



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification⁶ : A61K 31/44, 38/00</p>	<p>A1</p>	<p>(11) International Publication Number: WO 00/15224</p> <p>(43) International Publication Date: 23 March 2000 (23.03.00)</p>
<p>(21) International Application Number: PCT/US99/21055</p> <p>(22) International Filing Date: 14 September 1999 (14.09.99)</p> <p>(30) Priority Data: 60/100,687 17 September 1998 (17.09.98) US</p> <p>(71) Applicant (for all designated States except US): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).</p> <p>(72) Inventor; and (75) Inventor/Applicant (for US only): RINELLA, Joseph, Vincent, Jr. [US/US]; 3640 Romar Drive, Brownsburg, IN 46112 (US).</p> <p>(74) Agent: MACIAK, Ronald, S.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).</p>	<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: PROTEIN FORMULATIONS</p> <p>(57) Abstract</p> <p>The present invention discloses a stable, soluble formulation comprising a medically useful peptide or protein, a hydrophobic preservative, and nicotinamide. Said storage-stable, soluble formulation is useful as a multi-use pharmaceutical product.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PROTEIN FORMULATIONS

Field of Invention

The present invention is in the field of peptide and protein chemistry as it applies to human medicine. In particular, the invention relates to the preparation of soluble stabile peptide and protein formulations that include nicotinamide and hydrophobic preservatives.

Background of the Invention

Nicotinamide is not a widely-recognized excipient in pharmaceutical formulations. For example, it is not mentioned as an excipient in the *Handbook of Pharmaceutical Excipients*, 2nd ed., A. Wade & P. Weller, Eds. (1994). However, nicotinamide is known to increase the solubility of sparingly-soluble, non-protein, low molecular weight compounds, such as, certain piperazido and piperazino compounds [Fawzi, et al., *J. Pharmaceut. Sci.* 69:104-106 (1980)], anti-cancer nucleoside analogs [Truelove, et al., *Int. J. Pharmaceutics* 19:17-25 (1984)], paracetamol [Hamza, et al., *Drug Dev. Industr. Pharmacy* 11:1577-1596 (1985)], diazepam, griseofulvin, progesterone, 17 β -estradiol, and testosterone [Rasool, et al., *J. Pharmaceut. Sci.* 80:387-393 (1991)], the phenothiazine derivative, moricizine [Hussain, et al., *J. Pharmaceut. Sci.* 82:77-79 (1993)], and riboflavin [Coffman, et al., *J. Pharmaceut. Sci.* 85:951-954 (1996)].

In the above cited formulations, nicotinamide apparently operates as a hydrotropic agent to increase the solubility of another solute when nicotinamide is added at a high concentration. This hydrotropic phenomenon is in direct opposition to normal solution behavior where addition of a second solute to a solution of a sparingly soluble substance will cause the less soluble substance to precipitate.

A combination of insulin and nicotinamide, optionally containing a preservative, was previously

described by Jorgensen in U.S. Patent No. 5,382,574. The formulation was reported to promote faster absorption of insulin from an injection site. Jorgensen does not discuss any effect of nicotinamide on formulation stability.

5 Moreover, it is likely that the effect of nicotinamide was not observed or appreciated because the specification specifically recommends that known stabilizing agents such as phospholipids be added to stabilize the formulations. Also, it fails to mention any effect on insulin stability
10 produced by nicotinamide alone.

The molecular interactions in peptide and protein formulations are complex because a variety of factors such as choice of preservative, buffer, ionic strength, pH, temperature, and other excipients must be balanced to
15 produce a relatively stable formulation suitable for manufacturing, shipping, and storage that meets regulatory requirement for such products. The role that each factor contributes to aggregation is uncertain in view of the complexity of the given peptide or protein molecule as well
20 as the propensity for that peptide or protein to aggregate and precipitate in formulations containing preservatives. In view of this complexity and tendency to aggregate, the effect of nicotinamide on the stability of peptides and protein formulations containing a hydrophobic preservative
25 could not have been predicted from the art describing nicotinamide's effect as a hydrotropic agent for relatively small molecules, nor from its apparent ability to facilitate absorption of insulin from a subcutaneous injection.

Thus, the present invention provides conditions
30 that increase the physical stability of medically useful peptides and proteins in the presence of hydrophobic preservatives and makes possible commercially-viable, multi-use soluble pharmaceutical products to treat a variety of human diseases.

Summary of the Invention

This invention provides a stable soluble formulation comprising a medically useful peptide or protein, a hydrophobic preservative, and nicotinamide.

5 The invention further provides a process for preparing said formulation which comprises combining a peptide or protein, a hydrophobic preservative, and nicotinamide to produce said formulation.

Detailed Description and Preferred Embodiments

10 For purposes of the present invention, as disclosed and claimed herein, the following terms and abbreviations are defined as follows:

 Administering -- an act whose effect is to transfer a formulation of the present invention into the
15 body of a mammal in need thereof. Administration may be via any route known to be effective by the physician of ordinary skill. Parenteral administration is commonly understood in the medical literature as the injection of a dosage form
20 into the body by a sterile syringe or some other mechanical device such as an infusion pump. Peripheral parenteral routes of administration include, without limitation, intravenous, intramuscular, subcutaneous, and
intra-peritoneal routes of administration.

 Alkylparaben -- refers to a C₁ to C₄ alkyl paraben, or mixtures thereof. Preferably, alkylparaben is
25 methylparaben, ethylparaben, propylparaben, or butylparaben.

 Cresol - refers to meta-cresol, ortho-cresol, para-cresol, chloro-cresol, or mixtures thereof.

 Hydrophobic preservative -- refers to a
30 hydrophobic compound that is added to a pharmaceutical formulation to act as an anti-microbial agent. A parenteral formulation must meet guidelines for preservative effectiveness to be a commercially viable multi-use product. Among hydrophobic preservatives known in the art as being
35 effective and acceptable in parenteral formulations are the alkylparabens, the phenolic preservatives, benzyl alcohol,

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.