

Second Edition

Pharmaceutical Formulation Development of Peptides and Proteins

Edited by
Lars Hovgaard
Sven Frokjaer
Marco van de Weert

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Contents

Preface.....	vii
Editors.....	ix
Contributors.....	xi
Chapter 1 Peptide Synthesis.....	1
<i>Knud J. Jensen</i>	
Chapter 2 Protein Expression.....	17
<i>Nanni Din</i>	
Chapter 3 Protein Purification.....	35
<i>Lars Hovgaard, Lars Skriver, and Sven Frøkjær</i>	
Chapter 4 Characterization of Therapeutic Peptides and Proteins.....	49
<i>Marco van de Weert and Tudor Arvinte</i>	
Chapter 5 Chemical Pathways of Peptide and Protein Degradation.....	79
<i>Teruna J. Siahaan and Christian Schöneich</i>	
Chapter 6 Physical Instability of Peptides and Proteins.....	107
<i>Marco van de Weert and Theodore W. Randolph</i>	
Chapter 7 Peptide and Protein Derivatives.....	131
<i>Kristian Strømgaard and Thomas Høeg-Jensen</i>	
Chapter 8 Peptides and Proteins as Parenteral Solutions.....	149
<i>Michael J. Akers and Michael R. DeFelippis</i>	
Chapter 9 Peptides and Proteins as Parenteral Suspensions: An Overview of Design, Development, and Manufacturing Considerations.....	193
<i>Michael R. DeFelippis and Michael J. Akers</i>	

Chapter 10	Rational Design of Solid Protein Formulations	239
	<i>Bingquan (Stuart) Wang and Michael J. Pikal</i>	
Chapter 11	Peptide and Protein Drug Delivery Systems for Nonparenteral Routes of Administration	269
	<i>Ulrik Lyn Rahbek, František Hubálek, and Simon Bjerregaard</i>	
Chapter 12	Immunogenicity of Therapeutic Proteins	297
	<i>Grzegorz Kijanka, Wim Jiskoot, Melody Sauerhorn, Huub Schellekens, and Vera Brinks</i>	
Chapter 13	Biosimulation of Peptides and Proteins	323
	<i>Tue Søbørg, Christian Hove Rasmussen, Erik Mosekilde, and Morten Colding-Jørgensen</i>	
Chapter 14	Registration of Peptides and Proteins	339
	<i>Niamh Kinsella</i>	
Index	363

6 Physical Instability of Peptides and Proteins

Marco van de Weert and Theodore W. Randolph

CONTENTS

6.1	Introduction	107
6.2	Protein Structure.....	108
6.2.1	Peptides, Polypeptides, and Proteins	108
6.2.2	Protein Structure: Primary, Secondary, Tertiary, and Quaternary Structure	108
6.3	Protein Folding: Why Do Proteins Fold?	109
6.3.1	Role of Water and Stabilizing Interactions.....	109
6.3.2	The Energy Landscape of a Protein Molecule	111
6.4	Protein Physical Degradation	114
6.4.1	Protein Unfolding	114
6.4.2	Adsorption	117
6.4.3	Protein Aggregation.....	118
6.4.3.1	Aggregation Mechanisms and Kinetics.....	119
6.4.3.2	Fibrillation: A Special Case of Protein Aggregation.....	120
6.4.4	Protein Precipitation	121
6.5	Stabilization Strategies	122
6.6	Concluding Remarks	125
	References.....	126

6.1 INTRODUCTION

The biological function of peptides and proteins is highly dependent on their three-dimensional structure. Changes in that structure, which may arise due to chemical or physical processes, may alter or abolish that function, or even result in toxicity. Thus, it is of importance that a pharmaceutical formulation of therapeutic peptides and proteins retains the normal (native) structure of those peptides or proteins, or that any changes are fully reversible upon administration to the patient.

A major difference between proteins and low molecular weight drugs is the complexity of the three-dimensional structure and concomitant sensitivity toward external stress factors. The three-dimensional structure of proteins is mostly held together by noncovalent interactions, such as hydrogen bonds, salt bridges, and van der Waals forces. Any stress factor may alter these noncovalent interactions, possibly leading to new intra- or intermolecular interactions which may not be reversible upon removing the stress factor.

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