The Mechanics of Inhaled Pharmaceutical Aerosols

AN INTRODUCTION

Warren H. Finlay

Dallo Dal



Find authenticated court documents without watermarks at docketalarm.com.

The Mechanics of Inhaled Pharmaceutical Aerosols

An Introduction

Warren H. Finlay

University of Alberta Edmonton, Canada T6G 2G8



ACADEMIC PRESS

A Harcourt Science and Technology Company

San Diego San Francisco New York Boston London Sydney Tokyo

Find authenticated court documents without watermarks at docketalarm.com.

DOCKET

Α

LARM

This book is printed on acid-free paper.

Copyright © 2001 by ACADEMIC PRESS

All Rights Reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher.

> Academic Press A Harcourt Science and Technology Company Harcourt Place, 32 Jamestown Road, London NW1 7BY, UK http://www.academicpress.com

Academic Press A Harcourt Science and Technology Company 525 B Street, Suite 1900, San Diego, California 92101-4495, USA http://www.academicpress.com

ISBN 0-12-256971-7

Library of Congress Catalog Number: 2001090350

A catalogue record for this book is available from the British Library

Typeset by Paston PrePress Ltd, Beccles, Suffolk, UK Printed and bound in Great Britain by Bookcraft, Bath, Somerset

01 02 03 04 05 06 BC 9 8 7 6 5 4 3 2 1

LARM Find authenticated court documents without watermarks at <u>docketalarm.com</u>.

DOCKET

Δ

3. Motion of a Single Aerosol Particle in a Fluid

Here, v is the kinematic viscosity of the fluid surrounding the particle and is given by

$$v = \mu / \rho_{\text{fluid}} \tag{3.8}$$

where μ and ρ_{fluid} are the dynamic viscosity and mass density, respectively, of the fluid surrounding the particle. Various empirical equations for $C_d(Re)$ based on experimental data are normally used (Crowe *et al.* 1998), one such correlation being

$$C_{\rm d} = 24(1+0.15\ Re^{0.687})/Re \tag{3.9}$$

However, most inhaled pharmaceutical aerosol particles have very small diameters d and low velocities v_{rel} , so that Re is small. If $Re \ll 1$, the drag coefficient of a sphere is given by

$$C_{\rm d} = 24/Re$$
 (3.10)

which for Re < 0.1, gives a value of C_d that is accurate to within 1%.

Combining Eqs (3.4)–(3.10), for $Re \ll 1$ we can write

$$\mathbf{F}_{\rm drag} = -3\pi d\mu (\mathbf{v} - \mathbf{v}_{\rm fluid}) \tag{3.11}$$

Equation (3.11) is often referred to as Stokes law¹. It is derived from the continuum equations of fluid motion (since Eq. (3.10) comes by solving the Navier–Stokes equations), and so is valid only for particle diameters that are much greater than the mean free molecular path (which in air at typical inhalation conditions is near 0.07 μ m). Extension of Eq. (3.11) to particles with diameter *d* near the mean free path is considered later in this chapter, while extension to larger Reynolds number is readily accomplished with correlations such as Eq. (3.9).

3.2 Settling velocity

A particle in stationary air will settle under the action of gravity, and reach a terminal velocity quite rapidly. The settling velocity (also referred to as the 'sedimentation velocity') is defined as the terminal velocity of a particle in still fluid.

Because the particle's velocity does not change once it reaches the settling velocity, the acceleration on the particle is zero at this velocity, so that the net force on the particle must also be zero. Assuming the only forces on the particle are the aerodynamic drag and gravity, then for a solid, nonrotating, spherical particle only a vertical drag force will be present, which must balance gravity, i.e.

$$mg = F_{\rm drag} \tag{3.12}$$

where F_{drag} is the magnitude of the drag force. Assuming the Reynolds numbers $Re \ll 1$, we can use Eq. (3.11) for F_{drag} , in which the air velocity is zero ($\mathbf{v}_{fluid} = 0$), so that Eq. (3.11) reduces to

$$F_{\rm drag} = 3\pi d\mu v_{\rm settling} \tag{3.13}$$

Also, the gravity force is

DOCKE

$$mg = \rho_{\text{particle}} Vg \tag{3.14}$$

¹It is named after George Stokes, who first determined the flow field due to a rigid sphere in translational motion through a fluid for very low Reynolds number flow (Stokes 1851).

The Mechanics of Inhaled Pharmaceutical Aerosols

where $V = \pi d^3/6$ is the volume of the spherical particle and g is the acceleration of gravity. Equation (3.14) can thus be written

$$mg = \rho_{\text{particle}}(\pi d^3/6)g \tag{3.15}$$

Substituting Eqns (3.13) and (3.15) into Eq. (3.12), we have

$$3\pi d\mu v_{\text{settling}} = \rho_{\text{particle}}(\pi d^3/6)g \tag{3.16}$$

or

20

$$v_{\text{settling}} = \rho_{\text{particle}} g d^2 / 18 \mu \tag{3.17}$$

Equation (3.17) gives the settling velocity for a spherical particle settling under the action of gravity under the condition that $Re \ll 1$ and diameter \gg mean free path. Most inhaled pharmaceutical aerosols readily satisfy the condition diameter \gg mean free path, and many inhaled pharmaceutical aerosols also satisfy the condition that $Re \ll 1$, as seen in the example below. Exceptions to the condition $Re \ll 1$ are uncommon with inhaled pharmaceutical aerosols, but do occur in the entrainment of large carrier particles that occur in dry powder particles (discussed in Chapter 9), and high-speed metered dose propellant droplets (discussed in Chapter 10).

Example 3.1

What is the Reynolds number of a 10 micron diameter spherical, budesonide powder particle (a drug used in treating asthma, specific gravity = 1.26) settling in room temperature air?

Solution

We have

 $\rho_{\text{particle}} = 1.26 \times \text{density of water} = 1260 \text{ kg m}^{-3}$

viscosity of air $\mu = 1.8 \times 10^{-5}$ kg m⁻¹ s⁻¹

 $d = 10 \times 10^{-6} \,\mathrm{m}$

which gives

DOCKE.

 $\begin{aligned} \nu_{\text{settling}} &= (1260 \text{ kg m}^{-3})(9.81 \text{ m s}^{-2})(10 \times 10^{-6} \text{ m})^2 / (18 \times 1.8 \times 10^{-5} \text{ kg m}^{-1} \text{ s}^{-1}) \\ &= 3.8 \times 10^{-3} \text{ m s}^{-1} \\ &= 3.8 \text{ mm s}^{-1} \end{aligned}$

This gives us a Reynolds number of

$$Re = U_{rel}d/v$$

= (3.8 × 10⁻³ m s⁻¹) × (10 × 10⁻⁶ m)/(1.5 × 10⁻⁵ m² s⁻¹)

where we have used Eq. (3.8) for the kinematic viscosity of air with the density of air being $\rho = 1.2 \text{ kg m}^{-3}$. Calculating the numbers, we have

Re = 0.0025

DOCKET



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.

