

# **FORMULATION AND EVALUATION OF DRUG DELIVERY SYSTEMS BASED ON GEL FORMING POLYMERS**

**A Thesis**

**Presented to the Graduate School  
Faculty of Pharmacy, Alexandria University  
In Partial Fulfillment of the  
Requirements for the Degree**

**Of**

**Doctor of Philosophy**

**In**

**Pharmaceutics**

**By**

**Abeer Ahmed Kassem**

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

**2008**

# **FORMULATION AND EVALUATION OF DRUG DELIVERY SYSTEMS BASED ON GEL FORMING POLYMERS**

**Presented by**

**Abeer Ahmed Kassem**

M. Pharm. Sci., Alexandria University

**For the Degree**

**Of**

**Doctor of Philosophy**

**In**

**Pharmaceutics**

**Examiners' Committee**

**Approved**

**Prof. Dr. Nawal Khalafalla**

-----

-

**Prof. Dr. Samia A. Nour**

-----

-

## **Advisors' Committee**

**Prof. Dr. Viviane Fahim Naggar**

-----

-Professor of Pharmaceutics

Department of Pharmaceutics

**Prof. Dr. Fatma Ahmed Ismail**

-----

Professor of Pharmaceutics

Department of Pharmaceutics

**Dr. Elsayed Aboulmagd Elsayed**

-----

Lecturer of Microbiology

Department of Microbiology

*Dedicated to*

*ALLAH*

*The creator*

*My great Parents*

*My first two teachers*

*Dear husband*

*My support*

*Pretty Daughter*

*Innocent Son*

*My precious*

**Acknowledgment**

*First of all and above all great thanks to **ALLAH**, the lord of universe for granting me life, health and ability to learn.*

I would like to express my deepest thanks and appreciation to my advisor, **Prof. Dr. Viviane Fahim Naggar**, Professor of Pharmaceutics, Department of Pharmaceutics, Alexandria University, for her whole hearted guidance, valuable scientific interpretation and continuous pushing toward success.

No words can really express my gratitude to **Prof. Dr. Fatma Ahmed Ismail**, Professor of Pharmaceutics, Department of Pharmaceutics, Alexandria University, for her never ending help, valuable orientation and unlimited insistence for perfection.

I am also extremely grateful to **Dr. Elsayed Aboulmagd Elsayed**, Lecturer of Microbiology, Department of Microbiology, Alexandria University, for his support and his great effort in the accomplishment of the microbiological aspects of this research and his useful remarks.

Deep thanks for **Prof. Dr. Mohiey El-Deen El-Rasheedy** Professor of Periodontology, Oral Medicine, Oral diagnosis and Radiology, Faculty of Dentistry, Alexandria University, for his appreciable help and orientation in the clinical aspects of this research.

Special thanks to the staff members of the Department of Periodontology, Oral Medicine, Oral diagnosis and Radiology, Faculty of Dentistry, Alexandria University, for their valuable effort in the clinical evaluation of the selected formulae in this research, specially **Lecturer Assistants; Ghada Basuney, Marwa Mady, Nevine Abo El-Khair and Doaa El-Sayed.**

Finally, I would like to express my appreciation to all my colleagues, specially my real sisters, **Lecturer Assistants; Jihan Salah and Ragwa Farid** for their sincere and continuous cooperation and support. I would also like to extend my appreciation to all the patients participated in this work.

Thank you **Abeer Kassem**

# CONTENTS

LIST OF TABLES	i
LIST OF FIGURES	ii
LIST OF ABBREVIATIONS	v
GENERAL INTRODUCTION	
- Periodontal diseases	1
- Types of periodontal diseases	3
- Etiology of periodontal disease	5
- Treatment of periodontal disease	6
- Local sustained release devices for treatment of periodontal pockets; formulation parameters and considerations	8
- Drugs used in the treatment of periodontal diseases	9
- Dosage forms of local delivery devices intended for the treatment of periodontal pockets	14
- Novel technologies for periodontal disease management	19
AIM OF THE WORK	20
<b>PART ONE</b>	
<b><u>Chapter I</u></b> PREPARATION AND EVALUATION OF DEGRADABLE, GEL- FORMING TETRACYCLINE HCl FILMS FOR PERIODONTAL INTRA- POCKET APPLICATION	
1. Introduction	21
2. Experimental	26
2.1. Materials	26
2.2. Equipment	27
2.3. Methodology	28
2.3.1. Preparation of degradable films containing Tc HCl	28
2.3.1.1. Preparation of chitosan films	28
2.3.1.2. Preparation of PVA films	28
2.3.1.3. Preparation of pectin film	28
2.3.1.4. Preparation of Na CMC film	28

2.3.2. Film thickness	29
2.3.3. Swelling studies	29
2.3.3.1. Diameter method	29
2.3.3.2. Sponge method	29
2.3.4. Morphological characteristics of Tc HCl degradable films using SEM	29
2.3.5. <i>In vitro</i> release studies of Tc HCl from different degradable films	30
2.3.6. Kinetic analysis of release data	30
2.3.7. <i>In vitro</i> determination of the antibacterial activity of Tc HCl degradable films	30
2.3.7.1. Preparation of agar plates	30
2.3.7.2. Preparation of the micro-organism subculture	31
2.3.7.3. Determination of the standard curve and MIC of Tc HCl against <i>Staphylococcus aureus</i> ATCC 6538	31
2.3.8. Effect of ageing on the <i>in vitro</i> release and antibacterial activity of Tc HCl/Na CMC film	31
2.3.9. Clinical evaluation of Tc HCl/Na CMC film	31
	34
3. Results and discussion	
3.1. Evaluation of the <i>in vitro</i> performance of degradable films containing Tc HCl	34
3.1.1. Chitosan films	34
3.1.2. PVA films	41
3.1.3. Pectin film	52
3.1.4. Na CMC film	57
3.2. <i>In vitro</i> determination of the antibacterial activity of Tc HCl degradable films	62
3.3. Effect of ageing on the <i>in vitro</i> release and antibacterial activity of Tc HCl/Na CMC film	64
3.4. Clinical evaluation of Tc HCl/Na CMC film	69
<b>Chapter II</b> PREPARATION AND EVALUATION OF TETRACYCLINE HCl FILMS, BASED ON POLYELECTROLYTE COMPLEX FOR PERIODONTAL INTRA-POCKET APPLICATION	
1. Introduction	71
2. Experimental	74
2.1. Materials	74
2.2. Equipment	75
2.3. Methodology	76
2.3.1. Preparation of PEC films containing Tc HCl (Tc/PEC)	76
2.3.2. Film thickness	76
2.3.3. Swelling studies	76
2.3.3.1. Weighing method	76
2.3.3.2. Diameter method	77

2.3.4. Morphological characteristics of placebo <i>PEC</i> films and Tc/ <i>PEC</i> films using SEM	77
2.3.5. <i>In vitro</i> release studies of Tc HCl from Tc/ <i>PEC</i> films	77
2.3.6. Kinetic analysis of release data	77
2.3.7. <i>In vitro</i> determination of the antibacterial activity of Tc/ <i>PEC</i> films	77
2.3.8. Differential Scanning Calorimetry (DSC)	78
2.3.9. Effect of ageing on the <i>in vitro</i> release and antibacterial activity of Tc/ <i>PEC</i> films	78
2.3.10. Clinical evaluation of Tc/ <i>PEC</i> films	78
3. Results and discussion	80
3.1. Appearance, texture and thickness of the prepared <i>PEC</i> films containing Tc HCl	80
3.2. Morphological characteristics of the placebo and Tc HCl containing <i>PEC</i> films using SEM	83
3.3. Swelling behavior of Tc/ <i>PEC</i> films	88
3.3.1. Weighing method	88
3.3.2. Diameter method	88
3.4. <i>In vitro</i> release studies of the Tc/ <i>PEC</i> films	90
3.5. <i>In vitro</i> determination of the antibacterial activity of Tc/ <i>PEC</i> films	92
3.6. Differential Scanning Calorimetry (DSC)	94
3.7. Effect of ageing on the <i>in vitro</i> release and antibacterial activity of Tc/ <i>PEC</i> films	100
3.8. Clinical evaluation of Tc/ <i>PEC</i> films	103
<b>PART TWO</b>	
PREPARATION AND EVALUATION OF MELOXICAM AND MINOCYCLINE HCl STIMULI-RESPONSIVE GELS FOR INTRA-POCKET APPLICATION	
1. Introduction	105
2. Experimental	111
2.1. Materials	111
2.2. Equipment	112
2.3. Methodology	113
2.3.1. Preparation of thermo-sensitive gels "Pluronic <sup>®</sup> "	113
2.3.2. Preparation of pH-sensitive gels "Carbopol <sup>®</sup> "	113
2.3.3. <i>In vitro</i> drug release studies from Pl and C: H polymer system	113
2.3.4. Kinetic analysis of release data	114
2.3.5. <i>In vitro</i> determination of the antibacterial activity of MH in Pl gel	114
2.3.6. Clinical evaluation of thermo-sensitive Pl gels containing either Mx (3%) or MH (2%)	114



3. Results and discussion	118
3.1. Evaluation of thermo-reversible "PI" gels containing either Mx (3%) or MH (2%)	118
3.2. Evaluation of pH-sensitive "C: H" gels containing Mx (3%)	120
3.3. <i>In vitro</i> determination of the antibacterial activity of MH gel in PI	123
3.4. Clinical evaluation of thermo-sensitive "PI" gels containing either Mx (3%) or MH (2%)	125
<b>SUMMARY</b>	131
<b>REFERENCES</b>	135
<b>ARABIC SUMMARY</b>	

## LIST OF TABLES

<b>Table</b>		<b>Page</b>
<b>1</b>	Summary of some investigated local sustained delivery systems for antimicrobial agents	<b>11</b>
<b>2</b>	List of some commercially available local sustained delivery devices for treatment of periodontal diseases	<b>15</b>
<b>3</b>	Mean thickness of Tc HCl/ PVA films with different drug to polymer ratios	<b>43</b>
<b>4</b>	Kinetic parameters for the release data of Tc HCl from Tc HCl/Na CMC film under different storage conditions after five months	<b>68</b>

## LIST OF FIGURES

<b>Figure</b>		<b>Page</b>
<b>1</b>	Tooth anatomy	<b>2</b>
<b>2</b>	Types of periodontal diseases	<b>3</b>
<b>3</b>	Mobile teeth with intrabony pocketing	<b>4</b>
<b>4</b>	Teeth and bone in health	<b>4</b>
<b>5</b>	Type III periodontal disease	<b>3</b>
<b>6</b>	Gingival hyperplasia caused by Phenytoin	<b>5</b>
<b>7</b>	Scaling process	<b>6</b>
<b>8</b>	Teeth with plaque before and after scaling	<b>6</b>
<b>9</b>	The structural formula of polycyclic naphthacene carboxamide from which all Tetracyclines are derived	<b>13</b>
<b>10</b>	Some selected commercially available local sustained release devices for treatment of periodontal pockets	<b>16</b>
<b>11</b>	Structure of Tetracycline HCl	<b>21</b>
<b>12</b>	Structure of chitin (a) and chitosan (b)	<b>22</b>
<b>13</b>	Structure of PVA	<b>23</b>
<b>14</b>	Structure of pectin	<b>23</b>
<b>15</b>	Structure of cellulose (a) and Na CMC (b)	<b>24</b>
<b>16</b>	Measurement of periodontal pocket depth using sterile metered probe	<b>33</b>
<b>17</b>	Photographs of Tc HCl/chitosan films cast using different acidifiers	<b>36</b>
<b>18</b>	Effect of the acidifiers on the swelling behavior of Tc HCl/chitosan films on agar plate	<b>37</b>
<b>19</b>	Swelling profile; effect of the acidifiers on the swelling behavior of Tc HCl/chitosan films on agar plate	<b>38</b>
<b>20</b>	Release profile; effect of the acidifiers on the release behavior of Tc HCl from Tc HCl/chitosan films in Sørensen phosphate buffer, pH 6.6	<b>40</b>
<b>21</b>	Photographs of Tc HCl/PVA films with different drug: polymer ratios	<b>42</b>
<b>22</b>	Swelling profile; effect of drug: polymer ratio on the swelling profiles of Tc HCl from PVA films in Sørensen phosphate buffer, pH 6.6	<b>44</b>
<b>23</b>	Release profile; effect of drug: polymer ratio on the release behavior of Tc HCl from Tc HCl/PVA films in Sørensen phosphate buffer, pH 6.6	<b>46</b>
<b>24</b>	Scanning electron micrographs for Tc HCl/PVA (1:4) film	<b>48</b>
<b>25</b>	Scanning electron micrographs for Tc HCl/PVA (1:8) film	<b>49</b>
<b>26</b>	Scanning electron micrographs for Tc HCl/PVA (1:15) film	<b>50</b>
<b>27</b>	Scanning electron micrographs for Tc HCl/PVA (1:25) film	<b>51</b>
<b>28</b>	Photograph of Tc HCl/ pectin film	<b>53</b>
<b>29</b>	The swelling profile of Tc HCl/ pectin film in Sørensen phosphate buffer, pH 6.6	<b>54</b>
<b>30</b>	Release behavior of Tc HCl from Tc HCl /pectin film in Sørensen phosphate buffer, pH 6.6	<b>54</b>
<b>31</b>	Scanning electron micrographs for Tc HCl/ pectin film	<b>56</b>
<b>32</b>	Photograph of Tc HCl/ Na CMC film	<b>59</b>
<b>33</b>	Scanning electron micrographs for Tc HCl/ Na CMC film	<b>60</b>
<b>34</b>	The swelling profile of Tc HCl/Na CMC film in Sørensen phosphate buffer, pH 6.6	<b>61</b>
<b>35</b>	The release profile of Tc HCl from Tc HCl/Na CMC film in Sørensen	<b>61</b>

	phosphate buffer, pH 6.6	
<b>36</b>	Inhibition zones of different Tc HCl degradable films	<b>63</b>
<b>37</b>	Effect of ageing on the release profiles of Tc HCl from Tc HCl/Na CMC films stored in freezer	<b>65</b>
<b>38</b>	Effect of ageing on the inhibition zones of Tc HCl/Na CMC films stored in freezer	<b>65</b>
<b>39</b>	Effect of ageing on the release profiles of Tc HCl from Tc HCl/Na CMC films stored in fridge	<b>66</b>
<b>40</b>	Effect of ageing on the inhibition zones of Tc HCl/Na CMC films stored in fridge	<b>66</b>
<b>41</b>	Effect of ageing on the release profiles of Tc HCl from Tc HCl/Na CMC films stored at ambient conditions	<b>67</b>
<b>42</b>	Effect of ageing on the inhibition zones of Tc HCl/Na CMC films stored at ambient conditions	<b>67</b>
<b>43</b>	Mean pocket depth in patients treated with Tc HCl/ Na CMC film	<b>70</b>
<b>44</b>	Structure of sodium alginate	<b>72</b>
<b>45</b>	Clinical application of Tc/ ChA film	<b>79</b>
<b>46</b>	Photograph for Tc/ChA <i>PEC</i> film cast from 0.5 % acetic acid	<b>81</b>
<b>47</b>	Photograph for Tc /ChA <i>PEC</i> film cast from 0.01N HCl	<b>81</b>
<b>48</b>	Photograph for Tc/ChA <i>PEC</i> film cast from 1 % lactic acid	<b>81</b>
<b>49</b>	Photograph for Tc/ChP <i>PEC</i> film cast from 0.5 % acetic acid	<b>82</b>
<b>50</b>	Scanning electron micrographs for placebo ChA <i>PEC</i> film cast from 0.5% acetic acid	<b>84</b>
<b>51</b>	Scanning electron micrographs for Tc/ ChA <i>PEC</i> film cast from 0.5% acetic acid	<b>85</b>
<b>52</b>	Scanning electron micrographs for placebo ChP <i>PEC</i> film cast from 0.5% acetic acid	<b>86</b>
<b>53</b>	Scanning electron micrographs for Tc/ ChP <i>PEC</i> film cast from 0.5 % acetic acid	<b>86</b>
<b>54</b>	The swelling behavior of Tc/ChA and Tc/ChP films on agar plate by weighing method	<b>89</b>
<b>55</b>	The swelling behavior of Tc/ChA and Tc/ChP films on agar plate by diameter method	<b>89</b>
<b>56</b>	The release behavior of Tc HCl from Tc /ChA and Tc/ChP films in Sørensen phosphate buffer, pH 6.6	<b>91</b>
<b>57</b>	The inhibition zones of Tc /ChA and Tc/ChP films against <i>Staphylococcus aureus</i> ATCC 6538 for 21 days	<b>93</b>
<b>58</b>	Thermograms for (a) Chitosan film, (b) Sodium alginate film and (c) ChA <i>PEC</i>	<b>95</b>
<b>59</b>	Thermograms for (a) Chitosan film, (b) Pectin film and (c) ChP <i>PEC</i>	<b>96</b>
<b>60</b>	DSC Thermograms for (a) ChA <i>PEC</i> , (b) Tc/ChA <i>PEC</i> and (c) Tc: Chitosan: Sodium alginate physical mixture	<b>97</b>
<b>61</b>	DSC Thermograms for (a) ChP film, (b) Tc/ ChP film and (c) Tc: Chitosan: Pectin physical mixture	<b>98</b>
<b>62</b>	DSC Thermograms for (a) Chitosan film, (b) Tc/ Chitosan film and (c) Tc: Chitosan physical mixture	<b>99</b>
<b>63</b>	Effect of ageing on the release profile of Tc HCl from Tc/ChA film stored in freezer	<b>101</b>
<b>64</b>	Effect of ageing on the inhibition zones of Tc/ChA film stored in freezer	<b>101</b>

<b>65</b>	Effect of ageing on the release profile of Tc HCl from Tc/ChP film stored in freezer	<b>102</b>
<b>66</b>	Effect of ageing on the inhibition zones of Tc/ChP film stored in freezer	<b>102</b>
<b>67</b>	Mean pocket depth in patients treated with Tc/ChA film	<b>104</b>
<b>68</b>	Mean pocket depth in patients treated with Tc/ChP film	<b>104</b>
<b>69</b>	Preparation and application of Atridox <sup>®</sup> gel	<b>106</b>
<b>70</b>	Schematic presentation of the association mechanism of Poloxamer 407 in water	<b>107</b>
<b>71</b>	Chemical structure of Meloxicam	<b>109</b>
<b>72</b>	Chemical structure of Minocycline HCl	<b>109</b>
<b>73</b>	Meloxicam / Pluronic <sup>®</sup> gel preparation and application	<b>116</b>
<b>74</b>	Minocycline HCl / Pluronic <sup>®</sup> gel preparation and application	<b>117</b>
<b>75</b>	Release profile of Meloxicam and Minocycline HCl from Pluronic <sup>®</sup> gel (35%) in Sørensen phosphate buffer, pH 6.6	<b>119</b>
<b>76</b>	Release profile of Meloxicam from Pluronic <sup>®</sup> gel (35%) and Carbopol <sup>®</sup> : HPMC gel (1:2.5) in Sørensen phosphate buffer, pH 6.6	<b>122</b>
<b>77</b>	Inhibition zones for Minocycline HCl gel	<b>124</b>
<b>78</b>	% Decrease in pocket depth of group I (Meloxicam gel in 35% Pluronic <sup>®</sup> ) and group II (Minocycline HCl gel in 35% Pluronic <sup>®</sup> )	<b>126</b>
<b>79</b>	% Decrease in gingival index of group I (Meloxicam gel in 35% Pluronic <sup>®</sup> ) and group II (Minocycline HCl gel in 35% Pluronic <sup>®</sup> )	<b>127</b>
<b>80</b>	% Increase in bone density of group I (Meloxicam gel in 35% Pluronic <sup>®</sup> ) and group II (Minocycline HCl gel in 35% Pluronic <sup>®</sup> )	<b>128</b>
<b>81</b>	Follow-up of pocket depth and bone density in a patient after treatment with Meloxicam gel in 35% Pluronic <sup>®</sup> (group I)	<b>129</b>
<b>82</b>	Follow-up of pocket depth and bone density in a patient after treatment with Minocycline HCl gel in 35% Pluronic <sup>®</sup> (group II)	<b>129</b>

## LIST OF ABBREVIATIONS

<b>PD</b>	Probing depth	
<b>BP</b>	Bleeding on probing	
<b>CAL</b>	Loss of clinical attachment level	
<b>MIC</b>	Minimum inhibitory concentration	
<b>GCF</b>	Gingival crevicular fluid	
<b>PHBA</b>	Poly(hydroxybutyric acid)	
<b>PMM</b>	Polymethyl methacrylate	
<b>EC</b>	Ethyl cellulose	
<b>PHEMA</b>	Poly(2-hydroxyethyl)-methacrylate	
<b>PMA</b>	Poly(methacrylic acid);	
<b>HPC</b>	Hydroxypropyl cellulose	
<b>PLGA</b>	Poly(lactide/ glycolide);	
<b>PEG</b>	Polyethylene glycol	
<b>PLA</b>	Poly(lactide)	
<b>TPP</b>	Tripolyphosphate	
<b>HEC</b>	Hydroxyethyl cellulose	
<b>PVP</b>	Polyvinylpyrrolidone	
<b>CMC</b>	Carboxymethyl cellulose	
<b>MC</b>	Methyl cellulose	
<b>HPMC</b>	Hydroxypropylmethyl cellulose	
<b>POE</b>	Poly(ortho ester)	
<b>PCA</b>	Pyridone carboxylic acid	
<b>Tc</b>	Tetracycline	
<b>Tc HCl</b>	Tetracycline hydrochloride	
<b>EVA</b>	Ethylene vinyl acetate	
<b>NSAI</b>	Non-steroidal anti-inflammatory	
<b>PVA</b>	Polyvinyl alcohol	
<b>Na CMC</b>	Carboxymethyl cellulose sodium	
<b>SEM</b>	Scanning Electron Microscope	
<b>SGF</b>	Simulated Gingival Fluid	
<b>CAP</b>	Cellulose acetate phthalate	
<b>Ch</b>	Chitosan	
<b>A</b>	Sodium alginate	
<b>P</b>	Pectin	
<b>PEC</b>	Polyelectrolyte Complex	
<b>ChA PEC</b>	Chitosan-Sodium alginate Polyelectrolyte Complex	
<b>ChP PEC</b>	Chitosan-Pectin Polyelectrolyte Complex	
<b>FTIR</b>	Fourier-Transform Infrared spectroscopy	
<b>Tc/PEC</b>	Polyelectrolyte complex film containing Tc HCl	
<b>Tc/ChA</b>	Chitosan-Sodium alginate film containing Tc HCl	
<b>Tc/ChP</b>	Chitosan-Pectin film containing Tc HCl	
<b>DSC</b>	Differential Scanning Calorimetry	
<b>LCST</b>	Lower Critical Solution Temperature	
<b>UCST</b>	Upper Critical Solution Temperature	
<b>EO</b>	Ethylene oxide	

<b>PO</b>	Polypropylene oxide	
<b>PAA</b>	Polyacrylic acid	
<b>COX-1</b>	Cyclooxygenase-1 enzyme	
<b>COX-2</b>	Cyclooxygenase-2 enzyme	
<b>MMP8</b>	Matrix metalloproteinase 8	
<b>Mx</b>	Meloxicam	
<b>MH</b>	Minocycline HCl	
<b>PI</b>	Pluronic <sup>®</sup>	
<b>C:H</b>	Carbopol <sup>®</sup> : Hydroxypropylmethyl cellulose	