OPIC
Office de la propriété intellectuelle du Canada

CIPO
Canadian Intellectual Property Office

(12) (19) (CA) **Brevet-Patent**

(11) (21) (C) **2,024,651**
(22) 1990/09/05
(43) 1991/03/12
(45) 2000/08/01

(72) Fujii, Takeru, JP
(72) Sakoh, Seiichi, JP
(72) Hibi, Toru, JP
(72) Takama, Shigeyuki, JP
(72) Yamada, Akiya, JP
(73) Teikoku Seiyaku Kabushiki Kaisha, JP
(73) Asahi Kasei Kabushiki Kaisha, JP

(51) Int.Cl.[6] A61K 38/22, A61K 47/34
(30) 1989/09/11 (235186/1989) JP

(54) **PREPARATION TRANSVAGINALE HAUTEMENT ABSORBABLE CONTENANT UN POLYPEPTIDE BIOLOGIQUEMENT ACTIF**

(54) **HIGH-ABSORBABLE TRANSVAGINAL PREPARATION CONTAINING BIOLOGICALLY ACTIVE POLYPEPTIDE**

(57) The present invention is directed to a high-absorbable transvaginal preparation having excellent active ingredient absorbability, which comprises a biologically active polypeptide and an absorption promoter comprising a polyoxyethylenealkylphenyl ether and one or more compounds selected from the group consisting of an N-acylamino acid, cholic acids, pectic acid, taurine, saccharin, glycyrrhizic acid, aspartame, or a salt thereof. The preparation of the present invention is suitable for use in administering biologically active polypeptides.

Abstract

The present invention is directed to a high-absorbable transvaginal preparation having excellent active ingredient absorbability, which comprises a biologically active polypeptide and an absorption promoter comprising a polyoxyethylenealkylphenyl ether and one or more compounds selected from the group consisting of an N-acylamino acid, cholic acids, pectic acid, taurine, saccharin, glycyrrhizic acid, aspartame, or a salt thereof. The preparation of the present invention is suitable for use in administering biologically active polypeptides.

HIGH-ABSORBABLE TRANSVAGINAL PREPARATION CONTAINING BIOLOGICALLY ACTIVE POLYPEPTIDE

The present invention relates to a high-absorbable transvaginal preparation containing a biologically active polypeptide, more particularly to a high-absorbable preparation for transvaginal administration which comprises a biologically active polypeptide and a mixture of polyoxyethylenealkylphenyl ether and a specific compound as an absorption promoter for the purpose of enhancing the absorbability of said polypeptide.

Polypeptide hormones, e.g. insulin, calcitonin, and the like, are a water-soluble high molecular weight compound which is easily decomposed by gastric juice or a protease, e.g. pepsin, trypsin, and the like. Accordingly, when these polypeptide are orally administered, they are almost always decomposed without being absorbed and hence, they show very little effective physiological activity. Therefore, at present, pharmaceutical compositions of these polypeptides are usually prepared in a form suitable for injection in order to obtain the desired biological activity thereof. However, when the polypeptides need to be administered at regular intervals and repeatedly, the injection route is inconvenient and painful for patients, and hence, recent attention has been given to efforts for developing another administration method.

Pharmaceutical compositions for administration into the nasal cavity, the vagina or the rectum have been disclosed in Hirai et al., U.S. Patent No. 4,659,696 and Uda et al., U.S. Patent No. 4,670,419, which comprises a hydrophilic drug which is hardly absorbed in the gastrointestinal tract and cyclodextrin. The hydrophilic drug used in the said pharmaceutical composition includes polypeptides, e.g. insulin, LH-RH analogue, oxytocin, TRH, and the like. The cyclodextrin used in this pharmaceutical preparation is preferably α-cyclodextrin. This composition also contains various additives.

Further, a pharmaceutical composition for administration into the rectum or the vagina is disclosed in Morishita et al., U.S. Patent No. 4,609,640, which comprises a water-soluble drug and a specific type water-soluble chelating agent. It shows excellent drug absorbability. The water-soluble drug used in the said pharmaceutical composition includes polypeptides, e.g. insulin, somatostatin, calcitonin, and the like. When a chelating agent with low molecular weight such as a polycarboxylic acid is used together, a water-soluble high molecular weight base which does not have chelating activity, for example, gelatin, casein, albumin, globulin, is also used.

Other conventional additives which are necessary

for this administration dosage form, for example, a surfactant may also be contained therein.

Moreover, a transnasal powder preparation is disclosed in European Patent Publication EP-A-0193372, which comprises a physiologically active polypeptide, a quaternary ammonium compound and a lower alkyl ether of cellulose, and will have excellent preservability and chemical stability. The preferred powder preparation comprises insulin or calcitonin, benzalkonium chloride and hydroxypropyl cellulose. Various conventional additives, for example, lubricants, waxes, binding agents, diluents, colorants, flavoring agents, antioxidants, fillers, isotonic agents, surfactants, and the like are also contained therein.

Further, an absorbable intranasal preparation of calcitonin is disclosed in European Patent Publication EP-A-0183527, which comprises a calcitonin and at least one absorption promoter selected from the group consisting of acids or a salt thereof, benzilic acid or a salt thereof, capric acid or a salt thereof, polyethylene glycol 400, pyridoxal or a salt thereof, malic acid or a salt thereof and pyrophosphoric acid or a salt thereof. Other conventional additives for intranasal preparations may be added thereto. It is thought that by using one of specific absorption promoters, the efficiency of absorbing through the nasal cavity membrane is improved. The above mentioned

patent application discloses that a surfactant had been used as an absorption promoter in order to improve the absorbability through the nasal cavity of a large polypeptide, e.g. calcitonin, in the beginning. Both amphoteric and cationic surfactants, especially a nonionic surfactant like polyoxyethylenelauryl ether had been used in the early studies. However, it is assumed that such a desirable ether-type surfactant enhances the absorbability of a medicament by destroying the nasal cavity membrane.

British Patent Application No. 8326436 which has been published as GB-2127689A discloses an intranasal preparation, which comprises calcitonin incorporated into a suitable liquid diluent or carrier for administration into a nasal cavity mucous membrane, benzalkonium chloride and/or a surfactant being suitable for administration into the nasal cavity. When the said preparation contains a surfactant, the surfactant is preferably a nonionic surfactant, more preferably a polyoxyalkylene higher alcohol ether. It is reported that by these transnasal preparations of calcitonin, the bioavailability of calcitonin and the stability thereof are improved.

Moreover, a pharmaceutical composition of LH-RH or an analogue thereof for administration into the rectum or the vagina is disclosed in Matsuzawa et al. U.S. Patent No. 3,917,825. In the said composition, it is preferable that nonapeptide or decapeptide is uniformly dispersed into an oil base (e.q. oil, wax or fatty acid triglyceride)

containing a nonionic surfactant, e.g. a polyoxyethylene higher alcohol ether, and the like. Various administration methods including a transvaginal route of nonapeptide or decapeptide are disclosed in numerous patent applications and patent publications, see for example, Beddell et al., U.S. Patent No. 4,083,967, Immer et al., U.S. Patent No. 3,888,838, Nestor et al., U.S. Patent No. 4,234,571, Schally et al., U.S. Patent Nos. 4,010,125 and 4,018,726, and Saito et al., Fertility and Sterility, Vol. 28, No. 3, March 1977, 240-245.

Further, there is disclosed potent transvaginal adsorption of LH-RH analogue (leuprolide), LH-RH itself, and insulin in Okada et al., J. Pharm. Sci., Vol. 72, No. 1, January 1983, 75 - 78. The increase in absorbability thereof is obtained by using an organic acid. The enhancing effect on the absorbability seems to correlate with the chelation property of the organic acid to be used [cf. Okada et al., J. Takeda Res. Lab. 42 (1/2), 150 (1983)].

Touitou et al. developed a hydrophilic preparation for administration into the rectum or the vagina of insulin, heparin, phenol red and gentamicin which comprises as an nonionic surfactant polyethylene glycol together with Cetomacrogol* 1000 (polyethylene glycol 1000 monocetyl ether) (cf. J. Pharm. Pharmac., 1978, 30, 663). IL 54041 of the Jerusalem University seems to relate to a similar study, which discloses an enteric coated preparation and

*Trade Mark

a transvaginal preparation of peptide hormone or heparin containing a nonionic surfactant.

Morimoto et al. reported in J. Pharm. Pharmacol. 1985, 37, 759 - 760 the effect of nonionic surfactants, polyoxyethylene sorbitan monooleate and polyoxyethylene(9)lauryl ether, and the absorption promoting property of polyacrylic acid gel base on the adsorption at the rectum of semi-synthesized analogue of eel calcitonin. It was discovered at an early stage that polyacrylic acid gel base improves the absorption of insulin administered into the rectum, the vagina and the nasal cavity, and also adsorption of calcitonin administered into the rectum or the nasal cavity. The early report indicates that the absorbability of a difficultly absorbable drug is improved by administering it together with enamine, carboxylic acid and a surfactant.

There is disclosed an intrarectal preparation of calcitonin in Japanese Patent Publication No. 56-122309, wherein calcitonin and a surfactant (e.g. cholic acid, saponin, phospholipid, polyoxyethylenealkyl ether, glycerin fatty acid ester, sorbitan fatty acid ester, etc.) are dispersed uniformly in a suppository base.

Moreover, there is disclosed an absorption in the intestine of a drug by various compositions which promote absorption of a drug to be absorbed through the cell lining up on the surface of the mucous membrane in Muranishi, S.,

"Absorption Barriers and Absorption Promoters in the Intestine" of Topics in Pharmaceutical Sciences, 1987. A mixed micelle is also disclosed therein, wherein a nonionic surfactant and an unsaturated aliphatic carboxylic acid are used.

Although many studies have been conducted on the administration methods of polypeptides as mentioned above, these methods generally still have numerous defects. That is, when a drug is administered by one of the above-mentioned methods, it is necessary to administer the drug at a higher dose thereof than when it is administered by an injection route. As a result, the amount of the drug absorbed fluctuates widely. Thus, it is desirable that dosage forms of polypeptide have excellent storage stability, and that the polypeptide therein is easily absorbed without stimulating the mucous membrane of the administered region, and is stable at the administered region. Hitherto, although there have been many attempts to discover an alternative administration method of a biologically active polypeptide, e.g. insulin, calcitonin and the like, instead of the conventional injection route, no attention has been given to the problem that the biologically active polypeptide tends to lose the biological activity thereof during the storage thereof. The requisite to obtain a stable pharmaceutical dosage form containing a biologically active polypeptide is important for preparing the above pharmaceutical compositions. Moreover, in the study on the alternatives

to injection route, the above mentioned references do not suggest the way to avoid the enzymolysis of polypeptide which occurs during the process of absorption at the administered region.

Taking into consideration the above mentioned problems, that is, in order to reduce the pain of patients by injection and to suppress the decomposition of polypeptide as much as possible, the present inventors have intensively studied an improved dosage form of a biologically active polypeptide, e.g. insulin, calcitonin, and the like, instead of injection preparation, they had found that a transvaginal preparation containing only polyoxyethylenealkyphenyl ether alone hardly shows the required absorbability improvement, and that although transvaginal preparations containing N-acylamino acid, cholic acids, pectic acid, taurine, saccharin, glycyrrhizic acid, or aspartame alone show absorbability improvement, the absorption rate thereof is not sufficient. Hence, they have many problems, e.g. the necessity to increase the dose of biologically active polypeptide. As a result of further studies, the present inventors have unexpectedly found that the desired transvaginal preparation of a biologically active polypeptide having excellent absorbability can be obtained by incorporating polyoxyethylene-alkylphenyl ether together with one or more

compounds selected from the group consisting of N-acylamino acids, cholic acids, pectic acid, taurine, saccharin, glycyrrhizic acid, aspartame or a salt thereof. That is, the present invention relates to a high-absorbable transvaginal preparation which comprises a biologically active polypeptide and as an absorption promoter polyoxy-ethylenealkylphenyl ether and one or more compounds selected from the group consisting of N-acylamino acids, cholic acids, pectic acid, taurine, saccharin, glycyrrhizic acid, aspartame or a salt thereof.

An object of the present invention is to provide a pharmaceutical dosage form of a biologically active polypeptide which has excellent storage stability, and shows easy absorption of the polypeptide without irritating the mucous membrane of the administered region, and is stable at the administered region.

The biologically active polypeptide used in the present invention is a polypeptide having a comparatively lower molecular weight. Preferred biologically active polypeptides of the present invention are, for example, insulin, angiotensin, vasopressin, desmopressin, LH-RH (luteinizing hormone-releasing hormone), somatostatin, calcitonin, glucagon, oxytocin, gastoline, somatomedin, secretin, h-ANP (human atrial natriuretic polypeptide), ACTH (adrenocorticotropic hormone), MSH (melanocyte stimulating

hormone), β-endorphin, muramyldipeptide, enkephalin, neurotensin, bombesin, VIP (vasoactive intestinal polypeptide), CCK-8 (cholecystokinin-8), PTH (parathyroid hormone), CGRP (calcitonin gene relating polypeptide), TRH (thyrotropin-releasing hormone), endothelin, or a derivative (including an analogue) thereof. The various polypeptides which can be used in the present invention also include either naturally occurring polypeptides or synthesized derivatives (including analogues) thereof. Thus, for example, the calcitonin which is used in the present invention and has a reducing activity on serum calcium level includes not only natural calcitonins, e.g. salmon calcitonin, human calcitonin, porcine calcitonin, eel calcitonin or chicken calcitonin but also analogues, e.g. [Asu1,7]-eel calcitonin (e.g. elcatonin), and the like. The most preferred polypeptides of the present invention are calcitonin, insulin and LH-RH.

The amount of biologically active polypeptide contained in the transvaginal preparations of the present invention depends on the kind of polypeptide, but it should be an effective amount to exhibit the desired pharmaceutical activity thereof. For example, when calcitonin is employed as a biologically active polypeptide of the present invention, it should be contained therein in an effective amount thereof for treating such conditions as Paget's disease, hypercalcemia or osteoporosis, and

the like. For example, when porcine calcitonin is used, the amount thereof contained in the typical preparation may be in the range of about 0.01 - about 0.8 I.U./mg, and when elcatonin is used, the amount thereof may be in the range of about 0.01 - about 0.2 I.U./mg. When insulin is used as a biologically active polypeptide of the present invention, the effective amount for regulating the glucose level in blood and treating diabates is usually employed. Further, when LH-RH or an analogue thereof is used as a biologically active polypeptide of the present invention, the effective amount for treating various diseases of female genital organs, the effective amount for contraception and the effective amount for inducing other known biological responses to LH-RH are employed. When PTH, CGRH, somatomedin or an analogue thereof is used, the effective amount thereof for treating bone metabolic disorder is employed. The amount of other biologically active polypeptides which can be used in the present invention are also determined in the same manner as above.

The absorption promoter of the present invention comprises a mixture of polyoxyethylenealkylphenyl ether and one or more compounds selected from the group consisting of N-acylamino acids, cholic acids, pectic acid, taurine, saccharin, glycyrrhizic acid, aspartame (N-L-α-aspartyl-L-phenylalanine 1-methyl ester) or a salt thereof.

Preferred polyoxyethylenealkylphenyl ether is poly-

oxyethylene(5-30)alkylphenyl ether, for example, polyoxyethylene(9)octylphenyl ether, polyoxyethylene(10)octylphenyl ether, polyoxyethylene(30)octylphenyl ether, polyoxyethylene(10)nonylphenyl ether, polyoxyethylene(15)nonylphenyl ether or polyoxyethylene(20)nonylphenyl ether. The most preferred polyoxyethylenealkylphenyl ether is polyoxyethylene(9)octylphenyl ether [Nonidet P-40 (trade mark), hereinafter referred to as NP-40].

Preferred N-acylamino acids are amino acids N-acylated with an aliphatic carboxylic acid having 6 - 14 carbon atoms, especially having 8, 10 or 12 carbon atoms. A more preferred N-acylamino acid or a salt thereof is, for example, N-n-hexanoylglycine, N-n-octanoylglycine, N-n-decanoylglycine, N-n-dodecanoylglycine, N-n-decanoylglutamic acid, N-n-decanoylphenylalanine, N-n-decanoylaspartic acid, or an alkali metal salt thereof , e.g. sodium salt, and the like.

The cholic acid includes, for example, deoxycholic acid, chenodeoxycholic acid, taurocholic acid, or an alkali metal salt thereof, e.g. sodium salt, and the like.

Further, saccharin, taurine, glycyrrhizic acid and pectic acid may also be used in the form of a suitable alkali metal salt thereof, e.g. sodium salt, and the like.

The amount of the absorption promoter contained in the transvaginal preparation of the present invention depends on the type thereof, but usually, to the total

weight of the transvaginal preparation, polyoxyethylene-alkylphenyl ether is used in the range of about 0.1 to about 20 % by weight, preferably about 0.5 to about 5 % by weight, and one or more compounds selected from the group consisting of N-acylamino acids, cholic acids, pectic acid, taurine, saccharin, glycyrrhizic acid, aspartame or a salt thereof are used in the range of about 0.01 to about 5 % by weight, preferably about 0.05 to about 2 % by weight.

The transvaginal preparation of the present invention may contain, if necessary, animal protein and/or vegetable protein in order to enhance the stability of the biological active polypeptide. The animal protein and/or vegetable protein are preferably selected from ones which have usually been used for foods or pharmaceutical compositions. Preferred animal protein is, for example, albumin (e.g. bovine serum albumin, human serum albumin, etc.), casein and gelatin, and the like. Among these, the most preferable animal protein is albumin. The vegetable protein which can be used in the present invention is, for example, gluten, zein, soybean protein, and the like. The animal protein and the vegetable protein may be used either alone or together in the appropriate ratio.

In the present invention, the animal protein and the vegetable protein are used only when it is necessary, e.g. when the biologically active polypeptide or a derivative thereof is unstable. The stability of various polypeptides is well known by persons skilled in this field. For

example, elcatonin is a modified eel calcitonin which is prepared by modifying eel calcitonin so as to increase the stability thereof, and hence, the above animal or vegetable protein is not essential for a pharmaceutical composition containing elcatonin. On the other hand, natural eel calcitonin is not so stable as elcatonin, and hence, it is necessary to use the animal protein and/or the vegetable protein in a pharmaceutical composition thereof in order to maintain the stability of the polypeptide. Most polypeptides and derivatives thereof are unstable. There is available information as to the stability of specific polypeptides from ordinary text books or specifications supplied by manufacturers.

The amount of the animal protein and/or the vegetable protein used in the transvaginal preparation of the present invention is an amount effective for maintaining the stability of the polypeptide, and depends on the type of polypeptide, but is usually in the range of about 0.001 to 25% (w/v).

The transvaginal preparation of the present invention is prepared in conventional pharmaceutical dosage forms, for example, liquids, gels (preferably high viscosity gels), suppositories, films, tablets, soft capsules, tampons, creams, and the like, which usually comprise a biologically active polypeptide, an absorption promoter and, if necessary, animal protein and/or vegetable protein.

The transvaginal preparation of the present invention can be prepared by a conventional method. For instance, a liquid preparation can be prepared by dissolving a biologically active polypeptide, an absorption promoter and if necessary, animal protein and/or vegetable protein in a pharmaceutically acceptable liquid carrier or diluent, e.g. purified water, a physiological saline solution or a buffer, optionally followed by subjecting the resulting solution to various forming processes. The gel preparation having a high viscosity can be prepared adding a conventional thickening agent into the above liquid preparation. The thickening agent is, for example, cellulose lower alcohol ether, PVA (polyvinyl alcohol), PVP (polyvinylpyrrolidone), polyoxyethyleneoxypropylene glycol block copolymer [Pluronic (trade mark)], and the like. Since the pH value of the transvaginal preparation of the present invention has preferably a pH value closest to that of the vagina, after dissolving a biologically active polypeptide, an absorption promoter and optionally animal protein and/or vegetable protein in purified water, a physiological saline solution or a buffer, the resulting solution is adjusted to a pH range of 3 to 7, preferably 4 to 6. The agent to be used to adjust the pH value may be a conventional acid or base which is non-toxic and non-irritative to humans, for example, an organic acid (e.g. acetic acid, citric acid, etc.) and a weak base (e.g. sodium hydrogen carbonate, sodium acetate, etc.).

The suppositories of the present invention can be prepared by using a conventional suppository base, e.g. Witepsol (trade mark), macrogol, glycerogelatin, and the like. Firstly, a liquid preparation containing a biologically active polypeptide is well mixed with a suppository base by a mechanical mixing apparatus (e.g. Vortex Mixer, etc.) at a suitable temperature, that is, at the lowest temperature sufficient to obtain a suitable fluidity of the suppository base, and then the mixture is cooled in a suppository mold.

The film preparation of the present invention may be prepared by mixing well the above mentioned liquid preparation with a film base, e.g. hydroxypropylmethyl cellulose, chitosan, pullulan, glucomannan, polyacrylate ester, and the like, followed by casting the mixture and then by evaporating or drying thereof.

The cream preparation of the present invention may be prepared in the form of either water-in-oil type or oil-in-water type which contains the composition of the present invention .

The tablets of the present invention may be prepared by mixing well a liquid preparation containing a biologically active polypeptide with an appropriate additive , e.g. fillers, binding agents, disintegrators, and the like, followed by drying, and if necessary, by adding thereto other additives, e.g. a lubricant, and the like, and then by tabletting the mixture with a tablet machine.

If necessary, a gas-releasing agent, for example, carbonates (e.g. $NaHCO_3$, etc.) or acid salts (e.g. tartrate, citrate, etc.) may be used as an additive to prepare an effervescent preparation.

When the tablets of the present invention are non-disintegrable, it is necessary to use a base which can form a hydrogel in the vagina. The base suitable for the above mentioned hydrogel is, for example, glucomannan, alginic acid and a calcium salt thereof, pectin, hydroxypropylmethyl cellulose, and the like. The disintegrable tablets show a rapid-release property, but the non-disintegrable tablets usually show a slow-release property.

The soft capsule preparation of the present invention may be prepared by encapsulating an oily preparation or polyethylene glycol preparation containing a biologically active polypeptide into soft capsules.

The tampon-shaped preparation of the present invention may be prepared by various processes. The typical process comprises, for example, coating a tampon-shape core made of silicone resin with a polymer film containing a biologically active peptide, e.g. chitosan, polyacrylate-methacrylate copolymer, and the like.

In order to improve the quality and the appearance of the transvaginal preparation of the present invention, it may be incorporated with one or more additives, e.g. excipients, colorants, isotonic agents or antioxidants, for example, excipients, e.g. starch, dextrin, mannitol,

cyclodextrin, tragacanth, and the like; colorants, e.g. β-carotin, red color No. 2, blue color No.1, and the like; isotonic agents, e.g. sodium chloride, glucose, and the like; and antioxidants, e.g. ascorbic acid, erythorbic acid or a salt or ester thereof [cf. Remington's Pharmaceutical Sciences, 17th, 1985, edited by Alfonso R. Gennaro, Mack Publishing Company, Easton, Pennsylvania 18042].

By administering the transvaginal preparation of the present invention, the biologically active polypeptide therein is easily and effectively absorbed through the vaginal mucous membrane and shows the characteristic biological activity thereof. Moreover, the biologically active polypeptides, especially insulin and calcitonin are stable in the transvaginal preparation of the present invention, and the activity thereof does not change after long term storage. If necessary, the transvaginal preparation of the present invention may be kept in a cold place in order to maintain the stability thereof. Further, the transvaginal preparation of the present invention is low irritative to the vaginal mucous membrane.

The present invention is illustrated in more detail by the following Experiments and Preparations, but should not be construed to be limited thereto.

Experiment 1 The promotion effect of a combination of polyoxyethylenealkylphenyl ether and N-acylamino acid on absorption of elcatonin:

The ovaries of female Wistar rats (5 - 6 weeks old) were removed , and the rats were fed for about one month, which was used as a model animal for postmenopausal woman in this Experiment. Age of the thus fed animals was between 17 - 21 weeks.

To elcatonin (400 ng) was added to bovine serum albumin (3 mg) and to the mixture was added as an absorption promoter a mixture of polyoxyethylenealkylphenyl ether (20 µl) and an N-acylamino acid (10 µg) in the ratios as shown in Table 1. The mixture was diluted with 0.1 M acetic acid/sodium acetate buffer solution (pH 5.0) to give an elcatonin solution (1 ml).

The above rats were anesthetized with ether, and the required amount of blood was collected therefrom through the right external jugular vein prior to administration of elcatonin.

After inserting a small cotton ball into the rat vagina, the above mentioned elcatonin solution (50 µl) was administered thereto. Blood was collected again two hours after the administration of elcatonin.

The serum was separated from the whole blood, and the calcium level thereof was determined by using Calcium C Test Kit (trade mark) (Wako Pure Chemical Industries, Ltd.). The results are shown in Table 1.

Table 1

Absorption promoter			Reduction rate of serum calcium level (%)
N-Acylamino acid (1.0 %)		Polyoxyethylenalkyl-phenyl ether* (2.0 %)	
N-n-Hexanoylglycine sodium salt	+	NP-40	6.1±1.5
N-n-Octanoylglycine sodium salt	+	NP-40	5.3±1.6
N-n-Decanoyl glycine sodium salt	+	NP-40	5.0±1.6
N-n-Dodecanolyglycine sodium salt	+	NP-40	4.3±0.6
N-n-Decanoylglutamic acid sodium salt	+	NP-40	8.0±2.9
N-n-Decanoylphenylalanine sodium salt	+	NP-40	6.7±2.1
N-n-Decanoylaspartic acid sodium salt	+	NP-40	7.3±1.7
N-n-Decanoylaspartic acid sodium salt	+	NP-15	6.0±2.0
N-n-Decanoylaspartic acid sodium salt	+	NP-10	5.6±2.2

*Trademarks NP-40: Polyoxyethylene(9)octylphenyl ether

NP-15: Polyoxyethylene(15)nonylphenyl ether

NP-10: Polyoxyethylene(10)nonylphenyl ether

Using as an absorption promoter polyoxyethylene-alkylphenyl ether, N-acylamino acids, or other components alone, the control preparations for reference were prepared, and administered to the above mentioned rats in the same manner as above, and then, the decrease in serum calcium level was determined likewise. The results are shown in Table 2.

Table 2

Absorption promoter	Reduction rate of serum calcium level (%)
1.0 % N-n-Decanoylglycine sodium salt	2.3±2.4
1.0 % Deoxycholic acid sodium salt	2.3±1.2
1.0 % aspartame	0.3±1.5
2.0 % NP-40	0±2.6

As is clear from Tables 1 and 2 above, when a combination of polyoxyethylenealkylphenyl ether and N-acylamino acid is used as an absorption promoter, the preparation shows much higher reduction rate of serum calcium level than the preparation wherein they are used alone, and the absorption promoter composed of the above combination can promote to a considerable degree the absorption of elcatonin.

Experiment 2

In the same manner as described in Experiment 1 except that various combinations of N-n-decanoylglycine

sodium salt and NP-40 in the various ratios as shown in Table 3 were used as the absorption promoter, the reduction rate of serum calcium level was examined. The results are shown in Table 3.

Table 3

Absorption promoter		Reduction rate of serum calcium level (%)
N-n-Decanoylglycine sodium salt (%)	NP-40 (%)	
0.01	2.0	2.8±2.3
0.05	2.0	7.0±2.3
0.1	2.0	8.0
0.5	2.0	4.8±1.4
1.0	2.0	3.6
1.0	1.0	6.7
1.0	0.5	6.1±1.6

Experiment 3 Promotion effect of absorption promoters comprising other combinations on absorption of elcatonin :

In the same manner as described in Experiment 1 except, as an absorption promoter, a component (A) selected from cholic acids, pectic acid, taurine, saccharin sodium, glycyrrhizic acid and aspartame was used instead of the N-acylamino acid, and NP-40 [polyoxyethylene(9)octylphenyl ether] was used as polyoxyethylene-alkylphenyl ether (B), the promotion effect thereof on the absorption of elcatonin was examined. The results are shown in Table 4.

Table 4

Absorption promoter			Reduction Rate of serum calcium level (%)
(A) 1.0%		(B) 2.0%	
Taurocholic acid sodium salt	+	NP-40	7.0±2.4
Deoxycholic acid sodium salt	+	NP-40	5.3±2.0
Chenodeoxycholic acid sodium salt	+	NP-40	4.6±1.0
Pectic acid	+	NP-40	6.9±0.8
Taurine	+	NP-40	6.7±1.1
Saccharin sodium	+	NP-40	6.7±2.6
Glycyrrhizic acid	+	NP-40	8.8
Aspartame	+	NP-40	8.2±1.8

As is clear from Table 4 above in comparison with Table 2, the preparation using the absorption promoter comprising the combination of the present invention showed a higher reduction rate of serum calcium level than that of preparations using each of the components alone.

Preparation 1

In the following formulation, transvaginal suppositories are prepared in a conventional manner.

Components	Amount
Elcatonin	40 µg
NP-40	200 mg
N-n-Hexanoylglycine sodium salt	100 mg
Bovine serum albumin	30 mg

0.1 M Acetic acid/ sodium acetate buffer (pH 5)	0.5 ml
Witepsol	q.s.
	Totally 10 g (for 5 pieces)

Preparation 2

In the following formulation, transvaginal suppositories are prepared in a conventional manner.

Component	Amount
Insulin	1000 I.U.
NP-40	200 mg
N-n-Octanoylglycine sodium salt	100 mg
Bovine serum albumin	30 mg
0.1 M Acetic acid/ sodium acetate buffer (pH 5)	0.5 ml
Macrogol	q.s.
	Totally 10 g (for 10 pieces)

Preparation 3

In the following formulation, transvaginal suppositories are prepared in a conventional manner.

Component	Amount
h-PTH (1-34)	200 µg
NP-40	200 mg
N-n-Decanoylglycine sodium salt	100 mg
Bovine serum albumin	30 mg
0.1 M Acetic acid/	

sodium acetate buffer (pH 5)	0.5 ml
Glycerogelatin	q.s.
	Totally 10 g (for 10 pieces)

Preparation 4

In the following formulation, transvaginal suppositories are prepared in a conventional manner.

Component	Amount
Porcine calcitonin	600 I.U.
NP-40	200 mg
Taurocholic acid sodium salt	100 mg
Bovine serum albumin	30 mg
0.1 M Acetic acid/ sodium acetate buffer (pH 5)	0.5 ml
Witepsol	q.s.
	Totally 10 g (for 5 pieces)

Preparation 5

In the following formulation, transvaginal suppositories are prepared in a conventional manner.

Component	Amount
Salmon calcitonin	50 µg
NP-40	200 mg
Taurocholic acid sodium salt	100 mg
Bovine serum albumin	30 mg
0.1 M Acetic acid/ sodium acetate buffer (pH 5)	0.5 ml

Witepsol	q.s.
	Totally 10 g (for 5 pieces)

Preparation 6

In the following formulation, transvaginal suppositories are prepared in a conventional manner.

Component	Amount
Salmon calcitonin	50 µg
NP-40	200 mg
Pectic acid	100 mg
Bovine serum albumin	30 mg
0.1 M Acetic acid/ sodium acetate buffer (pH 5)	0.5 ml
Macrogol	q.s.
	Totally 10 g (for 5 pieces)

Preparation 7

In the following formulation, transvaginal suppositories are prepared in a conventional manner.

Component	Amount
Porcine calcitonin	600 I.U.
NP-15*	200 mg
N-n-Decanoylaspartic acid sodium salt	100 mg
Bovine serum albumin	30 mg
0.1 M Acetic acid/ sodium acetate buffer (pH 5)	0.5 ml
15 % PVA	q.s.
	Totally 10 g (for 5 pieces)

*) Polyoxyethylene(15)nonylphenyl ether

Preparation 8

In the following formulation , a transvaginal tablet is prepared in a conventional manner.

Component	Amount
Elcatonin	8 µg
NP-40	20 mg
N-n-Hexanoylglycine sodium salt	10 mg
Bovine serum albumin	3 mg
Carboxymethyl cellulose Na (CMC·Na)	20 mg
Cornstarch	300 mg
Lactose	q.s.
Totally	1 g

Preparation 9

In the following formulation, a transvaginal tablet is prepared in a conventional manner.

Component	Amount
Elcatonin	6 µg
NP-40	20 mg
N-n-Hexanoylglycine sodium salt	10 mg
Bovine serum albumin	3 mg
CMC·Na	20 mg
Cornstarch	200 mg
Citric acid	100 mg
Sodium hydrogen carbonate	100 mg

Magnesium stearate	50 mg
Lactose	q.s.
Totally	1 g

Preparation 10

In the following formulation, a transvaginal cream is prepared in a conventional manner.

Component	Amount
Elcatonin	50 µg
NP-40	200 mg
N-n-Octanoylglycine sodium salt	100 mg
Bovine serum albumin	30 mg
White petrolatum	2.5 g
Stearyl alcohol	2.0 g
Propylene glycol	1.0 g
Monostearic acid glycerin	0.5 g
Methylparaben	10 mg
Purified water	q.s.
Totally	10 g

Claims:

1. A high-absorbable transvaginal preparation which comprises a biologically active polypeptide and an absorption promoter comprising a polyoxyethylenealkyl-phenyl ether and one or more compounds selected from the group consisting of an N-acylamino acid, cholic acids, pectic acid, taurine, saccharin, glycyrrhizic acid, aspartame, or a salt thereof.

2. The high-absorbable transvaginal preparation according to claim 1, wherein the biologically active polypeptide is a hormone selected from the group consisting of insulin, angiotensin, vasopressin, desmopressin, luteinizing hormone-releasing hormone, somatostatin, calcitonin, glucogan, oxytocin, gastoline, somatomedin, secretin, human atrial natriuretic polypeptide, adrenocorticotropic hormone, melanocyte stimulating hormone, ß-endorphin, muramyldipeptide, enkephalin, neurotensin, bombesin, vasoactive intestinal polypeptide, cholecystokinin-8, parathyroid hormone, calcitonin gene relating polypeptide, thyrotropin-releasing hormone, endothelin and derivatives thereof.

3. The high-absorbable transvaginal preparation according to claim 2, wherein calcitonin or a derivative thereof is selected from the group consisting of salmon calcitonin, human calcitonin, porcine calcitonin, eel calcitonin, chicken calcitonin and derivatives thereof.

4. The high-absorbable transvaginal preparation according to claim 3, wherein the derivative of eel

calcitonin is (Asu1,7)-eel calcitonin (elcatonin).

5. The high-absorbable transvaginal preparation according to claim 1, wherein the polyoxyethylenealkyl-phenyl ether is polyoxyethylene(5-30)alkylphenyl ether.

6. The high-absorbable transvaginal preparation according to claim 5, wherein the polyoxyethylenealkyl-phenyl ether is polyoxyethylene(9)octylphenyl ether.

7. The high-absorbable transvaginal preparation according to claim 5, wherein the polyoxyethylenealkyl-phenyl ether is selected from the group consisting of polyoxyethylene(10)octylphenyl ether, polyoxyethylene(30)-octylphenyl ether, polyoxyethylene(10)nonylphenyl ether, polyoxyethylene(15)nonylphenyl ether and polyoxyethylene-(20)nonylphenyl ether.

8. The high-absorbable transvaginal preparation according to claim 1, wherein the absorption promoter comprises a polyoxyethylenealkylphenyl ether and an N-acylamino acid or a salt thereof.

9. The high-absorbable transvaginal preparation according to claim 8, wherein the acyl moiety of N-acylamino acid or a salt thereof is an acyl group of an aliphatic carboxylic acid having 6 to 14 carbon atoms.

10. The high-absorbable transvaginal preparation according to claim 9, wherein the N-acylamino acid or a salt thereof is selected from the group consisting of N-n-hexanoylglycine, N-n-oxtanoylglycine, N-n-decanoylglycine, N-n-dodecanoylglycine, N-n-decanoylglutamic acid, N-n-decanoylphenylalanine, N-n-decanoylaspartic acid and a

metallic salt thereof.

11. The high-absorbable transvaginal preparation according to claim 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, wherein the absorption promoter is incorporated in an amount of about 0.1 to 20 % by weight of polyoxyethylene-alkylphenyl ether, and about 0.01 to 5 % by weight of one or more compounds selected from the group consisting of an N-acylamino acid, cholic acids, pectic acid, taurine, saccharin, glycyrrhizic acid, aspartame and a salt thereof, based on the whole weight of the preparation.

12. The high-absorbable preparation according to claim 1, which is in a pharmaceutical dosage form selected from a liquid preparation, a gel preparation having a high viscosity, a suppository, a film preparation, a tablet, a tampon-shape preparation, and a cream preparation.