

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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**LUYE PHARMA GROUP LTD., LUYE PHARMA (USA) LTD.,  
SHANDONG LUYE PHARMACEUTICAL CO., LTD., and NANJING  
PHARMACEUTICAL CO., LTD.,  
Petitioners,**

**v.**

**ALKERMES PHARMA IRELAND LTD and ALKERMES CONTINENTAL  
THERAPEUTICS, INC.,  
Patent Owners.**

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Case IPR2016-01096  
U.S. Patent No. 6,667,061

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**PATENT OWNERS' DEMONSTRATIVES  
ORAL HEARING – AUGUST 28, 2017**



(12) **United States Patent**  
**Ramstack et al.**

(10) **Patent No.:** US 6,667,061 B2  
(45) **Date of Patent:** \*Dec. 23, 2003

(54) **PREPARATION OF INJECTABLE SUSPENSIONS HAVING IMPROVED INJECTABILITY**

(75) Inventors: **J. Michael Ramstack**, Lebanon, OH (US); **M. Gary L. Riley**, Cambridge, MA (US); **Stephen E. Zale**, Hopkinton, MA (US); **Joyce M. Hotz**, Cincinnati, OH (US); **Olufunmi L. Johnson**, Cambridge, MA (US)

(73) Assignee: **Alkermes Controlled Therapeutics, Inc.**

(\*) Notice: Subj. patent U.S.C. This claim

(21) Appl. No.: 10/225

(22) Filed: Sep.

(65) Prior US 2003/0113380.

Related U

(63) Continuation of ap 25, 2000, now Pat

(51) Int. Cl.

(52) U.S. Cl.

(58) Field of Search

(56) Re U.S. PAT

3,523,906	A	8/
3,691,090	A	9/
3,700,215	A	10/
3,737,337	A	6/
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5,656,299 A \* 8/1997 Kino et al. 424/489

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The inventors have unexpectedly discovered that injectability is improved, and in vivo injectability failures are significantly and unexpectedly reduced, by increasing the viscosity of the fluid phase of an injectable suspension, in contrast to conventional teachings that an increased viscosity hinders injectability and syringeability.

Col. 4, ll. 57-62.

(74) *Attorney, Agent, or Firm*—Andrea U. Reister, Covington & Burling

(57) **ABSTRACT**

Injectable compositions having improved injectability. The injectable compositions include microparticles suspended in an aqueous injection vehicle having a viscosity of at least 20 cp at 20° C. The increased viscosity of the injection vehicle that constitutes the fluid phase of the suspension significantly reduces in vivo injectability failures. The injectable compositions can be made by mixing dry microparticles with an aqueous injection vehicle to form a suspension, and then mixing the suspension with a viscosity enhancing agent to increase the viscosity of the fluid phase of the suspension to the desired level for improved injectability.

23 Claims, No Drawings

LUYE1001  
IPR of Patent No. 6,667,061

Decision (Paper 13) at 3; Patent Owners' Response, 5-6, 8, 32, 39, 41; Exh.

## POSA Did Not Want to Increase Vis



DeLuca 1<sup>st</sup> Dep. Tr.  
Exh. 2016 at  
97:10-13

“ . . . A particle in water’s going to s  
pretty fast. In honey, it’s going to ta  
long time. But it would be difficult to  
the honey over water.”

Petitioners' Reply (Paper 40) at 5-6 Exh. 1024 at ¶ 21

### TEST EXAMPLE 1

Each of the bromperidol-containing microsphere preparations obtained in Examples 1 to 3 was suspended in physiological saline and administered into the femoral muscle of male SD rats (15 weeks of age) in a dose of 12.5 mg as bromperidol. After a predetermined period of time, microspheres which remained in the administered area were periodically recovered to measure remaining amount of bromperidol. As the result, release of the drug at an almost constant rate was confirmed as shown in FIG. 1.

United States  
Kino et al.

[54] SUSTAINED  
PREPARATION  
ANTIPSYCHOTIC  
PROCESS

[75] Inventor: S

[73] Assignee: I

[21] Appl. No.: 4

[22] Filed: I

#### Refer

[63] Continuation-in-part of PCT/JP93/01673, Nov. 15, 1993.

[30] Foreign Application Priority Data

Nov. 17, 1992 [JP] Inps ..... 4-332441

[51] Int. Cl.<sup>4</sup> ..... A61K 9/30

[52] U.S. Cl. .... 424/489; 424/490; 424/497; 424/426

[58] Field of Search ..... 424/426, 490, 424/497, 480, 529, 530; 514/938

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..... examiner—Thurman K. Page  
Assistant Examiner—Sharon Howard  
Attorney Agent, or Firm—Sughrue, Mion, Zinn, Macpeak  
& Serr

#### ABSTRACT

A sustained release microsphere preparation which is produced by including a hydrophobic antipsychotic drug such as bromperidol, haloperidol or the like into a base composed of a high molecular weight polymer having in vivo biocompatibility such as polylactide acid, poly(lactide-co-glycolide) acid or the like, and a process for the production thereof.

4 Claims, 4 Drawing Sheets

120  
110

● EXAMPLE 1  
▲ EXAMPLE 2

### TEST EXAMPLE 4

A 15 mg portion of each of the haloperidol-containing microsphere preparations obtained from the following Formulations C and D was dispersed in 20 ml of physiological saline and shaken at 37° C. and at 80 revolutions per minute using a constant temperature shaker (manufactured by Taitech), and samples were periodically collected to calculate drug releasing ratio by ultraviolet absorption photometry (245 nm). As shown in the FIG. 4, it was confirmed that the microsphere preparation of Formulation C which comprises finely ground haloperidol can release the drug at a rate of almost 0 order.

### TEST EXAM

A 25 mg portion of each of the microsphere preparations obtained in Examples A and B was dispersed in physiological saline and shaken at 37° C. and at 80 revolutions per minute using a constant temperature shaker (manufactured by Yamato Kagaku). Thereafter, samples were periodically collected to calculate drug releasing ratio by ultraviolet absorption photometry (245 nm). It was confirmed that the microsphere preparation of Formulation A which comprises finely ground haloperidol can release the drug at a rate of almost 0 order.



US006667061B2

(12) United States Patent  
Ramstack et al.

(10) Patent No.: US 6,667,061 B2  
(45) Date of Patent: \*Dec. 23, 2003

(54)	PREPARATION OF INJECTABLE SUSPENSIONS HAVING IMPROVED INJECTABILITY	5,656,299 A	*	8/1997	Kino et al.	424,489
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					Moscos et al.	

(75) Inventors: J. Michael Ramstack, Lebanon, OH (US); M. Gary L. Riley, Cambridge, MA (US); Stej M.A. (US); Joy OH (US); Oh Cambridge, M.

(73) Assignee: Alkermes Corporation, Cambridge, MA

(\* ) Notice: Subject to any patent is extended U.S.C. 154(b)

This patent is claimed.

(21) Appl. No.: 10/259,949

(22) Filed: Sep. 30, 2002

(65) Prior Publication: US 2003/0113380 A1 Jun. 15

Related U.S. Appl

(63) Continuation of application of Pat. No. 6,495,25, 2000, now Pat. No. 6,495,25

(51) Int. Cl. 7

(52) U.S. Cl. 4, 4

(58) Field of Search 42

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- 5,656,297 A 8/1997 Berstein et al.

23 Claims, No Drawings

LUYE1001  
IPR of Patent No. 6,667,061

'061

Ex

1. A composition suitable for injection through a needle into a host, comprising:

- microparticles comprising a polymeric binder and an injection vehicle, wherein said microparticles are suspended in said injection vehicle at a concentration of greater than about 30 to form a suspension,
- wherein a fluid phase of said suspension has a viscosity greater than about 20 cp and less than about 600 cp at 20°C.,
- wherein the viscosity of said fluid phase of said suspension provides injectability of the composition through a needle ranging in diameter from

Decision (Paper 13) at 4; Patent Owners' Response (Paper 33) at 5

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