Pancreatin ECSM Process
Possibilities to obtain a higher Protease / Lipase ratio

Grinding

Autolysis

Sieving

Precipitation

Wash

Filtration

Drying

Milling

pH Adjustment
Inactivation of Lipase
pH 5.6 for 30 min

or

Lipase / Protease
Ratio 1 : 3

Pancreatin ECSM

Lipase 80,000 USP/g

Protease 250,000 USP/g

Abstract: A method for preparing a high concentration protease formulation comprising the following steps: a) grinding a frozen pancreas gland; b) autolysis of the mixture of pancreas gland obtained in a); c) separating the insoluble fibres in order to obtain a filtrate; d) mixing the filtrate with isopropanol in order to obtain a precipitate; e) purifying the precipitate by washing it with isopropanol and f) isolating the precipitate of step e) by filtration. The process allows the preparation of a formulation having a content of protease having at least 100,000 USP U/g of residual protease activity. This formulation may be used for the treatment of pancreatic disorders.

Title: HIGH PROTEASE CONTENT PANCREATIN
Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
HIGH PROTEASE CONTENT FORMULATION

FIELD OF THE INVENTION

The invention concerns a new protease formulation useful in the treatment of pancreatic disorders.

BACKGROUND OF THE INVENTION

Chronic pancreatitis is characterized by episodes of severe epigastric and back pain, which often requires regular doses of narcotics. During these episodes, the pain lasts for hours and occurs every day. Moreover, it recurs periodically for years. Pain is usually epigastric, sometime also felt in the left upper quadrant with radiation to the back between T12 and L2 or to the left shoulder (Pitchumoni 1998). Many patients are chronically debilitated because of the pain. It can be quite frustrating to take care of these patients because they return again and again to the emergency room with severe pain, some of them intoxicated, others denying any ongoing alcoholism, others addicted to narcotics. Excessive alcohol consumption causes about 70% of all cases of chronic pancreatitis while 10-40% is idiopathic (Ectors et al 1997).

The only prospective study on the incidence and prevalence of chronic pancreatitis was performed in Copenhagen in 1978 and 1979. It showed an incidence of 8.2 new cases/100,000 inhabitants per year and a prevalence of 26.4 cases/100,000 inhabitants. Alcohol consumption is considered to be a major factor in the development of chronic pancreatitis. Japan has traditionally had a very low alcohol intake, which may well explain the low incidence (rate) of chronic pancreatitis. Environmental or hereditary factors may influence the susceptibility to alcohol-induced pancreatitis. Alternatively, this may be related to regional differences in diagnostic criteria for chronic pancreatitis. Thus, the figures for frequency
of chronic pancreatitis differ markedly from one center to another. Most likely, this does not reflect a real difference in frequency but point strongly to regional differences in patient selection and diagnostic criteria. Valid and comparable figures for incidence and prevalence of chronic pancreatitis are pending for careful prospective epidemiologic studies based on uniformly accepted diagnostic criteria.

In chronic pancreatitis, the gland usually undergoes extensive atrophy with fibrosis and inflammatory cell infiltration. Somewhere along the evolution of the atrophy of the gland, there is an increase in protein secretion associated with protein precipitation in the smaller ductules, the formation of protein plugs, and the subsequent blockage of the smaller ductules. As the disease progresses, blockage of the larger ductules and central ducts takes place and stone formation and calcification can occur. Many of these changes probably involve the production of pain, as we know it in the syndrome of chronic pancreatitis.

The treatment of chronic pancreatitis is usually influenced by the presence of large or small duct disease. Patients with large duct disease should be referred for an attempt at endoscopic or surgical drainage. On the other hand, small duct disease is often characterized by minimal changes on X-rays, ultrasounds, and CT-scans (Hayakawa 1992, Walsh 1992). The exocrine function may be intact or only partially diminished (Hayakawa 1992). Since there is no effective way to treat these patients, one should proceed from the least invasive to the most invasive approach.

The American Gastroenterological Association (AGA 1998) has published guidelines for the treatment of chronic pancreatitis. The first step is to avoid the use of any type of irritant for the pancreas, such as alcohol, and to prescribe a low-fat diet and non-narcotic analgesics, such as acetaminophen. Secondly, when the patient suffers from refractory
pains, the use of high dose pancreatic enzymes plus acid suppression is advocated.

These new guidelines confirm the increasing evidences that chronic pancreatitis can be managed by the use of large doses of pancreatic enzymes, especially to relieve the pain associated with this condition. The mechanism seems to involve a reduction in the secretion of pancreatic enzymes mediated by the presence of ingested enzymes in the duodenum, a process called negative feedback inhibition. The ability of ingested enzymes to initiate changes in pancreatic exocrine secretion, and therefore, possibly modify pain, appears to involve a peptide in the mucosa of the small intestine, called CCK-releasing peptide (CCK-RP), that releases CCK into the circulation.

Trypsin is capable of denaturing this peptide and thereby prevents the release of CCK.

In the fasting state, basal pancreatic secretion supplies just enough enzyme to denature CCK-RP and thus limits the steady state of release of CCK to small amounts.

In chronic pancreatitis, trypsin out-put is diminished. As a result, CCK-RP is not denatured and is available to release excessive amounts of CCK. The pancreas remains under strong stimulation from this hormone and this mechanism is thought to cause pancreatic pain. However, the mechanism remains to be elucidated. Oral enzyme therapy provides increased trypsin within the duodenum and trypsin denatures CCK-RP, thereby reducing CCK release. The result is a decrease in pancreatic stimulation and less pain. Oral enzyme also reduces CCK release in response to food.
There are several published studies on the use of pancreatic enzymes for the relief of pain associated with chronic pancreatitis and one meta-analysis. Most of these studies were carried out and suggested that non-coated enzymes preparation should be useful in the treatment of painful chronic pancreatitis.

Moreover, the active component of these preparations is the protease fraction, more specifically trypsin and chymotrypsin, which can denature the CCK releasing peptide. It is then logical to think that enzymes preparations that would contain higher concentration of proteases would be ideal to treat chronic, painful pancreatitis.

Thus, there is a need to develop a new process for preparing a non-enteric coated formulation having a high content of protease.

SUMMARY OF THE INVENTION

An object of the present invention is to provide a new process for preparing a formulation having a high content of protease.

Accordingly, the process of the present invention comprises the following steps:

a) a grinding step which comprises grinding a predetermined amount of a frozen pancreas gland;

b) an autolysis step which comprises mixing the pancreas gland obtained in a) with water, isopropanol, sodium bicarbonate and trypsin, thereby obtaining a first mixture;
c) a separation step which comprises pumping the first mixture into a screening kettle thereby separating the insoluble fibers thereby obtaining a filtrate;

d) a precipitation step which comprises mixing the filtrate with isopropanol thereby forming a second mixture, and allowing the second mixture to settle thereby obtaining a precipitate;

e) a purification step which comprises washing the precipitate with isopropanol; and

f) an isolation step which comprises isolating the precipitate obtained in e) by filtration.

The process being characterized by adjusting the pH to at least 4 after the autolysis step b) or the separation step c).

Another object of the present invention is to provide a non-enteric coated formulation having a high content of protease. Accordingly, the formulation comprises protease having at least 100,000 USP U/g of residual protease activity and a pharmaceutically acceptable carrier.

A further object of the present invention is the use of the non-enteric formation of the instant invention for the treatment of pancreatic disorders.

Advantageously, the formulation of the invention provides a higher ratio of protease/lipase and higher protease residual activity.

Furthermore, the process of the present invention allows production of such formulation thanks to the lipase inactivation steps resulting in the pH adjustment.
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is flowchart illustrating a process for manufacturing a high protease content formulation according to a preferred embodiment of the present invention.

Figure 2 is a table summarizing the pH values that may be used in the process of Figure 1.

DETAILED DESCRIPTION OF THE INVENTION

The pancreatin formulation according to the present invention may be prepared by a process comprising:

a) a grinding step which comprises grinding a predetermined amount of a frozen pancreas gland;

b) an autolysis step which comprises mixing the pancreas gland obtained in a) with water, isopropanol, sodium bicarbonate and trypsin, thereby obtaining a first mixture;

c) a separation step which comprises pumping the first mixture into a screening kettle thereby separating the insoluble fibers thereby obtaining a filtrate;

d) a precipitation step which comprises mixing the filtrate with isopropanol thereby forming a second mixture, and allowing the second mixture to settle thereby obtaining a precipitate;

e) a purification step which comprises washing the precipitate with isopropanol; and
f) an isolation step which comprises isolating the precipitate obtained in e) by filtration.

It should be noted that the process of the instant invention is characterized by a pH adjustment after step b) or c). It has been discovered that the pH adjustment allows inactivation of lipase.

Thus according to the present invention, the pH must be at least 4. In a preferred embodiment, the pH may range between 4 and 7. Such conditions give rise to a composition having a residual lipase activity which varies from 20,000 to 100,000 USP U/g; a residual amylase activity which is greater than 75,000 USP U/g; and a residual protease activity which varies from 100,000 to 300,000 USP U/g.

Thus, the present invention is also concerned with a pancreatin, pancrealipase or pharmaceutical formulation comprising protease which has a residual protease activity of at least 100,000 USP U/g. Preferably, such formulation has a residual protease activity ranging from about 150,000 USP U/g to 300,000 USP U/g.

The formulation according to the present invention may also contain amylase and lipase. The feasible ratio of protease/lipase is around 3 to 15 in the final product. The lipase will then be between 25,000 to 35,000 USP U/g. The residual lipase activity is about 2,000 USP U/g for pancreatin and for pancrealipase, 24,000 USP U/g.

According to another preferred embodiment, the lipase inactivation may be carried out for up to 60 minutes, and preferably for 30 minutes.

The pancreatin or pharmaceutical formulation according to the present invention may be used for the treatment of digestive deficiencies and
pancreatic disorders such as chronic pancreatitis and non-ulcerous dyspepsia.

Dyspepsia is a common clinical symptom, associated with a potentially profound impact on health care resource utilization and patient quality of life. There are many possible causes for dyspepsia including acid-related disease, motility disturbances, abnormal visceral sensitivity, and neoplastic disorders of the esophagus, stomach, and duodenum. However, the majority of patients with dyspepsia have no identifiable upper gastrointestinal pathology after standard test (1-8). Furthermore, whether or not structural or functional abnormalities are documented, symptoms persist in >50% patients despite treatment with potent acid suppressants, prokinetics, drugs affecting visceral pain thresholds, and/or antibiotics against *H. pylori*. (9-10) Biliary tract disease may account for symptoms in some patients with dyspepsia, but it is well known that cholecystectomy and/or biliary sphincterotomy often fail to relieve symptoms in patients without classic biliary colic or objective evidence of biliary obstruction.

The role of pancreatic disease in dyspepsia is unclear. A number of studies have documented abnormal pancreatic function in patients with dyspepsia. Lundh meal tests were abnormal in 20/72 (28%) uninvestigated dyspeptics studied by Schulze et al. (11) and in 159/460 (35%) studied by Anderson et al. (12) Smith et al. also found significantly reduced mean tryptic activity after a Lundh test meal in 6/27 (27%) patients with endoscopically confirmed non ulcer dyspepsia (13) and Skude et al. found abnormal serum pancreatic isoamylase levels in 7/36 (19%) consecutive males seeking primary care for dyspepsia (14).

Mild pancreatic disease is difficult to diagnose since duodenal intubation tests may be impractical to perform outside of referral centers and because endoscopic retrograde pancreatography may be considered too invasive. Some authors have suggested that mild pancreatic disease may present as
dyspepsia (15) and abnormal pancreatic function has been found in up to 35% of patients with dyspepsia (11-14). There are no published data on pancreatographic finding in patients classified prospectively as suffering from dyspepsia.

5 EXAMPLES

1.0) Manufacturing process for pancreatin formula for 235 to 370 kg*

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<tr>
<th>Material</th>
<th>Mass</th>
<th>Addition</th>
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<tr>
<td>Pancreas glands</td>
<td>2,000-3,000 kg</td>
<td>at step 1 Mincing: frozen material is minced</td>
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<tr>
<td>Sodium bicarbonate</td>
<td>25-40 kg</td>
<td>at step 2 Autolysis: as buffer substance</td>
</tr>
<tr>
<td>Simethicone emulsion</td>
<td>0-12 kg</td>
<td>at step 2 Autolysis: in case of foaming</td>
</tr>
<tr>
<td>Pancreatin for starting</td>
<td>40-80 Mio FIP-Units</td>
<td>at step 2 Autolysis: to activate Trypsin for autolysis</td>
</tr>
<tr>
<td>Isopropanol 88% (v/v)</td>
<td>250-350 L</td>
<td>at step 2 Autolysis (start) to reduce microbiological contamination</td>
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<td></td>
<td>1,500-1,700 L</td>
<td>at step 2 Autolysis (end) to dissolve fat</td>
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<td></td>
<td>6,500-7,500 L</td>
<td>at step 4 Precipitation to precipitate pancreatin</td>
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<td>4,000-6,000 L</td>
<td>at step 5 Purification to wash pancreatin and to reduce</td>
</tr>
<tr>
<td>Drinking water</td>
<td>600-750 L</td>
<td>at step 2 Autolysis: to dissolve buffer and pancreas glands</td>
</tr>
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* Batch size is 470 to 740 Kg after addition of two sub-batches of this size to step 8 shredding.

1.1) Detailed description of the process

Step 1: Mincing

2,500 kg (2,000 to 3,000 kg) of deep frozen Porcine Pancreas Glands are minced with a meat grinder.

Step 2: Autolysis

The minced material is pumped with 500 L of drinking water to a stirred mixture of 300 L (250 to 350 L) of Isopropanol 88%, 150 L (100 to 250 L) of drinking water and 32.5 kg (25 to 40 kg) of Sodium bicarbonate in a autolysis kettle. Then 40 to 80 million FIP trypsin units and 0 to 1.2 kg of Simethicone emulsion (if foaming occurs) are added.

This mixture is heated in stages to a maximum of 25°C, while stirring. Samples are taken to determine the end of autolysis. To stop the autolysis (after 12 to 96 h) 1,600 L (1,500 to 1,700 L) of Isopropanol 88% (v/v) is added, while stirring.

Step 3: Separation
The mixture is pumped into the screening kettle and insoluble fibers are separated by sieving.

Step 4: Precipitation

The filtrate is charged to 7,000 L (6,500 to 7,500 L) of isopropanol 88% (v/v) in the precipitation kettle and stirred for a minimum of 30 minutes. The precipitate is allowed to settle during a minimum of 30 minutes and the upper layer of solvent is removed.

This solvent is distilled to recycle isopropanol.

Step 5: Purification

The remaining precipitate is stirred with 4,000 to 6,000 L of isopropanol 88% (v/v) at a maximum temperature of 25°C for a minimum of 60 minutes.

Step 6: Isolation

The purified product is isolated by filtration on a filter press.

Step 7: Cold storage

In a cold storage room the product is stored in closed containers at a max temperature of 0°C.

Step 8: Shredding

The wet filter cake of two autolysis sub-batches, produced as described above, are combined and shredded in a screw-type extruder.

Step 9: Drying
The sized product is dried in a vacuum double-cone dryer. The drying of pancreatin is performed in vacuum at temperatures between 0 and 85°C over a period of minimum 16 h, at least 1 h with a minimum temperature of 60°C.

5 Step 10: Milling

The dried product is milled in a cylinder mill and sieved.

Step 11: Sifting

To remove residual fibers the material is sieved on a 0.6 mm sifting system.

Step 12: Homogenizing

10 Before taking samples for analysis the material is collected in an aluminum container and homogenized with the container mixer.

Step 13: Quarantine Storage

The drug substance is stored in aluminum containers until released by Quality Control.

15 Optional: Standardizing

The digestive power of the drug substance can be standardized to customer requirements by blending material in a container mixer with a higher digestive power with material of a lower digestive power.

Step 14: Packaging and Labelling
Pancreatin / Pancrealipase is weighed into PE bags, sealed up tightly together with a desiccant in an Al-laminated foil and packaged in a corrugated cardboard box.
CLAIMS

1. A process for preparing a high concentration protease pancreatic formulation, the process comprising:

5  
a) grinding a predetermined amount of a frozen pancreas gland;

b) mixing the pancreas gland obtained in a) with water, isopropanol, sodium bicarbonate and trypsin, thereby obtaining a first mixture;

10  
c) pumping the first mixture into a screening kettle and separating the insoluble fibers thereby obtaining a filtrate;

d) mixing the filtrate with isopropanol thereby forming a second mixture, and allowing the second mixture to settle thereby obtaining a precipitate;

15  
e) washing the precipitate with isopropanol; and

 g) isolating the precipitate obtained in f) by filtration,

the process being characterized in that after step b) or c), the pH of the reaction mixture is adjusted to at least 4.

2. The process of claim 1, characterized in that the pH varies between 4 and 7.

20  

3. The process of claim 2, wherein the pH varies between 5 and 6.

4. The process of claim 1, wherein the pH is maintained for up to 60 minutes.
5. The process of claim 4, wherein the pH is maintained at 5 for 30 minutes.

6. The process of claim 4, wherein the pH is maintained at 6 for 30 minutes.

7. A pancreatin formulation obtained from the process of claim 1, characterized in that it comprises a residual protease activity of at least 100,000 USP U/g.

8. The pancreatin formulation according to claim 7, wherein the protease has a residual activity ranging from about 150,000 USP U/g to 300,000 USP U/g.

9. The pancreatin formulation according to claim 7 or 8, having a protease/lipase ratio ranging from about 3 to 10.

10. A pharmaceutical composition comprising protease having at least 100,000 USP U/g of residual protease activity and a pharmaceutically acceptable carrier.

11. The pharmaceutical composition of claim 10, characterized in that the residual protease activity ranges from 150,000 to 300,000 USP U/g.

12. The pharmaceutical composition of claim 10, characterized in that it has a protease/lipase ratio ranging from about 3 to 10.

13. Use of a pancreatin formulation as defined in any one of claims 7 to 12, for the treatment of digestive deficiencies and pancreatic disorders.

14. Use of a pancreatin formulation as defined in any one of claims 7 to 12, for the treatment of non-ulcerous dyspepsia or chronic pancreatitis.
15. Use of a pharmaceutical composition as defined in any one of claims 7 to 12, for the treatment of digestive deficiencies and pancreatic disorders.

16. Use of a pharmaceutical composition as defined in any one of claims 7 to 12, for the treatment of non-ulcerous dyspepsia or chronic pancreatitis.
Pancreatin ECSM Process

Possibilities to obtain a higher Protease/Lipase ratio

Grinding
Autoysis
Sieving
Precipitation
Wash
Filtration
Drying
Milling

FIG. 1

Lipase
Amylase
Protease

Pancratrin ECSM

30,000 USP/g
200,000 USP/g
250,000 USP/g

pH Adjustment
Inactivation of Lipase
pH 5-6 for 30 min

or

Lipase/Protease Ratio 1:3
pH Adjustment
Possibilities to obtain a higher Protease / Lipase ratio

- Minor process change
- Fast availability of (test) material in large quantities
- Higher ratio but similar protease concentration

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<td>268000</td>
<td>190000</td>
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<td>4</td>
<td>&lt; 1000</td>
<td>&lt; 10000</td>
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USP U/g
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

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According to International Patent Classification (IPC) or to both national classification and IPC.

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

**Electronic data base consulted during the international search (name of data base and, where practical, search terms used)**

EPO–Internal, MEDLINE, BIOSIS, EMBASE, WPI Data, PAJ

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>US 4 623 624 A (SCHULTZE HANS) 18 November 1986 (1986-11-18) column 7 - column 8</td>
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<td>DE 42 03 315 A (KALI CHEMIE PHARMA GMBH) 20 August 1992 (1992-08-20) page 3, line 55 - line 60 page 5, line 7 - line 9; claim 1</td>
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

"Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"S" document member of the same patent family

Date of the actual completion of the international search

6 July 2004

Date of mailing of the international search report

30/07/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5816 Patentlaan 2 NL – 2280 HV Rijswijk

Tel. (+31-70) 340-2040, Tx 31 651 apo nl, Fax: (+31-70) 340-2015

Authorized officer

Ury, A
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<td>SAYARI ADEL ET AL: &quot;Characterization of turkey pancreatic lipase&quot; BIOCHIMIE (PARIS), vol. 82, no. 2, February 2000 (2000-02), pages 153-159, XP002286876 ISSN: 0300-9084 paragraph 3.3.2.</td>
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<td>O'KEEFE S J ET AL: &quot;The exacerbation of pancreatic endocrine dysfunction by potent pancreatic exocrine supplements in patients with chronic pancreatitis.&quot; JOURNAL OF CLINICAL GASTROENTEROLOGY. UNITED STATES APR 2001, vol. 32, no. 4, April 2001 (2001-04), pages 319-323, XP009033039 ISSN: 0192-0790 Whole document, in particular page 320, left hand column, last full paragraph.</td>
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