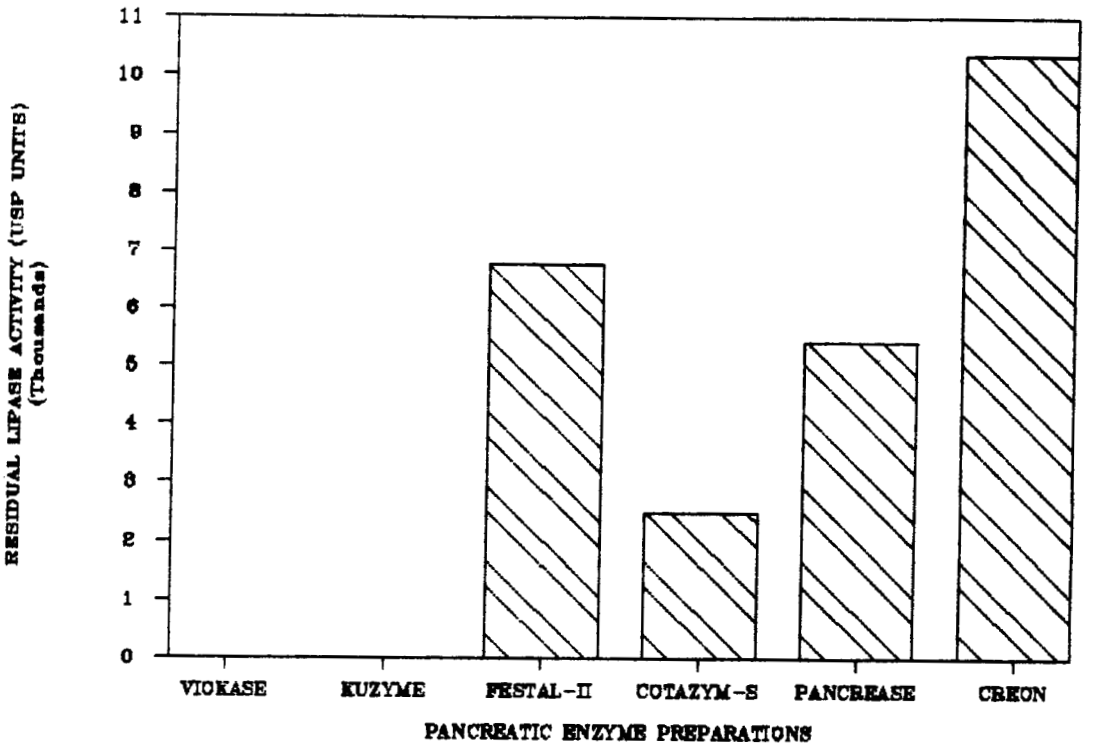

Figure 1: Comparative Acid Resistance
Residual Lipase Activity

The release rate of enzyme, and the pH level at which release begins, is shown to vary among different enteric coated products (Table 3). The rate of release for enteric coated tablets (Festal-II) evaluated in this study, was negligible in the pH ranges of 4.0-6.0. The rate of release for the enteric coated microsphere preparations varied, but was rapid in each case, once the pH-threshold was reached. Both the rate of release and the pH at which that release begins have been shown to be relevant factors in clinical management. Dutta et al (11) have shown that patients with pancreatic insufficiency, while fasting as well as

TABLE-3

DISSOLUTION CHARACTERISTICS OF ENTERIC COATED MICROSPHERES

PRODUCT	ACTUAL RELEASE OF LIPASE ACTIVITY* (USP UNITS)							
pH	Time (Minutes)							
Cotazym-S Capsules	15	30	45	60	75	90	105	120
5.5	0	0	0	0	0	0	0	0
5.6	0	0	0	0	0	0	2606 (56.4%)	3793 (82.1%)
6.0	0	0	2158 (46.7%)	4611 (99.8%)	4389 (95.0%)	4093 (88.6%)	3296 (70.9%)	N.D.
Pancrease Capsules								
5.5	0	0	0	694 (11.6%)	741 (12.4%)	1339 (22.4%)	921 (15.4%)	855 (14.3%)
5.6	0	0	0	759 (12.7%)	885 (14.8%)	771 (12.9%)	1782 (29.8%)	1291 (21.6%)
6.0	903 (15.1%)	1638 (27.4%)	2954 (49.4%)	4215 (70.5%)	4215 (70.5%)	4897 (81.9%)	5124 (85.7%)	4574 (76.5%)
Creon Capsules								
5.5	0	0	0	0	0	0	1668 (16.1%)	3698 (35.7%)
5.6	0	0	0	0	1191 (11.5%)	1854 (17.9%)	3460 (33.4%)	3584 (34.6%)
6.0	0	3854 (37.2%)	6744 (65.1%)	7707 (74.4%)	7759 (74.9%)	8805 (85.0%)	9406 (90.8%)	9882 (95.4%)

N.D. = None Detected

* Percent release is shown in parentheses.

post-prandially, have a lower than normal intraluminal pH. In view of these findings, it is important that enteric coated preparations release their enzyme activities at a pH that is not too low, such that denaturing of enzymes will occur, and not too high, such that enzymes are unlikely to be released within the small intestine. A threshold of release between pH 5.5 and pH 6.0 would seem to be ideal. Comparison of results in Table 3 indicate that all enteric coated microsphere preparations release their enzymes (as measured by lipase release) in the pH range of 5.5 - 6.0. Figure 2 shows a comparative dissolution profile of

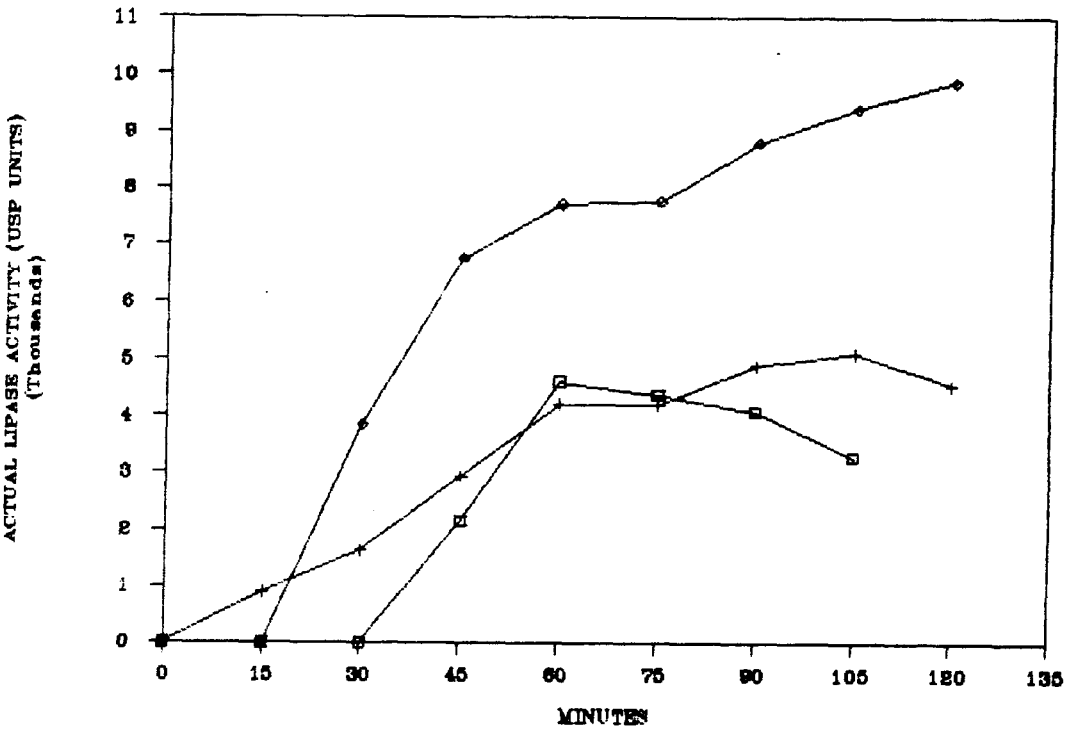

Figure 2: Dissolution Characteristics
Actual Lipase Activity at pH 6.0
□Cotazym-S + Pancrease ◇Creon

actual lipase activity for all three enteric coated microsphere preparations at pH 6.0, at which all products have rapid, though different, rates of release.

This study has highlighted the differences among the pancreatic enzyme preparations available in the United States. Since lipase is the principal enzyme for effective management of exocrine insufficiency, these preparations have declared lipase activity from 4000 USP units to 8000 USP units per dose, have varying resistance to acid and show varying degree of lipase availability in the pH range of 5.5 - 6.0. The preparation that

has high lipase content; shows resistance to gastric secretions; and has high lipase availability in the pH range of the duodenum (pH 5.5 - 6.0) would appear to be most desirable for the effective management of exocrine insufficiency (7-9). It is important for clinicians to take into account these in-vitro parameters when selecting a pancreatic enzyme product.

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