



شبكة المعلومات الجامعية

بسم الله الرحمن الرحيم



شبكة المعلومات الجامعية  
@ ASUNET



# شبكة المعلومات الجامعية التوثيق الالكتروني والميكروفيلم



شبكة المعلومات الجامعية

# جامعة عين شمس

التوثيق الالكتروني والميكرو فيلم

## قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها  
علي هذه الأفلام قد أعدت دون أية تغيرات



## يجب أن

تحفظ هذه الأفلام بعيدا عن الغبار

في درجة حرارة من ١٥-٢٥ مئوية ورطوبة نسبية من ٢٠-٤٠%

To be Kept away from Dust in Dry Cool place of  
15-25- c and relative humidity 20-40%

# بعض الوثائق الأصلية تالفة

# بالرسالة صفحات لم ترد بالاصل

**A PHARMACEUTICAL STUDY ON  
SOME BIOADHESIVE DRUG DELIVERY SYSTEMS**

**Presented by**

**Ragwa Mohamed Farid Mansour**

**M. Pharm. Sci., Alexandria University**

**For the Degree**

**Of**

**Doctor of Philosophy**

**In**

**Pharmaceutics**

**Examiners' Committee Approved**

**Prof. Dr.**

*Geni*

**Prof. Dr.**

*Ismael*

**Prof. Dr.**

*Elmaghrabi*

**Prof. Dr.**

*Elmar*



## **Advisors' Committee**

**Prof. Dr. Abd El-Azeem Ebian** Ebian

Professor of Pharmaceutics

Department of Pharmaceutics

**Prof. Dr. Mohamed Ahmed Etman** -----

Professor of Pharmaceutics

Department of Pharmaceutics



## ACKNOWLEDGEMENT

First of all, thank you ALLAH for helping me through this work.

I would like to thank my supervisor *Professor Dr. Abd-El Azeem Ebian* Professor of Pharmaceutics, Faculty of Pharmacy, Alexandria University for his encouragement and guidance.

I am deeply indebted to my supervisor *Professor Dr. Mohamed Etman* Professor of Pharmaceutics, Faculty of Pharmacy, Alexandria University for his kind advice, wise guidance and valuable supervision and without his assistance this study would not have been successful.

Special thanks go to *Professor Dr. Viviane Fahim Naggar*, Professor of Pharmaceutics, Faculty of Pharmacy, University of Alexandria, for her kind help and guidance have been of great value.

I wish to thank *Professor Dr. Ali Hazzah* Professor of Organic Chemistry, Faculty of Pharmacy, Alexandria University for his guidance in interpretation of IR spectra and *Professor Dr. Iman Fawazy* Professor of Physiology, Faculty of Medicine, Alexandria University for her essential assistance in the histological part in this study.

During this work I have collaborated with many colleagues for whom I have great regards especially Abir Kassem & Jihan Salah and I wish to extend my warmest thanks to all those who have helped me with my work in the Department of Pharmaceutics.

I would like also to thank the secretarial staff, technicians, and workers in the Department of Pharmaceutics for their great assistance.

Lastly, and most importantly, I wish to thank my family members to whom I dedicate this thesis for their patience and continuous support.

Above all, I thank my husband, who stood beside me and encouraged me constantly. Without my husband's encouragement, I would not have finished the degree.

*Thank you,  
Ragwa*



## TABLE OF CONTENTS

|                                                              |              |
|--------------------------------------------------------------|--------------|
| <b>ACKNOWLEDGEMENT</b>                                       | <b>i</b>     |
| <b>TABLE OF CONTENTS</b>                                     | <b>ii</b>    |
| <b>LIST OF TABLES</b>                                        | <b>vii</b>   |
| <b>LIST OF FIGURES</b>                                       | <b>ix</b>    |
| <b>LIST OF ABBREVIATIONS</b>                                 | <b>xiii</b>  |
| <br><b>GENERAL INTRODUCTION</b>                              | <br><b>1</b> |
| – Mucosal Surface                                            | 1            |
| – Mechanisms and Theories of Bioadhesion                     | 2            |
| – Factors affecting Bioadhesion                              | 3            |
| A. Bioadhesive Polymer-related Factors                       | 3            |
| B. Environment – related Factors                             | 4            |
| C. Physiological Variables                                   | 5            |
| – Bioadhesive (Mucoadhesive) Polymers                        | 6            |
| 1. First-generation Bioadhesives                             | 6            |
| 2. Second- generation Bioadhesives                           | 6            |
| 3. Thiolated Polymers or Thiomers                            | 7            |
| 4. Miscellaneous                                             | 7            |
| – Test Methods Used to Study Bioadhesion                     | 8            |
| A. In-vitro / ex-vivo Methods                                | 8            |
| B. In-vivo Methods                                           | 10           |
| – Applications of Bioadhesive Dosage Forms                   | 10           |
| – Nasal Drug Delivery                                        | 12           |
| – Nasal Drug Delivery: Advantages, Limitations and Solutions | 12           |
| – Function of the nose                                       | 15           |
| – Anatomy and Physiology of the Nose                         | 16           |
| I. Nasal cavity                                              | 16           |
| II. Cilia and Ciliary beating Frequency                      | 17           |
| III. Mucus and Mucociliary Clearance (MCC)                   | 18           |
| IV. Nasal Metabolism                                         | 20           |

|                                                              |               |
|--------------------------------------------------------------|---------------|
| <b>V. Vasculature and Innervations</b>                       | <b>20</b>     |
| – <b>Mechanism of Drug Absorption</b>                        | <b>21</b>     |
| – <b>Factors Affecting Drug Absorption</b>                   | <b>22</b>     |
| 1. Anatomical and physiological factors                      | 22            |
| 2. Drug Related Factors                                      | 23            |
| 3. Formulation Related Factors                               | 25            |
| – <b>Strategies for improving drug absorption</b>            | <b>26</b>     |
| – <b>Applications of Nasal Drug Delivery Systems</b>         | <b>29</b>     |
| 1. Local Delivery                                            | 29            |
| 2. Vaccine delivery                                          | 30            |
| 3. Delivery of drugs to brain                                | 32            |
| 4. Systemic Delivery                                         | 33            |
| – <b>Nasal Dosage Forms</b>                                  | <b>34</b>     |
| 1. Nasal Solutions                                           | 34            |
| 2. Nasal Suspensions and Emulsions                           | 35            |
| 3. Nasal Gels                                                | 35            |
| 4. Nasal Powders                                             | 36            |
| 5. Nasal Liposomes                                           | 37            |
| 6. Nasal Microspheres                                        | 37            |
| 7. Nasal Nanoparticles                                       | 37            |
| <br><b>AIM OF THE WORK</b>                                   | <br><b>41</b> |
| <br><b>CHAPTER I</b>                                         |               |
| <b>Formulation and Evaluation of In-situ Gelling Systems</b> |               |
| <b>INTRODUCTION</b>                                          | <b>42</b>     |
| <b>EXPERIMENTAL</b>                                          | <b>46</b>     |
| 1. Materials                                                 | 46            |
| 2. Equipment                                                 | 46            |
| 3. Methodology                                               | 47            |
| 3.1. Preparation of Gellan Gum In -situ Gels                 | 47            |
| 3.2. Evaluation of the formulations                          | 47            |
| 3.2.1. Drug Content                                          | 47            |

|                                                                         |        |
|-------------------------------------------------------------------------|--------|
| 3.2.2. Gelation studies                                                 | 47     |
| 3.2.3. Rheological studies                                              | 47     |
| 3.2.4.a. In-Vitro release studies                                       | 48     |
| 3.2.4.b. Kinetic analysis                                               | 48     |
| 3.2.5. Mucoadhesion Testing:                                            | 48     |
| 3.2.5.a. In-Vitro mucoadhesion Testing                                  | 48     |
| 3.2.5.b. In-vivo mucoadhesiveness                                       | 49     |
| 3.2.6. In-vivo nasal deposition                                         | 50     |
| 3.2.6.a. Surgical technique                                             | 50     |
| 3.2.6.b. Deposition of drug solution                                    | 50     |
| 3.2.7. Mucosa Histopathology                                            | 51     |
| 3.2.8. Infrared spectroscopy study                                      | 51     |
| 3.2.9. Stability study                                                  | 51     |
| <br>RESULTS AND DISCUSSION                                              | <br>52 |
| – In-vitro hydrogel formation                                           | 52     |
| – Drug content.                                                         | 55     |
| – Rheological study                                                     | 55     |
| – In-vitro release study                                                | 63     |
| – Kinetic analysis                                                      | 65     |
| – In-vitro bioadhesion                                                  | 70     |
| – In-vivo mucoadhesiveness                                              | 72     |
| – In-vivo nasal deposition                                              | 75     |
| – Histopathology of nasal mucosa                                        | 80     |
| – IR examination                                                        | 82     |
| – Stability study                                                       | 82     |
| <br>CONCLUSION                                                          | <br>92 |
| <br>CHAPTER II                                                          |        |
| Formulation And Evaluation Of In-Situ Gelling Bioadhesive Nasal Inserts |        |
| INTRODUCTION                                                            | 93     |
| EXPERIMENTAL                                                            | 98     |
| 1. Materials                                                            | 98     |

|                                                                              |         |
|------------------------------------------------------------------------------|---------|
| 2. Equipment                                                                 | 98      |
| 3. Methodology                                                               | 99      |
| 3.1. Insert preparation                                                      | 99      |
| 3.2. Characterization of inserts                                             | 99      |
| 3.2.1. Drug Content Uniformity                                               | 99      |
| 3.2.2. Thickness                                                             | 99      |
| 3.2.3. Surface pH                                                            | 99      |
| 3.2.4. Water uptake                                                          | 100     |
| 3.2.5.a. In-vitro drug release                                               | 101     |
| 3.2.5.b. Analysis of drug release data                                       | 101     |
| 3.2.6. Hydrophilicity of inserts                                             | 102     |
| 3.2.7. In-vitro Bioadhesion Testing                                          | 102     |
| 3.2.7.a. Modified Balance Method                                             | 102     |
| 3.2.7.b. Displacement Method                                                 | 102     |
| 3.2.8. Differential Scanning Calorimetry                                     | 103     |
| <br>RESULTS AND DISCUSSION                                                   | <br>104 |
| – Hydrophilicity of the inserts                                              | 106     |
| – Water uptake and swelling                                                  | 106     |
| – Bioadhesion                                                                | 112     |
| – In-vitro drug release                                                      | 117     |
| – Kinetic analysis                                                           | 123     |
| – Thermal Analysis                                                           | 124     |
| <br>CONCLUSION                                                               | <br>130 |
| <br>CHAPTER III                                                              |         |
| Formulation and Evaluation of Nasal Bioadhesive Sodium Alginate Microspheres |         |
| INTRODUCTION                                                                 | 131     |
| EXPERIMENTAL                                                                 | 135     |