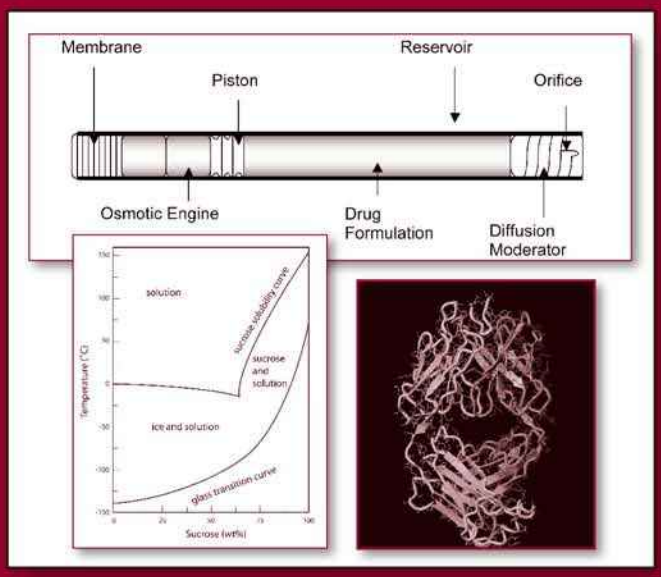
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 175

Protein Formulation and Delivery

Second Edition



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New York London

Informa Healthcare USA, Inc.
52 Vanderbilt Avenue
New York, NY 10017

Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 0-8493-7949-0 (Hardcover)
International Standard Book Number-13: 978-0-8493-7949-9 (Hardcover)

Library of Congress Cataloging-in-Publication Data

Protein formulation and delivery / edited by Eugene J. McNally, Jayne E. Hastedt. -- 2nd ed.
p. ; cm. -- (Drugs and the pharmaceutical sciences ; 175)
Includes bibliographical references and index.
ISBN-13: 978-0-8493-7949-9 (hardcover : alk. paper)
ISBN-10: 0-8493-7949-0 (hardcover : alk. paper)
1. Protein drugs--Dosage forms. I. McNally, Eugene J., 1961- II. Hastedt, Jayne E. III. Series: Drugs and the pharmaceutical sciences ; v.175.
[DNLM: 1. Protein Conformation. 2. Drug Delivery Systems. 3. Drug Design. 4. Drug Stability. 5. Proteins--administration & dosage. W1 DR893B v.175 2007 / QU 55.9 P9667 2007]

RS431.P75P77 2007
615'.19--dc22 2007023435

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Rational Choice of Excipients for Use in Lyophilized Formulations

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INTRODUCTION

The majority of protein drugs are delivered by the injection route, although there is an increasing interest in alternative delivery routes, e.g., pulmonary. Ready-to-use liquid formulations are preferred injectable dosage forms because they are considered easier to manufacture and administer. However, the majority of proteins are not sufficiently stable in aqueous media to provide adequate commercial shelf-life and this limits the development of protein pharmaceuticals as ready-to-use injectables. Freeze-drying is an established process to increase long-term stability of proteins and achieve an acceptable shelf-life (1). In some cases, as with proteins intended for administration by inhalation, spray-drying is used (2). It is also possible to simply dry protein solutions slowly at ambient temperatures under vacuum (3). This chapter deals with freeze-dried protein formulations as they are the most common commercial dosage forms. However, general principles can be applied to other dehydration processes such as spray-drying and vacuum-drying.

Essentially all protein formulations contain one or more inactive ingredients (excipients). Excipients are used to facilitate the formulation manufacturing process, ensure stability of the active ingredient during processing, storage, and administration, minimize adverse effects upon administration (e.g., minimize pain upon injection), and ensure desirable bioavailability and (for sustained release dosage forms) release profiles. Each excipient in the formulation requires justification for its use and an appropriate rationale for the level selected. Only excipients that are essential for performance and/or stability of a dosage form and suitable for injectable products are allowed to be included.

The majority of lyophile protein dosage forms contain buffer and a bulking agent, the latter often playing a dual role for both pharmaceutical elegancy and cryo- and lyoprotection, to achieve stability during processing and the shelf-life. In addition, many protein formulations contain additional stabilizers, e.g., a surfactant, and occasionally an antioxidant or a chelating agent. In some cases, a tonicity modifier, a solubilizer, a processing aid, or an antimicrobial agent may be used. It is notable that the active ingredient level in the formulation can range from as high as close to 100% to as low as a few parts per million. Therefore, it is also possible to have a large range of excipient levels in the final formulation. It should be mentioned also that excipients, which are important for the reconstituted solution, e.g., antimicrobial agents or tonicity modifiers, can be added with the diluent rather than being incorporated into the lyophile cake. Generally, selection of a proper excipient should take into account (*i*) the type of product, (*ii*) the delivery route, dose, and administration frequency, (*iii*) the chemical and physical properties of the excipient, (*iv*) potential interactions with other product components, and (*v*) the container/closure system.

It is typically advantageous to choose formulation excipients that will not only enable the product to meet its critical quality parameters but also facilitate the freeze-drying process because of the high cost/long processing times for this unit operation. This is especially critical when developing formulations for unique package systems such as dual chamber syringes, because of the difficulties encountered in uniform drying in these packages. Therefore, selection of excipients that can potentially increase the collapse or eutectic temperatures of the frozen solution can greatly facilitate the drying process, thereby reducing cost and processing times. It is also important to select excipients whose vapor pressure is sufficiently low so as not to permit its removal during the lyophilization process.

There are a number of reviews available on different aspects of protein freeze-drying (1,4–10). In particular, it has been recognized that understanding phase behavior is a key for lyophile formulation and process development. Therefore, we start with a discussion of phase behavior of excipients during manufacturing and storage. Phase transitions have a major impact on stability and performance of protein dosage forms. For example, crystallization of a lyoprotector may result in protein destabilization during freeze-drying and storage. Description of excipients based on their functional role in protein formulations is given in the section titled Role and Properties of Excipients, followed by practical

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