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Research Article

Creon 10k vs Pancrelip 10k: A Comparative *In vitro* Analysis of Lipase Activity of Pancreatin EC Pellets

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Abstract

Pancreatin enzyme replacement therapy, particularly in the form of Enteric coated (EC) Pancreatin Pellets/Capsules is essential in the treatment of exocrine pancreatic insufficiency (EPI). Several brands of Enteric-coated Pancreatin 10k enzyme in oral dosage forms are available on the market, and Creon 10k was chosen for the comparative study with Pancrelip 10k. The objective of this study was to evaluate and compare the enzymatic activity and in vitro dissolution profiles of the Enteric-coated Pancreatin pellets/capsules from Creon 10k (Abbott India Pvt Ltd) and Pancrelip 10k (Umang Global Pvt Ltd) across a range of phosphate buffers at pH levels of 1.2, 4.0, 4.5, 6.8, and 7.4. All these methods are performed as described in US Pharmacopeia (USP44-NF42). The marketed formulation Creon 10k (Abbott India Pvt Ltd) was compared with Pancrelip 10k, which is manufactured by Umang Global Pvt Ltd. The comparative analysis of enzymatic activity of Creon 10k and Pancrelip 10k focusing on Lipase, Amylase, and Protease shows that both products exhibit relatively comparable enzymatic activity. Furthermore, the dissolution characteristics for both Creon 10k and Pancrelip 10k also demonstrates a comparable release. Studies have shown that Pancrelip 10k, when compared to Creon 10k, is a possible substitute for treating EPI, as it shows a comparable enzymatic activity for Amylase, Lipase and Protease as well as in vitro dissolution for Lipase release.

Keywords: Exocrine Pancreatic Insufficiency; EC Pancreatin Pellets; Comparison Study; Enzymatic Activity; In Vitro Dissolution; Lipase Activity

Abbreviations

EC: Enteric Coated; USP: United State Pharmacopeia.

Introduction

Pancreatic Exocrine Insufficiency (PEI) is characterized by the pancreas's failure to release enzymes and bicarbonate necessary for effective digestion in the intestinal lumen, leading to maldigestion and Absorption of nutrients [1]. PEI symptoms range from weight loss, diarrhea, steatorrhea (fatty stools), abdominal pain, and nutritional deficiencies. The symptoms of PEI can have an enormous impact on a patient's quality of life and nutrition. Symptoms may include fatty stools, weight loss, malnutrition, abdominal pain and discomfort, diarrhea, nausea, vomiting, flatulence, and vitamin deficiencies (A, D, E, and K) [2,3]. PEI impacts 5-10% of the general population, with much greater incidence rates for specific populations, such as those with chronic pancreatitis (80-90%) and cystic fibrosis. The condition impacts more in men compared to women and typically develops between the ages of 35 and 40. In addition, diabetes mellitus is usually related with PEI in chronic pancreatitis patients, accounting for around 29% of cases [4-6].

Chronic pancreatitis, defined by long-term inflammation, is the major cause, accounting for around half of all instances. It is frequently caused by recurrent acute pancreatitis episodes or severe alcohol use, which gradually destroys pancreatic tissue [1,7]. Inherited disorders also play an important role, with cystic fibrosis being particularly remarkable since it causes thick mucus to obstruct pancreatic ducts, as well as other genetic illnesses such as hereditary pancreatitis and Shwachman-Diamond syndrome. Surgical techniques such as partial pancreatectomy and gastric bypass surgery can directly cause PEI by diminishing functional pancreatic tissue. PEI can also be caused by a variety of medical illnesses, including type 1 and long-term type 2 diabetes, pancreatic cancer, celiac disease, and inflammatory bowel disease [6-8].

The current therapy for PEI involves supplementing the pancreatic enzymes with extracts from the porcine pancreas. The pancreatin preparations that are now on the market are enteric-coated granules, which are microspheres coated with an acid-resistant layer that dissolves at higher pH values and remains intact at pH values below 4 [9,10]. Manufacturers often use a release threshold of 5.0–5.5. Once the threshold is met, the release rate should be as rapid as feasible. Pancreatin's enteric coating was established after it was discovered that only a limited quantity of enzymes passed through the stomach [9,11,12].

An appropriate pancreatic enzyme supplement should meet the following characteristics based on the physiological digestion process.

- Rapid enzyme release in the small intestine at roughly 6 pH, with a 2-hour effectiveness.
- Particles smaller than 1.7 mm can pass through the pylorus.
- Large specific surface area.
- Ingredients must conform to the label declaration.
- Excellent batch-to-batch uniformity [12,13].

In 2004, the US Food and Drug Administration (FDA) mandated that manufacturers of prescription pancreatic enzyme products (PEPs) file new drug applications (NDAs) in order to maintain regulatory monitoring and quality control. This requirement prompted the FDA to set minimum guidelines for enzyme quantity and stability, as well as to specify the studies needed to confirm effectiveness (FDA, 2004). Only PEPs approved by the FDA would be authorized to enter the market after the initial 2008 deadline, which was subsequently extended to 2010. The primary efficacy measure required was a comparison of the active PEP to a placebo, which resulted in a relatively low efficacy level [14,15].

The present study aims to compare Creon10k (Abbott India Pvt Ltd) and Pancrelip 10k (Umang Global Pvt Ltd) for lipase, protease, and amylase activity, as well as conduct *in vitro* release analysis of lipase in different pH range of 1.2 to 7.4.

Materials and Methods

The following pancreatin preparations were studied: Creon10k (Abbott India Pvt Ltd) and Pancrelip 10k (Umang Global Pvt Ltd). Both Creon 10k and Pancrelip 10k consist of an Enteric coated pellet. Pancrelip 10k is Enteric coated pancreatin pellets that are manufactured by Umang global Pvt Ltd.

Dissolution study

Dissolution release tests were performed according to the methods described in the USP. Standard preparations of both the Pancreatin pellets were place in 900ml buffer solution, at RPM 100 and 37±10 C and pH 1.2 to 7.4 in USP dissolution testing apparatus (Lab India DS8000 with Autosampler). Phosphate buffers were adjusted at pH 1.2, pH 4.0, pH 4.5, pH 6.8, and pH 7.4 using laboratory pH meter (DBK- Digital pH meter). Progress of dissolution was monitored for 120min by taking 2ml sample and measured Lipase activity. All measurements were carried out at least three times for each formulation at each pH and results were calculated.

Enzymatic activity

Lipase Activity

Lipase Activity was performed using an Automatic potentiometric titrator with A controlled water bath and an analytical method based on the USP Monograph. The amount of substrate hydrolysis was compared to a standard with a known activity. The enzymatic assay was performed by mixing olive oil substrate, buffer solution, bile salts solution, and 9ml in water a 50-mL jacketed glass vessel connected to a thermostatically controlled water bath at 37 ± 0.1°C. The mixture was stirred mechanically under a covered system.

Using a microburet, 0.1 N sodium hydroxide was added to adjust the pH to 9.20, monitored with a calomel-glass electrode. 0.1 N sodium hydroxide was added to maintain pH 9.0 for 5 minutes after adding 1.0 mL of the assay test dilution. The volume added was recorded at 1-minute intervals to assess enzymatic activity.

Protease Activity

Protease is the casein digestive enzyme which is determined by UV-Spectrometer. These enzymes are made by animals, Plants, fungi, and bacteria. Activity protease activity will be determined by Casein Substrate of pH 8.0, Buffer Solution of pH 7.5 ± 0.2 and Trichloroacetic acid solution Label test tubes in duplicate as S1, S2, S3 (standard series) and U (sample). Add the following to the tubes: 2.0 mL of buffer to S1, 1.5 mL to S2 and U, 1.0 mL to S3; 1.0 mL of Standard test dilution to S1, 1.5 mL to S2, 2.0 mL to S3; 1.5 mL of

Assay test dilution to U. Add 5.0 mL of Trichloroacetic acid solution to each tube and mix. Assign the tubes the corresponding designations S1B, S2B, S3B, and UB.

Prepare a blank by mixing 3.0 mL buffer and 5.0 mL Trichloroacetic acid in a separate tube (B). Place all tubes in a 40°C water bath and equilibrate. At time zero, add 2.0 mL of preheated Casein substrate to each tube and mix thoroughly. After 60 minutes, stop the reaction by adding 5.0 mL of Trichloroacetic acid to each tube, stir, and remove from the bath. Allow the tubes to stand for 10 minutes at room temperature, filter, and ensure the filtrates are clear. Measure the absorbance of each filtrate at 280 nm using the blank to set the instrument.

Calculation of potency

Subtract the absorbance of the blank tubes (S1B, S2B, S3B) from the standard tubes (S1, S2, S3) to obtain corrected values. Plot the corrected absorbance against the corresponding volumes of Standard test dilution. Using the corrected absorbance for tube U (U - UB), compare the protease activity of Pancreatin to the standard curve, accounting for dilution factors, and express the activity in USP units based on the label potency of USP Pancreatin Amylase and Protease RS.

Amylase Activity

Amylase activity in samples was the iodometric determination of reducing sugar formed in the hydrolysis of starch by amylase enzyme. To prepare a buffer solution, a fixed volume of dibasic sodium phosphate solution and monobasic potassium phosphate solution were mixed, and the final solution was adjusted to a pH of 6.8.

The substrate solution is prepared by soluble starch solution in hot water and cooled to room temperature. Another regent to be prepared in the Amylase Activity procedure is, 0.1 N iodine, 0.1 N NaOH, 2N H_2SO4 0.1 N Sodium thiosulphate, Sodium chloride Solution. Each flask was filled with 25 mL of substrate solution, 10 mL of pH 6.8 phosphate buffer, and 1 mL of sodium chloride solution. The flasks were labeled S, U, BS, and BU. After equilibration at 25±0.1◦C, 2 mL of 1 N HCl was added to BS and BU. Flasks S and BS were given 1 mL of standard preparation, while Flasks U and BU were given 1 mL of assay preparation. After mixing and a 10-minute incubation, 2 mL of 1 N HCl was added to S and U.

Subsequently, 10 mL of 0.1 N iodine VS and 45 mL of 0.1 N NaOH were added to all flasks, followed by dark incubation for 15 minutes at 15–25°C. 4 mL of 2 N H_2SO_4 was added, and the solutions were titrated with 0.1 N sodium thiosulphate VS until the blue colour vanished.

Result and Discussion

Result

Enzyme activity

To determine the enzymatic activity of both pancreatin EC pellets, a procedure is carried out as per USP. A comparison of the enzymatic activity of amylase, lipase, and protease in Pancrelip 10k and Creon 10k was conducted. The results of this comparison demonstrate that both pancreatin pellets exhibited nearly identical levels of enzymatic activity. Pancrelip 10k was found to have an amylase activity of 14251.6 EP Unit than Creon 10k (10498.1 EP. Unit). Similarly, Pancrelip 10k (14885.0 EP. Unit) demonstrated almost identical levels of lipase activity as compared to Creon 10k (15112.5 EP. Unit), which indicates that it has a greater capacity for fat digestion. When comparing the protease activity of Pancrelip 10k (855.12 EP Unit) to that of Creon 10k (635.6 EP Unit), Pancrelip 10k demonstrates a marginal difference in protease activity.

Enzyme release

The enzyme release rate and pH value at which release begins were found almost similar between the two products. The *in vitro* dissolution release profile for Lipase of Creon 10k and Pancrelip 10k was observed for 120min under different pH. At pH 1.2 the release of Lipase enzyme of Pancrelip 10k was found to be almost similar with Creon 10k, which shows that effective enzyme protection in highly acidic conditions. At pH 4.0-4.5, Pancrelip 10k shows a marginally higher lipase release compared to Creon 10k, showing better enzyme release compared to Creon10k. Pancrelip 10k dissolve completely (≥95%) at pH 6.8 and 7.4, while Creon 10k also shows a lipase release profile at (≥95%) at these pH levels.

This shows that Pancrelip 10k provides reliable and efficient enzymatic release, Comparable to Creon 10k, in supporting digestion

Pancreatin EC Pellets	Amylase	Lipase	Protease
Creon 10k	10498.1 EP UNIT	15112.5 EP UNIT	635.6 EP UNIT
Pancrelip 10k	14251.6 EP UNIT	14885.0 EP UNIT	855.12 EP UNIT

Table 1: Enzymatic activity of Pancreatin EC Pellets.

in the small intestine. At a pH of 7.4 during in vitro dissolution, both products demonstrate good lipase release activity. These findings suggest that both formulations provide consistent enzyme release in conditions relevant to gastrointestinal functions. The *in vitro* dissolution profile for Lipase for Pancreatin 10k is found to be stable and similar compared to Creon 10k.

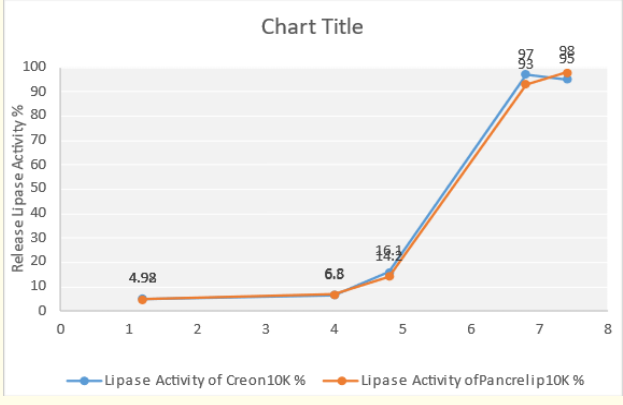

Figure 1: Comparative data for *in vitro* dissolution of Lipase release.

Sr.no	Dissolution pH	Dissolution time	Dissolution (Lipase)	
			Creon10k	Pancrelip10k
1	1.2	120min	4.98	4.92
2	4.0		6.5	6.8
3	4.5		16.1	14.2
4	6.8		97	93
5	7.4		95	98

Table 2: Comparison of *in vitro* dissolution profile at different pH of Lipase with Creon 10k.

In summary, Pancrelip 10k exhibited performance comparable to Creon 10k in enzymatic activity and dissolution profile provides an appropriate alternative for digestive enzyme supplementation.

Discussion

This study provides an *in vitro* comparison of Pancreatin EC Pellets of Pancrelip 10k (Umang Global Pvt Ltd), and Creon 10k (Abbott India Pvt Ltd) emphasizing their efficacy in facilitating diges-

tive enzyme release and activity across various physiological pH conditions. The output of pancreatic enzymes throughout the entire dissolution period was assessed by measuring the enzymatic activity in the solution. The comparative analysis of both the pancreatin EC pellets demonstrates their efficacy in enzyme protection and release across different physiological pH levels.

Enzymatic activity

The data indicated that the Lipase activity of Pancrelip 10k (14885.0 EP Unit) is nearly equivalent to that of Creon 10k (15112.5 EP Unit) demonstrating that both products provide comparable level of lipase. Regarding Amylase activity both the EC pellets exhibit good activity with marginal difference with Pancrelip 10k at 14251.6 EP Unit and Creon 10k at 10498.1 EP Unit. Both formulations show adequate amylase level, supporting their effectiveness in promoting overall digestive function. For the Protease activity, Creon 10k shows an activity of 635.6 EP Unit, while Pancrelip 10k shows an activity of 855.12 EP Unit, reflecting a modest difference in their protease activities. The Pancrelip 10k demonstrated comparable enzymatic activities for lipase, amylase, and protease when compared to Creon 10k.

Enzyme release

The lipase release dissolution studies were conducted at various physiological pH levels ranging from 1.2 to 7.4. Both formulations exhibited minimal lipase release at pH 1.2, indicating effective protection under acidic conditions. At pH 4.5, both pancreatin EC pellets exhibit comparable Lipase release, confirming that it releases in the small intestine. At the optimal duodenal pH of 6.8-7.4, Pancrelip 10k and Creon 10k demonstrate a complete release of the lipase enzyme. The Pancreatin EC pellets (Pancrelip 10k and Creon 10k) demonstrate significant efficacy in enzyme release and stability across various pH levels pertinent to gastrointestinal conditions. The data collected confirms that Pancrealip 10k (Umang Global Pvt Ltd) is a reliable alternative for managing exocrine pancreatic insufficiency when compared to the marketed Creon 10k (Abbott India Pvt Ltd).

The comparative study of two distinct pancreatin EC pellets, Pancrelip10k and Creon 10k, reveals that both Pancreatin EC pellets exhibit nearly similar enzymatic activity and in vitro dissolution for lipase release. In comparison to Creon 10k, which is a formulation that is currently on the market for enzyme replacement therapy, it has been demonstrated that Pancrelip 10k, which is manufactured by Umang global Pvt. Ltd., is a dependable and efficient alternative.

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