US009987229B2

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

(10) **Patent No.: US 9,987,229 B2**
(45) **Date of Patent: *Jun. 5, 2018**

(54) **PROCESS FOR PREPARING A MEDICAMENT**

(71) Applicant: **Norton Healthcare Ltd.**, London (GB)

(72) Inventors: **Xian-Ming Zeng**, London (GB); **Seah Kee Tee**, London (GB)

(73) Assignee: **Norton Healthcare Ltd.**, London (GB)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days. days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/453,940**

(22) Filed: **Mar. 9, 2017**

(65) **Prior Publication Data**

US 2017/0172925 A1 Jun. 22, 2017

Related U.S. Application Data

(60) Continuation of application No. 15/137,671, filed on Apr. 25, 2016, now Pat. No. 9,616,024, which is a division of application No. 10/594,473, filed as application No. PCT/US2004/028345 on Sep. 1, 2004, now Pat. No. 9,345,664.

(60) Provisional application No. 60/499,582, filed on Sep. 2, 2003.

(51) **Int. Cl.**

A61K 9/14	(2006.01)
A61M 15/00	(2006.01)
A61K 31/58	(2006.01)
A61K 9/00	(2006.01)
A61K 31/167	(2006.01)
A61K 31/137	(2006.01)
A61K 9/16	(2006.01)
A61K 31/56	(2006.01)

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

CPC ***A61K 9/1623*** (2013.01); ***A61K 9/0075*** (2013.01); ***A61K 31/167*** (2013.01); ***A61K 31/56*** (2013.01); ***A61K 31/58*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,957,965 A		5/1976	Hartley et al.	
4,161,516 A		7/1979	Bell	
5,518,998 A	*	5/1996	Backstrom	A61K 9/0075 424/489
6,030,604 A		2/2000	Trofast	
6,045,828 A	*	4/2000	Bystrom	A61K 9/0075 424/404
6,371,171 B1		4/2002	Trofast et al.	
2002/0106332 A1		8/2002	Walz et al.	
2003/0068278 A1		4/2003	Boeck et al.	

FOREIGN PATENT DOCUMENTS

GB	1242211	8/1971
WO	9500128	1/1995
WO	9521015	8/1995
WO	0230390	4/2002
WO	03024396	3/2003
WO	2004017918	3/2004

OTHER PUBLICATIONS

Ikegami, et al., "In vitro inhalation behavior of spherically agglomerated steroid particles with carrier lactose," Advanced Powder Technology, (2000) 11: 323-332.

Ikegami, et al., "Simultaneous particulate design of primary and agglomerated crystals of steroid by spherical agglomeration in liquid for dry powder inhalation," Powder Technology, (2003) 130: 290-297 (including preface).

De Villiers, et al., "Dissolution rate a measurement of the deaggregation of furosemide agglomerates during an interactive mixing process," Drug Development and Industrial Pharmacy (1990) 16: 1391-1397.

Cartilier, et al., "Effect of flowing adjuvants on the homogeneity and the kinetics of mixing of low dosage cohesive powder mixtures," Drug Development and Industrial Pharmacy (1986) 12: 1203-1218.

De Villiers, "Description of the kinetics of the deagglomeration of drug particle agglomerates during powder mixing," International Journal of Pharmaceutics (1997) 151: 1-6.

Vazquez, et al., "Assessment of the bronchodilator effect of inhaled furosemide compared to salbutamol in asthmatic patients," J Invest Allergol Clin Immunol (1998) 8: 115-118.

Begat, et al., "The role of force control agents in high-dose dry powder inhaler formulations," American Pharmacists Association J Pharma Sci (2009) 98: 2770-2783.

Morishima, et al., "Micromeritic characteristics and agglomeration mechanisms in the spherical crystallization of bucillamine by the spherical agglomeration and the emulsion solvent diffusion methods," Powder Technology, (1993) 76: 57-64.

Letter from Norton Healthcare Ltd. to Dr. Zeng, dated Aug. 25, 1998.

(Continued)

Primary Examiner — Robert A Wax
Assistant Examiner — Randeep Singh
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

The present invention provides a process for preparing a particulate medicament that has greater homogeneity and a lower adhesion between the particles of the active ingredient and the carrier. The process comprises the steps of: (a) combining a pharmaceutically active ingredient in the form of an agglomerate of primary particles having an agglomerate particle size such that the agglomerate is capable of passing through a sieve having a mesh of 50-3000 .mu.m with a pharmaceutically acceptable particulate carrier, and (b) mixing the resultant material in a mixer to break up the agglomerate into primary particles dispersed in the pharmaceutically acceptable particulate carrier such that 90% or more of the pharmaceutically active ingredient exists as primary particles having a particle size of 50 .mu.m or less.

12 Claims, 5 Drawing Sheets