

Description

The present invention relates to pharmaceutical compositions adapted for intravaginal administration comprising a biologically active polypeptide, namely calcitonin, an absorption promoter, optionally an animal and/or vegetable protein and a nontoxic pharmaceutically acceptable carrier or diluent therefor, in a formulation suitable for intravaginal administration.

Polypeptide hormones such as insulin and calcitonin are water-soluble, relatively small molecular weight compounds which are readily decomposed by gastric juices and by intestinal proteinases such as pepsin and trypsin. As a result, when these polypeptides are orally administered, they are barely absorbed and produce no effective pharmacological action. In order to obtain the desired biological activity, the polypeptides are at present usually dispensed in injectable dosage forms. However, the injectable route is inconvenient and painful to the patient, particularly when administration must occur on a regular and frequent basis; consequently, efforts have focused recently on alternative methods for administration of the polypeptide hormones.

US 4,659,696 and US 4,670,419 describe pharmaceutical compositions for nasal, vaginal or rectal administration comprising a hydrophilic therapeutic agent poorly absorbable in the gastrointestinal tract, together with cyclodextrin. Among the therapeutic agents present in the compositions are polypeptides, e.g., insulin, LH-RH analogs, oxytocin and TRH. The cyclodextrin is preferably alpha-cyclodextrin. Various pharmaceutical additives may also be present in the formulations.

US 4,609,640 describes a therapeutic composition for rectal or vaginal administration, said to have excellent absorption properties, which contains a water-soluble therapeutic agent and a water-soluble chelating agent of a particular type. The therapeutic agent may be a peptide hormone such as insulin, somatostatin, calcitonin, etc. Water-soluble base polymers having no chelating activity, such as gelatin, casein, albumin and globulin, may be employed if used in conjunction with a chelating agent of low molecular weight, i.e., one of a number of polycarboxylic acids or the like. Other conventional ingredients for such dosage forms, e.g., a surfactant, may also be present.

EP 0193372 discloses a nasal powder comprising a physiologically active polypeptide, a quaternary ammonium compound and a lower alkyl ether of cellulose, purportedly having excellent preservability and chemical stability. Preferred powders comprise insulin or calcitonin, benzalkonium chloride and hydroxypropyl cellulose. Various conventional additives may also be present, e.g., lubricants, waxes, binders, diluents, coloring agents, odor improvers, anti-oxidants, bulk fillers, isotonic agents and surfactants.

EP 0183527 describes an absorbable nasal calcitonin medicament comprising calcitonin and at least one absorption enhancer selected from benzyl acid and salts thereof, capric acid and salts thereof, polyethylene glycol 400, pyridoxal and salts thereof, malic acid and salts thereof and pyrophosphoric acid and salts thereof. Other ingredients conventional for nasal formulations may be added. Use of one of the specific absorption enhancers is said to improve efficiency of absorption across the membrane of the nasal cavity. The patent publication indicates that earlier attempts to improve the nasal absorbability of a large polypeptide such as calcitonin utilized surface active agents as absorption enhancers. The earlier work employed both amphoteric and cationic surface active agents, especially the nonionic surface active agent polyoxyethylene lauryl ether; unfortunately, the preferred ether type surface active agent is said to promote drug absorption by destroying the nasal membrane.

GB 2127689A, relates to pharmaceutical compositions for nasal administration comprising calcitonin, benzalkonium chloride and/or a surfactant suitable for nasal application, in a liquid diluent or carrier suitable for application to the nasal mucosa. When the compositions comprise a surfactant, it is preferably a non-ionic one, most preferably a polyoxyalkylene higher alcohol ether. Improved bioavailability and good stability are said to be achieved by these calcitonin inhalation compositions.

US 3,917,825 discloses pharmaceutical preparations for rectal or vaginal administration of LH-RH or its analogs. The nona- or decapeptide is dispersed homogeneously in an oleaginous base (e.g., oil, wax or fatty acid triglyceride) preferably containing a non-ionic surfactant such as a polyoxyethylene higher alcohol ether. Administration of nonapeptides and decapeptides by a variety of routes, including intravaginal, is described in numerous patents and publications, e.g., US 4,083,967; US 3,888,838; US 4,234,571; US 4,010,125; US 4,018,726; and Saito et al, *Fertility and Sterility*, Vol. 28, No. 3, March 1977, 240-245.

Okada et al, *J. Pharm. Sci.*, Vol. 72, No. 1, January 1983, 75-78, describe vaginal absorption of a potent LH-RH analog (leuprolide), of LH-RH itself and of insulin. Absorption enhancement is provided by use of organic acids. The enhancing potency appears to correlate with the chelating ability of the organic acids. See also Okada, *J. Takeda Res. Lab.* 42 (1/2), 150 (1983).

Touitou et al, *J. Pharm. Pharmac.*, 1978, 30, 663, have developed a hydrophilic vehicle for rectal or vaginal administration of insulin, heparin, phenol red and gentamicin comprising the non-ionic surfactant,

Cetomacrogol 1000 (polyethylene glycol 1000 monocetyl ether) in combination with polyethylene glycols. JERUSALEM UNIVERSITY's IL 54041 directed to pharmaceutical compositions containing a non-ionic surfactant for enteral or vaginal administration of peptide hormone or heparin appears to be related to the same work.

5 Morimoto et al, J. Pharm. Pharmacol. 1985, 37, 759-760, have reported on the effect of non-ionic surfactants, polyoxyethylene sorbitan monooleate and polyoxyethane 9 lauryl ether, on the enhancement of polyacrylic acid gel base in the rectal absorption of a semisynthetic analog of eel calcitonin. The polyacrylic acid gel base had been found earlier to improve absorption of insulin by rectal, vaginal and nasal routes and that of calcitonin by rectal and nasal routes. Earlier reports also indicated that the absorption of poorly
10 absorbable drugs can be enhanced by co-administering the drug with enamine, carboxylic acid and surface-active agents.

JP 56122309 also JP Patent Bulletin (B2) SHO62-36498, describes calcitonin compositions for rectal administration in which calcitonin and a surfactant (cholic acid, saponin, phospholipid, polyoxyethylene alkyl ether, glycerin fatty acid ester, sorbitan fatty acid ester or the like) are homogeneously dispersed in a
15 suppository base.

Muranishi, S., "Absorption Barriers and Absorption Promoters in the Intestine", in Topics in Pharmaceutical Sciences 1987, describes the absorption of drugs through the intestine using a variety of compositions which aid in the absorption of the drug through the cells that line the mucosal surface. A mixed micelle system was disclosed which involved the use of an unsaturated aliphatic carboxylic acid with a nonionic
20 surfactant.

DE 37 23 781 discloses a pharmaceutical composition comprising G-CSF and sodium lauryl sulfate or sorbitan fatty acid ester. Said preparation is suitable for intravaginal administration. FR 2 456 522 describes a vaginal suppository comprising insulin. Similar compositions containing certain biologically active polypeptides are described in Chemical Abstracts, Vol. 96 (10), 1982, Abstr. No. 74626n), EP 0 231 816 and FR 2
25 202 678.

It is the object of the present invention to provide dosage forms of calcitonin which are storage stable, which are non-irritating to and readily absorbed by the target mucosa, and which are stable at the site of administration.

The need to produce stable pharmaceutical dosage forms containing biologically active polypeptides is
30 an important problem in manufacturing these drugs. Moreover, in the search for alternatives to administration by injection, the art as a whole has not taught how to avoid enzymatic decomposition of the polypeptides both at their administration sites and during the absorption process.

The present inventors have now developed a proper non-injectable pharmaceutical dosage form containing a biologically active polypeptide namely calcitonin, aimed at alleviating the pain of injection and
35 minimizing decomposition of the polypeptide.

According to the present invention the above object is achieved by a pharmaceutical composition adapted for intravaginal administration, which is characterized by containing calcitonin, an absorption promoter namely an an-ionic and/or nonionic surfactant or a combination of a nonionic surfactant and a medium chain aliphatic carboxylic acid or its salt and a non-toxic pharmaceutically acceptable carrier or
40 diluent therefor, in a formulation suitable for intravaginal administration.

According to a preferred embodiment of the present invention said pharmaceutical composition is characterized by the additional content of an animal and/or vegetable protein.

FIG. 1 is a plot showing the absorption enhancing effects of increasing concentrations of sodium lauryl sulfate (SDS) on porcine calcitonin administered intravaginally to young, oophorectomized female rats;

45 FIG. 2 is a dose response curve of porcine calcitonin absorption from the vaginal mucosa of young, oophorectomized female rats;

FIG. 3 is a graph showing that serum calcitonin increased proportionally to the increase of the dosage of calcitonin administered intravaginally, and serum calcium decreased correspondingly with increase of calcitonin dosage, following administration of human calcitonin to young, oophorectomized female rats;

50 FIG. 4 is a bar graph illustrating that, in administration of porcine calcitonin (P-CT) to aged oophorectomized rat with 1% sodium lauryl sulphate (SDS) showed a similar ratio of decreased serum calcium against control to that of an intramuscular injection group;

FIG. 5 is a bar graph depicting the effect of human serum albumin (HSA) on the stability of porcine calcitonin (P-CT) at selected pH levels following intramuscular administration to young male rats;

55 FIG. 6 is a graph showing the serum calcium profile following administration of a suppository and a film comprising porcine calcitonin (P-CT), sodium lauryl sulfate (SDS), bovine serum albumin (BSA) and a nontoxic pharmaceutically acceptable carrier or diluent.

FIG. 7 is a graph showing that the serum calcium decreased correspondingly with the increase of serum human calcitonin (H-CT) following the vaginal liquid administration of H-CT, Nonidet P-40 and sodium caprate and bovine serum albumin to young, oophorectomized female rats.

FIG. 8 is a graph showing that the serum calcium decreased correspondingly with the increase of serum salmon calcitonin (S-CT) following the vaginal suppository administration of S-CT, Nonidet P-40® and sodium caprate and BSA to young, oophorectomized female rats.

The calcitonin for use herein includes not only the naturally occurring polypeptide but also pharmacologically active derivatives and analogs thereof. Thus, calcitonin intended for use in the present invention includes not only naturally occurring products such as salmon calcitonin, human calcitonin, porcine calcitonin, eel calcitonin and chicken calcitonin, but also analogs such as [Asu^{1,7}]-eel calcitonin or elcatonin, a product of Toyo Jozo Company, Ltd., as well.

The amount of the calcitonin in the intravaginal pharmaceutical preparations will vary, depending upon the particular polypeptide employed, but will be an amount sufficient to elicit the desired pharmacological effect. Thus, calcitonin, will be present in an amount sufficient to treat a condition such as Paget's disease or hypercalcemia or osteoporosis. A typical preparation may contain, for example, from 0.01 to 0.04 I.U./mg for porcine calcitonin.

The absorption promoter for use in the present invention is an anionic and/or nonionic surfactant or a combination of a nonionic surfactant and a medium chain aliphatic carboxylic acid or its salt.

The anionic and nonionic surfactants for use in the present invention may be used singly or in a combination of two or more from one or both categories. Preferred anionic surfactants include sodium lauryl sulfate, polyoxyethylenealkylphenyl ether sodium sulfate, sodium alkylnaphthalenesulfonate and sodium alkylbenzene sulfonate, as well as other sulfuric acid esters of higher primary alcohols and other salts of alkylnaphthalenesulfonic acid. Particularly preferred anionic surfactants are sodium lauryl sulfate and sodium alkylnaphthalenesulfonate (Pelex NBL®), most especially sodium lauryl sulfate. These anionic surfactants are usually in the form of their alkali metal salts. Preferred nonionic surfactants are exemplified by sorbitan fatty acid esters, polyoxysorbitan fatty acid esters and polyoxyalkylene higher alcohol ethers. The most preferred nonionic surfactant is polyoxyethylene (23) lauryl ether (Emulgen®).

The combination absorption promoter is a nonionic surfactant and a medium chain aliphatic carboxylic acid or its salt. The nonionic surfactant is preferably a polyoxyethylenealkylphenylether. The polyoxyethylene component can be depicted as $(OCH_2CH_2)_n$ where n ranges from 5 to 30. The alkyl component is preferably a C₈-C₉ straight chain alkyl, i.e., polyoxyethyleneoctylphenylether or polyoxyethylenononylphenylether. The more preferred polyoxyethylenealkylphenylethers are polyoxyethylene (9) or (10) or (30) octylphenylether, polyoxyethylene (10) or (15) or (20) nonylphenylether. A particularly preferred polyoxyethylenealkylphenylether is Nonidet P-40®, i.e. polyoxyethylene (9) octylphenylether by Sigma Chemical Company.

The medium chain aliphatic carboxylic acid is preferably saturated and may be depicted as R-COOH where R is preferably a C₅-C₁₅ straight chain saturated alkyl. Preferred medium chain aliphatic carboxylic acids are sodium caproate, sodium caprylate, sodium caprate and sodium laurate. The most preferred medium chain aliphatic carboxylic acid salt is sodium caprate.

The amount of the absorption promoter in the intravaginal pharmaceutical preparation of this invention will vary, depending upon the particular absorption promoter selected. Generally speaking, however, the usual concentration of absorption promoter such as an anionic and/or nonionic surfactant or the combination of a nonionic surfactant such as polyoxyethylenealkylphenylether and medium chain aliphatic carboxylic acid or its salt is between 0.01 and 5% (w/v%), preferably between 0.05 and 2% (w/v%).

The animal and vegetable proteins used in the practice of the present invention are preferably selected from among proteins which have previously been used in food or medical preparations. Preferred examples of animal protein are albumin, e.g., bovine serum albumin (BSA) or human serum albumin (HSA), casein, gelatin and the like. Albumin is particularly preferred. Examples of vegetable proteins contemplated for use herein are gluten, zein, soybean protein and the like. Either animal or vegetable protein may be employed, or a combination of an appropriate ratio of animal protein and vegetable protein may be used.

The animal or vegetable protein is merely optional in the practice of the present invention. The protein is only necessary when the biologically active polypeptide or derivative thereof is unstable. The stability of the various polypeptides are well known to those in the art. Elcatonin, for instance, is eel calcitonin which has been modified to improve the stability. Thus, a protein is not essential in a composition containing elcatonin. Natural eel calcitonin, on the other hand, is not as stable as elcatonin and an animal or vegetable protein must be present in the composition to maintain the stability of the polypeptide. Most polypeptides and polypeptide derivatives are unstable. Reference may be made to standard textbooks and manufacturer specifications to describe the stability of a particular polypeptide.

The amount of the animal or vegetable protein used in the composition of the present invention is an amount sufficient to maintain the stability of the polypeptide. The amount of the animal or vegetable protein generally ranges from 0.001 to 25% (w/v%) depending on the polypeptide being stabilized.

Administration of the formulation of the present invention can be via any of the accepted modes of vaginal administration. The intravaginal pharmaceutical preparation of this invention is typically a liquid, gel (preferably highly viscous), cream, suppository, film, tablet, soft capsule or tampon-type device consisting of a biologically active polypeptide, absorption promoter and optionally an animal or vegetable protein. The intravaginal pharmaceutical preparation of this invention can be prepared by dissolving the polypeptide, absorption promoter and protein in either purified water, physiological saline solution or a buffered solution as a carrier or diluent therefor and then formulate that mixture into each dosage form.

Since the pH of the intravaginal pharmaceutical preparation of this invention is desirably as close as possible to the pH of the inner vagina, after the biologically active polypeptide, absorption promoter and optionally animal or vegetable protein are dissolved in purified water or physiological saline solution or buffered solution, the pH of the preparation is adjusted to a pH between 3 and 7, preferably between 4 and 6. The chemicals used for adjusting the pH are known acids or bases which are nontoxic and non-irritating to humans, preferred examples being organic acids such as acetic acid and citric acid, and weak bases such as sodium bicarbonate and sodium acetate.

In order to improve the properties and appearance of the pharmaceutical preparation of the present invention, one or more excipients, coloring agents, isotonic agents and antioxidants may be added to the intravaginal pharmaceutical preparation of this invention, for example, excipients such as starch, dextrin, mannitol, sorbitol, cyclodextrin and tragacanth, coloring agents such as betacarotene, red color No. 2 and blue color No. 1, isotonic agents such as sodium chloride and glucose, and antioxidants such as ascorbic acid and erythorbic acid and their salts or esters. Actual methods of preparing such dosage forms are known or will be apparent, to those skilled in the art. For example, see Remington's Pharmaceutical Sciences, 17th edition, 1985, ed. Alfonso R. Gennaro, Mack Publishing Company, Easton, Pennsylvania 18042.

The nature of the excipient(s) will preferably aid in the manufacture of the dosage form selected. As will be demonstrated hereinafter, certain dosage forms provide a more extended release of the biologically active polypeptide. These extended release dosage forms are particularly useful and offer increased flexibility in the administration of the polypeptide.

When the compositions according to the invention are prepared in suppository form, typical suppository bases will include triglycerides (for example Witepsol, a product of Dynamit Nobel), polyethylene glycols, glycerogelatin, polyvinyl alcohol (PVA), and the like. Suppository bases selected from triglycerides and the like will provide a "quick-release" suppository, whereas suppositories formed from glycerogelatin and the like will provide suppositories having more sustained release characteristics.

An aqueous preparation containing the biologically active peptide can be mixed with a suppository base using a mechanical mixing device such as a Voltex mixer at a suitable temperature to allow the suppository base to become fluid and then the mixture can be cooled in a suppository mold.

When the compositions according to the invention are prepared in film form, typical film bases may include:

- hydrophilic polymers such as polyvinyl alcohol, chitosan, polyhydroxyethylmethacrylate, glucomannan, pullulan and the like; and/or
- hydrophobic polymers such as ethylcellulose, polyacrylate ester, for example, Eudragit, a registered trademark of Röhm, Pharma GmbH, silicone and the like.

For making a film, an aqueous preparation of the biologically active peptide can be mixed with a film base such as hydroxypropylmethylcellulose, chitosan, pullulan, glucomannan, polyacrylate ester and then it can be cast and evaporated (dried).

When the compositions according to the present invention are prepared in gel form, typical gel bases may include:

- anionic polymers such as polyacrylic acid sodium salt, carboxymethylcellulose sodium salt and the like; and
- nonionic polymers such as polyvinyl alcohol, polyoxyethylene-propyleneglycol block copolymer, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose and so on. The gel formulations will invariably display quick-release activity.

For making a highly viscous gel preparation, a known viscosity enhancer may be added as needed. Some examples of suitable viscosity enhancers include cellulose lower alcohol ether, polyvinyl alcohol, polyvinyl pyrrolidone (PVP), polyoxyethyleneoxypropyleneglycol block copolymer (Pluronic®), and the like.

When a cream-type dosage form is prepared, both water-in-oil type cream and oil-in-water type cream can be prepared with the compositions according to the invention. Again, cream formulations will display quick-release activity.

When the compositions according to the present invention are prepared in tablet form, it should first be noted that both disintegrating and non-disintegrating tablets can be prepared. For disintegrating tablets, a strong disintegrant is preferred, such as PVP-XL, Ac-di-sol (a registered trademark of FMC Corporation) explotab, HPC-L and the like. For non-disintegrating tablets, there is needed a base capable of forming in the vagina a hydrogel matrix for the compositions of the invention. Such bases include glucomannan, alginic acid and its calcium salt, pectin, hydroxypropylmethylcellulose and the like. The disintegrating tablets provide quick-release action, whereas the non-disintegrating tablets usually provide sustained release action.

For making a tablet, the aqueous preparation containing the biologically active peptide can be mixed well with a suitable excipient such as a filler, binder and/or disintegrant and then dried, and further excipients such as a lubricant may be added, if necessary. The final mixture may be compressed into a tablet by a tableting machine. In addition, foaming agents such as sodium bicarbonate as a carbonate agent and citric or tartaric acid as a acidifying agent may be used alone or in combination for the disintegrating tablets, if necessary.

For making a soft capsule, an oily or polyethyleneglycol formulation containing the biologically active peptide may be incorporated into a soft capsule gel.

For making a tampon-type device, several methods may be used. For instance, a tampon shaped core of silicone resin may be covered with a polymer film such as chitosan and a polyacrylate-methacrylate copolymer containing a biologically active peptide.

Further information concerning preparation of the various intravaginal dosage forms may be found in Remington's Pharmaceutical Sciences, supra. When the pharmaceutical preparation of the present invention is administered intravaginally, the biologically active polypeptide is readily and effectively absorbed through the vaginal mucosa and exhibits its characteristic biological activity. Furthermore, the biologically active polypeptide, especially calcitonin or insulin, is stable in this preparation and unchanged after a long period of storage. (When appropriate, the compositions of the invention are stored in a cool place to secure their stability.) Moreover, the intravaginal preparation of the invention is not irritative to the vaginal mucosa. Still further, it has been surprisingly discovered that absorption promoters, such as anionic and/or nonionic surfactants act as inhibitors to vaginal proteinase when incorporated in the compositions of this invention; hence, the biologically active polypeptide is stable at its administration site.

In order further to illustrate the present invention and the advantages thereof, the following specific examples are given.

EXAMPLE 1

Absorption-Enhancing Effect of Sodium Lauryl Sulfate on Calcitonin

Oophorectomy was performed on 5- to 6-week old female Wister rats which, after about one month, were used in this experiment as an animal model for postmenopausal women.

To 20 I.U. porcine calcitonin, 3 mg of bovine serum albumin (BSA) was added. Sodium lauryl sulfate (hereinafter called "SDS") was then added to the above-prepared mixture to make 0.05, 0.1, 0.5 and 1 w/v% concentrations, respectively. The mixtures of different SDS concentrations were then each diluted with 0.1 M acetic acid/sodium acetate buffer solution (pH 5.0) to make 1 ml calcitonin solutions. Rats were anesthetized with ether, and a required amount of blood was taken from the right external jugular vein before the administration of calcitonin. After a small cotton ball was inserted into the vagina of the rat, each 50 microliters of calcitonin solution of different SDS concentrations was administered. Blood was again extracted 2 hours after calcitonin administration.

After the separation of blood serum, serum calcium concentration was determined with a Calcium C test kit, a registered trademark at Wako Chemical in Japan. The results are depicted in FIG. 1. The ratio of decreased serum calcium concentration against the control, which was treated with the preparation without SDS, was increased correspondingly with increasing concentration of SDS in the preparation.

EXAMPLE 2**Dose Response of Calcitonin Absorption From Vaginal Mucosa**

5 Oophorectomized menopausal model rats were used in this experiment, similarly to Example 1.

Bovine serum albumin was added to each 1 ml of 2, 10, 20, 40 and 80 I.U./ml of porcine calcitonin dissolved in acetic acid buffer solution (pH 5.0) to make 3 mg/ml. Then, SDS was added to each solution to make 1 w/v%. Similarly to Example 1, these preparations containing different concentrations of calcitonin were administered intravaginally to the rats, and the serum calcium concentration was determined. The ratio of decreased serum calcium against control exhibited an increase proportional to the increase of calcitonin concentration of the preparation administered. The largest ratio of decreased serum calcium against control noted in this experiment was 30%. In this experiment, it was found that the serum calcium concentration could be controlled by adjusting the dosage of calcitonin administered. See FIG. 2.

15 EXAMPLE 3**Evidence of the Absorption of Calcitonin Through Vaginal Mucosa**

20 This experiment was performed to confirm that calcitonin was actually absorbed through vaginal mucosa using the intravaginal dosage form of this invention.

Similarly to Examples 1 and 2, oophorectomized rats were used in this experiment. 1000 micrograms of Human calcitonin (HCT) was dissolved in 1 ml of 0.1 M acetate buffer (pH 5) containing 0.3 w/v% bovine serum albumin and 1 w/v% SDS. 10, 25, 50, 100 and 200 micrograms of HCT (protein weight) in solution per 1 kg body weight of rats were taken out of the HCT solution mentioned above, and each portion of the HCT solution was diluted up to 50 microliters with 0.1 M acetate buffer (pH 5) containing 0.3% (w/v%) bovine serum albumin and 1 w/v% SDS. Each 50 microliters of HCT solution with a different amount of HCT was administered into the vagina with a small cotton ball. Two hours after drug administration, blood was extracted from the right external jugular vein of the anesthetized rat, and serum calcium was determined with a Calcium C test kit. Serum calcitonin was also determined by a radioimmunoassay method (RIA method), using human calcitonin antibody. The results showed that serum calcitonin increased proportionally to the increase in the dosage of calcitonin administered into the vagina, and serum calcium decreased correspondingly with increase in calcitonin dosage. This result implied that the absorption of human calcitonin and its biological activity exhibited dose dependent response when the intravaginal preparation of this invention was administered. See FIG. 3.

35 EXAMPLE 4**Effectiveness in Aged Oophorectomized Rats**

40 Because many patients receiving calcitonin treatment are post-menopausal women, an experiment was designed to investigate the effectiveness of the intravaginal preparation of the present invention in aged, oophorectomized rats.

The ovaries of 30-week-old female Wister rats were excised about one month before use in the experiment. Prior to this experiment, a separate experiment was performed to investigate the susceptibility of aged, oophorectomized rats to porcine calcitonin. Different concentrations of calcitonin were injected into rats in the femoral bicipital muscle, and the decreasing serum calcium was determined. The susceptibility of aged rats to calcitonin was very low, and the largest ratio of decreased serum calcium against control was about 10%; this result differed significantly from the result of the experiment using young rats.

50 Following the procedure of Examples 1 and 2, a dose of 4 I.U. calcitonin per rat was prepared and administered intravaginally by inserting a small cotton ball in the vagina. Following the procedure of Examples 1 and 2, blood was extracted and the blood calcium concentration was determined. As a result of the addition of 1% of SDS to the intravaginal preparation of this invention, the intravaginal group showed a similar ratio of decreased serum calcium against control to that of the intramuscular injection group. See FIG. 4.

EXAMPLE 5**Effect of Sodium Lauryl Sulfate on the Stability of Calcitonin**

5 A porcine calcitonin (P-CT) pharmaceutical preparation according to the invention was prepared by the method described in Examples 1 and 2, and the stability of porcine calcitonin in the resultant preparation was investigated. Thus, 1 ml of 3 mg/ml bovine serum albumin (BSA) solution was added to 40 I.U. of porcine calcitonin, and the mixture was divided into two equal portions. SDS was added to one of the portions to make a final concentration of 0.1 w/v%; and no SDS was added to the other portion. The pH of
 10 both of the preparations was then adjusted to pH 5 with acetic acid/sodium acetate buffer (0.1M) solution. These two preparations were then stored at 37°C for 8 days. The biological activity of calcitonin of the 8-day stored preparations was then investigated using 5-week-old Wister male rats. A dosage of 0.12 I.U./kg calcitonin of these two preparations was administered to the rats by injection into the femoral muscle. One hour after drug administration, blood was extracted from the right external jugular vein, and the blood
 15 calcium content was determined. After the 8-day storage period, the biological activity of the preparation containing no SDS decreased to about half that of the freshly made preparation, while the preparation containing SDS did not lose any biological activity after being stored for 8 days. See TABLE 1 below.

TABLE 1**Effect of SDS on Calcitonin Stability****Ratio of Decreased Calcium
Concentration Against Control**

<u>Treatment</u>	<u>0 day</u>	<u>8 days (at 37°C)</u>
P-CT	20.7	11.1
P-CT + 0.1% SDS	22.6	22.4

P-CT(40 I.U.)/0.3% BSA/ml, at pH 5.0

EXAMPLE 6**Stabilizing Effect of Animal protein on Calcitonin**

Using blood calcium decreasing ratio as an indication, the effect of pH and human serum albumin (HSA) on the stability of calcitonin in the preparation of this invention was investigated using 5-week-old male Wister rats.

45 Purified porcine calcitonin (P-CT) was dissolved in 0.1 M acetic acid buffer solutions of pH 3.0 and pH 5.0 and 0.1 M phosphoric acid buffer solution of pH 6.8 so that each of the solutions contained 0.03 I.U./ml of porcine calcitonin. Each calcitonin solution (pH 3.0, 5.0, 6.8) was divided into two parts. In each case, to one portion of the calcitonin solutions 3 mg/ml of HSA was added, while no treatment was performed on the other portion. The resultant preparations were stored at 4°C for one week. These calcitonin preparations
 50 were then each injected into the femoral bicipital muscle of the rats at a dosage of 0.06 I.U. per kg body weight. An appropriate quantity of blood was extracted from the right external jugular vein, and blood calcitonin concentration was determined with a Calcium C-Test kit. As shown in FIG. 5, calcitonin in the buffer solutions without HSA was stable at pH 3.0 and 5.0, but unstable at pH 6.8. When HSA was added to the preparation, calcitonin in pH 6.8 solution became as stable as calcitonin in a solution of pH 3.0 or 5.0.

EXAMPLE 7**Inhibitory Effect of Sodium Lauryl Sulfate, a Surfactant, on Protease Activity**

The inhibitory effect of sodium lauryl sulfate (SDS) on protease activity was investigated in an *in vitro* study using trypsin, a typical serine protease possessing an optimum pH near neutral, and N-alpha-benzoyl-L-arginine ethyl ester (BAEE), a synthetic substrate. The calcitonin pharmaceutical preparation was prepared according to Examples 1 and 2. The preparation was inserted into the vagina with a small cotton ball. Two hours after the insertion, the inserted cotton ball was removed from the vagina. The vagina was then washed with a fixed quantity of phosphate buffered saline solution, the washed solution was combined with the cotton ball, and the protease activity was determined with BAEE as substrate. The result showed that protease activity decreased about 30% in the 1% SDS added group in comparison with the control group that had no SDS treatment. This result indicated that the SDS incorporated in the pharmaceutical preparation of this invention inhibited calcitonin decomposition by intravaginal protease when the preparation was administered intravaginally. See TABLE 2 below.

TABLE 2

Inhibition of Protease Activity by SDS	
Treatment	BAEE units/mg protein
control	23.4 (100.0)
1% SDS	6.84 (29.2)

EXAMPLE 8**The Serum Calcium Profile Following Intravaginal Administration of Suppository and Film Comprising P-CT, SDS, and BSA**

The pharmaceutical formulations used in this experiment are listed in Table 3.

TABLE 3

Dosage form	Amount of P-CT/Unit	Absorption Promoter	Protein	Base for Formulation
Suppository	1 I.U.	SDS (1%)	BSA (0.3%)	Glycero-gelatin (glycerin: gelatin:H ₂ O 70:20:10)
Suppository	1 I.U.	SDS (1%)	BSA (0.3%)	Polyvinyl alcohol
Film	5 I.U.	SDS (1%)	BSA (0.3%)	Chitosan + HPMC

HPMC represents hydroxypropylmethylcellulose. Each formulation listed in Table 3 was administered into the vagina of oophorectomized rats. Blood samples were taken at 2, 4, 8, 12 and 24 hours after vaginal administration, and serum calcium concentration was determined with a Calcium C test kit. The ratio of decreased serum calcium concentration against the control was plotted against time scale. The results are depicted in FIG. 6.

In this experiment, it was found that the formulations in table 3 could decrease the serum calcium concentration similar to the aqueous liquid formulation in example 2.

EXAMPLE 9**Evidence of the Absorption of Human Calcitonin Through Vaginal Mucosa**

This experiment was conducted to confirm that H-CT was actually absorbed through rat vaginal mucosa in the presence of sodium caprate and Nonidet P-40.

Oophorectomized rats were used in this experiment in a similar manner as Example 3. 1 mg of H-CT was dissolved in 400 microliters of 0.1 M acetate buffer (pH 5) containing 0.3 w/v% bovine serum albumin

(BSA) and 1% sodium caprate and 2% Nonidet P-40. 100 microliters of H-CT solution (250 micrograms H-CT) was administered into the vagina of the rat with a small cotton ball. Blood samples were taken from the right external jugular vein of the anesthetized rats at 1, 2 and 4 hours after administration. Serum calcium was determined with a Calcium C test kit. Serum H-CT was also determined by the RIA method using human calcitonin antibody. The results are shown in FIG. 7.

The results indicate that the serum calcitonin increased proportionally to the increase in the dosage of calcitonin administered into the vagina, and the serum calcium decreased correspondingly with an increase in calcitonin dosage. This result indicates that the absorption of H-CT and its biological activity exhibits a dose-dependent response when the composition of this invention containing the combination absorption promoter of sodium caprate and Nonidet P-40 was administered intravaginally.

EXAMPLE 10

The Profile of Serum Calcium and Salmon Calcitonin (S-CT) Concentration After Intravaginal Administration of Suppository Containing S-CT

The model animals and experimental procedures are similar to that described in Example 9. The suppositories used in this Example were prepared as follows. 1 mg of S-CT was dissolved in 100 microliters of 0.1 M acetate buffer solution (pH 5) containing 1.5 mg of BSA (bovine serum albumin), 10 mg of Nonidet P-40, and 5 mg of sodium caprate. 383 mg of suppository base composed of PEG 4000 (33%), PEG 6000 (47%) and distilled water (20%) was warmed to 45° to 50° C, then mixed well with the S-CT solution using a Vortex mixer for 1 min, then transferred into a brass suppository mold and cooled to approximately 4° C for 2 hrs. 125 mg of S-CT suppository contained 250 micrograms of S-CT. 250 micrograms of a S-CT suppository was administered into the rat vagina. 1, 2, and 4 hrs after administration, blood samples were taken, and the serum calcium concentration and the serum calcitonin were determined by the same method used in Example 9. The data is listed in FIG. 8.

The results indicate that the absorption of S-CT and its biological activity exhibit a dose-dependent response when the S-CT composition of this invention containing the combination absorption promoter of sodium caprate and Nonidet P-40 was administered intravaginally.

EXAMPLE 11

The Effect of the Combination Type Absorption Promoter

The animal model used in this experiment was basically similar to that of Example 1 except that the age of the oophorectomized rat was different. 100 microliters of the P-CT (4 I.U.) acetate buffer solution containing 0.3 w/v % BSA, the combination absorption promoter (2% polyoxyethylenealkylphenylether and 1% medium chain aliphatic carboxylic acid sodium salt) was administered into the oophorectomized rat vagina with the aid of a cotton ball. 2 hrs. after administration, blood samples were taken and the calcium concentration determined. The ratio of decreased calcium concentration against control was calculated. The data obtained is summarized in Table 4. Comparison data appears immediately below Table 4. NP-10 represents polyoxyethylene (10) nonylphenylether. NP-15 represents polyoxyethylene (15) nonylphenylether. OP-10 represents polyoxyethylene (10) octylphenylether.

TABLE 4

The Invention

Combination Absorption Promoters	The Ratio of Decreased Ca^{++}	Age (Weeks)
2% Nonidet P-40 + 1% Na caprylate	1.5	8-9
2% Nonidet P-40 + 1% Na caprate	13.7	8-9
2% Nonidet P-40 + 1% Na laurate	6.5	8-9
2% NP-10 + 1% Na caprate	5.9	32
2% NP-15 + 1% Na caprate	3.6	32
2% OP-10 + 1% Na caprate	4.3	32

Comparison data

Absorption Promoter	The Ratio of Decreased Ca^{++}	Age (Week)
1% Na caprylate	0.4	18
1% Na caprate	4.0	18
1% Na laurate	4.3	18
2% Nonidet P-40	0	18

From the data shown above, the combination of the polyoxyethylenealkylphenylether and medium chain aliphatic carboxylic acid sodium salt gave surprisingly better results in terms of biological response than either of the comparison absorption promoters.

EXAMPLE 12**The Effect of the Combination Type of Absorption Promotor on Elcatonin**

5 The animal model used in this experiment was similar to that of example 1 except for the age of oophorectomized rat. 100 microliters of the solution of elcatonin (400 ng) in 0.1M acetate buffer containing 0.3% w/v BSA and the combination absorption promotor (2% polyoxyethylenealkylphenylether and 1% sodium caprate) was administered into the oophorectomized rat vagina with the aid of cotton ball. 2 hours after administration, the blood samples were taken out and the calcium concentration determined. The ratio of decreased calcium concentration in serum against control was calculated. The data is presented in Table 5.

TABLE 5

Absorption Promoter	The Ratio of Decreased Ca ⁺⁺ Concentration in Serum
2% Nonidet P-40 + 1% Na caprate	11.9 ± 1.1
1% Na Caprate	4.2 ± 0.6
The age of rat: 25 weeks old.	

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A pharmaceutical composition adapted for intravaginal administration characterized by containing calcitonin, an absorption promoter namely an anionic and/or nonionic surfactant or a combination of a nonionic surfactant and a medium chain aliphatic carboxylic acid or its salt and a non-toxic pharmaceutically acceptable carrier or diluent therefor, in a formulation suitable for intravaginal administration.
2. A composition according to claim 1, characterized by the additional content of an animal and/or vegetable protein.
3. The composition according to claim 1 or 2, wherein the calcitonin is salmon calcitonin, human calcitonin, porcine calcitonin, eel calcitonin or chicken calcitonin.
4. The composition according to claims 1 to 3, wherein the anionic surfactant is sodium lauryl sulfate, polyoxyethylenealkylphenylether sodium sulfate, sodium alkylphenylsulfonate or sodium alkylbenzenesulfonate.
5. The composition according to claims 1 to 4, wherein the nonionic surfactant is a sorbitan fatty acid ester, a polyoxysorbitan fatty acid ester and a polyoxyalkylene higher alcohol ether.
6. The composition according to claims 1 to 3 or 5, wherein the absorption promoter comprises a combination of non-ionic surfactant and a saturated medium chain aliphatic carboxylic acid or alkali salt thereof.
7. The composition according to claim 6, wherein the nonionic surfactant is polyoxyethylenealkylphenylether.
8. The composition according to claim 7, wherein the polyoxyethylenephenylether is polyoxyethylene (5 to 30) alkyl (C-8 or C-9) phenylether.
9. The composition according to claim 8, wherein the polyoxyethylenealkylphenylether is selected from the group consisting of polyoxyethylene (9) or (10) or (30) octylphenylether or polyoxyethylene (10) or (15) or (20) nonylphenylether.

**EXAMPLE 12****The Effect of the Combination Type of Absorption Promotor on Elcatonin**

5 The animal model used in this experiment was similar to that of example 1 except for the age of oophorectomized rat. 100 microliters of the solution of elcatonin (400 ng) in 0.1M acetate buffer containing 0.3% w/v BSA and the combination absorption promotor (2% polyoxyethylenealkylphenylether and 1% sodium caprate) was administered into the oophorectomized rat vagina with the aid of cotton ball. 2 hours after administration, the blood samples were taken out and the calcium concentration determined. The ratio of decreased calcium concentration in serum against control was calculated. The data is presented in Table 5.

TABLE 5

Absorption Promoter	The Ratio of Decreased Ca ⁺⁺ Concentration in Serum
2% Nonidet P-40 + 1% Na caprate	11.9 ± 1.1
1% Na Caprate	4.2 ± 0.6
The age of rat: 25 weeks old.	

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A pharmaceutical composition adapted for intravaginal administration characterized by containing calcitonin, an absorption promoter namely an anionic and/or nonionic surfactant or a combination of a nonionic surfactant and a medium chain aliphatic carboxylic acid or its salt and a non-toxic pharmaceutically acceptable carrier or diluent therefor, in a formulation suitable for intravaginal administration.
2. A composition according to claim 1, characterized by the additional content of an animal and/or vegetable protein.
3. The composition according to claim 1 or 2, wherein the calcitonin is salmon calcitonin, human calcitonin, porcine calcitonin, eel calcitonin or chicken calcitonin.
4. The composition according to claims 1 to 3, wherein the anionic surfactant is sodium lauryl sulfate, polyoxyethylenealkylphenylether sodium sulfate, sodium alkyl naphthalenesulfonate or sodium alkylbenzenesulfonate.
5. The composition according to claims 1 to 4, wherein the nonionic surfactant is a sorbitan fatty acid ester, a polyoxysorbitan fatty acid ester and a polyoxyalkylene higher alcohol ether.
6. The composition according to claims 1 to 3 or 5, wherein the absorption promoter comprises a combination of non-ionic surfactant and a saturated medium chain aliphatic carboxylic acid or alkali salt thereof.
7. The composition according to claim 6, wherein the nonionic surfactant is polyoxyethylenealkylphenylether.
8. The composition according to claim 7, wherein the polyoxyethylenephenylether is polyoxyethylene (5 to 30) alkyl (C-8 or C-9) phenylether.
9. The composition according to claim 8, wherein the polyoxyethylenealkylphenylether is selected from the group consisting of polyoxyethylene (9) or (10) or (30) octylphenylether or polyoxyethylene (10) or (15) or (20) nonylphenylether.



10. The composition according to claim 9, wherein the polyoxyethylenealkylphenylether is polyoxyethylene (9) octylphenylether or polyoxyethylene (10) nonylphenylether.
- 5 11. The composition according to claims 1 to 10, wherein the saturated medium chain aliphatic carboxylic salt is selected from the group consisting of sodium caproate, sodium caprylate, sodium caprate, sodium laurate, sodium myristate and sodium palmitate.
12. The composition according to claim 11, wherein the salt is the sodium salt of capric acid.
- 10 13. The composition according to claims 1 to 12, wherein the concentration of the absorption promoter is between 0.01 to 5 w/v %.
14. The composition according to claim 13, wherein the concentration of the absorption promoter is between 0.05 and 2 w/v %.
- 15 15. The composition according to claims 2 to 14, wherein the protein is animal protein.
16. The composition according to claim 15, wherein the animal protein is albumin, casein or gelatin.
- 20 17. The composition according to claim 16, wherein the animal protein is albumin.
18. The composition according to claim 17, wherein the albumin is bovine serum albumin.
19. The composition according to claims 2 to 14, wherein the protein is vegetable protein.
- 25 20. The composition according to claims 2 to 14, wherein the protein is a combination of animal protein and vegetable protein.
- 30 21. The composition according to claims 1 to 20, wherein the saturated medium chain carboxylic acid has from 8 to 16 carbon atoms.

Claims for the following Contracting States : ES, GR

- 35 1. Process for enhancing the absorbability and the storage stability of intravaginally administered calcitonin characterized by mixing said calcitonin with 0.01 to 5 w/v % of an absorption promoter namely an anionic and/or nonionic surfactant or a combination of a nonionic surfactant and a medium chain aliphatic carboxylic acid or its salt and a non-toxic pharmaceutically acceptable carrier or diluent therefor, adjusting the pH of the mixture to a value between 3 and 7 with acids or bases which are non-toxic and non-irritating to humans and formulating the mixture into a form suitable for intravaginal administration.
- 40 2. The process according to claim 1, characterized by adding an animal and/or vegetable protein.
- 45 3. The process according to claim 1 or 2, wherein the calcitonin is salmon calcitonin, human calcitonin, porcine calcitonin, eel calcitonin or chicken calcitonin.
- 50 4. The process according to claims 1 to 3, wherein the anionic surfactant is sodium lauryl sulfate, polyoxyethylenealkylphenylether sodium sulfate, sodium alkyl naphthalenesulfonate or sodium alkyl benzenesulfonate.
- 55 5. The process according to claims 1 to 4, wherein the nonionic surfactant is a sorbitan fatty acid ester, a polyoxysorbitan fatty acid ester and a polyoxyalkylene higher alcohol ether.
6. The process according to claims 1 to 3 or 5, wherein the absorption promoter comprises a combination of nonionic surfactant and a saturated medium chain aliphatic carboxylic acid or alkali salt thereof.
7. The process according to claim 6, wherein the nonionic surfactant is polyoxyethylenealkylphenylether.



8. The process according to claim 7, wherein the polyoxyethylenephénylether is polyoxyethylene (5 to 30) alkyl (C-8 or C-9) phenylether.
9. The process according to claim 8, wherein the polyoxyethylenealkylphenylether is selected from the group consisting of polyoxyethylene (9) or (10) or (30) octylphenylether or polyoxyethylene (10) or (15) or (20) nonylphenylether.
10. The process according to claim 9, wherein the polyoxyethylenealkylphenylether is polyoxyethylene (9) octylphenylether or polyoxyethylene (10) nonylphenylether.
11. The process according to claims 1 to 10, wherein the saturated medium chain aliphatic carboxylic salt is selected from the group consisting of sodium caproate, sodium caprylate, sodium caprate, sodium laurate, sodium myristate and sodium palmitate.
12. The process according to claim 11, wherein the salt is the sodium salt of capric acid.
13. The process according to claims 1 to 12, wherein the concentration of the absorption promoter is between 0.05 and 2 w/v %.
14. The process according to claims 2 to 13, wherein the protein is animal protein.
15. The process according to claim 14, wherein the animal protein is albumin, casein or gelatin.
16. The process according to claim 15, wherein the animal protein is albumin.
17. The process according to claim 16, wherein the albumin is bovine serum albumin.
18. The process according to claims 2 to 13, wherein the protein is vegetable protein.
19. The process according to claims 2 to 13, wherein the protein is a combination of animal protein and vegetable protein.
20. The process according to claims 1 to 19, wherein the saturated medium chain carboxylic acid has from 8 to 16 carbon atoms.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Pharmazeutisches Präparat, angepaßt an die intravaginale Verabreichung, dadurch **gekennzeichnet**, daß es Calcitonin, eine resorptionsfördernde Substanz, nämlich ein anionisches und/oder nichtionisches grenzflächenaktives Mittel oder eine Kombination eines nichtionischen grenzflächenaktiven Mittels mit einer mittelkettigen aliphatischen Carbonsäure oder ihrem Salz und einen nichttoxischen pharmazeutisch annehmbaren Träger oder ein nichttoxisches pharmazeutisch annehmbares Verdünnungsmittel dafür in einer Zubereitung, geeignet für die intravaginale Verabreichung, enthält.
2. Präparat nach Anspruch 1, dadurch **gekennzeichnet**, daß es zusätzlich ein Tier- und/oder Pflanzenprotein enthält.
3. Präparat nach Anspruch 1 oder 2, dadurch **gekennzeichnet**, daß das Calcitonin Lachscalctonin, menschliches Calcitonin, Schweinecalcitonin, Aalcalcitonin oder Hühnercalcitonin ist.
4. Präparat nach den Ansprüchen 1 bis 3, dadurch **gekennzeichnet**, daß das anionische grenzflächenaktive Mittel Natriumlaurylsulfat, Polyoxyethylenalkylphenylethernatriumsulfat, Natriumalkylnaphthalinsulfonat oder Natriumalkylbenzolsulfonat ist.
5. Präparat nach den Ansprüchen 1 bis 4, dadurch **gekennzeichnet**, daß das nichtionische grenzflächenaktive Mittel ein Sorbitanfettsäureester, ein Polyoxysorbitanfettsäureester und ein Polyoxyalkylenether eines höheren Alkohols ist.



6. Präparat nach den Ansprüchen 1 bis 3 oder 5, dadurch **gekennzeichnet**, daß die resorptionsfördernde Substanz eine Kombination eines nichtionischen grenzflächenaktiven Mittels und einer mittelkettigen aliphatischen Carbonsäure oder eines Alkalisalzes davon umfaßt.
- 5 7. Präparat nach Anspruch 6, dadurch **gekennzeichnet**, daß das nichtionische grenzflächenaktive Mittel Polyoxyethylenalkylphenylether ist.
8. Präparat nach Anspruch 7, dadurch **gekennzeichnet**, daß der Polyoxyethylenphenylether Polyoxyethylen-(5 bis 30)-alkyl-(C-8 oder C-9)-phenylether ist.
- 10 9. Präparat nach Anspruch 8, dadurch **gekennzeichnet**, daß der Polyoxyethylenalkylphenylether aus der Gruppe, bestehend aus Polyoxyethylen-(9)- oder -(10)- oder -(30)-octylphenylether oder Polyoxyethylen-(10)- oder -(15)- oder -(20)-nonylphenylether, ausgewählt ist.
- 15 10. Präparat nach Anspruch 9, dadurch **gekennzeichnet**, daß der Polyoxyethylenalkylphenylether Polyoxyethylen-(9)-octylphenylether oder Polyoxyethylen-(10)-octylphenylether ist.
11. Präparat nach den Ansprüchen 1 bis 10, dadurch **gekennzeichnet**, daß das Salz einer mittelkettigen gesättigten aliphatischen Carbonsäure ausgewählt ist aus der Gruppe, bestehend aus Natriumcaproat, Natriumcaprylat, Natriumcaprat, Natriumlaurat, Natriummyristat und Natriumpalmitat.
- 20 12. Präparat nach Anspruch 11, dadurch **gekennzeichnet**, daß das Salz das Natriumsalz von Caprinsäure ist.
13. Präparat nach den Ansprüchen 1 bis 12, dadurch **gekennzeichnet**, daß die Konzentration der resorptionsfördernden Substanz zwischen 0,01 bis 5 Gew./Vol.-% ist.
14. Präparat nach Anspruch 13, dadurch **gekennzeichnet**, daß die Konzentration der resorptionsfördernden Substanz zwischen 0,05 und 2 Gew./Vol.-% liegt.
- 30 15. Präparat nach den Ansprüchen 2 bis 14, dadurch **gekennzeichnet**, daß das Protein ein Tierprotein ist.
16. Präparat nach Anspruch 15, dadurch **gekennzeichnet**, daß das Tierprotein Albumin, Casein oder Gelatine ist.
- 35 17. Präparat nach Anspruch 16, dadurch **gekennzeichnet**, daß das Tierprotein Albumin ist.
18. Präparat nach Anspruch 17, dadurch **gekennzeichnet**, daß das Albumin Rinderserumalbumin ist.
- 40 19. Präparat nach den Ansprüchen 2 bis 14, dadurch **gekennzeichnet**, daß das Protein ein pflanzliches Protein ist.
20. Präparat nach den Ansprüchen 2 bis 14, dadurch **gekennzeichnet**, daß das Protein eine Kombination von Tierprotein und pflanzlichem Protein ist.
- 45 21. Präparat nach den Ansprüchen 1 bis 20, dadurch **gekennzeichnet**, daß die gesättigte mittelkettige Carbonsäure 8 bis 16 Kohlenstoffatome besitzt.

Patentansprüche für folgende Vertragsstaaten : ES, GR

- 50 1. Verfahren zur Erhöhung des Resorptionsvermögens und der Lagerstabilität von intravaginal verabreichtem Calcitonin, dadurch **gekennzeichnet**, daß man das Calcitonin mit 0,01 bis 5 Gew./Vol.-% einer resorptionsfördernden Substanz, nämlich einem anionischen und/oder nichtionischen grenzflächenaktiven Mittel oder einer Kombination eines nichtionischen grenzflächenaktiven Mittels mit einer mittelkettigen aliphatischen Carbonsäure oder ihrem Salz, und einem nichttoxischen pharmazeutisch annehmbaren Träger oder einem nichttoxischen pharmazeutisch annehmbaren Verdünnungsmittel dafür mischt, den pH-Wert des Gemisches auf einen Wert zwischen 3 und 7 mit Säuren oder Basen einstellt, die beim Menschen nichttoxisch und nichtreizend wirken, und daß man das Gemisch in einer Form
- 55



formuliert, die für die intravaginale Verabreichung geeignet ist.

2. Verfahren nach Anspruch 1, dadurch **gekennzeichnet**, daß man ein tierisches und/oder pflanzliches Protein zugibt.
3. Verfahren nach Anspruch 1 oder 2, dadurch **gekennzeichnet**, daß das Calcitonin Lachscalctonin, menschliches Calcitonin, Schweinecalcitonin, Aalcalcitonin oder Hühnercalcitonin ist.
4. Verfahren nach den Ansprüchen 1 bis 3, dadurch **gekennzeichnet**, daß das anionische grenzflächenaktive Mittel Natriumlaurylsulfat, Polyoxyethylenalkylphenylethernatriumsulfat, Natriumalkylnaphthalinsulfonat oder Natriumalkylbenzolsulfonat ist.
5. Verfahren nach den Ansprüchen 1 bis 4, dadurch **gekennzeichnet**, daß das nichtionische grenzflächenaktive Mittel ein Sorbitanfettsäureester, ein Polyoxysorbitanfettsäureester und ein Polyoxyalkylenether eines höheren Alkohols ist.
6. Verfahren nach den Ansprüchen 1 bis 3 oder 5, dadurch **gekennzeichnet**, daß die resorptionsfördernde Substanz eine Kombination eines nichtionischen grenzflächenaktiven Mittels und einer gesättigten mittelkettigen aliphatischen Carbonsäure oder eines Alkalisalzes davon umfaßt.
7. Verfahren nach Anspruch 6, dadurch **gekennzeichnet**, daß das nichtionische grenzflächenaktive Mittel Polyoxyethylenalkylphenylether ist.
8. Verfahren nach Anspruch 7, dadurch **gekennzeichnet**, daß der Polyoxyethylenphenylether Polyoxyethylen-(5 bis 30)-alkyl-(C-8 oder C-9)-phenylether ist.
9. Verfahren nach Anspruch 8, dadurch **gekennzeichnet**, daß der Polyoxyethylenalkylphenylether aus der Gruppe, bestehend aus Polyoxyethylen-(9)- oder -(10)- oder -(30)-octylphenylether oder Polyoxyethylen(10)- oder -(15)- oder -(20)-nonylphenylether, ausgewählt wird.
10. Verfahren nach Anspruch 9, dadurch **gekennzeichnet**, daß der Polyoxyethylenalkylphenylether Polyoxyethylen-(9)-octylphenylether oder Polyoxyethylen(10)-nonylphenylether ist.
11. Verfahren nach den Ansprüchen 1 bis 10, dadurch **gekennzeichnet**, daß das Salz der gesättigten mittelkettigen aliphatischen Carbonsäure ausgewählt wird aus der Gruppe, bestehend aus Natriumcaproat, Natriumcaprylat, Natriumcaprat, Natriumlaurat, Natriummyristat und Natriumpalmitat, ist.
12. Verfahren nach Anspruch 11, dadurch **gekennzeichnet**, daß das Salz das Natriumsalz von Caprinsäure ist.
13. Verfahren nach den Ansprüchen 1 bis 12, dadurch **gekennzeichnet**, daß die Konzentration der resorptionsfördernden Substanz zwischen 0,05 und 2 Gew./Vol.-% liegt.
14. Verfahren nach den Ansprüchen 2 bis 13, dadurch **gekennzeichnet**, daß das Protein ein tierisches Protein ist.
15. Verfahren nach Anspruch 14, dadurch **gekennzeichnet**, daß das tierische Protein Albumin, Casein oder Gelatine ist.
16. Verfahren nach Anspruch 15, dadurch **gekennzeichnet**, daß das tierische Protein Albumin ist.
17. Verfahren nach Anspruch 16, dadurch **gekennzeichnet**, daß das Albumin ein Rinderserumalbumin ist.
18. Verfahren nach den Ansprüchen 2 bis 13, dadurch **gekennzeichnet**, daß das Protein ein pflanzliches Protein ist.
19. Verfahren nach den Ansprüchen 2 bis 13, dadurch **gekennzeichnet**, daß das Protein eine Kombination eines tierischen Proteins mit einem pflanzlichen Protein ist.



20. Verfahren nach den Ansprüchen 1 bis 19, dadurch gekennzeichnet, daß die gesättigte mittelkettige Carbonsäure 8 bis 16 Kohlenstoffatome besitzt.

Revendications

5 Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composition pharmaceutique adaptée à l'administration intravaginale, caractérisée en ce qu'elle contient de la calcitonine, un promoteur d'absorption, à savoir un tensioactif anionique et/ou non ionique, ou une combinaison d'un tensioactif non ionique et d'un acide carboxylique aliphatique à chaîne moyenne ou de son sel, et un véhicule non toxique, pharmaceutiquement acceptable, ou un diluant pour cette composition, dans une formulation convenant à l'administration intravaginale.
10
2. Composition selon la revendication 1, caractérisée par une teneur supplémentaire en protéine animale et/ou végétale.
15
3. Composition selon la revendication 1 ou 2, dans laquelle la calcitonine est la calcitonine de saumon, la calcitonine humaine, la calcitonine porcine, la calcitonine d'anguille ou la calcitonine de poulet.
4. Composition selon les revendications 1 à 3, dans laquelle le tensioactif anionique est le laurylsulfate de sodium, un sulfate sodique de polyoxyéthylènealkylphényléther, un alkyl-naphtalènesulfonate de sodium ou un alkylbenzènesulfonate de sodium.
20
5. Composition selon les revendications 1 à 4, dans laquelle le tensioactif non ionique est un ester d'acide gras et de sorbitane, un ester d'acide gras et de polyoxysorbitane et un éther d'alcool supérieur et de polyoxyalkylène.
25
6. Composition selon les revendications 1 à 3 ou 5, dans laquelle le promoteur d'absorption comprend une combinaison de tensioactif non ionique et d'un acide carboxylique aliphatique saturé à chaîne moyenne ou d'un de ses sels alcalins.
30
7. Composition selon la revendication 6, dans laquelle le tensioactif non ionique est un polyoxyéthylènealkylphényléther.
8. Composition selon la revendication 7, dans laquelle le polyoxyéthylènealkylphényléther est un polyoxéthylène (5 à 30) alkyl (en C₈ ou C₉) phényléther.
35
9. Composition selon la revendication 8, dans laquelle le polyoxyéthylènealkylphényléther est choisi dans le groupe constitué par le polyoxyéthylène (9) ou (10) ou (30) octylphényléther ou le polyoxyéthylène (10) ou (15) ou (20) nonylphényléther.
40
10. Composition selon la revendication 9, dans laquelle le Polyoxyéthylènealkylphényléther est le polyoxyéthylène (9) octylphényléther ou le polyoxyéthylène (10) nonylphényléther.
11. Composition selon les revendications 1 à 10, dans laquelle le sel carboxylique aliphatique saturé à chaîne moyenne est choisi dans le groupe constitué par le caproate de sodium, le caprylate de sodium, le caprate de sodium, le laurate de sodium, le myristate de sodium et le palmitate de sodium.
45
12. Composition selon la revendication 11, dans laquelle le sel est le sel de sodium d'acide caprique.
- 50 13. Composition selon les revendications 1 à 12, dans laquelle la concentration du promoteur d'absorption est comprise entre 0,01 et 5 % en poids/volume.
14. Composition selon la revendication 13, dans laquelle la concentration du promoteur d'absorption est comprise entre 0,05 et 2 % en poids/volume.
55
15. Composition selon les revendications 2 à 14, dans laquelle la protéine est une protéine animale.



16. Composition selon la revendication 15, dans laquelle la protéine animale est l'albumine, la caséine ou la gélatine.
17. Composition selon la revendication 16, dans laquelle la protéine animale est l'albumine.
18. Composition selon la revendication 17, dans laquelle l'albumine est la sérum-albumine bovine.
19. Composition selon les revendications 2 à 14, dans laquelle la protéine est une protéine végétale.
20. Composition selon les revendications 2 à 14, dans laquelle la protéine est une combinaison d'une protéine animale et d'une protéine végétale.
21. Composition selon les revendications 1 à 20, dans laquelle l'acide carboxylique saturé à chaîne moyenne possède de 8 à 16 atomes de carbone.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour améliorer la capacité d'absorption et la stabilité au stockage de calcitonine administrée par voie intravaginale, caractérisé en ce que l'on mélange ladite calcitonine avec 0,01 à 5 % en poids/volume d'un promoteur d'absorption, à savoir d'un tensioactif anionique et/ou non ionique, ou d'une combinaison d'un tensioactif non ionique et d'un acide carboxylique aliphatique à chaîne moyenne ou de son sel, et un véhicule non toxique, pharmaceutiquement acceptable, ou un diluant pour cette composition, on ajuste le pH du mélange à une valeur comprise entre 3 et 7 avec des acides ou des bases qui sont non toxiques et non irritantes pour l'homme, et on formule le mélange sous une forme convenant à l'administration intravaginale.
2. Procédé selon la revendication 1, caractérisé en ce que l'on ajoute une protéine animale et/ou végétale.
3. Procédé selon la revendication 1 ou 2, dans lequel la calcitonine est la calcitonine de saumon, la calcitonine humaine, la calcitonine porcine, la calcitonine d'anguille ou la calcitonine de poulet.
4. Procédé selon les revendications 1 à 3, dans lequel le tensioactif anionique est le laurylsulfate de sodium, un sulfate sodique de polyoxyéthylènealkylphényléther, un alkylnaphtalènesulfonate de sodium ou un alkylbenzènesulfonate de sodium.
5. Procédé selon les revendications 1 à 4, dans lequel le tensioactif non ionique est un ester d'acide gras et de sorbitane, un ester d'acide gras et de polyoxysorbitane et un éther d'alcool supérieur et de polyoxyalkylène.
6. Procédé selon les revendications 1 à 3 ou 5, dans lequel le promoteur d'absorption comprend une combinaison de tensioactif non ionique et d'un acide carboxylique aliphatique saturé à chaîne moyenne ou d'un de ses sels alcalins.
7. Procédé selon la revendication 6, dans lequel le tensioactif non ionique est un polyoxyéthylènealkylphényléther.
8. Procédé selon la revendication 7, dans lequel le polyoxyéthylènealkylphényléther est un polyoxyéthylène (5 à 30) alkyl (en C₈ ou C₉) phényléther.
9. Procédé selon la revendication 8, dans lequel le polyoxyéthylènealkylphényléther est choisi dans le groupe constitué par le polyoxyéthylène (9) ou (10) ou (30) octylphényléther ou le polyoxyéthylène (10) ou (15) ou (20) nonylphényléther.
10. Procédé selon la revendication 9, dans lequel le Polyoxyéthylènealkylphényléther est le polyoxyéthylène (9) octylphényléther ou le polyoxyéthylène (10) nonylphényléther.
11. Procédé selon les revendications 1 à 10, dans lequel le sel carboxylique aliphatique saturé à chaîne moyenne est choisi dans le groupe constitué par le caproate de sodium, le caprylate de sodium, le



caprate de sodium, le laurate de sodium, le myristate de sodium et le palmitate de sodium.

12. Procédé selon la revendication 11, dans lequel le sel est le sel de sodium d'acide caprique.

5 13. Procédé selon les revendications 1 à 12, dans lequel la concentration du promoteur d'absorption est comprise entre 0,05 et 2 % en poids/volume.

14. Procédé selon les revendications 2 à 13, dans lequel la protéine est une protéine animale.

10 15. Procédé selon la revendication 14, dans lequel la protéine animale est l'albumine, la caséine ou la gélatine.

16. Procédé selon la revendication 15, dans lequel la protéine animale est l'albumine.

15 17. Procédé selon la revendication 16, dans lequel l'albumine est la sérum-albumine bovine.

18. Procédé selon les revendications 2 à 13, dans lequel la protéine est une protéine végétale.

20 19. Procédé selon les revendications 2 à 13, dans lequel la protéine est une combinaison d'une protéine animale et d'une protéine végétale.

20. Procédé selon les revendications 1 à 19, dans lequel l'acide carboxylique saturé à chaîne moyenne possède de 8 à 16 atomes de carbone.

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