UNITED STATES PATENT AND TRADEMARK OFFICE

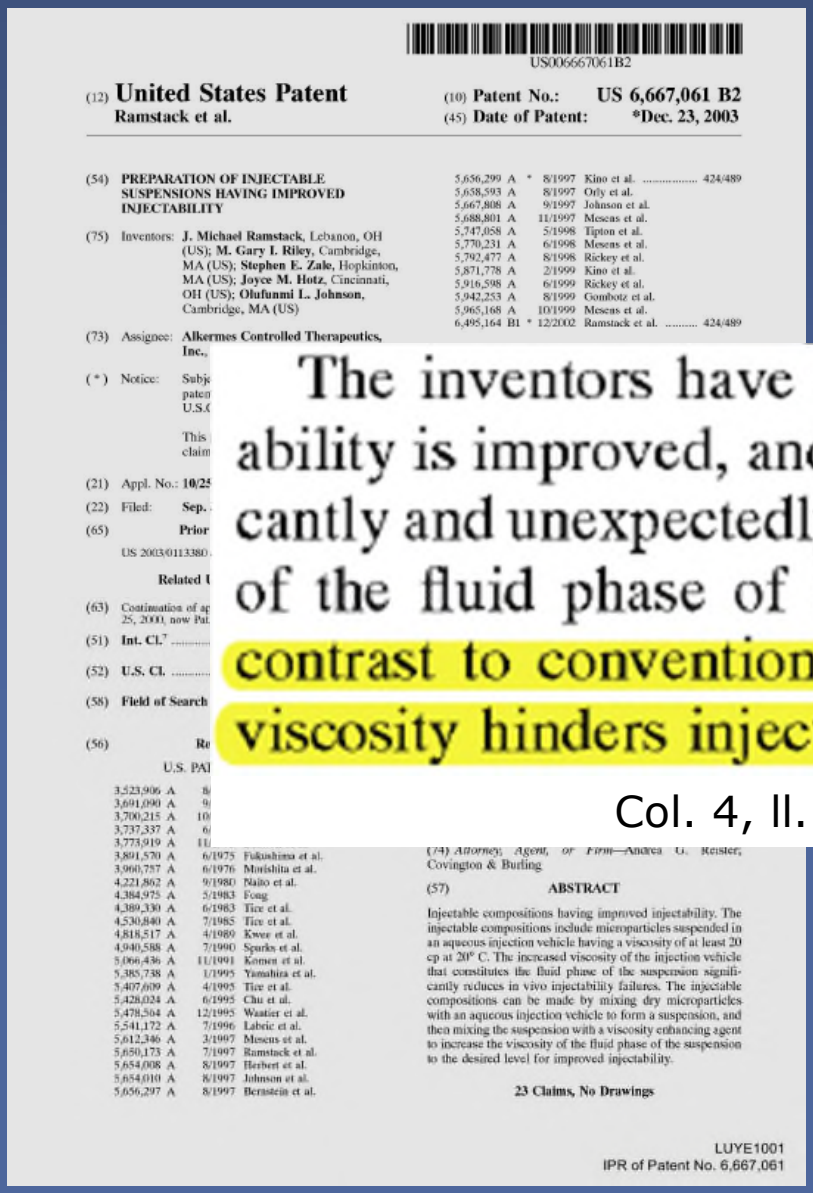
BEFORE THE PATENT TRIAL AND APPEAL BOARD

**LUYE PHARMA GROUP LTD., LUYE PHARMA (USA) LT
SHANDONG LUYE PHARMACEUTICAL CO., LTD., and NANJI
PHARMACEUTICAL CO., LTD.,
Petitioners,
v.
ALKERMES PHARMA IRELAND LTD and ALKERMES CONT
THERAPEUTICS, INC.,
Patent Owners.**

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

PATENT OWNERS' DEMONSTRATIVES
ORAL HEARING – AUGUST 28, 2017

’061 P
Ex



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**

(75) Inventors: **J. Michael Ramstack**, Lebanon, OH (US); **M. Gary I. 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
paten
U.S.C
This
claim

(21) Appl. No.: **10/25**

(22) Filed: **Sep.**

(65) **Prior**
US 2003/0113380

Related U

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

(51) **Int. Cl.**[7]

(52) **U.S. Cl.**

(58) **Field of Search**

(56) **Re**
U.S. PA

3,523,906	A	8/		
3,691,090	A	9/		
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(74) *Attorney, Agent, or Firm*—Andrea G. 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

The inventors have unexpectedly discovered
ability is improved, and in vivo injectability fai
cantly and unexpectedly reduced, by increasing
of the fluid phase of an injectable suspensio
contrast to conventional teachings that an inc
viscosity hinders injectability and syringeabili

Col. 4, ll. 57-62.

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

Petitioners' Expert's Testimon

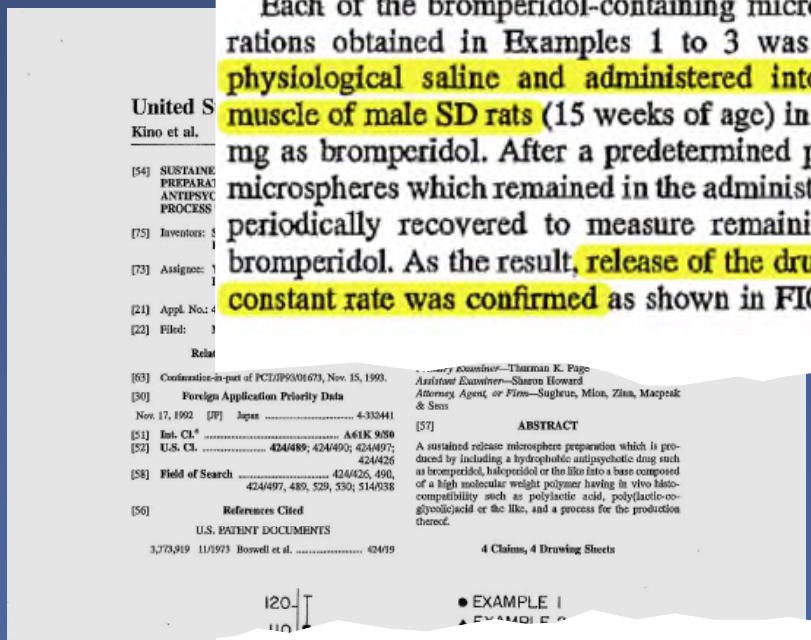
DeLuca 1st Dep. Tr. Exh. 2016 at 97:10-13

" . . . 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 S
Kino et al.

[54] SUSTAINE
PREPARA
ANTIPSYC
PROCESS

[75] Inventors:

[73] Assignee:

[21] Appl. No.:

[22] Filed:

Rela

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

[30] Foreign Application Priority Data

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

[51] Int. Cl.[6] A61K 9/50

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

[58] Field of Search 424/426, 490, 424/497, 489, 529, 530; 514/938

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

[57] 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 histocompatibility such as polylactic acid, poly(lactic-co-glycolic)acid or the like, and a process for the production thereof.

4 Claims, 4 Drawing Sheets

120

● EXAMPLE 1

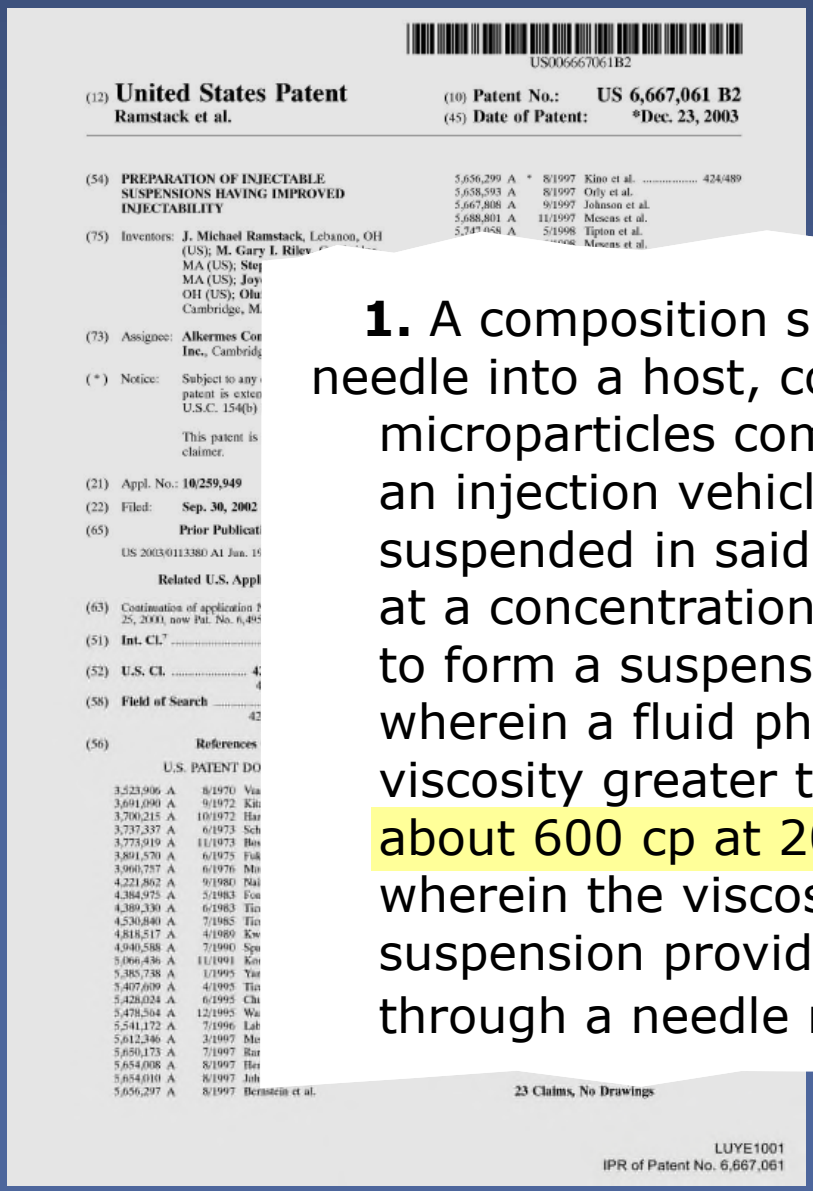
TEST EXAM

A 25 mg portion of each of th
microsphere preparations obtaine
mulations A and B was dispersed
saline and shaken at 37° C. and at
using a constant temperature
Yamato Kagaku). Thereafter, sa
collected to calculate drug rele
absorption photometry (245 nm).
confirmed that the microsphere p
A which comprises finely ground
the drug at a rate of almost 0 or

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.

Patent Owners' Response (Paper 33) at 11; Exh. 2014 at ¶¶ 83-84; Exh. 208



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

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(75) Inventors: **J. Michael Ramstack**, Lebanon, OH (US); **M. Gary I. Riley** [illegible] MA (US); **Ste** [illegible] MA (US); **Joy** [illegible] OH (US); **Olu** [illegible] Cambridge, M[illegible]

(73) Assignee: **Alkermes Co** [illegible] **Inc.**, Cambrid[illegible]

(*) Notice: Subject to any [illegible] patent is exten[illegible] U.S.C. 154(b)

This patent is [illegible] claimer.

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

(22) Filed: **Sep. 30, 2002**

(65) **Prior Publicat**[illegible]

US 2003/0113380 A1 Jun. 1[illegible]

Related U.S. Appl[illegible]

(63) Continuation of application [illegible] 25, 2000, now Pat. No. 6,49[illegible]

(51) **Int. Cl.**[7] .....

(52) **U.S. Cl.** ..... 4[illegible] [illegible]

(58) **Field of Search** ..... [illegible] 42[illegible]

(56) **References**

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4,384,975	A	5/1983	Fo	
4,389,330	A	6/1983	Tic	
4,530,840	A	7/1985	Tic	
4,818,517	A	4/1989	Kw	
4,940,588	A	7/1990	Sp	
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5,747,058	A	5/1998	Tipton et al.	
			Meseas et al.	

23 Claims, No Drawings

LUYE1001
IPR of Patent No. 6,667,061

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Ex

1. A composition suitable for injection throu
needle into a host, comprising:
microparticles comprising a polymeric binde
an injection vehicle, wherein said micropart
suspended in said injection vehicle
at a concentration of greater than about 30
to form a suspension,
wherein a fluid phase of said suspension ha
viscosity greater than about 20 cp and less
about 600 cp at 20°C.,
wherein the viscosity of said fluid phase of
suspension provides injectability of the com
through a needle ranging in diameter from

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

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