(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 386 951 A2**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: **90302236.6**

(22) Date of filing: **02.03.90**

(51) Int. Cl.5: **A61K 37/02, A61K 9/08, A61K 47/04**

(30) Priority: **06.03.89 US 319248**

(43) Date of publication of application:
12.09.90 Bulletin 90/37

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(71) Applicant: **ELI LILLY AND COMPANY**
Lilly Corporate Center
Indianapolis Indiana 46285(US)

(72) Inventor: **Inman, Eugene Lee**
8061 Castle Cove Road
Indianapolis, Indiana 46256(US)
Inventor: **Kirsch, Lee Edwin**
7630 Camelback Drive
Indianapolis, Indiana 46250(US)

(74) Representative: **Hudson, Christopher Mark et al**
Eri Wood Manor
Windlesham Surrey GU20 6PH(GB)

(54) **An improved diluent formulation for daptomycin.**

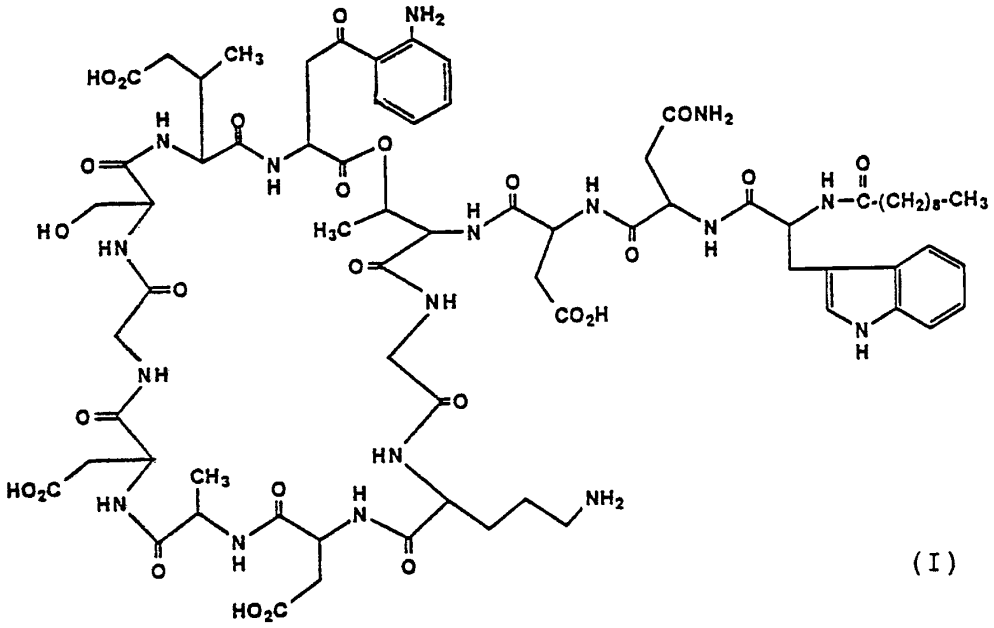
(57) Improved formulations for the lipopeptide antibiotic, daptomycin, are provided. Also provided are an improved kit for parenteral administration of daptomycin and a buffered pharmaceutical composition comprising daptomycin and a parenterally-acceptable buffer.

EP 0 386 951 A2

AN IMPROVED DILUENT FORMULATION FOR DAPTOMYCIN

In the field of antibiotics, particularly in the field of lipopeptide antibiotics, searches are constantly ongoing for new and improved formulations for delivery of the active ingredients into the subject under antimicrobial treatment. In this regard, it is of paramount importance that the formulation of the active ingredient be one that allows the drug to be bioavailable, while at the same time inhibiting, or at least not contributing to, premature degradation of the active ingredient. Further, it is of equal, if not greater, importance that the formulation itself be one that does not unacceptably enhance toxicity or any other untoward effect to the subject.

The present invention provides a solution to the problem of the premature "in solution" degradation of the known lipopeptide antibiotic daptomycin. Daptomycin is represented by the following structural Formula (I)



(I)

and is described in U.S. Patent No. 4,537,717. Stabilized daptomycin formulations are provided herein which allow the antibiotic to be prepared for parenteral administration in commonly used diluents such as 5% dextrose solution, with minimal degradation. Following the realization that daptomycin, when dissolved in a 5% dextrose solution, undergoes 15-20% degradation in 24 h at 25° C or in 7 days at 5° C, it was discovered that formulations with sufficient buffer capacity in the pH range 6-8 reduce the degradation to approximately 1%.

The present invention provides stabilized formulations of daptomycin (I) which possess sufficient buffer capacity to allow for storage of daptomycin solutions in 5% dextrose without significant degradation.

It has recently been discovered that daptomycin, when dissolved in 5% dextrose solution, undergoes 15-20% degradation into two unidentified products in 24 h at 25° C or 7 days at 5° C. The degradation, which also was found to be unique to reducing sugars and especially aldoses (e.g., glucose, mannose, galactose, arabinose, etc.), appears to be pH related and is accompanied by a significant loss of antibiotic potency. As an illustration of this phenomenon, the following study was conducted:

First, 8 vials of daptomycin (100 mg each) were reconstituted to a concentration of 1 mg/ml with normal saline and 5% dextrose (4 each). Next, the solutions were stored at room temperature (approximately 25° C) and refrigerated temperatures and assayed at the 6 h and 24 h timepoints.

Time			Clarity		Potency	
(hrs.)	Temp.	pH	(NTU)	Visual	(mg/mL)	Total Appearance of Degradation Products
0.9% NaCl:						
Initial	--	4.2	1.0	ACPL*	1.026	5.2
6	A	4.2	0.9	1111**	1.025	5.1
	B	4.2	0.8	1111	1.025	5.6
24	A	4.2	0.9	1111	1.019	5.6
	B	4.2	0.7	1111	1.002	7.5
5% Dextrose:						
Initial	--	4.5	1.7	ACPL	1.023	8.9
6	A	4.5	1.6	1111	1.001	12.6
	B	4.5	0.7	1111	0.963	16.6
24	A	4.5	1.5	1111	0.975	16.2
	B	4.5	1.1	1111	0.848	24.9

*Inspection for appearance, color, package and clarity.
**1 indicates no change from initial.

In sum, solutions of daptomycin and dextrose held at refrigerated temperature demonstrated a potency loss of about 5% at the 24 h timepoint, while solutions held at room temperature showed a 17% loss over the same time period.

Further, a series of degradation kinetic studies demonstrate that the rate of appearance of degradation products is pH-dependent. For example, the appearance half-life for the degradation products at 25° C and pH 4.5 was 6 h, while at 25° C and pH 7.0, the half-life was 63 h.

The nature of the degradation products has as yet not been determined; although, as indicated by the loss in potency of unstabilized solutions of daptomycin, these products exhibit far less antibiotic activity than the present antibiotic.

The stabilized formulations provided herein are suitable for administration by the parenteral routes and comprise an antibiotically effective amount of daptomycin, a pharmaceutically acceptable buffer and a pharmaceutically acceptable diluent. In addition, the formulations can contain excipients.

Pharmaceutically acceptable buffers which can be used include sodium or potassium salts of phosphoric acid, boric acid, citric acid, carbonic acid, hydroxide, and the like; tris(hydroxymethyl)aminomethane (TRIS® buffer), amino acids, and like buffers.

Diluents which can be used include water for injection, 5% dextrose, 0.9% saline, Ringer's solution and like commonly used diluents for the parenterally administered antibiotics.

Excipients which can be used include, for example, mannitol, tonicity modifiers (e.g., sodium chloride or glycerol), preservatives and solubilizing agents. Further examples of acceptable diluents and excipients can be found in Remington's Pharmaceutical Sciences, 17th Ed., A. R. Gennaro, Ed., Mack Publishing Co., Easton, PA, 1985, incorporated herein by reference; particularly relevant are pages 1518-1552.

Preferred buffers of this invention are dibasic sodium phosphate and TRIS® (tris(hydroxymethyl)-aminomethane buffer.

Thus, in broadest terms, the present invention provides an improved formulation comprising daptomycin and a parenterally-acceptable buffer possessing sufficient buffer capacity to maintain the pH of the reconstituted daptomycin between a pH of between about 6.0 to about 8.0.

Specific examples of preferred parenterally acceptable buffer systems are provided in the following Table 1:

Table 1

Formulation A	Isotonic Sodium Phosphate Dibasic Solution (8.73 mg/mL)
Formulation B	Isotonic Sodium Phosphate Dibasic Solution (15.76 mg/mL)
Formulation C	TRIS® (Tris(hydroxymethyl)aminomethane) Solution (3.30 mg/mL)
Formulation D	TRIS® (Tris(hydroxymethyl)aminomethane) Solution (3.74 mg/mL)
Formulation E	TRIS® (Tris(hydroxymethyl)aminomethane) Solution (4.96 mg/mL)

Formulations comprising the buffers in Table 1 were tested by reconstituting freeze-dried daptomycin (150 mg) and 50 mg mannitol (50 mg) in 10 mL of each buffer, then diluting the resultant solution in 100 mL of 5% dextrose solutions. The effectiveness of the buffered diluents in suppressing the appearance of degradation products is shown below in Table 2:

Table 2:

Summary Stability Results . Percent Increase in Daptomycin Degradation Products at 1 day storage (25° C) and 7 days storage (5° C).

		% Increase in Dextrose Related Degradation Products	
Formulation	pH	1 day (25° C)	7 days (5° C)
5% dextrose (control)	4.4	16.9	17.3
A	6.9	1.1	1.1
B	7.3	0.6	0.5
C	6.9	1.8	0.8
D	7.4	0.5	0.4
E	7.9	0.3	0.3

Further examples of buffer systems meant by the term "pharmaceutically-acceptable buffer" include sodium or potassium salts of phosphoric acid, boric acid, citric acid, carbonic acid, hydroxide, and the like; tris(hydroxymethyl)aminomethane (TRIS® buffer) and all amino acids and like buffers.

In the case where sodium phosphate dibasic is used as buffer, it is preferred that the concentration be in the range of about 0.02 mMolar to about 0.13 mMolar, most preferably about 0.05 mMolar to about 0.10 mMolar. One skilled in the art will appreciate that the amount of buffer necessary to maintain the pH in the desired range is directly related to the amount of daptomycin present in solution. Thus, the above ranges are preferred when daptomycin is present in a concentration of about 6×10^{-4} mMolar.

The following is a nonexhaustive list of examples of unit dose formulations for daptomycin:

	Ingredient	Amount
1)	Daptomycin	150 mg
	Mannitol	50 mg
	Isotonic Sodium Phosphate Dibasic Solution (8.73 mg/ml)	10 ml
	Dextrose (5%)	90 ml
2)	Daptomycin	200 mg
	Mannitol	66 mg
	Isotonic Sodium Phosphate Dibasic Solution (8.73 mg/ml)	13 ml
	Dextrose (5%)	87 ml
3)	Daptomycin	250 mg
	Mannitol	82 mg
	Isotonic Sodium Phosphate Dibasic Solution (8.73 mg/ml)	16 ml
	Dextrose (5%)	84 ml
4)	Daptomycin	300 mg
	Mannitol	100 mg
	Isotonic Sodium Phosphate Dibasic Solution (8.73 mg/ml)	20 ml
	Dextrose (5%)	80 ml

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.