



Universiteit  
Leiden  
The Netherlands

## Pharmaceutical aspects of subvisible particles in protein formulations

Weinbuch, D.

### Citation

Weinbuch, D. (2016, December 13). *Pharmaceutical aspects of subvisible particles in protein formulations*. Retrieved from <https://hdl.handle.net/1887/44780>

Version: Not Applicable (or Unknown)

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/44780>

**Note:** To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/44780> holds various files of this Leiden University dissertation.

**Author:** Weinbuch, D.

**Title:** Pharmaceutical aspects of subvisible particles in protein formulations

**Issue Date:** 2016-12-13

# **Pharmaceutical aspects of subvisible particles in protein formulations**

**DANIEL WEINBUCH**

The research in this thesis was performed at and financially supported by  
**Coriolis Pharma** Research GmbH, Munich, Germany

Printed by Gildeprint, Enschede, The Netherlands

Pharmaceutical aspects of subvisible particles in protein formulations

Daniel Weinbuch

PhD thesis, with a summary in Dutch

Leiden University, the Netherlands

November 2016

ISBN: 978-94-6233-468-7

Copyright: © 2016 Daniel Weinbuch. All rights reserved. No part of this thesis may be reproduced or transmitted in any form or by any means without written permission of the author.

# **Pharmaceutical aspects of subvisible particles in protein formulations**

Farmaceutische aspecten van microscopisch fijne deeltjes in eiwitformuleringen  
(met een samenvatting in het Nederlands)

## **Proefschrift**

ter verkrijging van  
de graad van Doctor aan de Universiteit Leiden,  
op gezag van Rector Magnificus Prof. Mr. C.J.J.M. Stolker,  
volgens besluit van het College voor Promoties  
te verdedigen op 13. December 2016 des middag te 12.30 uur.

door

**Daniel Weinbuch**

Geboren op 1 mei 1985 te Illertissen, Duitsland

## **Promotor**

Prof. Dr. W. Jiskoot

## **Co-promotor**

Dr. A. Hawe

## **Promotiecommissie**

Prof. Dr. J.A. Bouwstra, Leiden University, Chair

Prof. Dr. M. Danhof, Leiden University, Secretary

Prof. Dr. W. Friess, Ludwig Maximilian University of Munich, Germany

Prof. Dr. A.M. Juppo, University of Helsinki, Finland

Prof. Dr. C.J. Roberts, University of Delaware, USA

Prof. Dr. A.P. IJzerman, Leiden University

“I am a part of all that I have met.”  
(Alfred Lord Tennyson)





---

## Table of contents

---

|            |  |     |
|------------|--|-----|
| Chapter 1  | General introduction   | 9   |
| Chapter 2  | Introduction into formulation development of biologics   | 19  |
| Chapter 3  | Preclinical model used for the immunogenicity prediction of therapeutic proteins   | 43  |
| Chapter 4  | Light obscuration measurements of highly viscous solutions:<br><i>Sample pressurization overcomes underestimation of subvisible particle counts</i>                        | 67  |
| Chapter 5  | Micro–flow imaging and resonant mass measurement (Archimedes):<br><i>Complementary methods to quantitatively differentiate protein particles and silicone oil droplets</i> | 77  |
| Chapter 6  | Flow imaging microscopy for protein particle analysis:<br><i>A comparative evaluation of four different analytical instruments</i>   | 107 |
| Chapter 7  | Nanoparticulate impurities in pharmaceutical-grade sugars and their interference with light scattering-based analysis of protein formulations                              | 135 |
| Chapter 8  | Nanoparticulate impurities in pharmaceutical-grade sucrose are a potential threat to protein stability   | 155 |
| Chapter 9  | Summary and perspectives   | 179 |
| Appendices | Nederlandse samenvatting   | 189 |
|            | Abbreviations  | 195 |
|            | List of publications   | 201 |
|            | <i>Curriculum vitae</i>  | 203 |

---

