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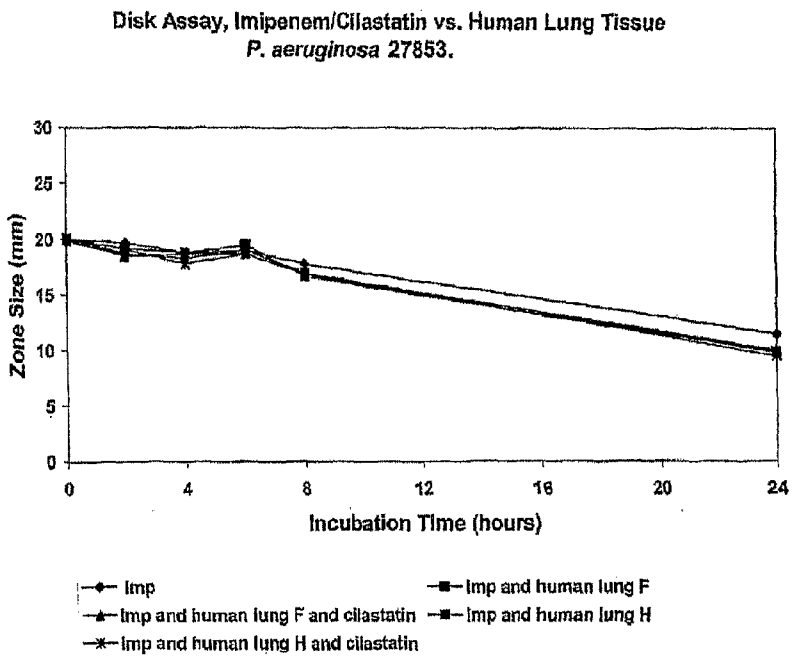
(54) Title: INHALED IMIPENEM



(57) Abstract: The present invention relates to inhaled formulations containing imipenem for increased efficacy and decreased toxicity in treating microbial infections.

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INHALED IMIPENEM

FIELD OF THE INVENTION

The present invention relates to inhaled formulations containing imipenem without cilastatin for increased efficacy and decreased toxicity in treating microbial infections.

BACKGROUND

Imipenem (N-formimidoylthienamycin) is an antibiotic derived from thienamycin which is produced by *Streptomyces cattleya*. Imipenem was found to be subject to metabolism by a dipeptidase (dehydropeptidase I) located on the luminal surface of the proximal tubular cells. This metabolic liability results in nephrotoxic biotransformation products and very low levels of the drug intact in the kidney and urine of many mammalian species, including man. Imipenem is highly active against Gram-positive and Gram-negative organisms. Thus attempts were made to overcome this metabolic liability and was successfully achieved by co-formulating imipenem with a potent inhibitor of dehydropeptidase, known as cilastatin. The 1:1 combination of cilastatin sodium and imipenem is available for intravenous administration and is used for treatment of several infections, including lower respiratory tract infection. Imipenem is also available in this combination with cilastatin for intramuscular injection. To date, there is no oral formulation of imipenem or in combination with cilastatin.

When administered alone, imipenem is metabolized in the kidneys resulting in relatively low levels in urine. Cilastatin effectively prevents renal metabolism of imipenem so that when imipenem and cilastatin are given together, imipenem remains active and this is due to matching pharmacokinetic profiles of the two drugs.

After I.V. or I.M. administration, imipenem appears to show high levels in the plasma and relatively good concentration in tissues, including lung tissues. The effective plasma half-life in humans after I.V. administration is about one hour and even longer (2-3 hours) after I.M. administration.

It is clear that in utilizing I.V. or I.M. administration routes, a combination with cilastatin is necessary to result in higher levels of the drug in the kidney and urine. However, post mortem studies have shown that dehydropeptidase I enzyme levels in the lung tissues are extremely low (0.14 to 1.6 specific activity) as compared with that of renal cortex tissues (74 to 346 specific activity) in humans.

As such, it is an object of the present invention to provide a route for direct and localized administration of imipenem to the site of a bacterial infection without the need for coadministration of cilastatin.

The present invention overcomes the disadvantages of conventional modes of imipenem administration that require coadministration with cilastatin, by inhalation and offers new advantages that can enhance its therapeutic index.

SUMMARY

This summary is provided to introduce a selection of concepts in a simplified form that are further described below in the Detailed Description. This summary is not intended to identify key features of the claimed subject matter, nor is it intended to be used as an aid in determining the scope of the claimed subject matter.

The present invention provides for inhaled imipenem compositions free of (i.e. without) cilastatin, suitable for drug delivery. The composition may be delivered alone or with other salts and/or excipients. The compositions and methods of administration described herein have superior properties beyond existing methods know in the art.

In particular, the compositions and methods of the present invention provide greater efficacy, with decreased toxicity as compared with conventional administration methods of imipenem. By administering imipenem directly to the lungs through inhalation, higher concentrations of the drug are reaching the site of infection and less of the drug is being distributed to the kidneys where unfavorable biotransformation reactions are known to occur. Additionally, the present invention overcomes the need for co-administration with cilastatin.

In addition to compositions and methods of use, the present invention provides methods of preparation and manufacture of inhalable antimicrobial compositions comprising imipenem free of cilastatin; or pharmaceutically acceptable salts or excipients thereof for use in the methods of the invention.

Further embodiments of the invention include those described in the detailed description.

DESCRIPTION OF THE DRAWINGS

The foregoing aspects and many of the attendant advantages of this invention will become more readily appreciated as the same become better understood by reference to

the following detailed description, when taken in conjunction with the accompanying drawings, wherein:

Figure 1 shows the effect of human lung tissue on imipenem alone and in conjunction with cilastatin in zone size reduction of *P. aeruginosa* (#27853).

Figure 2: shows the effect of human kidney tissue on imipenem alone and in conjunction with cilastatin in zone size reduction of *P. aeruginosa* (#27853).

Figure 3 shows the effect of human lung tissue on imipenem alone and in conjunction with cilastatin in zone size reduction of *E. coli* (#25922).

Figure 4 shows the effect of human kidney tissue on imipenem alone and in conjunction with cilastatin in zone size reduction of *E. coli* (#25922).

DETAILED DESCRIPTION

Imipenem is a carbapenem that shows broad spectrum activity against bacterial strains, including gram positive and gram negative organisms, particularly *P. aeruginosa*. Such spectrum makes it attractive as a candidate for inhaled administration.

Previously it was thought that imipenem was only effective if administered in conjunction with cilastatin to prevent metabolism from dipeptidase enzymes. The present invention provides a route of administration for imipenem that permits efficacious amounts of drug to reach the site of infection without the need for cilastatin. More particularly, the present invention provides a composition for inhalation comprising aerosolizable imipenem, without cilastatin.

One embodiment of the invention provides a composition for inhalation comprising aerosolizable imipenem substantially free (less than 1%), or free of cilastatin. A more particular embodiment thereof provides a composition for inhalation consisting essentially of or consisting of aerosolizable imipenem.

In a more particular embodiment the composition comprises a pharmaceutically acceptable salt of imipenem and/or an excipient. In a more particular embodiment still, said excipient is selected from the group consisting of hydrophobic amino acids, water soluble polypeptides, and phospholipids. In another embodiment said excipient is a hydrophobic amino acid selected from the group consisting of alanine, isoleucine, leucine, methionine, phenylalanine, proline, tryptophan, and valine.

In another embodiment the composition has a residual moisture content is less than 5.0 % by weight.

In another embodiment said composition comprises particles having a geometric diameter less than 5.0 microns.

In another embodiment said composition comprises particles having a mass median aerodynamic diameter less than 5.0 microns.

In another embodiment the composition comprises 35.0 – 99.0 % by weight of imipenem; or a pharmaceutically acceptable salt thereof.

In another the composition has an emitted dose greater than 70%.

Another embodiment of the invention provides a method of treating a patient suffering from an endobronchial infection comprising administering the composition for inhalation comprising aerosolizable imipenem. In another more particular embodiment said infection is caused by at least one of Gram-positive, Gram-negative, aerobic, or anaerobic organisms. More particular still, said infection is caused by *P. aeruginosa.*

Another embodiment of the invention provides a method of treating a patient suffering from exposure to anthrax comprising administering the composition for inhalation comprising aerosolizable imipenem free of cilastatin.

In a more particular embodiment said composition is a dispersible dry powder form of imipenem.

Another embodiment of the invention provides a method of treating a patient having a lower respiratory tract infection comprising administering a therapeutically effective amount of an inhaled composition comprising aerosolizable imipenem. In another more particular embodiment said infection is caused by at least one of Gram-positive, Gram-negative, aerobic, or anaerobic organisms. More particular still, said infection is caused by *P. aeruginosa.*

In a more particular embodiment said composition does not contain cilastatin and said patient remains substantially free of imipenem-related nephrotoxic biotransformation products.

In another more particular embodiment, said composition is a dry powder and further comprises an excipient selected from the group consisting of hydrophobic amino acids, water soluble polypeptides, and phospholipids.

In another embodiment, said composition comprises or consists of particles having a geometric diameter and a mass median aerodynamic diameter less than 5.0 microns and a residual moisture content of less than 5.0 % by weight.

In another embodiment, the composition is administered through a dry powder inhaler and results in an emitted dose greater than 70%.

One embodiment of the invention provides a dispersible dry powder antimicrobial composition comprising at least 35.0 % by weight, or at least 50.0 % by weight, or at least 65.0 % by weight, or at least 70.0 % by weight, or at least 75.1 % by weight, or at least 80.0 % by weight, or at least 85.0 % by weight, or at least 90.0 % by weight, or at least 95.0 % by weight, or at least 97.0 % by weight of imipenem; or a pharmaceutically acceptable salt thereof. A more particular embodiment provides said composition further comprising an excipient. In a more particular embodiment still, said excipient is selected from the group consisting of hydrophobic amino acids, water soluble polypeptides, and phospholipids. Alternatively, said excipient is a hydrophobic amino acid selected from the group consisting of alanine, isoleucine, leucine, methionine, phenylalanine, proline, tryptophan, and valine. Preferably, said excipient is leucine.

Another embodiment provides the dispersible dry powder antimicrobial composition comprising at least 35.0 % by weight, or at least 60.0 % by weight, or at least 65.0 % by weight, or at least 70.0 % by weight, or at least 75.1 % by weight, or at least 80.0 % by weight, or at least 85.0 % by weight, or at least 90.0 % by weight, or at least 95.0 % by weight, or at least 97.0 % by weight of imipenem alone or with leucine, further comprising HCl as a pharmaceutically acceptable salt.

Another embodiment provides the dispersible dry powder antimicrobial composition comprising at least 35.0 % by weight, or at least 60.0 % by weight, or at least 65.0 % by weight, or at least 70.0 % by weight, or at least 75.1 % by weight, or at least 80.0 % by weight, or at least 85.0 % by weight, or at least 90.0 % by weight, or at least 95.0 % by weight, or at least 97.0 % by weight of imipenem; or a pharmaceutically acceptable salt thereof, wherein the residual moisture content is less than 10.0 %, or 9.0%, or 8.0%, or 7.0%, or 6.0%, or 5.0%, or 4.0%, or 3.0%, or 2.0%, or 1.0% by weight.

Another embodiment provides the dispersible dry powder antimicrobial composition comprising at least 35.0 % by weight, or at least 60.0 % by weight, or at least 65.0 % by weight, or at least 70.0 % by weight, or at least 75.1 % by weight, or at least 80.0 % by weight, or at least 85.0 % by weight, or at least 90.0 % by weight, or at least 95.0 % by weight, or at least 97.0 % by weight of imipenem; or a pharmaceutically acceptable salt thereof, wherein said composition comprises particles having a geometric diameter less than 5.0 microns, or less than 4.0 microns, or less than 3.8 microns, or less

than 3.5 microns, or less than 3.0 microns, or less than 2.5 microns. In a more particular embodiment said composition comprises particles having a geometric diameter between about 1.0 and about 5.0 microns, or between about 2.0 and about 4.0 microns, or between about 2.0 and about 3.5 microns, or between about 2.5 and about 3.0 microns.

Another embodiment provides the dispersible dry powder antimicrobial composition comprising at least 35.0 % by weight, or at least 60.0 % by weight, or at least 65.0 % by weight, or at least 70.0 % by weight, or at least 75.1 % by weight, or at least 80.0 % by weight, or at least 85.0 % by weight, or at least 90.0 % by weight, or at least 95.0 % by weight, or at least 97.0 % by weight of imipenem; or a pharmaceutically acceptable salt thereof, wherein said composition comprises particles having a mass median aerodynamic diameter less than 5.0 microns, or less than 4.0 microns, or less than 3.8 microns, or less than 3.5 microns, or less than 3.0 microns, or less than 2.5 microns. In a more particular embodiment said composition comprises particles having a mass median aerodynamic diameter between about 1.0 and about 5.0 microns, or between about 2.0 and about 4.0 microns, or between about 2.1 and about 3.1 microns, or between about 2.5 and about 3.0 microns.

Another more particular embodiment provides a dispersible dry powder antimicrobial composition comprising 65.0 – 85.0 % by weight of imipenem; or a pharmaceutically acceptable salt thereof.

Another embodiment provides the dispersible dry powder antimicrobial composition comprising at least 35.0 % by weight, or at least 60.0 % by weight, or at least 65.0 % by weight, or at least 70.0 % by weight, or at least 75.1 % by weight, or at least 80.0 % by weight, or at least 85.0 % by weight, or at least 90.0 % by weight, or at least 95.0 % by weight, or at least 97.0 % by weight of imipenem; or a pharmaceutically acceptable salt thereof, having an emitted dose of greater than 50%, or greater than 60%, or greater than 70%, or greater than 80%, or greater than 90%.

A further embodiment of the invention provides a method of treating a patient with a microbial infection comprising:

providing a dispersible dry powder composition comprising imipenem, or a pharmaceutically acceptable salt thereof;

loading said composition into a dry powder inhaler;

inhaling the composition from said dry powder inhaler, wherein upon inhalation said patient is treated for the microbial infection.

In a more particular embodiment of said method of treating a patient with a microbial infection, said imipenem, or a pharmaceutically acceptable salt thereof is present in at least 35.0 % by weight, or at least 60.0 % by weight, or at least 65.0 % by weight, or at least 70.0 % by weight, or at least 75.1 % by weight, or at least 80.0 % by weight, or at least 85.0 % by weight, or at least 90.0 % by weight, or at least 95.0 % by weight, or at least 97.0 % by weight.

In a more particular embodiment of said method of treating a patient with a microbial infection, said composition further comprises an excipient selected from the group consisting of hydrophobic amino acids, water soluble polypeptides, and phospholipids. In a preferred embodiment said excipient is leucine.

In a more particular embodiment of said method of treating a patient with a microbial infection, with or without leucine as an excipient, said composition consists of particles having a geometric diameter and a mass median aerodynamic diameter less than 5.0 microns, or less than 4.0 microns, or less than 3.8 microns, or less than 3.5 microns, or less than 3.0 microns, or less than 2.5 microns and a residual moisture content of less than 10.0 %, or 9.0%, or 8.0%, or 7.0%, or 6.0%, or 5.0%, or 4.0%, or 3.0%, or 2.0%, or 1.0% by weight.

In a more particular embodiment of said method of treating a patient with a microbial infection, said step of inhaling the composition from said dry powder inhaler results in an emitted dose greater than 50%, or greater than 60%, or greater than 70%, or greater than 80%, or greater than 90%.

In a more particular embodiment of said method of treating a patient with a microbial infection, said dry powder inhaler has a resistance less than about 0.6 cm $H_2O^{0.5}$/LPM, or less than about 0.5 cm $H_2O^{0.5}$/LPM, or less than about 0.4 cm $H_2O^{0.5}$/LPM, or less than about 0.2 cm $H_2O^{0.5}$/LPM, or less than about 0.1 cm $H_2O^{0.5}$/LPM, or less than about 0.08 cm $H_2O^{0.5}$/LPM.

In a more particular embodiment of said method of treating a patient with a microbial infection, said dry powder inhaler has a flow rate between about 20 and about 90 LPM, or about 20 and about 80 LPM, or about 30 and about 80 LPM, or about 40 and about 80 LPM, or about 50 and about 80 LPM, or about 20 and about 70 LPM, or about 20 and about 60 LPM, or about 20 and about 50 LPM, or about 30 and about 70 LPM, or about 40 and about 60 LPM, or about 45 and about 60 LPM.

In a more particular embodiment of said method of treating a patient with a microbial infection, said dry powder inhaler is a passive dry powder inhaler.

Another embodiment provides a method of treating a patient suffering from an endobronchial infection comprising administering a compound of embodiment 1.

Another embodiment of the invention provides a method of treating a patient having an endobronchial infection comprising administering a therapeutically effective amount of an inhaled dry powder composition comprising, imipenem, or a pharmaceutically acceptable salt or excipient thereof.

Another embodiment provides a dispersible dry powder antimicrobial composition comprising imipenem; or a pharmaceutically acceptable salt thereof, having a AUC_{12} value below about 10 ug hr/ml when given in a dose of between 400 and 600 mg, or 300 and 600 mg, or 200 and 500 mg, or 300 and 400 mg, or 350 and 400mg, or 500 and 600 mg, or 400 and 500 mg, or 400 and 450 mg, or 200 and 300 mg, or 250 and 300mg, or 100 and 200mg, or 150 and 200mg, or 100 and 300 mg, or 50 and 100 mg.

Another embodiment provides a dispersible dry powder antimicrobial composition comprising imipenem; or a pharmaceutically acceptable salt thereof, having a AUC_{12} value below about 5 ug hr/ml when given in a dose of between 400 and 600 mg, or 300 and 600 mg, or 200 and 500 mg, or 300 and 400 mg, or 350 and 400mg, or 500 and 600 mg, or 400 and 500 mg, or 400 and 450 mg, or 200 and 300 mg, or 250 and 300mg, or 100 and 200mg, or 150 and 200mg, or 100 and 300 mg, or 50 and 100 mg.

In a more particular embodiment thereof, the AUC_{12} is below 25, or 24, or 23, or 22, or 21, or 20, or 19, or 18, or 17, or 16, or 15, or 14, or 13, or 12, or 11, or 10, or 9, or 8, or 7, or 6, or 5, or 4, or 3, or 2, or 1, or 0.5, or 0.25, or 0.125 ug hr/ml.

Another embodiment provides a dispersible dry powder antimicrobial composition comprising imipenem; or a pharmaceutically acceptable salt thereof, having a AUC_{24} value below about 20 ug hr/ml when given in a dose of between 400 and 600 mg, or 300 and 600 mg, or 300 and 500 mg, or 300 and 400 mg, or 350 and 400mg, or 500 and 600 mg, or 400 and 500 mg, or 400 and 450 mg, or 200 and 300 mg, or 250 and 300mg, or 100 and 200mg, or 150 and 200mg, or 100 and 300 mg, or 50 and 100 mg.

In a more particular embodiment thereof, the AUC_{24} is below 35, or 30, or 25, or 24, or 23, or 22, or 21, or 20, or 19, or 18, or 17, or 16, or 15, or 14, or 13, or 12, or 11, or 10, or 9, or 8, or 7, or 6, or 5, or 3, or 2, or 1 ug hr/ml.

Another embodiment provides a dispersible dry powder antimicrobial composition comprising imipenem; or a pharmaceutically acceptable salt thereof, having an AUC_{24}/MIC ratio less than about 1. In a more particular embodiment said MIC corresponds to inhibition of bacteria selected from the group consisting of *P. aeruginosa*, *E. coli*, *S. pneumoniae*, *S. aureus*, and *H. influenzae*.

Another embodiment provides a dispersible dry powder antimicrobial composition comprising imipenem; or a pharmaceutically acceptable salt thereof, having an AUC_{24}/MIC ratio less than about 200. In a more particular embodiment said MIC corresponds to inhibition of bacteria selected from the group consisting of *P. aeruginosa*, *E. coli*, *S. pneumoniae*, *S. aureus*, and *H. influenzae*.

Another embodiment of the invention provides a method of treating a patient suffering from anthrax exposure comprising administering a dry powder composition comprising at least 35.0 % by weight of imipenem; or a pharmaceutically acceptable salt thereof.

It is contemplated that the invention encompasses all possible combinations of the embodiments described herein. Further, it is contemplated that any of the compositions or methods of the invention may be used to treat a patient suffering from anthrax exposure.

The formulations described herein may be delivered using any suitable dry powder inhaler (DPI), i.e., an inhaler device that utilizes the patient's inhaled breath as a vehicle to transport the dry powder drug to the lungs. Preferred is the T-326 Dry Powder Inhaler (T-326 Inhaler, Nektar Therapeutics, San Carlos, CA). The T-326 Inhaler is a hand-held, manually operated, breath-activated, dry powder inhaler which uses no stored power sources or electronics. The T-326 inhaler has a flow resistance of approximately 0.09 cm $H_2O^{0.5}$/LPM or about 8 cm H_2O at 30 LPM (a pneumotachometer has a flow resistance of approximately 1 cm at the 30 LPM).

Further inhalers include Inhale Therapeutic Systems' dry powder inhalation devices as described in Patton, J. S., et al., U.S. Pat. No. 5,458,135 (1995) Smith, A. E., et al., U.S. Pat. No. 5,740,794 (1998); and in Smith, A. E., et al., U.S. Pat. No. 5,785,049 (1998), herein incorporated by reference. When administered using a device of this type, the powder is contained in a receptacle having a puncturable lid or other access surface, preferably a blister package or cartridge, where the receptacle may contain a single dosage unit or multiple dosage units. Convenient methods for filling large numbers of

cavities (i.e., unit dose packages) with metered doses of dry powder medicament are described, e.g., in Parks, D. J., et al., WO 97/41031 (1997) incorporated herein by reference.

Also suitable for delivering the powders described herein are dry powder inhalers of the type described, for example, in Cocozza, S., et al. , U.S. Pat. No. 3,906,950 (1974), and in Cocozza, S., et al., U.S. Pat. No. 4,013,075 (1997), incorporated herein by reference, wherein a premeasured dose of dry powder for delivery to a subject is contained within a hard gelatin capsule.

Other dry powder dispersion devices for pulmonarily administering dry powders include those described, for example, in Newell, R. E., et al., European Patent No. EP 129985 (1988); in Hodson, P. D., et al., European Patent No. EP 472598 (1996); in Cocozza, S., et al., European Patent No. EP 467172 (1994), and in Lloyd, L. J. et al., U.S. Pat. No. 5,522,385 (1996), incorporated herein by reference. Also suitable for delivering the dry powders of the invention are inhalation devices such as the Astra- Draco "TURBUHALER". This type of device is described in detail in Virtanen, R., U.S. Pat. No. 4,668,281 (1987); in Wetterlin, K., et al. U.S. Pat. No. 4,667,668 (1987); and in Wetterlin, K., et al. U.S. Pat. No. 4,805,811 (1989), all of which are incorporated herein by reference. Other suitable devices include dry powder inhalers such as the Rotahaler® (Glaxo), Discus® (Glaxo), Spiros® inhaler (Dura Pharmaceuticals), and the Spinhaler® (Fisons). Also suitable are devices which employ the use of a piston to provide air for either entraining powdered medicament, lifting medicament from a carrier screen by passing air through the screen, or mixing air with powder medicament in a mixing chamber with subsequent introduction of the powder to the patient through the mouthpiece of the device, such as described in Mulhauser, P., et al., U.S. Pat. No. 5,388,572 (1997), incorporated herein by reference.

Dry powders may also be delivered using a pressurized, metered dose inhaler (MDI), e.g., the Ventolin® metered dose inhaler, containing a solution or suspension of drug in a pharmaceutically inert liquid propellant, e.g., a chlorofluorocarbon or fluorocarbon, as described in Laube, et al., U.S. Pat. No. 5,320,094 (1994), and in Rubsamen, R. M., et al., U.S. Pat. No. 5,672,581 (1994), both incorporated herein by reference. Alternatively, the powders described herein may be dissolved or suspended in a solvent, e.g., water, ethanol, or saline, and administered by nebulization. Nebulizers for

delivering an aerosolized solution include the AERx® (Aradigm), the Ultravent® (Mallinkrodt), and the Acorn II® (Marquest Medical Products).

Prior to use, dry powders are generally stored under ambient conditions, and preferably are stored at temperatures at or below about 25° C., and relative humidities (RH) ranging from about 30 to 60%. More preferred relative humidity conditions, e.g., less than about 30%, may be achieved by the incorporation of a desiccating agent in the secondary packaging of the dosage form.

Clinical Pharmacology for conventional imipenem formulation is obtained from Physicians Desk Reference, 58th Ed. (2004) 845, which is incorporated by reference.

DEFINITIONS:

AUC	Area under the curve
AUC_n	Area under the curve, wherein n is the time period in hours, such as 24
AUC/MIC or AUIC	Area under the curve inhibitory concentration
cm $H_2O^{0.5}$ /LPM	Unit of resistance to flow; the square root of pressure drop divided by flow rate.
C_{max}	Maximum concentration
C_{ss}	Steady state concentration
DPI	Dry Powder Inhaler
ED	Emitted Dose
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
HCl	Hydrochloride salt (derived from hydrochloric acid)
IT	Intratracheal (as a mode of administration)
IV	Intravenous (as a mode of administration)
LPM	Liters per minute
MBC	Minimum Bactericidal Concentration
MIC	Minimum Inhibitory Concentration
MMAD	Mass median aerodynamic diameter
PK	Pharmacokinetic
SAE	Serious Adverse Event
SCFM	Standard cubic feet per minute

SEM	Scanning electron microscopy
TPI	Tobramycin Powder for Inhalation

The term "effective amount" is an amount necessary or sufficient to realize a desired biological effect. For example, an effective amount of a compound to treat an bacterial infection may be an amount necessary to cause stasis, reduction, or inhibition in bacterial growth. The effective amount may vary, depending, for example, upon the condition treated, weight of the subject and severity of the disease. One of skill in the art can readily determine the effective amount empirically without undue experimentation.

As used herein "treatment" or "treated," as in being "treated for the microbial infection" refers to an amount sufficient to palliate, ameliorate, stabilize, reverse, slow or delay progression of a condition such as a microbial infection, and/or symptoms associated therewith.

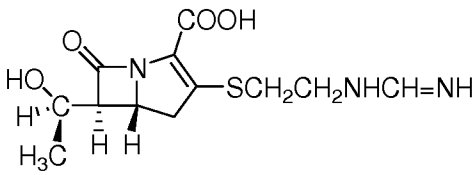
A "subject" or "patient" is meant to describe a human or vertebrate animal including a dog, cat, pocket pet, marmoset, horse, cow, pig, sheep, goat, elephant, giraffe, chicken, lion, monkey, owl, rat, squirrel, slender loris, mouse, or other vertebrate animal commonly found in a zoo, such as, for example the San Diego Zoo.

A "pocket pet" refers to a group of vertebrate animals capable of fitting into a commodious coat pocket such as, for example, hamsters, chinchillas, ferrets, rats, guinea pigs, gerbils, rabbits and sugar gliders.

The compositions of the present invention can be used in the form of salts as in "pharmaceutically acceptable salts" suitable for attachment to imipenem. A "pharmaceutically acceptable salt" includes a salt with an inorganic base, organic base, inorganic acid, organic acid, or basic or acidic amino acid. As salts of inorganic bases, the invention includes, for example, alkali metals such as sodium or potassium; alkaline earth metals such as calcium and magnesium or aluminum; and ammonia. As salts of organic bases, the invention includes, for example, trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, and triethanolamine. As salts of inorganic acids, the instant invention includes, for example, hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid. As salts of organic acids, the instant invention includes, for example, formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid. As salts of basic

amino acids, the instant invention includes, for example, arginine, lysine and ornithine. Acidic amino acids include, for example, aspartic acid and glutamic acid.

"Imipenem" or "N-formimidoylthienamycin" refers to a compound having the following structure:



or hydrates (e.g. monohydrate) thereof.

The term "aerosolizable imipenem" refers to imipenem which is for dispersal into particles for inhalation. Such particles can be liquid or solid suspended or dispersed in air or gas and generally range in size from 0.001 μm to more than 100 μm.

The pharmaceutical compositions containing the compounds described herein can include additives such as "excipients." Suitable pharmaceutically acceptable excipients include processing agents and drug delivery modifiers and enhancers, such as, for example, calcium phosphate, magnesium stearate, talc, monosaccharides, disaccharides, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, dextrose, hydroxypropyl-β-cyclodextrin, polyvinylpyrrolidinone, low melting waxes, ion exchange resins, surfactants, and the like, as well as combinations of any two or more thereof. Preferred excipients of the instant invention include amino acids (preferably hydrophobic, such as leucine), water soluble polypeptides, sugars, and phospholipids. Preferred phospholipids for use as excipients include dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, diarachidoylphosphatidylcholine dibehenoylphosphatidylcholine, diphosphatidyl glycerol, short-chain phosphatidylcholines, long-chain saturated phosphatidylethanolamines, long-chain saturated phosphatidylserines, long-chain saturated phosphatidylglycerols, and long-chain saturated phosphatidylinositols.

Other suitable pharmaceutically acceptable excipients are described in "Remington's Pharmaceutical Sciences," Mack Pub. Co., New Jersey (1991), and PCT applications WO 95/31479, WO 96/32096, and WO 96/32149, which are incorporated herein by reference.

As used herein, the term "dry powder" refers to a composition that contains finely dispersed, or "dispersible" solid particles that are capable of (i) being readily dispersed in or by means of an inhalation device and (ii) inhaled by a subject so that a portion of the particles reach the lungs. Such a powder is considered to be "respirable" or suitable for pulmonary delivery. Suitable agents to enhance dispersion, which are disclosed in PCT applications WO 95/31479, WO 96/32096, and WO 96/32149, are hereby incorporated in their entirety by reference.

As used herein, "passive dry powder inhaler" refers to an inhalation device which relies upon the patient's inspiratory effort to disperse and aerosolize a drug formulation contained within the device and does not include inhaler devices which comprise a means for providing energy to disperse and aerosolize the drug formulation, such as pressurized gas and vibrating or rotating elements.

A dry powder typically contains less than about 15% moisture or "residual moisture content by weight," preferably less than 10% moisture, and more preferably contains less than 5% moisture.

"AUC" as used herein, means area under the plasma concentration-time curve, as calculated by the trapezoidal rule over a time period, such as a 24-hour interval (AUC_{24}), for the formulations.

The trapezoidal rule is expressed mathematically as follows (3):

$$\int_a^b f(x)dx \approx \frac{\Delta x}{2}\left(f(x_0) + 2f(x_1) + 2f(x_2) + \cdots + 2f(x_{n-1}) + f(x_n)\right). \qquad (3)$$

"AUC_{24}/MIC" ratios describe interactions of a drug with specific targets in a respective pathogen by occupying a specific number of critical binding sites. The ratio has been shown to effectively predict the therapeutic response of micro-organisms to antimicrobials, such as imipenem. Zhanel, G., *et al.* Drugs 2002, 62(1), 29.

As used herein, the term "emitted dose" or "ED" refers to the delivery of dry powder from a suitable inhaler device after a firing or dispersion event from a powder unit, capsule, or reservoir. ED is defined as the ratio of the dose delivered by an inhaler device to the nominal dose (i.e., the mass of powder per unit dose placed into a suitable inhaler device prior to firing). The ED is an experimentally-determined amount and is typically determined using an in-vitro device set up which mimics patient dosing.

To determine an ED value (further described in the Examples section), a nominal dose of dry powder (as defined above) is placed into a suitable passive dry powder inhaler. The resulting aerosol cloud is then drawn by vacuum from the device. The amount of powder that is released from the device constitutes the delivered dose. For example, for a 5 mg, dry powder containing capsule placed into an inhalation device, if dispersion of the powder results in 4 mg of powder as described above, then the ED for the dry powder composition is: 4 mg (delivered dose)/5 mg (nominal dose) x 100 = 80%.

As used herein, the term "geometric diameter" is a measure of geometric particle size and is determined using, for example, a Malvern Spraytec laser diffraction analyzer.

As used herein the term "mass median aerodynamic diameter" or "MMAD" is a measure of the aerodynamic size of a dispersed particle. The aerodynamic diameter is used to describe an aerosolized powder in terms of its settling behavior and is the diameter of a unit density sphere having the same settling velocity generally in air as the particle. The aerodynamic diameter encompasses particle shape density and physical size of a particle. As used herein mass median aerodynamic diameter or MMAD refers to the midpoint or median of the aerodynamic particle size distribution of an aerosolized powder determined by Anderson cascade impaction described in the Examples section.

As used herein "antimicrobial" refers to a composition, namely imipenem, that is harmful to microbes, or capable of destroying or inhibiting the growth of microorganisms. Microbes as described herein, include pathogenic bacteria, fungi, protozoans, microscopic algae, and viruses; alternatively, reference to a "microbial infection" involves infection with at least on of the following: bacteria, fungi, protozoans, microscopic algae, and/or viruses.

The term "dispersible dry powder antimicrobial composition" refers to a composition capable of (i) being readily dispersed in or by means of an inhalation device and (ii) inhaled by a subject so that a portion of the particles reach the lungs, which is harmful to microbes, or capable of destroying or inhibiting the growth of microorganisms, such as, pathogenic bacteria, fungi, protozoans, microscopic algae, and viruses.

The invention is described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of

noncritical parameters which can be changed or modified to yield essentially the same results.

EXAMPLES

Generalized Procedure: Animal tissues of interest (particularly rat, dog, and human tissue) were homogenized in a volume of saline equal to 3 times the weight of the tissue. The homogenates were distributed into 1mL volumes and frozen at -80°C until the day of testing.

On the day of testing, fresh solutions of imipenem were prepared, and combined with an equal volume of the tissue homogenates described above (final concentration of imipenem in incubated sample = 1mg/mL). These mixtures were incubated at 35°C for a 24 hour period. At several timepoints (0, 2, 4, 6, 8, and 24 hours) a 10μL volume of each test mixture was applied to sterile filter paper disks (7mm diam.). The disks were arranged on 150mm Mueller-Hinton agar plates, streaked in Kirby-Bauer fashion with ATCC QC strains of *E. coli* (#25922) or *P. aeruginosa* (#27853). The plates also received a disk with the imipenem solution alone (no tissue, incubated with the test mixtures of drug and tissue), and also a commercially available imipenem Kirby-Bauuer susceptibility disk.

The agar plates were then incubated overnight, and the resultant inhibition zones measured. The inhibition zone measurements thus provided an indirect measure of imipenem degradation by the tissue homogenates, in a bioassay format. Cilastatin was added to some mixtures, as a way to confirm that the decrease of imipenem antibacterial activity by a particular tissue was specific to dipeptidase activity. The zones for the imipenem/tissue mixtures were compared at each timepoint to the zones produced by the imipenem only condition. This allowed assessment of how much activity loss was due to enzyme degradation, compared to the loss from incubation in the absence of tissue. Note that the nominal imipenem content of each test disk was 10μg, the same as on the commercial imipenem disk.

RESULTS:

Studies with imipenem exposure to rat lung and kidney tissues confirmed the degrading effect of both tissues upon imipenem activity by 24 hours, although rat lung tissue degraded imipenem activity faster than rat kidney. Assay testing the effect of rat lung tissue, and dog lung, upon imipenem antibacterial activity demonstrated the same

negative effect upon imipenem activity, at the same rate as seen before for the rat lung and kidney studies.

In another study, exposure to dog lung tissue showed no significant effect on imipenem antibacterial activity, and rat lung showed the same rapid and significant negative effect on imipenem inhibition zone size. The addition of cilastatin to the imipenem/rat lung tissue test condition showed a significant slowing of the degradation of imipenem activity by rat tissue. Protection of imipenem activity by cilastatin in the presence of rat lung suggested that imipenem breakdown by rat lung tissue was caused by dipeptidase enzyme, as cilastatin inhibits this enzyme's activity upon imipenem.

Subsequent studies employed rat lung tissue as a positive control, and 4 human tissue homogenates (2 lung, and 2 kidney), each used as an individual specimen (not pooled). All imipenem/tissue specimens were also separately run in the presence of cilastatin. Human kidney homogenate produced a significant decline in imipenem activity (Figures 2 and 4). This decline was significantly lessened with the addition of cilastatin. Human lung homogenates showed little or no decline in imipenem activity (Figures 1 and 3). These results suggest that our human lung specimens contain very little dipeptidase enzyme compared to human kidney.

This assay provides a measure of the effect of animal tissues upon imipenem. It also offers the ability to compare the rate of imipenem degradation between samples. The results obtained with human tissue specimens show that imipenem is not significantly degraded by lung tissue-associated dipeptidase.

FORMULATION:

Compositions containing imipenem are prepared by mixing imipenem and excipient(s) (if used) with a liquid medium to form a solution. The pH of the solution is adjusted as appropriate to facilitate solubilization and/or stabilization of the components in the solution.

Spray Drying Preparation: The imipenem solutions are spray dried, for example, with Buchi 190 Mini Spray Dryers, having nozzles and cyclones that were designed to generate and catch very fine particles. (For formulations utilizing organic solvents, a modified Buchi 190 Mini Spray Dryer can be used that supplies nitrogen as the gas source and is equipped with an oxygen sensor and other safety equipment to minimize the possibility of explosion.) The solution feed rate is 5 ml/minute; and maintained at room

temperature, inlet temperature range is 120 - 131°C and is adjusted to obtain an outlet temperature of approximately 80°C, the drying gas flow rate is about 18 SCFM, and the atomizing air is supplied at 0.5 to 1.5 SCFM, typically at a pressure of about 100 PSI.

Characterization: Each powder is characterized in terms of moisture content, emitted dose (ED), and mass median aerodynamic diameter (MMAD). ED is a measure of efficiency for the powder package/device combination. MMAD refers to a measure of the particle size of the aerosolized powder. For these experiments, imipenem powders are formulated and manufactured (spray dried) preferably with leucine as an excipient. The residual water content of these formulations is determined by Karl Fisher titration. The stability of these formulations is demonstrated by comparing initial HPLC results to a four-month time point for samples stored at desiccated room temperature.

Morphology is determined by scanning electron microscopy (SEM).

To determine the ED, the spray-dried powders are first filled into capsules. The test can be performed by connecting a vacuum system to the mouthpiece of a passive dry powder inhaler. The vacuum system is set to have a flow rate of 60 liters/minute. A capsule containing, for example, 5 mg of the formulation to be evaluated is loaded into a device. The device is pumped which pierces the capsule and the aerosol cloud is then drawn out of the device chamber by vacuum. The difference in weight of the capsule is determined. Emitted dose is calculated as this weight, multiplied by one hundred, divided by the fill weight in the capsule. A higher number is a better result than a lower number.

MMAD can be determined with an Andersen cascade impactor. In a cascade impactor the aerosolized powder (which is aerosolized using an inhaler device as described in U.S. Patent No. 5,740,794) enters the impactor via an air stream, and encounters a series of stages that separate particles by their aerodynamic diameter (the smallest particles pass farthest down the impactor). The amount of powder collected on each stage is determined gravimetrically, and the mass median aerodynamic diameter is then calculated.

All of the above captioned citations are fully incorporated by reference as if set forth herein.

While illustrative embodiments have been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

CLAIMS

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A composition for inhalation comprising aerosolizable imipenem free of cilastatin.

2. The composition according to claim 1, comprising a pharmaceutically acceptable salt of imipenem and/or an excipient.

3. The composition according to claim 2, wherein said excipient is selected from the group consisting of hydrophobic amino acids, water soluble polypeptides, and phospholipids.

4. The composition according to claim 2, wherein said excipient is a hydrophobic amino acid selected from the group consisting of alanine, isoleucine, leucine, methionine, phenylalanine, proline, tryptophan, and valine.

5. The composition according to claim 1, wherein the composition has a residual moisture content is less than 5.0 % by weight.

6. The composition according to claim 1, wherein said composition comprises particles having a geometric diameter less than 5.0 microns.

7. The composition according to claim 1, wherein said composition comprises particles having a mass median aerodynamic diameter less than 5.0 microns.

8. The composition according to claim 1, comprising 35.0 – 99.0 % by weight of imipenem; or a pharmaceutically acceptable salt thereof.

9. The composition according to claim 1, comprising an emitted dose greater than 70%.

10. A method of treating a patient suffering from an endobronchial infection comprising administering the composition of claim 1.

11. A method of treating a patient suffering from exposure to anthrax comprising administering the composition of claim 1.

12. The method of claim 10, wherein said composition is a dispersible dry powder form of imipenem.

13. A method of treating a patient having a lower respiratory tract infection comprising administering a therapeutically effective amount of an inhaled composition comprising aerosolizable imipenem.

14. The method according to claim 13 wherein said composition does not contain cilastatin and said patient remains substantially free of imipenem-related nephrotoxic biotransformation products.

15. The method of claim 13, wherein said composition is a dry powder and further comprises an excipient selected from the group consisting of hydrophobic amino acids, water soluble polypeptides, and phospholipids.

16. The method of claim 13, wherein said composition comprises particles having a geometric diameter and a mass median aerodynamic diameter less than 5.0 microns and a residual moisture content of less than 5.0 % by weight.

17. The method of claim 13, wherein the inhalation of the composition is from a dry powder inhaler and results in an emitted dose greater than 70%.

18. The method of claim 10 or 13, wherein said infection is caused by at least one of Gram-positive, Gram-negative, aerobic, or anaerobic organisms.

19. The method of claim 18, wherein said infection is caused by *P. aeruginosa.*

FIGURE 1

Disk Assay, Imipenem/Cilastatin vs. Human Lung Tissue
P. aeruginosa 27853.

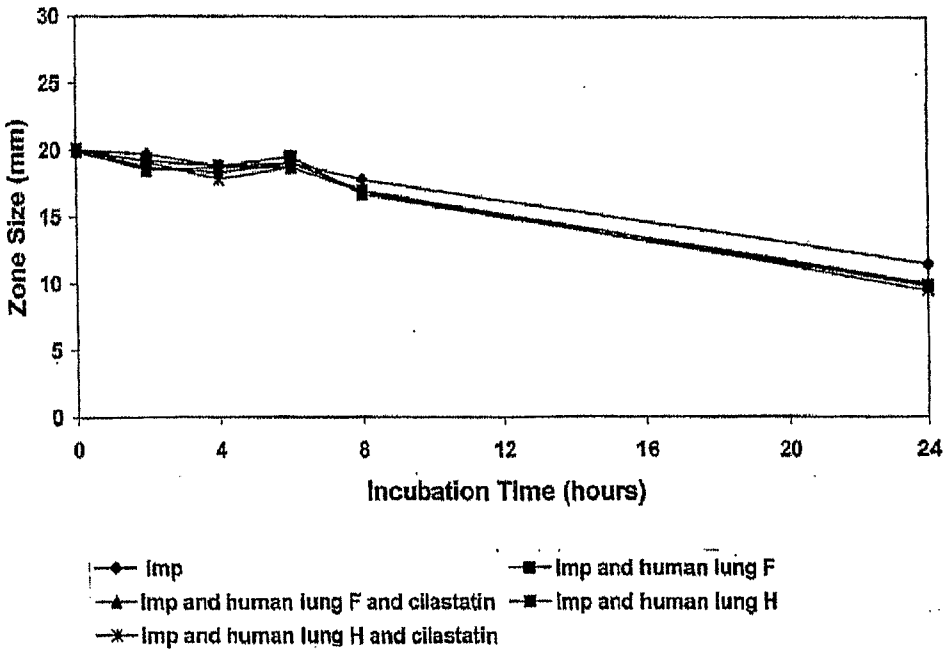


FIGURE 2

Disk Assay, Imipenem/Cilastatin vs. Human Kidney Tissue
***P. aeruginosa* 27853.**

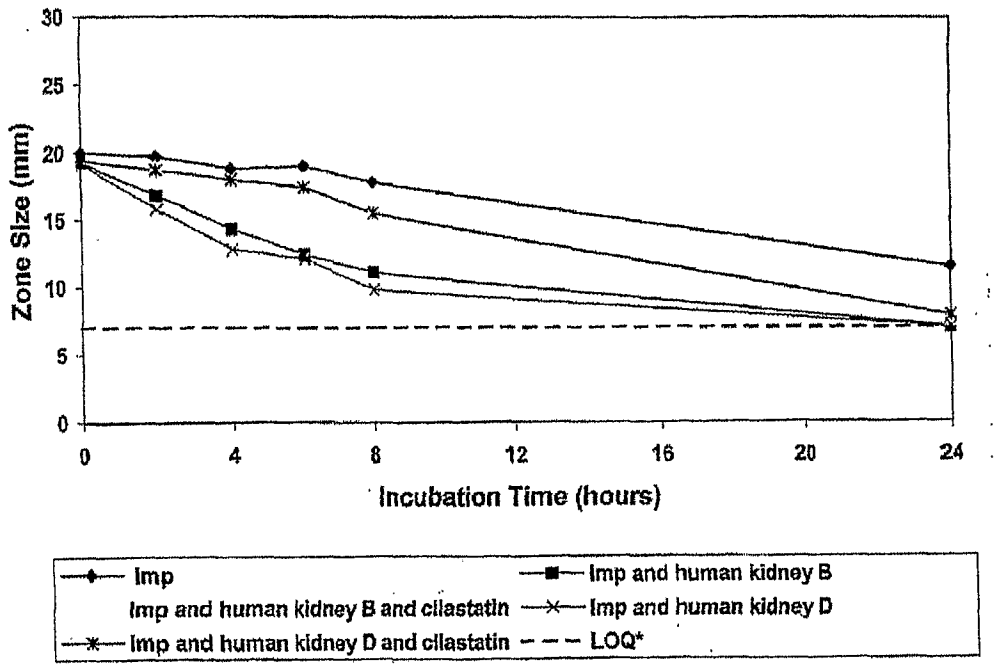


FIGURE 3

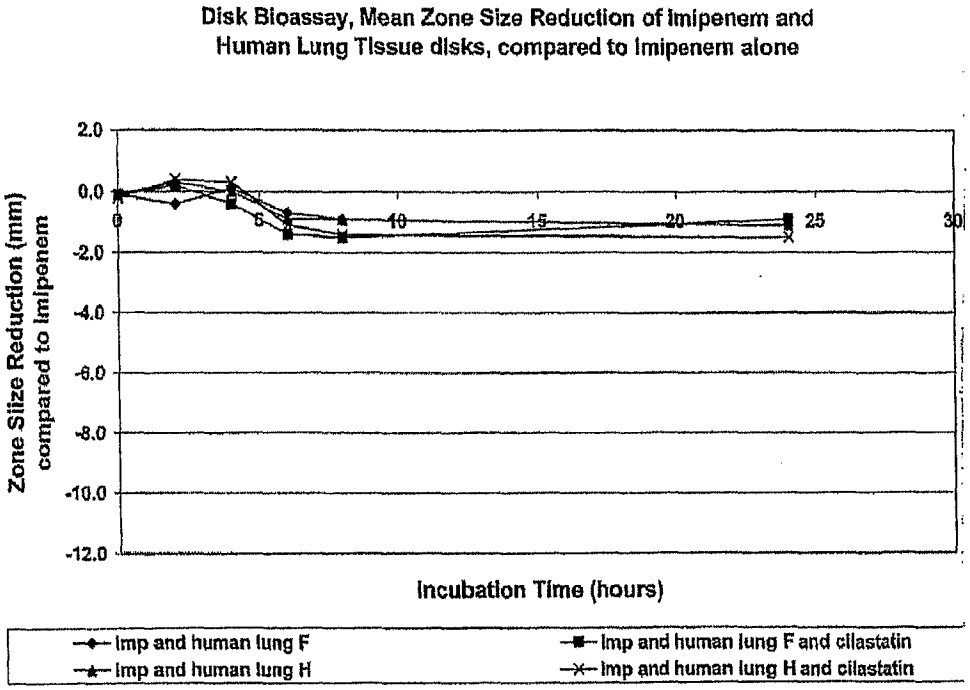
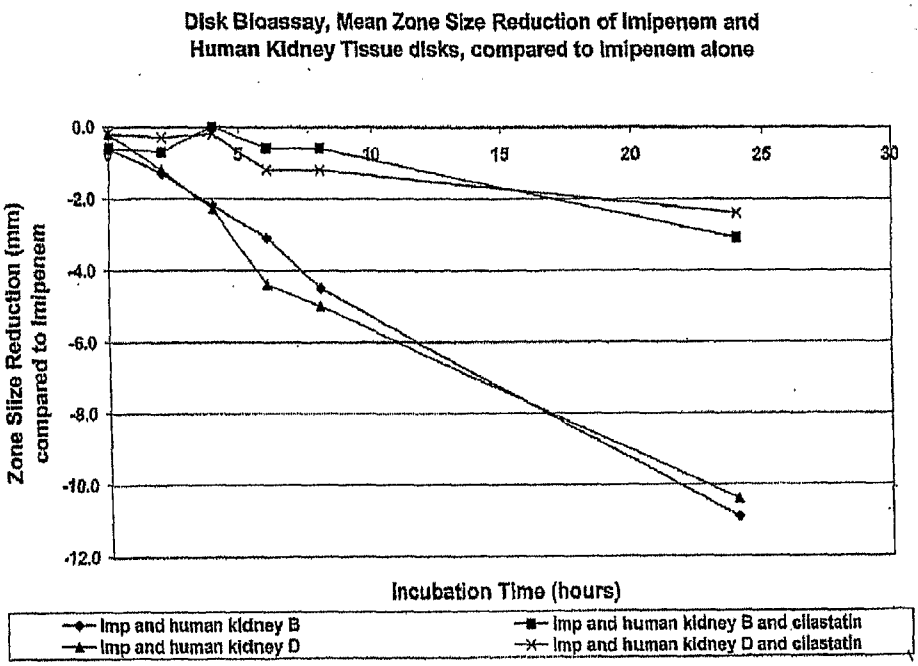

Disk Bioassay, Mean Zone Size Reduction of Imipenem and Human Lung Tissue disks, compared to Imipenem alone
Zone Size Reduction (mm) compared to Imipenem
2.0
0.0
-2.0
-4.0
-6.0
-8.0
-10.0
-12.0
0
5
10
15
20
25
30
Incubation Time (hours)
Imp and human lung F
Imp and human lung F and cilastatin
Imp and human lung H
Imp and human lung H and cilastatin

FIGURE 4


Disk Bioassay, Mean Zone Size Reduction of Imipenem and Human Kidney Tissue disks, compared to Imipenem alone
Zone Size Reduction (mm) compared to Imipenem
0.0
-2.0
-4.0
-6.0
-8.0
-10.0
-12.0
0
5
10
15
20
25
30
Incubation Time (hours)
Imp and human kidney B
Imp and human kidney D
Imp and human kidney B and cilastatin
Imp and human kidney D and cilastatin