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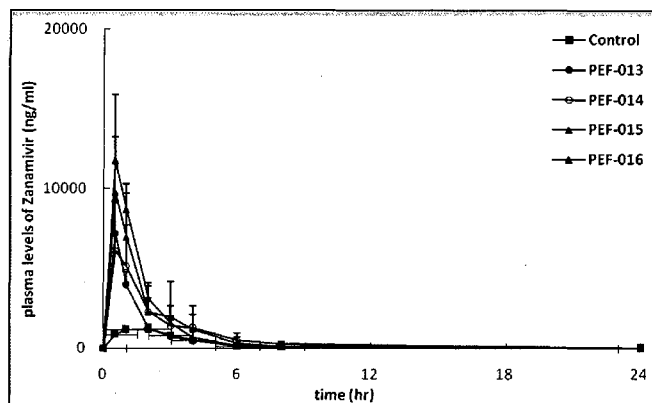
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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING ANTIVIRAL NEURAMINIDASE INHIBITOR AND PERMEATION ENHANCER FOR ENHANCED ORAL BIOAVAILABILITY

FIG. 4



(57) Abstract: Provided is a pharmaceutical composition comprising an antiviral neuraminidase inhibitor and a permeation enhancer with improved oral absorption and/or bioavailability, which can be useful in for preventing or treating viral infections, in particular, influenza A and B virus infections.

**PHARMACEUTICAL COMPOSITION COMPRISING ANTIVIRAL
NEURAMINIDASE INHIBITOR AND PERMEATION ENHANCER FOR
ENHANCED ORAL BIOAVAILABILITY**

5 **FIELD OF THE INVENTION**

The present invention related to a pharmaceutical composition comprising an antiviral neuraminidase inhibitor and a permeation enhancer with improved oral absorption and/or bioavailability.

10

BACKGROUND OF THE INVENTION

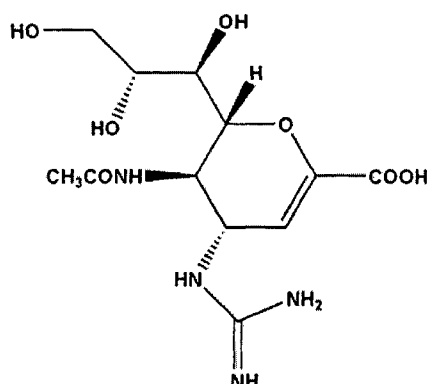
Influenza is a disease caused by viruses of three main subtypes, influenza A, B and C, which are classified according to their antigenic determinants. Influenza A and B viruses are the most common causes of influenza in a human being. Influenza has an enormous impact on public health with severe economic implications in addition to the devastating health problems, including morbidity and even mortality. Infection may be mild, moderate or severe, ranging from asymptomatic through mild upper respiratory infection and tracheobronchitis to a severe, occasionally lethal, viral pneumonia.

The sialidase (neuraminidase, acylneuraminyl hydrolase, EC 3.2.1.18) of influenza virus is involved in the elution of progeny virions from the surface of infected cells and may also assist in the movement of virus through the mucus within the respiratory tract. This enzyme, which catalyzes the cleavage of the a (2-6)- or (2-3)- ketosidic linkage between terminal sialic acid and adjacent galactose on glycoconjugates, thereby destroying the cell surface receptor for influenza virus.

A new class of a specific anti-influenza agent, zanamivir (RelenzaTM, GG167, 4-guanidino-2,4-dideoxy-2,3-dehydro-N-acetylneuraminic acid, *see* Formula. 1) is a potent and selective inhibitor of the neuraminidases of influenza

A and B viruses useful in the treatment or prevention of influenza virus infection. It is efficacious in shortening the duration and decreasing the severity of experimental infections in animals and humans when administered through the intranasal route. Inhaled zanamivir is therapeutically active in acute, uncomplicated, naturally occurring human influenza. Intranasal zanamivir is also efficacious in preventing experimental human influenza virus infection when administered before virus inoculation.

[Formula 1]



Commercially available zanamivir is an oral inhalation formulation applied using DiskhalerTM (a dry powder inhaler) due to its poor oral bioavailability in a human being (2%; range 1 to 5%). However, other routes of administration such as oral or systemic is warranted considering patients for whom inhalation may be difficult or may not effectively deliver the drug to sites of viral replication. Besides, oral delivery is a highly sought-after means of drug administration due to its convenience and positive effect on patient compliance. Unfortunately, zanamivir for oral delivery is still perceived as a problem due to its limited transport across the intestinal epithelium. Especially, the epithelial cells that are lining the lumen of the gastrointestinal tract (GIT) exert a barrier to oral drug delivery.

Zanamivir compositions and their oral dosage forms with improved systemic bioavailability would represent a considerable benefit for patients for whom inhalation may be difficult or may not effectively deliver the drug to sites

of viral replication. As a result new strategies for delivering drugs across the GIT cell layers are needed for the oral delivery of zanamivir.

Drugs are transported across the intestinal epithelium by passive diffusion either through transcellular pathway or paracellular pathway. Lipophilic drugs use the transcellular pathway to cross the epithelial barrier, while hydrophilic drugs are limited to use the paracellular pathway, which occupy less than 0.1% of the total surface area of the intestinal epithelium. Besides, the tight junctions (TJ) which connect the adjacent epithelial cells provide an extra barrier to the permeation of hydrophilic drugs. Due to this paracellular barrier, oral absorption of hydrophilic drugs is severely hampered.

Oral permeation enhancers aid oral drug absorption by altering the structure of the cellular membrane (transcellular route) and/or the TJs between cells (paracellular route) of the intestinal epithelium. Accordingly, numerous potential oral permeation and/or absorption enhancers have been identified including the categories of anionic surfactants, cationic surfactants, zwitterionic surfactants, nonionic surfactants, fatty acids, fatty esters, fatty amines, sodium salts of fatty acids, bile salts, nitrogen-containing rings, etc.

Hence, the present inventors have found a pharmaceutical composition containing zanamivir and an oral permeation enhancer which facilitates absorption of zanamivir through intestinal mucosa.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide a pharmaceutical composition comprising an antiviral neuraminidase inhibitor and a permeation enhancer with improved oral absorption and/or bioavailability.

In accordance with one aspect of the present invention, there is provided a pharmaceutical composition comprising an antiviral neuraminidase inhibitor and a permeation enhancer selected from the group consisting of anionic-, cationic-, zwitterionic- or nonionic surfactants, fatty acids or fatty acid derivatives, bile

acids or bile acid salts, cyclodextrins, chitosan or chitosan derivatives, phospholipids, nitrogen containing rings and a mixture thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

5

The above and other objects and features of the present invention will become apparent from the following description of the invention, when taken in conjunction with the accompanying drawings, in which:

10 FIG. 1 shows the effect of enhancers on apparent permeability (Papp) of zanamivir across the caco-2 monolayers;

FIG. 2 shows the plasma zanamivir concentration-time profiles after oral administration of the composition comprising zanamivir and various enhancers;

15 FIG. 3 shows the effect of sodium caprate amount on apparent permeability (Papp) of zanamivir across the caco-2 monolayers;

FIG. 4 shows the plasma zanamivir concentration-time profiles after oral administration of the composition comprising zanamivir and various amounts of sodium caprate enhancer; and

20 FIG. 5 shows the concentration of zanamivir in lung after oral or intravenous administration of the composition.

DETAILED DESCRIPTION OF THE INVENTION

25 As used herein, the singular forms “a”, “an”, and “the” include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to “an enhancer” includes a mixture of two or more enhancers.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. In addition, the materials, methods, and
30 Examples are illustrative only and not intended to be limited.

As used herein, the term “pharmaceutically acceptable” refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio.

As used herein, the term “drug” includes all forms thereof including optically pure enantiomers or mixtures, racemic or otherwise, as well as derivative forms, for example, salts, acids, esters, and the like. The drug may be provided in any suitable phase state including a solid, liquid, solution, suspension and the like. When provided in solid particulate form, the particles may be of any suitable size or morphology, and may assume one or more crystalline, semi-crystalline and/or amorphous forms.

The drug can be included in microparticulate or nanoparticulate forms in which the drug is, or is entrapped within, encapsulated by, attached to, or otherwise associated with, a microparticulate or nanoparticle.

As used herein, the term “effective amount” or “therapeutically effective amount” means a dosage or amount sufficient to provide treatment of influenza infection or to otherwise provide a desired pharmacologic and/or physiologic effect, for example, by reducing mortality or the severity of one or more symptoms. The precise dosage will vary according to a variety of factors such as subject-dependent variables (such as age, immune system health, other-related disease conditions and the like), and route of administration.

As used herein, the term “enhancer” refers to a compound or a mixture of compounds, which is capable of enhancing the transport of a drug, particularly hydrophilic and/or macromolecular drug across the GIT in an animal such as human. In the present invention, the enhancer may be among the categories of surfactants (anionic, cationic, zwitterionic, and nonionic), fatty acids or fatty acid derivatives, bile salts cyclodextrins, chitosan or chitosan derivatives, phospholipids, and nitrogen containing rings.

As used herein, the term “therapeutically effective amount of an enhancer” refers to an amount of enhancer that allows for uptake of therapeutically effective amounts of drug via oral administration. It has been shown that the effectiveness of an enhancer in enhancing the gastrointestinal
5 delivery of poorly permeable drugs is dependent on the drug, enhancer type, and/or route of administration and the like.

The present invention provides a pharmaceutical composition comprising antiviral neuraminidase inhibitor and a permeation enhancer selected from the
10 group consisting of anionic-, cationic-, zwitterionic- or nonionic surfactants, fatty acids or fatty acid derivatives, bile acids or bile acid salts, cyclodextrins, chitosan or chitosan derivatives, phospholipids, nitrogen containing rings and a mixture thereof.

15 The pharmaceutical composition of the present invention is useful for preventing or treating viral infections, in particular influenza (*e.g.*, influenza A and B viruses) infection.

Each ingredient of the inventive pharmaceutical composition is described
20 in detail as follows.

(1) Antiviral neuraminidase inhibitor

The active ingredient (drug) used in the pharmaceutical composition of
25 the present invention is an antiviral neuraminidase inhibitor selected from the group consisting of zanamivir, oseltamivir and peramivir, preferably zanamivir.

In each case the drug may be present in any amount which is sufficient to elicit a therapeutic effect. As will be appreciated by those skilled in the art, the actual amount of a drug compound used will depend on, among other things, the
30 potency of the drug, the specifics of the patient and the therapeutic purpose for

which the drug is being used.

The antiviral neuraminidase inhibitor may be contained in an amount ranging from 1 mg to 1,000 mg per 1 unit dosage form of the composition.

5 (2) Permeation enhancer

The permeation enhancer used in the pharmaceutical composition of the present invention interacts in a transient and reversible manner with the GIT cell lining increasing permeability and facilitating the absorption of otherwise poorly
10 permeable molecules.

In the present invention, the permeation enhancer may be selected from the group consisting of anionic-, cationic-, zwitterionic- or nonionic surfactants, fatty acids or fatty acid derivatives, bile acids or bile acid salts, cyclodextrins, chitosan or chitosan derivatives, phospholipids, nitrogen containing rings and a
15 mixture thereof.

The preferred permeation enhancer may include medium chain fatty acids and its salts, medium chain fatty acid esters of glycerol and propylene glycol, bile salts, and cyclodextrins.

In one embodiment, the enhancer may be a fatty acid or a fatty acid
20 derivative having a carbon chain length of 6 to 24 carbon atoms. Preferably, the enhancer may be a medium chain fatty acid, or a salt, ester, ether or other derivative thereof, which is solid at room temperature and which has a carbon chain length of 6 to 12 carbon atoms. More preferably, the enhancer may be a sodium salt of the medium chain fatty acid having a carbon chain length of 6 to
25 12 carbon atoms, wherein the sodium salt is solid at room temperature (*e.g.*, sodium caprylate, sodium caprate, and sodium laurate); or an esters of the medium chain fatty acid with glycerol and propylene glycol (*e.g.*, caprylocaproyl macrogol-8 glycerides (Labrasol[®])).

In another embodiment, the enhancer may be a bile acid or a bile acid salt,
30 preferably a salt of cholic acid (*e.g.*, sodium salt of cholic acid (sodium cholate)).

In another embodiment, the enhancer may be cyclodextrin, preferably hydroxypropyl β -cyclodextrin.

In the present invention, representative examples of the enhancer include sodium caprate, caprylocaproyl macrogol-8 glycerides, sodium cholate,
5 hydroxypropyl β -cyclodextrin and a mixture thereof.

The enhancer may be suitably present in any amount sufficient to allow for uptake of therapeutically effective amounts of the drug via oral administration. For example, the enhancer may be contained in an amount ranging from 30% to 70% by weight based on the total weight of the composition.

10

In the present invention, the pharmaceutical composition may comprise the antiviral neuraminidase inhibitor and the enhancer in a ratio ranging from 1:100,000 to 10:1, preferably from 1:1,000 to 10:1 by weight.

The actual ratio of the antiviral neuraminidase inhibitor to the enhancer
15 used will depend on, among other things, the potency of the articular drug and the enhancing activity of the particular enhancer.

In the present invention, the pharmaceutical composition may be formulated into a solid oral dosage form, which may be a tablet, a capsule or a
20 multiparticulate formulation, but is not limited thereto. A preferred solid oral dosage form is a delayed release dosage form, which minimizes the release of drug and enhancer in the stomach cavity, and hence the dilution of the local enhancer concentration therein, and releases the drug and enhancer in the intestine for enhanced absorption by the intestinal cells.

25 A particularly preferred solid oral dosage form is a delayed release rapid onset dosage form. Such a dosage form minimizes the release of the drug and enhancer in the stomach, and hence the dilution of the local enhancer concentration therein, but releases the drug and enhancer rapidly once the appropriate site in the intestine has been reached, maximizing the delivery of the
30 poorly permeable drug by maximizing the local concentration of the drug and

enhancer at the site of absorption.

As used herein, the term "tablet" includes, but is not limited to, conventional immediate release (IR) tablets, controlled release (CR) tablets, sustained release (SR) tablets, matrix tablets, multilayer tablets, multilayer matrix
5 tablets, extended release (ER) tablets, delayed release tablets, and pulsed release tablets.

Any or all of the inventive tablets may optionally be coated with one or more coating materials, including polymer coating materials, such as enteric coating materials, rate-controlling coating materials, semi-permeable coating
10 materials and the like, preferably enteric or rate-controlling coating materials. The coating process may be performed after the tablet is formed.

Tablet solid oral dosage forms particularly useful in the practice of the invention include those selected from the group consisting of IR tablets, CR tablets, SR tablets, coated IR tablets, matrix tablets, coated matrix tablets,
15 multilayer tablets, coated multilayer tablets, multilayer matrix tablets and coated multilayer matrix tablets.

A preferred tablet dosage form is an enteric coated tablet dosage form. A particularly preferred tablet dosage form is an enteric coated rapid onset tablet dosage form. In one embodiment of the present invention, the tablet may be IR
20 tablets, SR tablets, enteric coated IR tablets, enteric coated SR tablets or multilayer tablets.

As used herein, the term "capsule" includes instant release capsules, controlled release capsules, sustained release capsules, coated instant release capsules, coated sustained release capsules, delayed release capsules and coated
25 delayed release capsules. Any or all of the inventive capsules may optionally be coated with one or more coating materials, including polymer coating materials, such as enteric coatings, rate-controlling coatings, semi-permeable coatings and the like. A preferred capsule dosage form is an enteric coated capsule dosage form. A particularly preferred capsule dosage form is an enteric coated rapid
30 onset capsule dosage form. In one embodiment of the present invention, the

capsule may be IR capsules, SR capsules, enteric coated IR capsules or enteric coated SR capsules.

As used herein, the term “multiparticulate” means a plurality of discrete particles, pellets, mini-tablets and a combination thereof. If the oral form is a multiparticulate capsule, the multiparticulate can suitably be encapsulated into a hard or soft gelatin capsules. Alternatively the multiparticulate can suitably be incorporated into a sachet.

The multiparticulate may be coated with a layer containing rate-controlling polymer material. The multiparticulate oral dosage form may comprise a blend of two or more populations of particles, pellets, or mini-tablets having different *in vitro* and/or *in vivo* release characteristics. For example, a multiparticulate oral dosage form may comprise a blend of an instant release component and a delayed release component contained in a suitable capsule.

In one embodiment, the multiparticulate dosage form comprises a capsule containing delayed release rapid onset minitabets. In another embodiment, the multiparticulate dosage form comprises a delayed release capsule comprising instant release minitabets. In a further embodiment, the multiparticulate dosage form comprises a capsule comprising delayed release granules. In yet another embodiment, the multiparticulate dosage form comprises a delayed release capsule comprising instant release granules.

In another embodiment, the multiparticulate together with one or more auxiliary excipient materials may be compressed into tablet form such as a single layer or multilayer tablet. Typically, a multilayer tablet may comprise two layers containing the same or different levels of the same active ingredient having the same or different release characteristics. Alternatively, a multilayer tablet may contain different active ingredient in each layer. Such a tablet, either single layered or multilayered, can optionally be coated with a controlled release polymer so as to provide additional controlled release properties.

A number of embodiments of the invention will now be described.

In one embodiment of the present invention, the dosage form containing zanamivir, enhancer, and excipients is a solid oral dosage formulation chosen among tablet, capsule, or multiparticulate formulation. The dosage form can be
5 a controlled release dosage form, most preferably delayed release with rate-controlling polymer matrix or coating.

In one embodiment, there is provided a pharmaceutical composition and a solid oral dosage form prepared therefrom, which comprises zanamivir and the permeation enhancer to promote absorption of zanamivir at the GIT cell lining, a
10 medium chain fatty acid or a medium chain fatty acid derivative having a carbon chain length of from 6 to 12 carbon atoms, wherein the enhancer and the composition are solids at room temperature.

In another embodiment, there is provided a multilayer tablet comprising a composition of the present invention. Typically such a multilayer tablet may
15 comprise a first layer containing a drug and an enhancer in an instant release form and a second layer containing a drug and an enhancer in a modified release form.

As used herein, the term "modified release" includes sustained, delayed, or otherwise controlled release of a drug upon administration to a patient.

In an alternative embodiment, a multilayer tablet may comprise a first
20 layer containing a drug and a second layer containing an enhancer. Each layer may independently comprise further excipients chosen to modify the release of the drug or the enhancer. Thus the drug and the enhancer may be released from the respective first and second layers at rates which are the same or different. Alternatively, each layer of the multilayer tablet may comprise both drug and
25 enhancer in the same or different amounts.

In yet another embodiment, there is provided a multiparticulate comprising a composition of the present invention. The multiparticulate may comprise particles, pellets, mini-tablets or combinations thereof, and the drug and the enhancer may be contained in the same or different populations of particles,
30 pellets or mini-tablets making up the multiparticulate.

In multiparticulate embodiments, sachets and capsules such as hard or soft gelatin capsules can suitably be used to contain the multiparticulate. A multiparticulate dosage form may comprise a blend of two or more populations of particles, pellets or mini-tablets having different *in vitro* and/or *in vivo* release characteristics. For example, a multiparticulate dosage form may comprise a blend of an immediate release component and a delayed release component contained in a suitable capsule.

In the case of any of the above-mentioned embodiments, a controlled release coating may be applied to the final dosage form (capsule, tablet, multilayer tablet, etc.). The controlled release coating may typically comprise a rate controlling polymer material as defined above. The dissolution characteristics of such a coating material may be pH-dependent or independent.

The various embodiments of the solid oral dosage forms of the invention may further comprise auxiliary excipient materials such as, for example, diluents, lubricants, disintegrants, plasticizers, anti-tack agents, opacifying agents, pigments, flavorings and the like. As will be appreciated by those skilled in the art, the exact choice of excipients and their relative amounts will depend to some extent on the final dosage form.

Suitable diluents include, for example, pharmaceutically acceptable inert fillers such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose, lactose (lactose monohydrate, lactose anhydrous, etc.), dibasic calcium phosphate, mannitol, starch, sorbitol, sucrose, and glucose.

Suitable lubricants, including agents that act on the flowability of the powder to be compressed are, for example, colloidal silicon dioxide, talc, stearic acid, magnesium stearate and calcium stearate.

Suitable disintegrants include, for example, lightly cross-linked polyvinyl pyrrolidone, corn starch, potato starch, maize starch and modified starches,

croscarmellose sodium, cross-povidone, sodium starch glycolate and combinations and mixtures thereof.

Preferably, the diluent may be used in an amount ranging from 10 to 80% by weight; the lubricant may be used in an amount ranging from 0.1 to 5% by weight; and the disintegrant may be used in an amount ranging from 1 to 10% by weight, based on the total weight of the composition.

The following Examples are provided to illustrate preferred embodiments of the invention, and are not intended to limit the scope of the present invention.

10

Preparation of Immediate Release (IR) Tablets- (1)

Examples 1 to 3

Each of the tablets of Example 1 to 3 was prepared by using the composition described in Table 1. The ingredients described in the Table 6 were passed through #30 mesh and mixed well according to the corresponding amounts. The mixture was then formulated into direct-compression tablets.

The amount of sodium caprate contained in the tablets of Examples 1 to 3 was 70%, 60%, and 50% (w/w) based on the total weight of the tablet, respectively.

20

Comparative Example 1

The procedure of Example 1 was repeated except for without adding sodium caprate enhancer.

25

<TABLE 1>

Ingredients	Amount (mg)			
	Example 1	Example 2	Example 3	Comparative Example 1
Zanamivir	10.00	10.00	10.00	10.00
Sodium caprate	490.00	320.00	210.00	-
Microcrystalline cellulose	105.50	105.50	105.50	105.50
Anhydrous dicalcium phosphate	75.50	75.50	75.50	75.50
Carboxymethyl cellulose sodium	8.50	8.50	8.50	8.50
Magnesium stearate	4.50	4.50	4.50	4.50
Sodium stearyl fumarate	4.00	4.00	4.00	4.00

Preparation of IR Tablets by dry granulation (2)

5 Each of the tablets of Example 1 to 3, and Comparative Example 1 was prepared based on the procedure of Example 1 and Comparative Example 1 except that the dry granulation of the compositions was formed before tabulating.

The ingredients were mixed together except for magnesium stearate, and dry-granulated using a roller compactor to prepare the granules. The granules
 10 thus obtained were then mixed with lubricant, *e.g.*, magnesium stearate and mixed for 5 minutes. The resulting mixture was formulated into a tablet.

Preparation of Sustained Release (SR) Tablets

15 Examples 4 to 6

The procedure of Example 1 was repeated except for using the composition described in Table 2.

Comparative Example 2

20 The procedure of Comparative Example 1 was repeated except for using the composition described in Table 2.

<TABLE 2>

Ingredients	Amount (mg)			
	Example 4	Example 5	Example 6	Comparative Example 2
Zanamivir	10.00	10.00	10.00	10.00
Sodium caprate	490.00	320.00	210.00	-
Microcrystalline cellulose	105.50	105.50	105.50	105.50
Hydroxypropyl methylcellulose	75.50	75.50	75.50	75.50
Carboxymethyl cellulose sodium	8.50	8.50	8.50	8.50
Polyvinylpyrrolidone	12.50	12.50	12.50	12.50
Silicondioxide	2.50	2.50	2.50	2.50
Sodium stearyl fumarate	4.00	4.00	4.00	4.00

Preparation of Enteric Coated IR and SR Tablets

5 Examples 7 and 8

The IR and SR tablets prepared in Examples 1 and 4 were coated with the enteric coating material described in Table 3 with a weight gain of 5% of the tablet weight.

10 Comparative Examples 3 and 4

The IR and SR tablets prepared in Comparative Examples 1 and 2 were coated with the enteric coating material described in Table 3 with a weight gain of 5% of the tablet weight.

<TABLE 3>

Coating solution for 5% weight gain	
Ingredients	Amount (mg)
Eudragit L-30 D-55	7.4
Triethyl citrate	0.74
Talc	0.92
Purified water	q.s.

Preparation of IR Capsules

Example 9

(1) Granule preparation

IR capsule was prepared by using the composition described in Table 4.

5 Zanamivir, sodium caprate, microcrystalline cellulose, anhydrous dicalcium phosphate, and carboxymethylcellulose sodium were each passed through #30 mesh, and mixed in a high-speed mixer for 3 minutes. A mixture of water and ethanol solution containing polyvinylpyrrolidone was added to the mixture, and mixed again for another 5 minutes. The resulting mixture was deposited on the

10 inner wall of the high-speed mixer, scrapped off and further stirred for another 2 minutes. The final mixture was then dried in tray oven at 60 °C, granulated and then mixed with lubricants, *e.g.*, magnesium stearate and sodium stearyl fumarate, to obtain zanamivir granules.

15 (2) Encapsulation:

The zanamivir granules thus obtained were filled into hard gelatin capsules to an appropriate target fill weight.

Comparative Example 5

20 The procedure of Example 9 was repeated except for without adding sodium caprate enhancer.

<TABLE 4>

Ingredients	Amount (mg)	
	Example 9	Comparative Example 5
Zanamivir	10.00	10.00
Sodium caprate	490.00	-
Microcrystalline cellulose	105.50	105.50
Anhydrous dicalcium phosphate	75.50	75.50
Carboxymethyl cellulose sodium	8.50	8.50
Polyvinylpyrrolidone	12.50	12.50
Magnesium stearate	4.50	4.50
Sodium stearyl fumarate	4.00	4.00

Preparation of SR Capsules

Example 10

5 The granule preparation procedure of Example 9 was repeated except for using the composition described in Table 5, and the zanamivir granules thus obtained were encapsulated into hard gelatin capsules.

Comparative Example 6

10 The procedure of Example 10 was repeated except for using the composition described in Table 5.

<TABLE 5>		
Ingredients	Amount (mg)	
	Example 10	Comparative Example 6
Zanamivir	10.00	10.00
Sodium caprate	490.00	-
Microcrystalline cellulose	105.50	105.50
Hydroxypropyl methylcellulose	75.50	75.50
Carboxymethyl cellulose sodium	8.50	8.50
Polyvinylpyrrolidone	12.50	12.50
Silicondioxide	2.50	2.50
Sodium stearyl fumarate	4.00	4.00

15 Preparation of Enteric Coated IR Capsules

Example 11

The IR capsule prepared in Example 9 was coated with the enteric coating material in accordance with the procedure of Example 7.

20

Preparation of Enteric Coated SR Capsules

Example 12

The SR capsule prepared in Example 10 was coated with the enteric coating material in accordance with the procedure of Example 7.

Test Example 1: Effect of permeation enhancers on zanamivir permeation

5

Caco-2 Cell Monolayer Drug Transport Study

Caco-2 cell culture study was performed with liquid formulation as a preliminary study in order to investigate the effect of the permeation enhancers and concentration effect.

10

1-1: Monolayer Growth

The adenocarcinoma cell line caco-2 was obtained from the American Type Culture Collection (Rockville, MD). The cells were cultured at 37°C in an atmosphere of 95% relative humidity and 5% CO₂. The used medium was a standard medium consisting of Dulbecco's Modified Eagles Medium (DMEM) comprising 4.5 g/L glucose supplemented with 10% heat inactivated fetal bovine serum and 1% penicillin/streptomycin. The cells were grown as permanent cultures in 75 cm² culture flasks, and the medium was changed twice a week. The cells were trypsinized when they reach more than 90% confluency. The caco-2 cells were then seeded on 12-well polycarbonate filter inserts (Transwell, Costar, USA), with surface area of 1.12 cm² and pore size of 0.4 μm, with a density of 5 X 10⁵ cells/cm². The medium was changed every other day and the cell cultures were at no time found to be infected. All the related experiments were done with cell passage number between 28 to 40 and confluent monolayers between 21 to 30 days after seeding on filters.

1-2: Transport studies (Transepithelial transport)

The effects of permeation enhancers on the transport of zanamivir from

apical to basolateral were investigated using Hank's Balanced Salt Solution (HBSS) of pH 7.4 at 37°C.

Before the start of experiment, the DMEM was removed completely from the Transwell plate with caco-2 monolayer, and washed twice with pre-warmed phosphate buffer saline (37 °C). The plate was then filled with pre-warmed HBSS (37 °C) both apically and basolaterally of 0.5 ml and 1 ml, respectively, and transepithelial electrical resistance (TEER) of the monolayers were measured. Monolayers with TEER value of more than 250 ohms cm² were only selected for the experiment, and were incubated for 30 minutes in an orbital shaking incubator (rpm 50 and temperature 37 ± 0.5 °C).

Test solution samples which contain the zanamivir with or without the permeation enhancers were prepared in accordance with the composition described in Table 6. The test solution samples were prepared by dissolving 50 µM of zanamivir (ZMR) first in the appropriate amount of HBSS, and stirred well to obtain a clear ZMR solution. Each permeation enhancer in an amount of 0.01% by weight based on the total weight of the ZMR solution was then added to the ZMR solution, and stirred again until a clear solution is obtained, to prepare a resulting the test solution samples.

20

<TABLE 6>

Sample	Zanamivir (µM)	Permeation enhancer (0.01%)	Buffer Medium
Control	50	-	HBSS
PEF-001	50	Labrasol	HBSS
PEF-002	50	Sodium caprate	HBSS
PEF-003	50	Hydroxypropyl β-cyclodextrin	HBSS
PEF-004	50	Sodium cholate	HBSS

At the start of the experiment (time 0), apical HBSS was replaced with the prepared test solution samples described in Table 6. The transport across the monolayers was measured by sampling at basolateral well at 30, 60, 90, and 120 minutes. At each sampling, the inserts were transferred to a new plate containing 1 ml of fresh pre-warmed HBSS basolaterally. Apical test solution sample was

taken before and at the end of the experiment. The samples were analyzed by LC-MS/MS method mentioned below.

1-3: Zanamivir Analysis

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Analysis of zanamivir was performed using Agilent™ 1100series (USA). Zanamivir was separated on an Atlantis dC18 (2.0 X 100mm, 5µm). The isocratic mobile phase consisted of acetonitrile/10 mM ammonium acetate (20/80 (v/v %)). The flow rate of the mobile phase and the column oven temperature were set at 0.3 ml/min and 30 °C, respectively.

The LC system was coupled to an API 4000 Qtrap mass spectrometer equipped with turbo ion spray ionization source (AB MDS Sciex, Toronto, Canada). The turbo ion spray ionization source was operated in a positive mode. The curtain gas, nebulizer gas, and the turbo gas (nitrogen) pressures were set at 10, 50, and 40 psi, respectively. The turbo gas temperature was set at 600°C, and the ion spray needle voltage was adjusted to 5500 V.

The mass spectrometer was operated at a unit resolution for both Q1 and Q3 in the multiple reaction monitoring (MRM) mode with a dwell time of 300 ms in each transition. The transition of the precursors to the product ion was monitored at 333.2 → 60.1 for zanamivir, 278.2 → 152.0 for entacavir (as an internal standard). The collision energy was set at medium. Data acquisition was performed with the Analyst 1.4 software (AB MSD Sciex, Toronto, Canada). Mean values of 3 samples (n=3 wells) were calculated for the apical to basolateral solutions at each time point. The apparent permeability coefficients were calculated using the following Equation 1. The results are shown in FIG. 1.

<Equation 1>

$$\text{Permeability coefficient : } P_{\text{app}} = \left(\frac{dQ/dt}{C_0 \times A} \right)$$

30

wherein,

dQ/dt is the rate of permeation of the drug across the cells;

C_0 is the donor compartment concentration at time 0; and

A is the area of the cell monolayer.

5 C_0 is obtained from analysis of the dosing solution at the start of experiment.

FIG. 1 shows the effect of enhancers on apparent permeability (P_{app}) of zanamivir across the caco-2 monolayers. As shown in FIG. 1, all tested
10 enhancers showed a significant increase of zanamivir permeation, compared to that of the control with no enhancer. Most specifically, sodium caprate and Labrasol demonstrated most considerable permeation enhancement of zanamivir across the cell lines.

15 1-4: *In vivo* oral PK/BA study in rats

In vivo study was performed with the liquid formulation as a preliminary study to confirm the effect of enhancer effect in rats.

Male Sprague-Dawley (SD) rats weighing about 275–315 g were used for
20 this study. The rats were anaesthetized by intraperitoneal injection of ketamine and xylazine (90:10 mg/kg), and cannulated with a polyethylene (PE) tubing (0.58 mm i.d., 0.96 mm o.d., Natsume, Tokyo, Japan) in the left femoral artery and vein.

Test solution samples were prepared in accordance with the composition described in Table 7. The test solution samples were prepared by dissolving 30
25 mM of ZMR first in the appropriate amount of the purified water, and stirred well to obtain a clear ZMR solution. Each permeation enhancer in an amount of 5% by weight based on the total weight of the ZMR solution was then added to the ZMR solution, and stirred again until a clear solution is obtained, to prepare a resulting the test solution samples.

30 And the test solution samples were orally administered to the rats ($n = 3$

each) in a bolus dose equivalent to zanamivir in an amount of 50 mg/kg of animal body weight containing the permeation enhancers in an amount of 5% by weight based on the total solution.

5

<TABLE 7>

Sample	Zanamivir (mM)	Permeation enhancer (5%)	Solution Medium
Control	30	-	Purified water
PEF-005	30	Labrasol	Purified water
PEF-006	30	Sodium caprate	Purified water
PEF-007	30	Hydroxypropyl β -cyclodextrin	Purified water
PEF-008	30	Sodium cholate	Purified water

Then, blood samples were collected from femoral veins of the rats prior to and at 0.5, 1, 2, 3, 4, 6, 8, and 24 hr after administration. The oral administration was performed under conscious condition. Plasma samples were harvested by
 10 centrifugation at 1,500 g for 10 min and stored at -20 °C until analysis. The analysis was performed using LC-MS/MS method as mentioned in above. The results are shown in FIG. 2.

FIG. 2 shows the plasma levels of zanamivir-time profiles after administration. As shown in FIG. 2, the permeation enhancers except for
 15 hydroxypropyl β -cyclodextrin (PEF-007) showed a higher absorption compared to that of the control with no permeation enhancer.

The $C_{\max}$ was about 5 times higher for all permeation enhancers except hydroxypropyl β -cyclodextrin. The AUC was about two times higher for the sodium caprate and sodium cholate. The AUC was either similar or lower than
 20 the control for the labrasol and hydroxypropyl β -cyclodextrin, respectively. The bioavailability (BA)(%) of ZMR was about two folds higher for sodium caprate. The BA% of other enhancers was not significantly higher than control.

Test Example 2: Effect of sodium caprate enhancer concentration on
 25 **zanamivir permeation**

The objective of this study was to investigate the effect of amounts of sodium caprate enhancer on the permeability of zanamivir in caco-2 monolayer as well as on the oral bioavailability in the rats.

5 2-1: Transport studies (Transepithelial transport)

The effects of sodium cholate enhancer concentration on zanamivir permeation from apical to basolateral were investigated using Hank's Balanced Salt Solution (HBSS) of pH 7.4 at 37°C.

Test solution samples were prepared in accordance with the composition described in Table 8. The test solution samples were prepared by dissolving 50 μ M of ZMR first in the appropriate amount of HBSS, and stirred well to obtain a clear ZMR solution. Sodium cholate in an amount of 0%, 2.5%, 5%, 7.5% and 10% by weight based on the total weight of the ZMR solution was then added to the ZMR solution, and stirred again until a clear solution is obtained, to prepare a resulting the test solution samples.

<TABLE 8>

Sample	Zanamivir (μ M)	Sodium cholate (%)	Buffer
Control	50	-	HBSS
PEF-009	50	2.5	HBSS
PEF-010	50	5.0	HBSS
PEF-011	50	7.5	HBSS
PEF-012	50	10.0	HBSS

At the start of the experiment (time 0), apical HBSS was replaced with the prepared test solution samples described in Table 3. The transport across the monolayers was measured by sampling at basolateral well at 30, 60, 90, and 120 minutes. At each sampling, the inserts were transferred to a new plate containing 1 ml of fresh pre-warmed HBSS basolaterally. Apical test solution samples were taken before and at the end of experiment. The samples were analyzed by LC-MS/MS method mentioned in Test Example 1. The results are shown in FIG. 3.

The FIG. 3 shows the effect of sodium cholate amount on apparent permeability (P_{app}) of zanamivir across the caco-2 monolayers. As shown in

FIG. 3, compared to control, all tested samples comprising sodium cholate showed a significant increase of zanamivir permeation. However, there was no significant difference observed between the permeation with increased amount of enhancer, sodium cholate.

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2-2: In vivo oral PK/BA study in rats

The test solution samples were prepared in accordance with the composition described in Table 9. The test solution samples were prepared by dissolving 50 μ M of ZMR first in the appropriate amount of the purified water, and stirred well to obtain a clear ZMR solution. Sodium caprate in an amount of 0%, 2.5%, 5%, 7.5% and 10% by weight based on the total weight of the ZMR solution was then added to the ZMR solution, and stirred again until a clear solution is obtained, to prepare a resulting the test solution samples.

And the test solution samples described in Table 9 were orally administered to the rats (n = 3 each) in a bolus dose equivalent to zanamivir in an amount of 50 mg/kg of animal body weight containing the sodium caprate in an amount described in Table 9

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<TABLE 9>

Sample	Zanamivir (mM)	Sodium caprate (%)	Solution Medium
Control	30	-	Purified water
PEF-013	30	2.5	Purified water
PEF-014	30	5	Purified water
PEF-015	30	7.5	Purified water
PEF-016	30	10	Purified water

Then, blood samples were collected from the femoral vein of the rats prior to and at 0.5, 1, 2, 3, 4, 6, 8, and 24 hr after administration. The oral administration was performed under conscious condition. The results are shown in FIG. 4.

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FIG. 4 shows the plasma levels of zanamivir-time profiles after oral administration. Sodium caprate enhanced the permeation and BA (%) of

zanamivir in the rats compared to that of the control. Among the four concentrations tested, 7.5% and 10% of sodium caprate were comparable to each other and showed a higher BA compared to that of 2.5% and 5% of sodium caprate in PK/BA study.

5

Test Example 3: In vivo zanamivir lung content study in rats

The objective of this study was to investigate the concentration of zanamivir that reaches lung after oral or intravenous (i.v.) administration.

10 The zanamivir concentration in lung is vital for the therapeutic effect as the influenza virus replicates in the lung surface. For this study, male Sprague-Dawley (SD) rats weighing about 275–315 g were used. The test solution samples for oral or intravenous administration were prepared in accordance with the composition described in Table 10. LCF-001 formulation for intravenous
15 administration was prepared by dissolving 10 mg of ZMR in 10 ml (1 mg/ml) of saline solution. LCF-002 formulation for oral administration without enhancer (control) was prepared by dissolving 100 mg of ZMR in 10 ml (10 mg/ml) of the purified water. LCF-003 formulation for oral administration with enhancer was prepared by dissolving 100 mg of ZMR in 10 ml (10 mg/ml) of the purified water
20 to obtain a clear solution. Sodium caprate in an amount of 10% by weight based on the ZMR solution was added thereto, and stirred again until a clear solution is obtained. LCF-001 formulation was administered by intravenous route in 1 mg/kg dosage, and LCF-002 and LCF-003 formulations were administered by oral route in 10 mg/kg to the rats.

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<TABLE 10>

Sample	Route of administration	Dosage (mg/kg)	Formulation
LCF-001	intravenous	1	Saline solution
LCF-002	oral	10	Aqueous solution
LCF-003	oral	10	zanamivir with enhancer 10% sodium caprate

At each sampling points (0, 0.08, 0.25, 0.5, 1, 2, 4, 8 and 24 hr) after either oral or intravenous administration of the test solution samples, the rats were sacrificed and a chest incision was made to extract the lungs. The lungs were then washed with saline twice and weighed after removal of water by dry wipes.

5 The lungs were then transferred into E-tube containing 4% bovine serum albumin solution (5 time dilution), homogenized well, and stored in the freezer (-80°C) until analysis. Zanamivir from the homogenate was extracted and analyzed by the LC-MS/MS method described in above. The results are shown in FIG. 5.

FIG. 5 shows the concentration of zanamivir in lung after oral or

10 intravenous administration of the formulations. The formulation with sodium caprate enhancer (LCF-003) showed enhanced lung concentration in comparison to aqueous solution of zanamivir alone without enhancer (LCF-002). The enhanced lung concentration is possibly due to the enhanced absorption/BA of zanamivir by the permeation enhancer, sodium caprate.

15

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.

20

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising an antiviral neuraminidase inhibitor, and a permeation enhancer selected from the group consisting of anionic-, cationic-, zwitterionic- or nonionic surfactants, fatty acids or fatty acid derivatives, bile acids or bile acid salts, cyclodextrins, chitosan or chitosan derivatives, phospholipids, nitrogen containing rings and a mixture thereof.
2. The pharmaceutical composition of claim 1, wherein the enhancer is fatty acids or fatty acid derivatives having a carbon chain length of 6 to 24 carbon atoms.
3. The pharmaceutical composition of claim 2, wherein the enhancer is a medium chain fatty acid, or a salt, ester, ether or a derivative thereof, which has a carbon chain length of 6 to 12 carbon atoms.
4. The pharmaceutical composition of claim 3, wherein the enhancer is a sodium salt of a medium chain fatty acid selected from the group consisting of sodium caprylate, sodium caprate, and sodium laurate.
5. The pharmaceutical composition of claim 1, wherein the enhancer is selected from the group consisting of sodium caprate, caprylocaproyl macrogol-8 glycerides, sodium cholate, hydroxypropyl β -cyclodextrin and a mixture thereof.
6. The pharmaceutical composition of claim 1, which comprises the antiviral neuraminidase inhibitor and the permeation enhancer in a ratio ranging from 1:100,000 to 10:1 by weight.
7. The pharmaceutical composition of claim 1, wherein the antiviral neuraminidase inhibitor is selected from the group consisting of zanamivir,

oseltamivir and peramivir.

8. The pharmaceutical composition of claim 7, wherein the antiviral neuraminidase inhibitor is zanamivir.

9. A pharmaceutical formulation prepared by employing the pharmaceutical composition of claim 1.

10. The pharmaceutical formulation of claim 9, wherein the composition is a solid oral dosage form.

11. The pharmaceutical formulation of claim 10, wherein solid oral dosage form is a tablet, a capsule, or a multiparticulate.

12. The pharmaceutical formulation of claim 10, which is a delayed release dosage form.

13. The pharmaceutical formulation of claim 11, which is an intermediate release (IR) tablet, a sustained release (SR) tablet, or a multilayer tablet.

14. The pharmaceutical formulation of claim 9, which is coated with one or more coating materials selected from the group consisting of an enteric material, a rate-controlling material and a semi-permeable material.

15. The pharmaceutical formulation of claim 14, wherein the pharmaceutical formulation is a tablet and the coating is performed after a tablet is compressed.

16. The pharmaceutical formulation of claim 15, which is an IR tablet, a SR tablet, or a multilayer tablet.

17. The pharmaceutical formulation of claim 11, wherein the multiparticulate is selected from the group consisting of a discrete particle, a pellet, a minitabket and a combination thereof.

18. The pharmaceutical formulation of claim 17, wherein the multiparticulate comprises a blend of two or more populations of particles, pellets, or minitabkets.

19. The pharmaceutical formulation of claim 18, wherein the blend of two or more populations of particles, pellets or minitabkets in the multiparticulate have different *in vitro* or *in vivo* release characteristics.

20. The pharmaceutical formulation of claim 11, wherein the multiparticulate is encapsulated into a hard or soft gelatin capsule.

21. The pharmaceutical formulation of claim 20, wherein the capsule is coated with one or more coating materials selected from the group consisting of an enteric material, a rate-controlling material and a semi-permeable material.

22. The pharmaceutical formulation of claim 11, wherein the multiparticulate is incorporated into a sachet.

23. The pharmaceutical formulation of claim 11, wherein the multiparticulate is compressed into a tablet.

24. The pharmaceutical formulation of claim 23, wherein the tablet is coated with one or more coating materials selected from the group consisting of an enteric material, a rate-controlling material and a semi-permeable material.

25. The pharmaceutical formulation of claim 24, wherein the tablet is an IR tablet, a SR tablet, or a multilayer tablet.

26. The pharmaceutical formulation of claim 9, which is a delayed release enteric coated tablet.

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FIG. 1

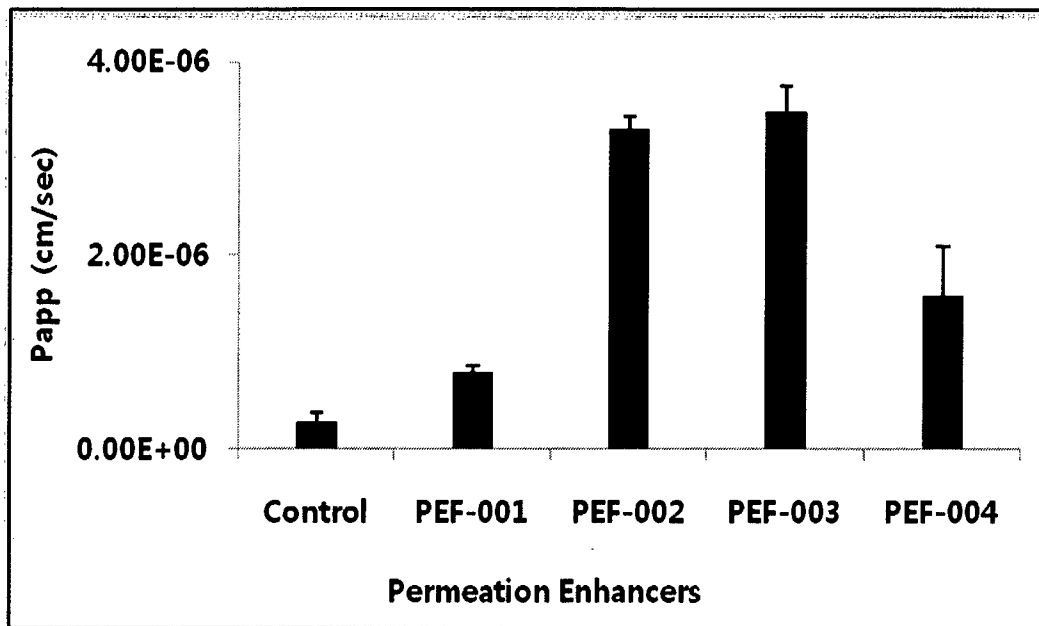
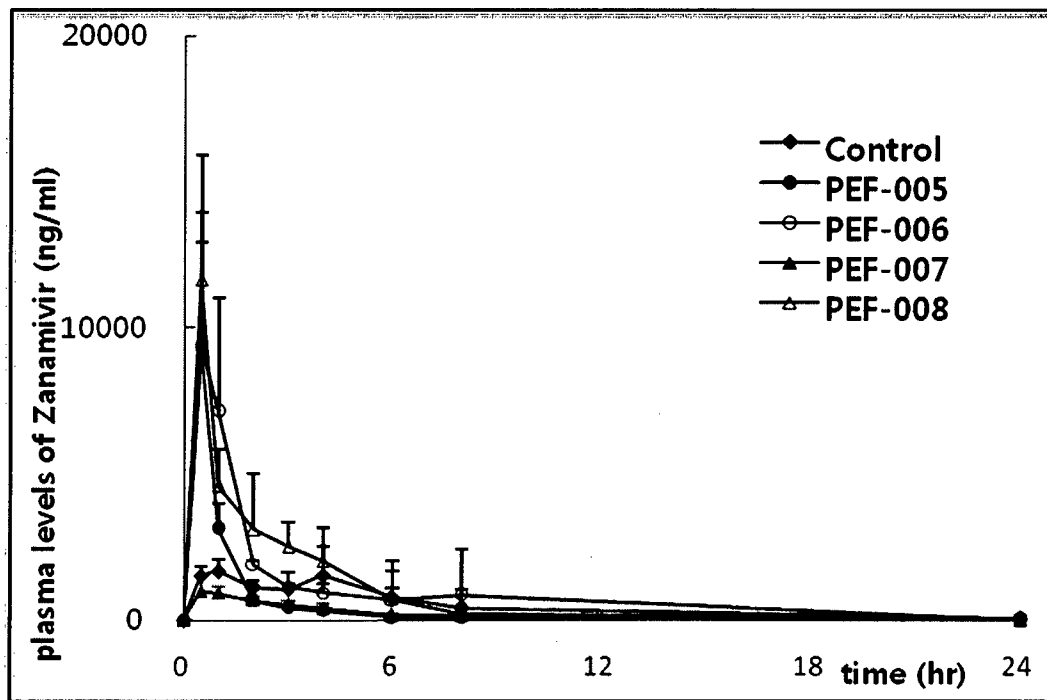


FIG. 2



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FIG. 3

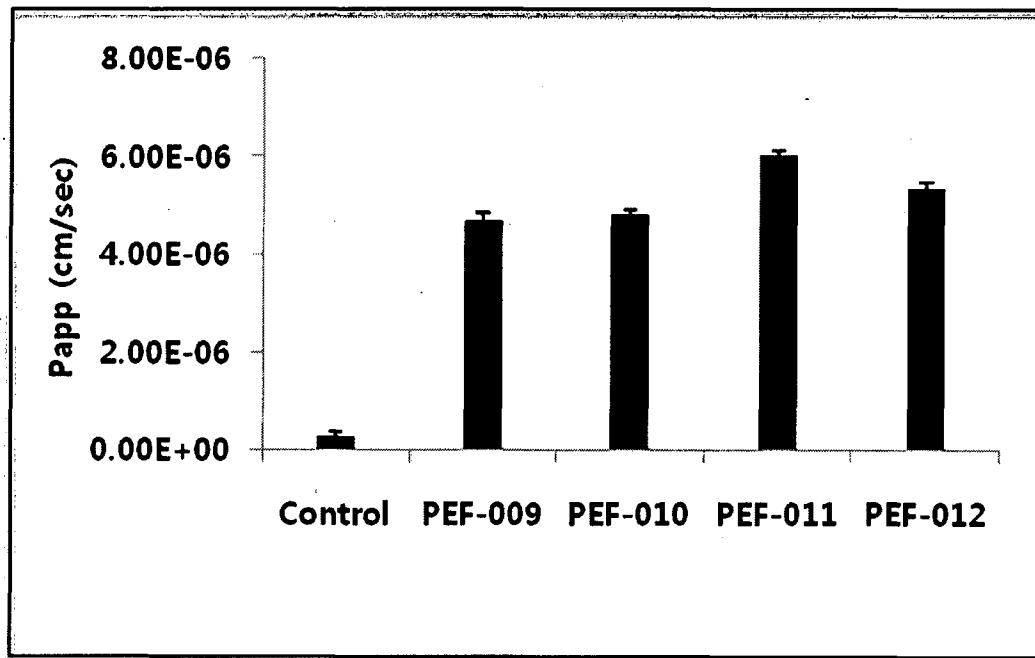
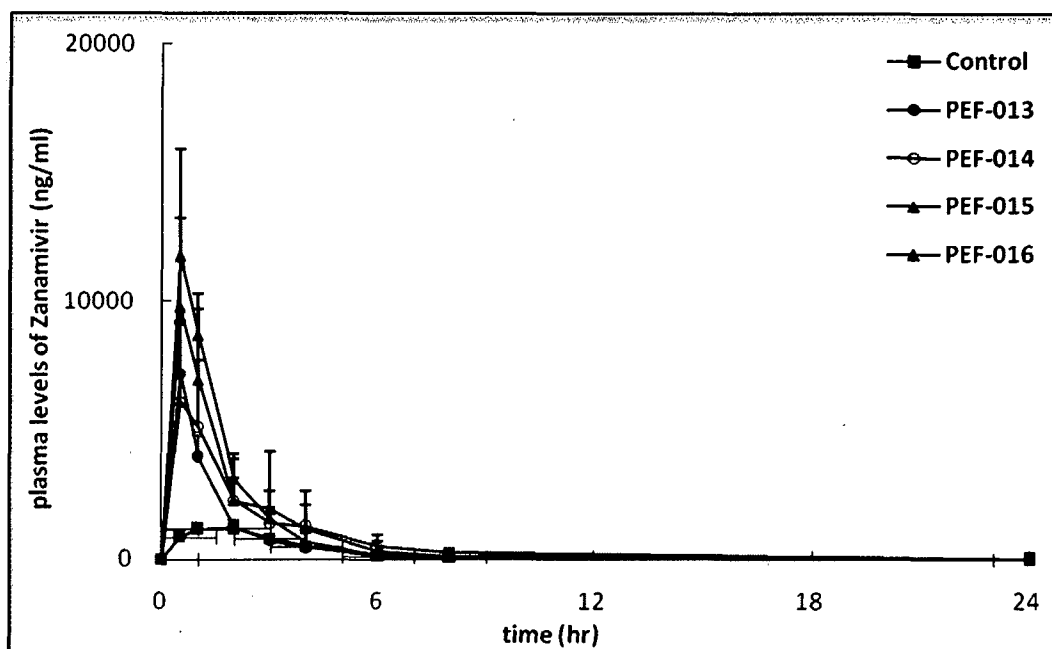
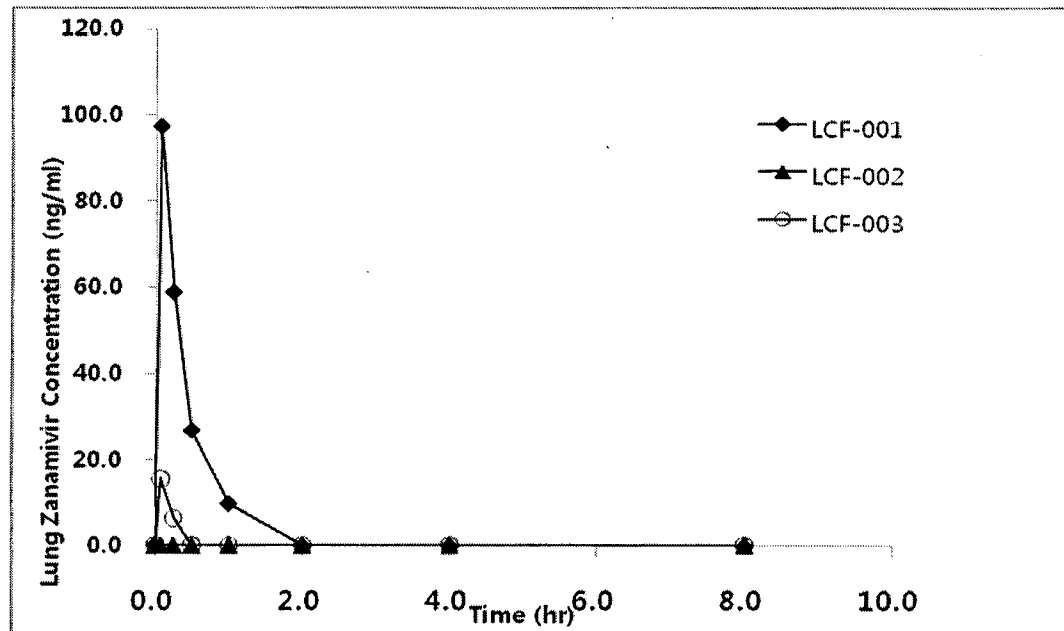


FIG. 4



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FIG. 5



A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/351(2006.01)i, A61K 31/185(2006.01)i, A61K 47/40(2006.01)i, A61K 9/24(2006.01)i, A61K 9/22(2006.01)i, A61K 9/20(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K31/351

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal) & keywords: antiviral, neuraminidase inhibitor, permeation enhancer, influenza, bioavailability, Caco, zanamivir, oseltamivir, peramivir

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011-0206764 A1 (HOLMES, E. et al.) 25 August 2011 See abstract, paragraphs [0003], [0019], [0023], [0027], [0038], [0041], [0044], [0047], [0048] and claims 1, 2, 7, 8.	1-26
Y	US 2004-0062801 A1 (FAOUR, J. et al.) 1 April 2004 See abstract paragraph [0023] and claims 1, 2, 3, 4, 13, 25, 31.	1-26
Y	SHAH, P. et al. 'Modulation of Ganciclovir intestinal absorption in presence of absorption enhancers' Pharmaceutical technology, October 2007, Vol. 96, No. 10, pp.2710-2722 See abstract and conclusion.	1-26
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Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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

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Date of the actual completion of the international search

15 MARCH 2013 (15.03.2013)

Date of mailing of the international search report

15 MARCH 2013 (15.03.2013)

Name and mailing address of the ISA/KR



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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2012/005828

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