

# NANOSCIENCE APPLICATIONS IN DIABETES TREATMENT

Editor:  
**Ali Rastegari**

**Bentham Books**

# **Nanoscience Applications in Diabetes Treatment**

Edited by

**Ali Rastegari**

*Department of Pharmaceutics and Pharmaceutical  
Nanotechnology, School of Pharmacy  
Iran University of Medical Sciences  
Tehran, Iran*

## **Nanoscience Applications in Diabetes Treatment**

Editor: Ali Rastegari

ISBN (Online): 978-981-5196-53-5

ISBN (Print): 978-981-5196-54-2

ISBN (Paperback): 978-981-5196-55-9

© 2023, Bentham Books imprint.

Published by Bentham Science Publishers Pte. Ltd. Singapore. All Rights Reserved.

First published in 2023.

## **BENTHAM SCIENCE PUBLISHERS LTD.**

### **End User License Agreement (for non-institutional, personal use)**

This is an agreement between you and Bentham Science Publishers Ltd. Please read this License Agreement carefully before using the ebook/echapter/ejournal (“**Work**”). Your use of the Work constitutes your agreement to the terms and conditions set forth in this License Agreement. If you do not agree to these terms and conditions then you should not use the Work.

Bentham Science Publishers agrees to grant you a non-exclusive, non-transferable limited license to use the Work subject to and in accordance with the following terms and conditions. This License Agreement is for non-library, personal use only. For a library / institutional / multi user license in respect of the Work, please contact: [permission@benthamscience.net](mailto:permission@benthamscience.net).

### **Usage Rules:**

1. All rights reserved: The Work is the subject of copyright and Bentham Science Publishers either owns the Work (and the copyright in it) or is licensed to distribute the Work. You shall not copy, reproduce, modify, remove, delete, augment, add to, publish, transmit, sell, resell, create derivative works from, or in any way exploit the Work or make the Work available for others to do any of the same, in any form or by any means, in whole or in part, in each case without the prior written permission of Bentham Science Publishers, unless stated otherwise in this License Agreement.
2. You may download a copy of the Work on one occasion to one personal computer (including tablet, laptop, desktop, or other such devices). You may make one back-up copy of the Work to avoid losing it.
3. The unauthorised use or distribution of copyrighted or other proprietary content is illegal and could subject you to liability for substantial money damages. You will be liable for any damage resulting from your misuse of the Work or any violation of this License Agreement, including any infringement by you of copyrights or proprietary rights.

### ***Disclaimer:***

Bentham Science Publishers does not guarantee that the information in the Work is error-free, or warrant that it will meet your requirements or that access to the Work will be uninterrupted or error-free. The Work is provided "as is" without warranty of any kind, either express or implied or statutory, including, without limitation, implied warranties of merchantability and fitness for a particular purpose. The entire risk as to the results and performance of the Work is assumed by you. No responsibility is assumed by Bentham Science Publishers, its staff, editors and/or authors for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products instruction, advertisements or ideas contained in the Work.

### ***Limitation of Liability:***

In no event will Bentham Science Publishers, its staff, editors and/or authors, be liable for any damages, including, without limitation, special, incidental and/or consequential damages and/or damages for lost data and/or profits arising out of (whether directly or indirectly) the use or inability to use the Work. The entire liability of Bentham Science Publishers shall be limited to the amount actually paid by you for the Work.

### **General:**

1. Any dispute or claim arising out of or in connection with this License Agreement or the Work (including non-contractual disputes or claims) will be governed by and construed in accordance with the laws of Singapore. Each party agrees that the courts of the state of Singapore shall have exclusive jurisdiction to settle any dispute or claim arising out of or in connection with this License Agreement or the Work (including non-contractual disputes or claims).
2. Your rights under this License Agreement will automatically terminate without notice and without the

need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.

3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

**Bentham Science Publishers Pte. Ltd.**

80 Robinson Road #02-00

Singapore 068898

Singapore

Email: [subscriptions@benthamscience.net](mailto:subscriptions@benthamscience.net)



## CONTENTS

<b>PREFACE</b> .....	i
<b>LIST OF ABBREVIATIONS</b> .....	ii
<b>LIST OF CONTRIBUTORS</b> .....	iv
<b>CHAPTER 1 THE STORY OF DIABETES AND ITS CAUSES</b> .....	1
<i>Ramin Malboosbaf and Neda Hatami</i>	
<b>INTRODUCTION</b> .....	1
<b>TYPE 1 DIABETES</b> .....	2
Role of Genetics .....	2
Role of the Environment .....	3
<i>Infection</i> .....	3
<i>Dietary Factors</i> .....	3
Natural History and Prognosis .....	3
Effects on Glucose Metabolism .....	6
Effect on Lipid Metabolism .....	6
Effects on Protein Metabolism .....	7
<b>PATHOPHYSIOLOGY OF TYPE 2 DIABETES</b> .....	7
Insulin-sensitive Tissues .....	8
Insulin Resistance and the Risk of Type 2 Diabetes Mellitus .....	10
Adipose Tissue and Insulin Resistance .....	11
Role of Gut Microbiome and Metabolome in Diabetes and Insulin Resistance .....	12
Role of Gut Hormones .....	13
Genetics .....	14
Environmental Influences .....	15
Sleeping .....	16
Natural History and Prognosis .....	16
Maturity-onset Diabetes of the Young, Latent Autoimmune Diabetes of Adults, and Double Diabetes .....	17
<b>CONCLUSION</b> .....	18
<b>REFERENCES</b> .....	18
<b>CHAPTER 2 TREATMENT APPROACHES AND CHALLENGES</b> .....	31
<i>Ramin Malboosbaf and Neda Hatami</i>	
<b>INTRODUCTION</b> .....	31
<b>PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 1 DIABETES</b> .....	32
Insulin Therapy .....	32
<b>PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES</b> .....	34
<b>NON-INSULIN TREATMENT FOR TYPE 2 DIABETES MELLITUS</b> .....	35
Insulin Secretagogues .....	35
<i>Sulfonylureas</i> .....	36
<i>Meglitinides</i> .....	37
Amylin Analogs .....	37
<i>Biguanides</i> .....	38
<i>Metformin</i> .....	38
<i>Insulin Sensitizers</i> .....	39
Alpha-glucosidase Inhibitors (AGIs) .....	40
<i>Incretin Mimetics</i> .....	41
<i>GLP-1 Agonists</i> .....	41
<i>DPP-4 Inhibitors</i> .....	43

Sodium-glucose Co-transporter Two Inhibitors .....	44
Insulin in Type 2 Diabetes .....	46
<b>CONCLUSION</b> .....	47
<b>REFERENCES</b> .....	47
<b>CHAPTER 3 NANOMEDICINE FOR INSULIN DELIVERY IN DIABETES</b> .....	57
<i>Morteza Rafiee-Tehrani, Somayeh Handali, Mohammad Vaziri, Sepideh Nezhadi and Farid Abedin Dorkoosh</i>	
<b>INTRODUCTION</b> .....	57
<b>NANOCARRIERS BASED INSULIN DELIVERY</b> .....	60
Liposome .....	61
Chitosan .....	62
PLGA .....	63
Solid Lipid Nanoparticle (SLN) .....	63
Hydroxyapatite (HAP) .....	64
Nanogels .....	64
Micelle .....	65
Dendrimer .....	65
Exosomes .....	65
<b>CONCLUSION</b> .....	66
<b>REFERENCES</b> .....	66
<b>CHAPTER 4 NANOSCIENCE FOR DRUG DELIVERY IN DIABETES</b> .....	70
<i>N. Vishal Gupta, M. Sharadha, K. Trideva Sastri, Souvik Chakraborty, Hitesh Kumar, Vikas Jain and Surajit Dey</i>	
<b>NANOMEDICINE IN DIABETES: NEED-BASED APPROACH</b> .....	70
Nanomedicine in the Management of Diabetes .....	72
<b>ORGANIC MATERIAL-BASED NANOMEDICINES</b> .....	72
Lipid-based Nanocarriers .....	72
<i>Liposomes and Pro-liposomes</i> .....	74
<i>Solid Lipid Nanoparticles (SLNs)</i> .....	75
<i>Nanostructured Lipid Carriers (NLCs)</i> .....	76
<i>Nano-emulsions</i> .....	76
<i>Microemulsions</i> .....	77
<i>Nano-capsules</i> .....	78
<i>Self-nano-and Micro-emulsifying Drug Delivery Systems (SMEDDS and SNEDDS)</i> .....	78
Natural Polymeric Nanoparticles .....	79
<i>Chitosan-Based Nanoparticles</i> .....	79
<i>Alginate-Based Nanoparticles</i> .....	80
<i>Dextran-Based Nanoparticles</i> .....	81
Synthetic Polymeric Nanoparticles .....	81
<i>PLGA (Poly Lactic-co-Glycolic Acid) Based Nanoparticles</i> .....	81
<i>PLA Based Nanoparticles</i> .....	82
Miscellaneous .....	82
<i>Nanosuspensions</i> .....	82
<i>Dendrimers</i> .....	83
<i>Micelles</i> .....	84
<i>Hydrogels</i> .....	85
<b>INORGANIC MATERIAL-BASED NANOMEDICINE</b> .....	86
Carbon Nanotubes (CNTs) .....	86
Metallic Nanoparticles (MNPs) .....	87
<b>SPECIALIZED NANOMEDICINES</b> .....	88

Natural Carrier Systems-based Nanomedicines .....	89
Erythrocytes-based Nanocarriers .....	89
Exosomes-based Nanocarriers .....	90
Phytosome-based Nanocarriers .....	90
Sphingosomes-based Nanocarriers .....	91
<b>CHALLENGES WITH NANOMEDICINE IN THE MANAGEMENT OF DIABETES .....</b>	<b>92</b>
<b>CONCLUSION AND FUTURE PERSPECTIVES .....</b>	<b>93</b>
<b>REFERENCES .....</b>	<b>94</b>
<b>CHAPTER 5 NANOSCIENCE FOR NUCLEOTIDE DELIVERY IN DIABETES .....</b>	<b>102</b>
<i>Ali Rastegari</i>	
<b>INTRODUCTION .....</b>	<b>102</b>
<b>DNA DELIVERY APPROACH .....</b>	<b>104</b>
<b>RNA DELIVERY APPROACH .....</b>	<b>106</b>
<b>FUTURE AND CHALLENGES .....</b>	<b>107</b>
<b>CONCLUSION .....</b>	<b>108</b>
<b>REFERENCES .....</b>	<b>108</b>
<b>SUBJECT INDEX .....</b>	<b>133</b>



## **PREFACE**

The book is structured in a manner that sequentially covers various aspects related to diabetes and the application of nanotechnology in its treatment. Chapters 1 and 2 extensively delve into the pathophysiology of diabetes, encompassing different types of the disease, and provide an overview of the diverse medical therapy approaches available for each type. Chapter 3 focuses on the utilization of nanomedicine for insulin delivery in diabetes treatment. It thoroughly explores the various nano-based vehicles that hold the potential for delivering insulin effectively. In Chapter 4, the book extensively discusses the potential of nanoscience in drug delivery for diabetes. This chapter presents a comprehensive review of different studies that have investigated the use of nanoparticles as carriers for drug delivery in diabetes treatment. The final chapter concentrates on nanotechnology approaches for nucleotide delivery and gene therapy in diabetes. It not only highlights the advancements in this field but also addresses the associated challenges and potential future developments. Overall, the book aims to provide a comprehensive understanding of diabetes, current medical therapies, and how nanotechnology can be harnessed to enhance treatment options, including insulin delivery, drug delivery, and gene therapy.

**Ali Rastegari**

Department of Pharmaceutics and Pharmaceutical Nanotechnology  
School of Pharmacy, Iran University of Medical Sciences  
Tehran, Iran

## List of Abbreviations

- AGIs** Alpha-glucosidase inhibitors
- BMI** Body mass index
- CDC** Centers for disease control and prevention
- CPPs** Cell-penetrating peptides
- CNTs** Carbon nanotubes
  - DM** Diabetes mellitus
  - DDs** Drug delivery systems
  - DPPi** Dipetidyl peptide inhibitor
  - DNA** Deoxyribonucleic acid
  - FDA** Food and drug administration
- G-CSF** Granulocyte colony-stimulating factor
  - GAD** Glutamic acid decarboxylase
  - GI** Gastrointestinal
- GLP-1** Glucagon-like peptide-1
  - GIP** Gastric inhibitory polypeptide
- GCK** Glucokinase
- GLB** Glibenclamide
- HLA** Human leukocyte antigen
  - IL** Interleukin
- ICAs** Islet cell antibodies
- IAAs** Insulin autoantibodies
  - LPL** Lipoprotein lipase
- LADA** Latent autoimmune diabetes of adults
- LNCs** Lipid nano-capsules
- MNPs** Metallic nanoparticles
- MODY** Maturity-onset Diabetes of the Young
- MCP1** Monocyte chemoattractant protein 1
  - MEs** Micro-emulsions
  - NPs** Nanoparticles
  - NEs** Nano-emulsions
- NLCs** Nanostructured Lipid Carriers
- PKC** Protein kinase C

<b>PLs</b>	Pro-liposomes
<b>PEG</b>	Poly ethylene glycol
<b>PLGA</b>	Poly (lactic-co-glycolic) acid
<b>RAA</b>	Rapid-acting analogs
<b>RNA</b>	Ribonucleic acid
<b>SiRNA</b>	Short interfering RNAs
<b>SGDC</b>	Sodium-glycodeoxycholate
<b>SLNs</b>	Solid lipid NPs
<b>SUR</b>	Sulfonylurea receptor
<b>SGLT2</b>	Sodium-glucose cotransporter 2
<b>TCA</b>	Tricarboxylic acid
<b>TZD</b>	Thiazolidinediones
<b>TNF</b>	Tumor necrosis factor
<b>T1DM</b>	Type 1 diabetes mellitus
<b>T2DM</b>	Type 2 diabetes mellitus
<b>UCP1</b>	Uncoupling protein 1

## List of Contributors

<b>Ali Rastegari</b>	Department of Pharmaceutics and Pharmaceutical Nanotechnology, School of Pharmacy, Iran University of Medical Sciences, Tehran, Iran
<b>Farid Abedin Dorkoosh</b>	Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
<b>Hitesh Kumar</b>	Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India
<b>K. Trideva Sastri</b>	Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India
<b>M. Sharadha</b>	Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India
<b>Mohammad Vaziri</b>	Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
<b>Morteza Rafiee-Tehrani</b>	Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
<b>N. Vishal Gupta</b>	Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India
<b>Neda Hatami</b>	Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran
<b>Ramin Malboosbaf</b>	Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran
<b>Sepideh Nezhadi</b>	Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
<b>Somayeh Handali</b>	Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
<b>Souvik Chakraborty</b>	Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India
<b>Surajit Dey</b>	Roseman University of Health Sciences, College of Pharmacy, Henderson, Nevada, USA
<b>Vikas Jain</b>	Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India

**CHAPTER 1****The Story of Diabetes and its Causes****Ramin Malboosbaf<sup>1,\*</sup> and Neda Hatami<sup>1</sup>**<sup>1</sup> *Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran*

**Abstract:** Diabetes mellitus (DM) is a complex metabolic disorder whose rising prevalence is terrible. A deeper knowledge of the pathophysiology of diabetes could assist in discovering possible therapeutic targets for treating diabetes and its associated problems. The common feature of diabetes, regardless of the specific pathology involved, is hyperglycemia brought on by the death or dysfunction of  $\beta$ -cell. As insulin deficiency gets worse over time, dysglycemia progresses in a continuum. This chapter has provided a brief review of the pathophysiology of diabetes. Also, the roles of genetics and environmental factors have been emphasized.

**Keywords:** Diabetes, Disease, Factor, Glucose, Pathophysiology.

**INTRODUCTION**

Diabetes mellitus is a complex metabolic disorder whose principal clinical and diagnostic feature is hyperglycemia [1]. Diabetes has reached epidemic proportions; the global diabetes prevalence in 20-79-year-old in the latest reports was estimated to be 10.5% (536.6 million people), rising to 12.2% (783.2 million) in 2045 [2]. Over the next 20 years, its prevalence is expected to double, affecting more than half a billion people, with more than 75% of patients living in low- and middle-income countries [3]. Additionally, the increase in prevalence in developing countries is believed to be greater due to the widespread adoption of Western lifestyle habits, such as sedentary behavior, inactivity, and a high-energy diet [4, 5].

The risk of a variety of cardiovascular disorders is roughly doubled by diabetes, particularly type 2 diabetes mellitus (T2DM) [6]. In addition, a wide range of non-vascular diseases, such as cancer, infections, liver disease, and mental and nervous system disorders, are linked to T2DM [7]. In a similar vein, type 1 diabetes mellitus (T1DM) is linked to an increased risk of both vascular and non-

---

\* **Corresponding author Ramin Malboosbaf:** Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran; E-mail: malboosbaf.r@gmail.com

vascular complications. A deeper knowledge of the pathophysiology of diabetes could assist in discovering possible therapeutic targets for treating diabetes and its associated problems [8, 9].

## **TYPE 1 DIABETES**

The prevalence of T1DM is increasing worldwide. Although T1DM is often diagnosed in childhood, 84% of people living with T1DM are adults [10]; 62% of all new T1D cases in 2022 were in people aged 20 years or older [11]. T1DM affects men and women equally [12] and reduces life expectancy by an estimated 13 years [9]. With some exceptions, the incidence of T1DM is positively related to geographic distance north of the equator [13]. Colder seasons correlate with the diagnosis and progression of T1DM. Both disease onset and the incidence of islet autoimmunity appear to be higher in autumn and winter than in spring and summer [14 - 16].

### **Role of Genetics**

The higher prevalence of T1DM in a family suggests a hereditary risk, which increases with the proband's degree of genetic similarity. Human leukocyte antigen (HLA) gene variations alter how the HLA protein binds to antigenic peptides and how the antigen is presented to T cells, contributing to 50-60% of the gene risk. Cell surface proteins involved in antigen presentation and self-tolerance are encoded by HLA genes, which are essential for controlling the immune response. As a result, genetic variations in these proteins' amino acid sequences may alter the repertoire of presented peptides and result in self-tolerance loss [17].

The autoimmune nature of diabetes is primarily due to its strong connection to HLA, the DQA and DQB genes, and its direct influence through the DRB genes [18]. Genome-wide association studies have demonstrated a strong link with the HLA-DR3 and HLA-DR4 haplotypes, as well as an exclusive link between the autoimmune destruction of  $\beta$ -cells and the DR4-DQB1\*0302 haplotype [19 - 21].

Smaller effects are caused by about additional 50 genes individually [22, 23], including gene variants that modulate immune regulation and tolerance, viral responses [24 - 29], responses to environmental signals, and endocrine function [30]. Some variants are expressed in pancreatic  $\beta$ -cell [31]. In relatives, the onset and progression of islet autoimmunity are influenced by genetics [32, 33]. These gene variants collectively are responsible for 80% of T1DM inheritance [34]. A patient's risk, C-peptide decline rates, and response to various therapies can all be predicted by genetic variants [35]. With a deeper comprehension of heredity profiles, new goals for individualized interventions may be realized.

## **Role of the Environment**

Numerous pieces of evidence suggest that environmental and genetic factors interact to cause autoimmunity and the development of T1DM, such as T1DM discordance rates in twins, the variance in geographic prevalence, and the adjustment of disease incidence rates as individuals migrate from low to high-incidence countries. The fact that most patients with the highest risk HLA haplotypes do not develop T1DM lends credence to this gene-environment interaction. Timing of environmental trigger exposure can also be very important. The investigation of environmental exposures is made more challenging by the variation in disease onset age. However, the early onset of islet autoantibodies linked to T1DM in children raises the possibility that early environmental exposures may play a role [10].

## ***Infection***

Congenital rubella infection has strong evidence to raise the possibility of T1DM development [36]. Enteroviruses are also thought to be associated with T1DM [37]. These infections are considered to alter gut microbiome composition [10].

## ***Dietary Factors***

$\beta$ -cell autoimmunity can be affected by the timing of exposure to foods like grains and nutrients like gluten [10], as some studies show that early initiation of (<3 months) cereals may have this effect [38]. Retrospective studies led to the hypothesis that early initiation of cow's milk or less breastfeeding could increase the risk of T1DM. However, it was not confirmed by prospective studies [39]. Vitamin D deficiency and low levels of omega-3 fatty acids have been probably linked to an increased risk of T1DM [40].

## **Natural History and Prognosis**

The common feature of diabetes, regardless of the specific pathology involved, is hyperglycemia brought on by the death or dysfunction of  $\beta$ -cell. As insulin deficiency gets worse over time, dysglycemia progresses in a continuum. The ability to categorize diseases and determine where and how to intervene best to stop or halt disease progression and complications depends on understanding the natural history of  $\beta$ -cell mass and function [10]. T1DM pathogenesis is influenced by both humoral and cellular immunity [41]. There is increasing evidence of significant overlap across the entire spectrum of diabetes, even though T1DM is caused by the immune system's destruction of beta cells, and T2DM is mostly associated with glucose-specific insulin secretion problems [42]. In both types of diabetes, the hyperglycemia-induced stress response may contribute to  $\beta$ -cell

## Treatment Approaches and Challenges

Ramin Malboosbaf<sup>1,\*</sup> and Neda Hatami<sup>1</sup>

<sup>1</sup> Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran

**Abstract:** Diabetes drugs are given in monotherapy or in combination. The significant challenges in effective diabetes management are optimizing current treatments to ensure optimal and stable glucose control with minimal side effects and reducing long-term complications of diabetes. This chapter reviews these conventional drugs with their mechanism of action, side effects, and efficacy and safety profile.

**Keywords:** Diabetes, Disease, Safety, Treatment.

### INTRODUCTION

Many people worldwide are affected by diabetes mellitus (DM), a significant public health problem [1]. The worldwide increase in diabetes patients, maybe primarily attributable to the trend toward sedentary living [2]. Retinopathy, nephropathy, neuropathy, and cardiovascular complications are DM-related complications [3].

Diabetes drugs are given in monotherapy or combination [4]. The significant challenges in effective diabetes management are optimizing current treatments to ensure optimal and stable glucose control with minimal side effects and reducing long-term complications of diabetes [5]. Nanoformulations can solve some of the disadvantages of current anti-diabetic drugs [5] and, more importantly, promote cellular uptake and enhance the pharmacokinetics and pharmacodynamics of drugs [6].

---

\* Corresponding author Ramin Malboosbaf: Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran; E-mail: malboosbaf.r@gmail.com



## PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 1 DIABETES

### Insulin Therapy

Insulin treatment is essential for these individuals because the absence or near-absence of  $\beta$ -cell function is the hallmark of T1DM [7]. Furthermore, during the past three decades, there has been growing evidence that the optimal combination of effectiveness and safety for patients with T1DM is provided by more intense insulin replacement, such as numerous daily insulin injections or continuous subcutaneous delivery *via* an insulin pump [8 - 10].

Basal insulin, prandial insulin, and correction insulin are frequently used in insulin replacement therapy [11]. NPH insulin, long-acting insulin analogs, and continuous rapid-acting insulin delivery *via* an insulin pump are all components of basal insulin. Compared to NPH insulin, basal insulin analogs have a longer duration of action and plasma concentration and activity profiles that are flatter and more constant. Compared to standard human insulin, rapid-acting analogs (RAA) have a quicker onset, peak, and duration of action. Compared to human insulin, treatment with insulin analogs is associated with lower HbA1C and less hypoglycemia, weight gain, and hypoglycemia in T1DM patients [12 - 14]. Compared to RAA, inhaled human insulin may cause less hypoglycemia and weight gain due to its rapid peak and shorter action duration [15]. Recently, two new formulations of injectable insulin were released with improved fast-acting profiles. Faster-acting insulin aspart and insulin lispro-aabc are better at reducing prandial excursions than RAA [16, 17]. In addition, compared to U-100 glargine, longer-acting basal analogs (U-300 glargine or degludec) may reduce the risk of hypoglycemia in T1DM patients [18, 19]. Despite the advantages of insulin analogs for T1DM patients, some people cannot afford the expense and level of care needed to utilize them [20].

There are numerous insulin treatment options. In order to prevent diabetic ketoacidosis, avoid severe hypoglycemia, and meet individual glycemic goals, the administration of some form of insulin in a planned, individualized regimen is essential for T1DM treatment [20]. By altering the original insulin molecule and changing its constituent parts, several other forms of insulin molecules have developed [20]. These insulin analogs' pharmacodynamic and pharmacokinetic profiles are diverse (Table 1). Based on their pharmacokinetic and pharmacodynamic properties, these insulins are characterized and administered [21].

Table 1. Different types of insulins.

Insulin Type	Examples	Onset of Action (min)	Time to Peak (hours)	Duration (hours)	Administration
Rapid-acting	Aspart Lispro Glulisine	10-20	0.5-1.5	3-5	0-15min before or just after meals
Short-acting	Regular human	30-45	2-4	4-8	15-30min before meals
Intermediate-acting	NPH	60-120	4-8	12-20	Once or twice daily
Long-acting	Detemir	60-120	6-10	16-24	Usually once daily
	Glargine	60-120	No pronounced peak	~24	
	Degludec	60-120	No pronounced peak	Up to 72	
premixed	70/30NPH/R	30-40	4-8	12-20	Usually twice daily, 0-30min before meals
	70/30 protamine-aspart/aspart	10-20			
Concentrated	U-300 glargine	60-120	No pronounced peak	Up to 72	Once daily
	U-500 human regular	30-45	6-12	12-24	Twice daily
	U-200 degludec	60-120	No pronounced peak	>24	Once daily

There are numerous drawbacks to conventional prandial and basal insulin preparations for insulin therapy. First, regular insulin is absorbed slowly by the subcutaneous tissue. After 30 to 60 minutes, the metabolic effect begins, and the highest concentration is reached after two to three hours of injection. As a result, people who take insulin regularly are more likely to experience postmeal hyperglycemia and late-postprandial hypoglycemia. Second, peak glucose is markedly reduced by the conventional basal insulin isophane (NPH). NPH is absorbed from subcutaneous tissue at varying rates [22]. Due to these pharmacodynamic limitations, users are more likely to experience hypoglycemia at night and elevated glucose levels before pre-breakfast. Insulin analogs based on a modified amino acid sequence from the human insulin molecule have been developed to address these issues.

## Nanomedicine for Insulin Delivery in Diabetes

Morteza Rafiee-Tehrani<sup>1</sup>, Somayeh Handali<sup>1</sup>, Mohammad Vaziri<sup>1</sup>, Sepideh Nezhadi<sup>1</sup> and Farid Abedin Dorkoosh<sup>1,\*</sup>

<sup>1</sup> Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

**Abstract:** Diabetes is one of the common diseases in the world and its treatment faces challenges. Insulin is the main therapeutic agent used in the treatment of diabetic patients. However, it has several side effects and during the day, patients may need several insulin injections, which is not pleasant for them. Therefore, a controlled and prolonged release system is required to decrease the injection frequency, improve the bioavailability of insulin, and enhance the compliance of patients. Nanoparticles (NPs) based drug delivery systems (DDSs) have been considered for insulin delivery. NPs can improve the permeability of insulin by opening the tight junctions between intestinal epithelial cells and can protect insulin from the action of enzymes existing in the gastrointestinal (GI) tract.

**Keywords:** Delivery, Diabetes, Insulin, Nanoparticle.

### INTRODUCTION

Diabetes is of two types in which the body cannot produce insulin (type 1) or is not sensitive to insulin (type 2) and; consequently, the blood glucose level is not well controlled [1]. Diabetes is one of the biggest global health challenges of the 21<sup>st</sup> century, and there are many people living with this disease [2, 3]. Diabetes is mainly caused by environmental influences, immune system dysfunction, mental factors, and genetics, which result in either insulin resistance or insufficient insulin secretion [4].

As mentioned, diabetes is a result of the inefficiency of insulin to convert glucose into energy. When this process is disrupted, blood glucose can rise to a level that has health consequences. Insulin is the main therapeutic agent used in the treatment of patients with diabetes [5]. Insulin is a globular protein with a molecular weight of 5808 Daltons, containing two chains, A (21 residues) and B

---

\* Corresponding author Farid Abedin Dorkoosh: Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran; E-mail: dorkoosh@tums.ac.ir

(30 residues) that are linked together by disulfide bonds (Fig. 1) [6]. Insulin is produced by  $\beta$  cells of the pancreas. When there is too much glucose in the blood, insulin converts extra glucose into glycogen and stores it in the liver [7].

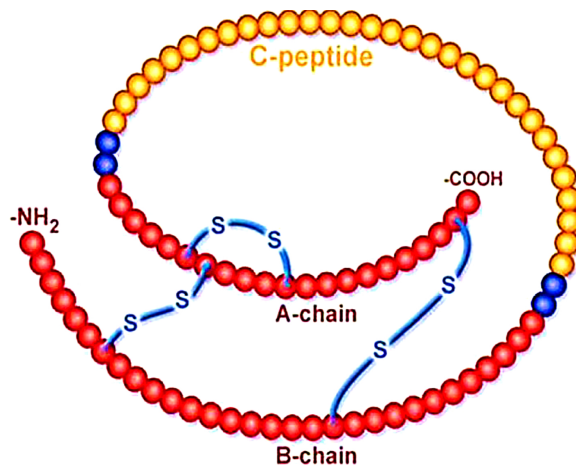
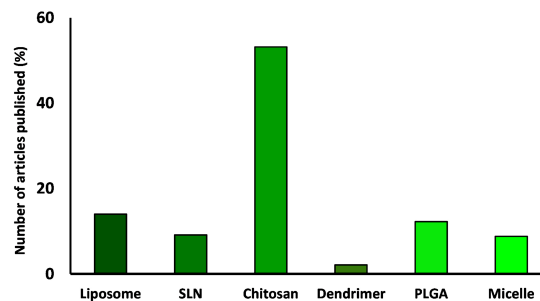


Fig. (1). Structure of insulin [8].

At present, the route of insulin administration is subcutaneous injection [9] which has several disadvantages including; lipohyperatrophy, obesity, retinopathy, hypoglycemia, neuropathy, lipodystrophy, allergic reactions and peripheral hyperinsulinemia [4, 10]. During the day, patients may need several insulin injections, which is not pleasant for most patients. Therefore, a controlled and prolonged release system is required to decrease the injection frequency and enhance the compliance of patients. According to the reports of Health Care Costs Institute, the cost of insulin for patients has doubled. Generally, oral delivery of peptide drugs is attractive due to patient compliance, patient adherence, and a cost-effective manufacturing process than injections. However, the gastrointestinal (GI) tract is a hostile milieu for the oral absorption of drugs due to low pH, existence of peptidases and proteases, and poor absorption through the intestinal epithelial layer. Furthermore, the hydrophilic nature of peptide drugs and the large molecular size further restrict their oral absorption [5, 11]. The bioavailability of insulin following oral delivery is usually lower than 1% owing to the enzymes existing in the GI tract and poor absorption *via* the intestinal epithelial cells [5].

Nanotechnology is a novel technology that will promote the next industrial revolution. Nanoparticles (NPs) based drug delivery systems (DDSs) have been considered to effectively transport various therapeutic agents to target cells. Nanocarriers are used for entrapment of drugs to limit their side effects and

improve their bioavailability. Organic and inorganic NPs have been employed for drug delivery. Various nanocarriers such as drug delivery system such as liposomes, polymeric NPs, solid lipid NPs (SLNs), chitosan, exosomes, micelles, nanogels and dendrimers have been widely investigated for encapsulation of insulin and increasing its bioavailability (Fig. 2). The structure of some nanocarriers for insulin delivery is shown in Fig. (3). These nanocarriers are biodegradable, biocompatible, non-toxic and can escape from the reticuloendothelial system. Insulin encapsulated in NPs can be protected from the action of the enzymes existing in the GI tract. Moreover, NPs can improve the permeability of insulin to the intestinal mucosa through opening the tight junctions between intestinal epithelial cells [12]. In recent years, long-acting NPs formulations containing insulin have been developed to diminish the frequency of injections. Additionally, nanocarriers are widely considered for oral delivery of insulin [13]. Smart nanocarrier-based drug delivery systems were also developed for insulin delivery. For example, glucose-responsive NPs (synthesized from dextran) were prepared for rapid and extended self-regulated insulin delivery. Results showed that these formulations could reduce the elevated blood glucose levels in mice and decrease the risk of hypoglycemia [1]. Glucose-responsive self-assembled polyamines as smart NPs were also used for insulin delivery. These smart NPs could appropriately regulate blood glucose concentration [14].



**Fig. (2).** Number of articles published in Elsevier, Springer, ACS, and Taylor & Francis journals from 2015 to 2022.

In oral insulin delivery, nanocarriers can improve the transport of insulin through the paracellular pathways. Chitosan can increase the paracellular transport of insulin through the interaction of positively charged polymers with the negatively charged cell membrane. Transcellular pathway is another mechanism for transporting insulin-loaded NPs. The transcellular pathway includes fusion, endocytosis, and adsorption. Moreover, receptor-mediated endocytosis is the major route for insulin-loaded nanocarriers to enter into cells [6, 15]. Fig. (4) illustrates the different delivery pathways of the insulin-loaded NPs.

## Nanoscience for Drug Delivery in Diabetes

N. Vishal Gupta<sup>1,\*</sup>, M. Sharadha<sup>1</sup>, K. Trideva Sastri<sup>1</sup>, Souvik Chakraborty<sup>1</sup>, Hitesh Kumar<sup>1</sup>, Vikas Jain<sup>1</sup> and Surajit Dey<sup>2</sup>

<sup>1</sup> Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India

<sup>2</sup> Roseman University of Health Sciences, College of Pharmacy, Henderson, Nevada, USA

**Abstract:** Current conventional diabetes mellitus (DM) therapies are inadequate and have poor patient compliance. Subsequently, it is necessary to explore nanomedicine in managing diabetes. In recent years, several nanocarrier systems have been proven effective in various aspects of diabetes treatment, increasing drug stability, overcoming different biological barriers, and in enhancing bioavailability. Nanomedicine can potentially improve the therapeutic effect of drug substances to gain the patient's belief and impart a greater level of acceptability. In the present scientific spectrum, nanomedicines promise to provide sustained and targeted delivery with potential physical stability for a prolonged period, rendering a safe and effective therapy for diabetes. This chapter comprehensively elaborates on trends in the drug delivery system in treating diabetes for improved delivery of different classes of antidiabetic agents compared to contemporary therapies.

**Keywords:** Diabetes, Drug delivery, Inorganic nanocarriers, Nanomedicine, Organic nanocarriers, Targeting.

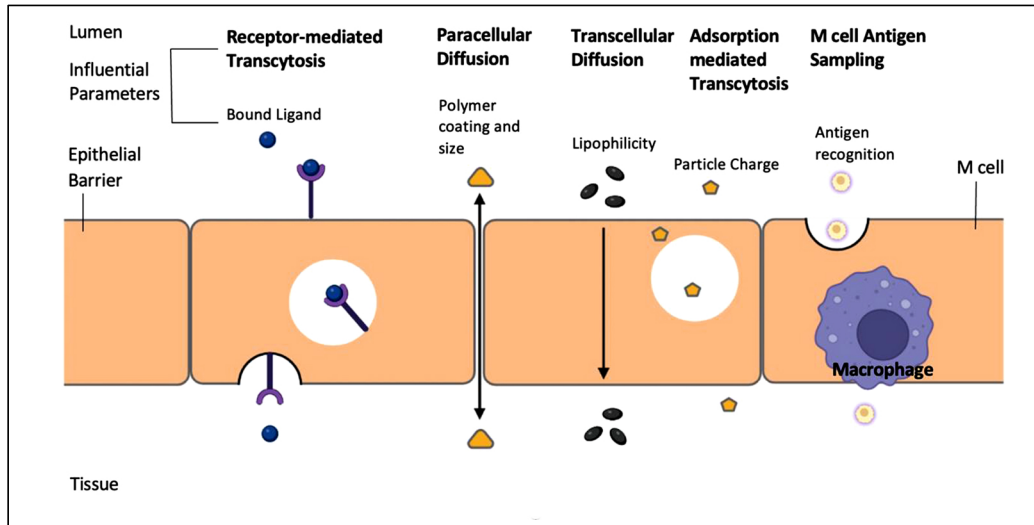
### NANOMEDICINE IN DIABETES: NEED-BASED APPROACH

Diabetes mellitus constitutes clusters of metabolic disorders associated with higher blood glucose levels propelled by insulin resistance or deficiency [1]. Every year a substantial number of individuals are affected by this disorder. When the islet  $\beta$ -cell in the pancreas is significantly affected mostly by autoimmune destruction, it leads to Type-1 diabetes [2]. In other circumstances, insulin fails to trigger any response, and insulin resistance contributes to hyperglycemia [3]. Constant monitoring of glucose levels is significant to avoid any downstream impediment in the patients. Studies indicated that sustained hyperglycemia conditions would lead to macrovascular or microvascular complications [4].

\* **Corresponding author N. Vishal Gupta:** Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India; E-mail: vkguptajss@gmail.com

Traditionally diabetes patient is rigorously monitored for their glucose levels and subsequently administered insulin [5]. Patients are exhaustive with tedious and painful procedures leading to erratic glucose monitoring and meagre adherence. These patient factors precedent to irregular doses ultimately result in seizures and altered glucose levels [6]. There have been tremendous efforts made by researchers to develop continuous glucose monitors along with insulin pumps to tackle these patient difficulties. However, it is necessary to enhance these types of equipment for better management of diabetes. Over the years, there has been exponential growth in nanoscience that deliberated promising results for managing diabetes conditions [7]. Nanotechnology has delivered many breakthroughs explicitly in the medical field by enabling researchers to develop proficient nanosystems for delivering potential therapeutic molecules with enhanced benefits [8]. The principles of nanotechnology are exercised to design nanomedicines as nanotherapeutics; these systems enable the loading of the therapeutic moiety, subsequently enhancing its physiochemical properties, and achieving enhanced therapeutic benefits with precise targeting [9]. Nanotechnology has played a vital role in developing new-age glucose-monitoring devices. Fascinatingly, nanotechnology has potentiated the efforts of scientists in developing numerous delivery systems for improving insulin molecules and other antidiabetic molecules in the systemic circulation, surpassing the usual harsh metabolic pathway that deliberately reduces the efficacy of these molecules; thus, these nanosystems offer a better approach than conventional methods to deliver anti-diabetic molecules [10]. Diabetes is a very peculiar disease, especially type-2, *i.e.*, severely affected by insulin resistance/deficiency. Interestingly, it was discovered that in a subcategory of type – 2, a significant number of patients experience varied blood–glucose levels due to obesity; these effects are independent of insulin. A certain number of patients suffer from insulin deficiency and other sections from insulin resistance [11]. These diabetic conditions have grabbed the attention of scientists, and it is believed that nanomedicine could play a potential role in managing these categories. In recent times, nanotechnological approaches have yielded new–age delivery systems capable of enhancing anti-diabetic molecules' potential [12]. Studies supported the vital role of various nano-formulations specially designed with novel smart polymers that successfully shield the drug molecules from harsh metabolic pathways; subsequently, these systems were instrumental in achieving a controlled release pattern of the loaded molecules, thus facilitating the maintained levels of insulin in patients [13]. The various transport mechanisms available for drug delivery of nanocarriers for the management of diabetes are illustrated in Fig. (1). Furthermore, constant monitoring of glucose levels is essential for diabetic patients. A more accurate, highly sensitive, robust nanosensors could be

deployed along with other nanomaterials in glucose monitoring devices which would drastically improve the patient's life [14].



**Fig. (1).** Various transport mechanisms are available for drug delivery of nanocarriers for the management of diabetes.

## Nanomedicine in the Management of Diabetes

Numerous types of nanomedicines have been studied as a drug delivery system for diabetes management as mentioned in Fig. (2).

### ORGANIC MATERIAL-BASED NANOMEDICINES

Organic nanomaterials are nanocarriers assembled smartly from organic compounds and have drawn significant attention, notably for drug delivery in developing organic frameworks used in biomedical and pharmaceutical nanotechnology. Solid evidence of organic nanocarriers was investigated with lipid-based, natural, and synthetic polymeric nanocarriers.

#### Lipid-based Nanocarriers

Lipid-based nanocarriers are widely explored as carriers of drugs owing to their remarkable advantages due to their less toxicity, high loading efficiency, good stability, good protectivity, controlled and sustained release, affordable scale-up manufacturing, and targeted site-specific delivery through oral, topical, dermal, parenteral and pulmonary routes. The word lipid-based nanocarriers include liposomes, Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers



## Nanoscience for Nucleotide Delivery in Diabetes

Ali Rastegari<sup>1,\*</sup>

<sup>1</sup> Department of Pharmaceutics and Pharmaceutical Nanotechnology, School of Pharmacy, Iran University of Medical Sciences, Tehran, Iran

**Abstract:** The convergence of nanoscience and nucleotide delivery holds tremendous promise in revolutionizing diabetes treatment. Nucleotide delivery emerged as a promising tool to modulate gene expression and cellular function in diabetes. Integration of nanoscience and nucleotide delivery in diabetes treatment opens avenues for efficient therapies. This approach has the potential to significantly improve glucose regulation and mitigate long-term complications associated with the disease. This chapter discussed DNA and RNA delivery approaches in diabetes treatment and the future and challenges of nucleotide delivery in diabetes.

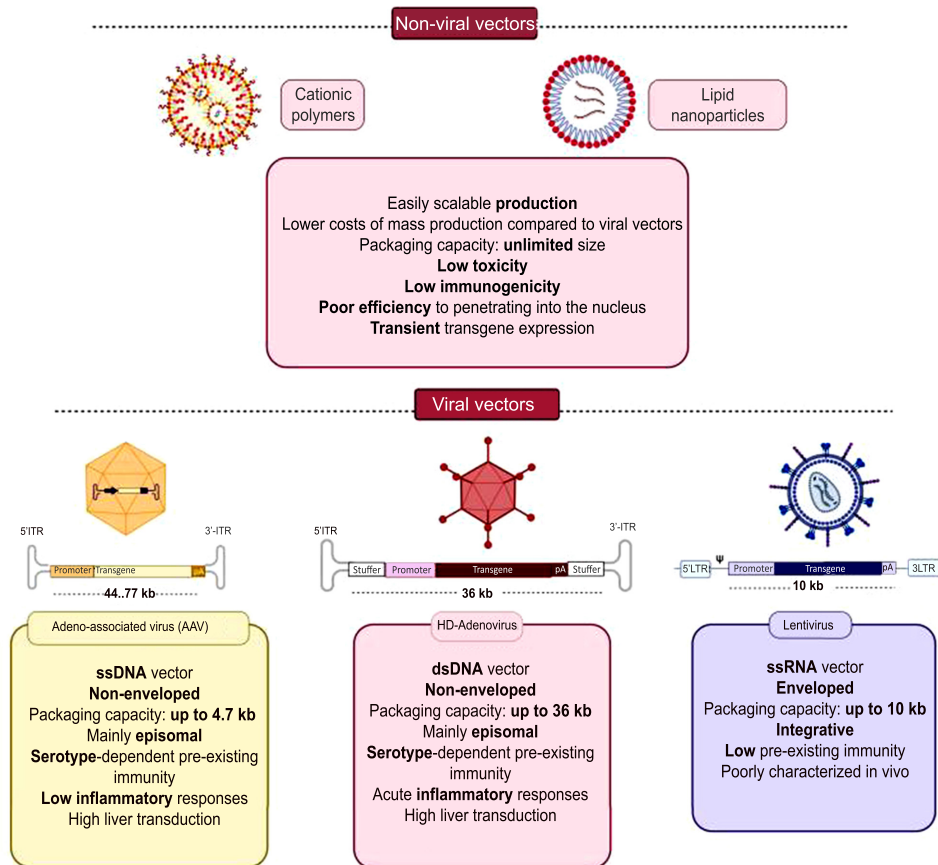
**Keywords:** Delivery, Diabetes, Gene, Nanotechnology.

### INTRODUCTION

Current treatments for diabetes often rely on insulin injections, oral medications, and lifestyle changes. However, gene therapy has emerged as a cutting-edge approach that has the potential to provide long-lasting solutions to this global health epidemic. Studies have shown that diabetes disease could be related to several genes [1, 2]. Furthermore, protein and small molecules delivery are limited and cannot be used for the treatment of every condition of disease. However, accordingly RNA and DNA are precursors of proteins, they can be used as a promising approach to the treatment of different diseases. Nucleotide delivery even can be used for gene editing of host's DNA to cure a genetic defect as opposed to just providing a simple treatment [3, 4]. Nucleotide delivery is defined as the delivery of genetic material including DNA plasmid, or RNA into the cell for production of desired proteins or inhibiting protein expression to correct or modulate a disease. Nucleic acids have a highly negative charge and their intracellular uptake is limited due to the presence of the force of repulsion between nucleic acids and the negatively charged plasma membrane. Furthermore, nucleic acids are rapidly cleared from the body due to degradation

\* Corresponding author Ali Rastegari: Department of Pharmaceutics and Pharmaceutical Nanotechnology, School of Pharmacy, Iran University of Medical Sciences, Tehran, Iran; E-mail: rastegari.a@iums.ac.ir

by endonucleases [5]. In this regard, studies have shown that cationic nanoparticles act as a powerful carrier for the protection of nucleic acids from degradation and also enhance the transfection efficiency and gene expression into the targeted tissue (Fig. 1) [6].



**Fig. (1).** Non-viral and viral vectors for nucleotide delivery [7].

Nanoscience has revolutionized the field of gene therapy, offering promising solutions to tackle complex diseases like diabetes. The integration of nanotechnology and gene therapy holds immense potential in transforming diabetes treatment [8].

The use of nanoparticles for nucleotide delivery could efficiently protect the degradation of nucleic acids and based on their chemical structure, increase nucleic acid cellular uptake and endosomal escape. In general, cationic

nanoparticles based on polymers or lipids will be used to electrostatically condense with the nucleic acid with negative charged [9]. The positive charge of nanoparticles is usually achieved by using amine groups in their structures which will be protonated at physiological pH ( $pK_a \sim 7.4$ ). Many studies investigated synthetic and natural polymers for nucleotide delivery, for example, chitosan, poly-L-lysine and polyethyleneimine [10, 11]. As mentioned in previous chapters, the use of conventional therapeutic agents and small molecule delivery for diabetes treatment and control of blood glucose has several limitations. Accordingly, newer physiological approaches like nucleotide delivery could be a good candidate for the treatment of diabetes. In this chapter, we briefly discussed DNA and RNA delivery by using nanoparticles for the treatment of different types of diabetes.

### **DNA DELIVERY APPROACH**

Plasmid DNA can encode information for the expression of therapeutic proteins in different diseases. In one study, biodegradable poly [ $\alpha$ -(4-aminobutyl)-L-glycolic acid] (PAGA) could efficiently protect plasmid DNA pCAGGS from degradation and reduce the development of insulinitis in non-obese diabetic (NOD) mice. Their results have shown that using this polymeric nanoparticle could increase the stability of plasmid DNA from 10 minutes to 60 minutes and make serum mIL-10 level peak at 5 days which could be detectable for 9 weeks. The study showed that using PAGA/plasmid DNA complex could prevent autoimmune diabetes. This formulation significantly decreased severe insulinitis in NOD mice, 15.7% insulinitis in treated group compared with 90.9% in non-treated group [12]. In other study, researchers used cationic nanoparticles by blending lactide-co-glycolide (PLGA) and methacrylate copolymer (Eudragit® E100) to deliver a therapeutic DNA encoding mouse interleukin-10 in the muscle of mice. Their results have shown that the prepared nanoparticles could effectively escape from the endosome and the transfection efficiency was significantly higher than PLGA nanoparticles. Elevation of interleukin-10 level can facilitate the suppression of interferon-gamma levels, which can reduce islet infiltration. By muscular injection of cationic nanoparticles containing DNA plasmid IL-10, a lower blood glucose level was achieved compared with alone plasmid and histological assessment showed no chronic inflammatory responses in the muscles [13]. Studies demonstrated that muscular injection could be an efficient route for gene delivery due to good accessibility, and vascularization, which make it as a suitable route for gene delivery to make long-lasting protein expression [14 - 16].

As mentioned previously, glucagon-like peptide-1 (GLP-1) is a treatment option in diabetes. Researchers are trying to produce GLP-1 endogenously by using GLP-1 plasmid to diminish the injection of GLP-1 in diabetic patients as a

## SUBJECT INDEX

### A

Absorption 11, 38, 40, 58, 61, 63, 64, 65, 76, 83, 88, 89  
 carbohydrate 40  
 insulin-mediated glucose 11  
 intestinal glucose 38  
 of insulin 63, 64  
 pulmonary 65  
 Acid(s) 6, 13, 62, 63, 64, 65, 81, 82, 84, 86, 87, 89, 102, 103, 104, 106  
 bile 13  
 boronic 87  
 cholic 81  
 folic 62  
 gluconic 89  
 itaconic 64  
 nucleic 64, 65, 102, 103, 104  
 pachymic 86  
 phenylboronic 64, 65  
 Polylactic 82  
 polysaccharide hyaluronic 84  
 targeted glycyrrhetic 106  
 tricarboxylic 6  
 Activity 12, 16, 37, 38, 61, 63, 64, 74, 75, 87, 88, 89, 90, 93  
 anti-hypertriglyceridemia 38  
 antibacterial 87  
 antihyperglycemic 88  
 antioxidant 74  
 enzymatic 61, 63, 64, 88  
 hypoglycaemic 74, 75  
 insulinotropic 89  
 tyrosine kinase 38  
 Acute 39, 44  
 pancreatitis 44  
 renal failure 39  
 Agents 42, 43, 46, 76  
 emulsifying 76  
 non-insulin 46  
 Alginate-based nanoparticles 80

Alpha-glucosidase inhibitors (AGIs) 40, 41  
 Amino acids 7, 13, 41  
   glucogenic 7  
 AMP-dependent protein kinase 38  
 Angiogenesis 90  
 Anti-diabetic activity 92  
 Anti-oxidant functions 92  
 Antidiabetic therapy 93  
 Apoptosis 4, 10, 90, 91  
   arrest 90  
 Atherosclerosis 9  
 Atherosclerotic 9, 35  
   lesions 9  
 Autoantibodies 5, 17  
   sensitive 17  
 Autoimmune diabetes 17, 104, 105  
 Autoimmunity 3, 5, 15

### B

Basal insulin 32, 33, 34, 42, 46  
   preparations 33  
 Bio-materialistic applications 81  
 Bioavailability of insulin 57, 58  
 Blood glucose 14, 57, 76, 89, 104, 105  
   downregulated 76

### C

Cancer, bladder 40  
 Carbohydrate intake 34  
 Carbon nanotubes (CNTs) 86, 87  
 Cardiac 45, 77  
   dysfunction 45  
   index 77  
 Cardiomyocytes 9  
 Cardiotoxicity 39  
 Cardiovascular 1, 16, 31, 35, 38, 39, 45  
   complications 31, 39  
   disease 35, 38  
   disorders 1  
   events, adverse 45

Ali Rastegari (Ed.)

All rights reserved-© 2023 Bentham Science Publishers

- health 45
- outcomes 45
- risk variables 16
- Cell-penetrating peptides (CPPs) 61
- Cerebrospinal fluids 66
- Chronic 35, 106
  - inflammation 106
  - kidney disease 35
- Chrysin suspension 78
- Copolymer 62, 81
  - thermosensitive 62
- Cytokines 12, 13, 16, 105
  - inflammatory 16
- Cytotoxicity 105

**D**

- Destruction 2, 3, 70, 106
  - autoimmune 2, 70
  - immune system's 3
- Development 3, 5, 8, 10, 11, 13, 15, 18, 82, 83, 84, 85, 104, 107
  - atherosclerosis 10
  - immune system 13
- Diabetes 1, 10, 12, 17, 18, 31, 35, 38, 41, 70, 71, 72, 74, 75, 76, 78, 79, 81, 83, 84, 91, 92, 102, 106, 107
  - and insulin resistance 12
  - disease 102, 106, 107
  - induced vascular dysfunction 83, 84
  - management 71, 72, 76, 78, 79, 81, 91, 92
  - mellitus (DM) 1, 10, 18, 31, 35, 38, 41, 70, 74, 75, 92
  - progressive insulin-dependent 17
- Diarrhea 38, 41
- Disorder 1, 18, 70
  - complex metabolic 1, 18
- DNA 102, 104, 105, 106, 107
  - plasmid 102, 105, 107
- Drug(s) 31, 37, 39, 41, 43, 44, 57, 58, 59, 61, 62, 63, 64, 65, 66, 70, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 88, 89, 92
  - absorption 65, 77
  - anti-diabetic 31
  - antihypertensive 75
  - biomolecule 92

- delivery systems (DDSs) 57, 58, 59, 63, 65, 66, 70, 72, 73, 74, 78, 81, 88, 89
- encapsulated 64, 80
- hydrophobic 61
- insoluble 82
- Drug release 75, 79, 80, 81, 93
  - sustained 75
- Dysglycemia 1, 3, 16, 18
- Dyslipidaemia 82

## E

- Edema 39
  - macular 39
- Effects 62, 70, 76, 81, 84, 91, 107, 108
  - anti-diabetic 91
  - antioxidant 84
  - hyperalgesia 76
  - therapeutic 70, 81, 84, 107, 108
  - toxic 62
- Egg phospholipid 91
- Electrolyte imbalance 45
- Emulsification, ultrasonic 76
- Endocytosis pathway 61
- Endonucleases 103
- Endosome hybrids 64
- Endothelial insulin sensitivity 9
- Energy 6, 12, 57, 76
  - burns 12
  - dietary 6
- Environmental influences 15
- Enzymatic degradation 106
- Enzymes 16, 38, 40, 41, 57, 58, 59, 85
  - diffusing 85
  - mitochondrial 38
- Erythrocyte-glucose-responsive system 89
- Euglycemia 8, 14
  - restoring 14
- Euglycemic bracketing 10
- Expression, insulin receptor 38

## F

- Fabrication methods 77, 81
- Facilitative glucose transporter 44
- Factors 1, 3, 5, 8, 11, 12, 17, 57, 93, 105
  - colony-stimulating 12
  - genetic 3
  - macrophages release 12
  - mental 57

## **Subject Index**

- nuclear 17
- tumor necrosis 5, 12
- Fasting glucose 8
- Fluorescence 87
  - signals 87
- Fluorescent biosensing 87
- Function 2, 3, 6, 9, 13, 15, 44, 45, 92
  - cardiac 45
  - endocrine 2
  - hepatic 44
  - vascular endothelial 9

**G**

- Gastric inhibitory polypeptide (GIP) 14, 41
- Gastrointestinal 38, 40, 41, 44, 57, 58
  - discomfort 38, 41
  - system 40
- Gene(s) 2, 3, 14, 15, 17, 84, 102, 103, 107, 108
  - delivery systems 107
  - editing 102
  - environment interaction 3
  - interactions 14
  - therapy 102, 103, 107, 108
  - vehicles 107
  - wound-repair-related 84
- Genetic 2, 5, 8
  - predisposition 8
  - profile 5
  - variations 2
- Glucagon 8, 14, 37, 42, 43
  - producing alpha cells 8
  - secretion 8, 37, 42
- Glucokinase 6, 17
  - hepatic 6
- Gluconeogenesis 6, 7, 11, 38, 91
  - downregulated 91
  - inhibiting 38
  - renal 7
- Glucose 4, 6, 7, 8, 10, 12, 13, 14, 15, 41, 57, 58, 64, 65, 66, 76, 77, 81, 85, 87, 89, 90, 91
  - dependent insulinotropic polypeptide 41
  - fluorescent 87
  - homeostasis 8, 12, 89
  - intolerance 8, 13
  - oxidase 81, 89
  - oxidation 10
  - responsive insulin 85

## **Nanoscience Applications in Diabetes Treatment 113**

- Glucose metabolism 6, 10, 88
  - influence 10
- Glycogenolysis 6
- Gut 8, 12, 13
  - microbiome 12, 13
  - microbiota 8, 12, 13

## **H**

- Heart failure 35, 39, 77
  - diabetic-induced 77
- Heat shock proteins (HSPs) 65
- Hepatic 15, 43, 44
  - dysfunction 44
  - gluconeogenesis 15
  - glucose 43
- Hepatocytes 6, 12, 17
- HLA protein 2
- Hormones 12, 13, 41
  - gut 13
  - metabolic 41
- Human leukocyte antigen (HLA) 2
- Hyperglycemia 1, 3, 4, 7, 8, 14, 16, 17, 18, 46, 70
- Hyperglycemic hypoinsulinemia 7
- Hyperinsulinemia 7, 11
- Hypersecretion 7
- Hypertriglyceridemia 6, 46
- Hypoglycaemia 77
- Hypoglycemic effect 63, 65

## **I**

- Immune system dysfunction 57
- Infections, urinary tract 45
- Inflammatory bowel disease 41
- Insulin 1, 3, 5, 6, 7, 8, 9, 11, 17, 18, 32, 33, 44, 46, 71, 89
  - deficiency 1, 3, 6, 18, 71
  - insensitivity 7
  - signaling 8, 9, 11
  - therapy 5, 17, 32, 33, 44, 46
  - transport 89
- Insulin resistance 7, 8, 10, 11, 12, 13, 14, 15, 16, 17, 70, 71
  - hepatic 8, 11
  - systemic 10
- Islet inflammation 15

**L**

Linear polysaccharide 62  
Lipase activity 10  
lipoprotein 10  
Lipid 6, 78  
metabolism 6  
nano-capsules (LNCs) 78  
Lipohyperatrophy 58  
Lipolysis 10  
Lipopolysaccharides 5  
Lipoprotein lipase 6, 16  
Liposomal 61, 62, 89  
chitosan gel 62  
formulations 61, 62  
system 89  
Lipotoxicity 16  
Liver 1, 11, 36, 41, 82  
cirrhosis 11, 41  
disease 1  
gluconeogenesis 36  
inflammation 82

**M**

Major adverse cardiovascular events (MACE)  
35, 42  
Metabolic 11, 13, 16, 33, 39, 70  
disorders 16, 70  
dysregulation 13  
effect 33  
homeostasis 11  
syndrome 13, 39  
Metabolism 7, 41  
carbohydrate 41  
protein 7  
Metabolites 12, 13  
toxic lipid 12  
Method 80, 82  
electrospinning 80  
nanoemulsification 82  
Modification of liposomes 61  
Myocardial infarction 35

**N**

Nanocarriers 58, 59, 60, 61, 62, 63, 64, 65, 66,  
72, 73, 75, 76  
insulin-loaded 59  
lipid-based 72

Nanoparticles 57, 58, 78, 79, 86, 87, 88, 92,  
103, 104, 106, 107, 108  
inorganic 86  
lipid-based 92, 108  
metallic 87  
polymeric 78, 79, 104, 106  
silica-based 86  
Nasopharyngitis 44

**P**

Pathways 38, 62, 76, 88  
endocytic 62  
insulin signalling 88  
Peroxisome proliferator-activated receptor  
(PPAR) 38, 39  
Phytosomes 89, 90, 91  
prepared natural flavonoid-loaded 91  
Polyethylenimine-based vehicles 107  
Polymers 79, 81, 105  
cytotoxic 105  
protein-based 79, 81  
Properties 39, 62, 75, 85, 107  
anti-diabetic 39  
biocompatible 85  
mucoadhesion 75  
rheological 85  
Protection 34, 103  
cardiovascular 34  
Proteins 2, 6, 11, 12, 64, 65, 81, 102, 106  
downregulate 106  
heat shock 65  
monocyte chemoattractant 12  
transporting glucose transporter 6

**R**

RAS-associated binding protein 65  
Reactive oxygen species (ROS) 5, 84  
Renal impairment 44  
Response 2, 3, 8, 12, 15, 16, 17, 41, 70, 87,  
104, 105, 107  
chronic inflammatory 104  
hyperglycemia-induced stress 3  
immune 2, 15, 107  
RNA interference technology 106

**S**

- Single-gene diseases 17
- Skin reactions 36
- Sleep 16
  - apnea 16
  - deprivation 16
- Smart nanocarrier-based drug delivery systems 59
- Synergistic therapy system 85
- Synthesis 7, 10, 63, 86
  - accelerating protein 7
- Systemic 12, 91, 92
  - inflammatory effects 12
  - lipid homeostasis 91, 92

**T**

- Therapies 2, 13, 37, 45, 70, 80, 82, 83, 84, 92
  - cardiovascular 45
  - contemporary 70
  - diabetic 80, 83
- Thermosensitive triblock copolymer 63
- Tumor necrosis factor (TNF) 5, 12

**W**

- Wound healing 62, 84, 90
  - augmented diabetic 90
- Wounds 84, 87
  - diabetic 87

**Z**

- Zinc transporter 4





**Ali Rastegari**

---

Prof. Ali Rastegari is Assistant Professor of Pharmaceutical Nanotechnology in Iran University of Medical Sciences. He is recognized as an expert in nanotechnology for drug and gene delivery. He obtained his PharmD from Isfahan University of Medical Sciences, and Ph.D. in pharmaceutical nanotechnology from Tehran University of Medical Sciences. He worked for several months at Paris-Sud University and was interested in the development of nano based formulation for treatment of diseases, like diabetes mellitus.