UNIVERSITÀ DEGLI STUDI DI SALERNO

**Department of Industrial Engineering**

Master's Degree in Industrial Engineering

# Mathematical modeling of urea absorption in a dialysis process with a wearable artificial kidney made of PGA

Thesis in

**Transport Phenomena**

Supervisors:

Prof. Ing. Gaetano Lamberti

Ing. Diego Caccavo

Prof. C. F. Van Nostrum

Dr. K.G.F. Gerritsen

Candidate:

Serena De Stefano

number 0622201193

**Academic Year 2021/2022**

Universiteit Utrecht

UMC Utrecht

The synthesis, the characterization of the polymer and the dynamic experiments were performed at the Department of Pharmaceutical Sciences, Faculty of Sciences, Utrecht Universiteit (Utrecht, Netherlands), under the supervision of Prof. C. F. Van Nostrum, dr. B.H Lentferink, and dr. K.G.F. Gerritsen during an Erasmus traineeship project.

*Eventuale dedica*

Questo testo è stato stampato in proprio, in Times New Roman

La data prevista per la discussione della tesi è il 19/12/2022
Fisciano, (data di stampa)

# Table of contents

**Table of contents** ..... I

**Table of Figures** ..... V

**Table of Tables** ..... IX

**Abstract** ..... XI

**Abstract (Italian)** ..... XIII

**Introduction** ..... 1

1.1 Kidney Function ..... 2

1.1.1 Kidney Disease ..... 3

1.1.2 Artificial Kidney ..... 4

1.2 Dialysis Process ..... 5

1.2.1 Dialysis types [4] ..... 6

1.2.2 Uremic toxins ..... 8

1.2.3 Urea ..... 9

1.2.4 Toxicity of urea ..... 11

1.3 Urea adsorption process ..... 11

1.3.1 Urea Binding Capacity ..... 12

1.3.2 Urea sorbents features ..... 13

1.4 Chemisorption process ..... 15

1.4.1 Chemisorption versus Physisorption ..... 15

1.4.2 Equilibrium Isotherm models ..... 15

1.4.3 Kinetic models 18
1.5 State of Art 19
1.5.1 Types of sorbents for Artificial Kidneys 19
1.5.2 Types of Artificial Kidneys 19
1.5.3 Mathematical modeling [4] 20
1.5.4 In-vivo urea distribution modeling 21
1.6 Aim of the work 23
**Materials and methods 25**
2.1 Materials 26
2.1.1 Styrene 26
2.1.2 Poly(methacrylic acid) sodium salt solution 26
2.1.3 55% technical grade divinylbenzene (DVB) 27
2.1.4 50% Benzoyl peroxide blend with dicyclohexyl phthalate 27
2.1.5 Aluminum Chloride 28
2.1.6 HBr 48% 28
2.2 Equipment 28
2.2.1 Glass Reactor 28
2.2.2 Oil bath 29
2.2.3 Vacuum Drying Oven 30
2.3 Synthesis of PGA 31
2.3.1 Suspension polymerization 31
2.3.2 Acetylation of polystyrene 32
2.3.3 Kornblum oxidation 33
2.4 Urea binding capacity measurements 34
2.4.1 Analysis of urea binding capacity 34
2.5 Dynamic Experiment set-up 35
2.5.1. Single column set-up 38
2.5.2. Multiple columns set-up 39
**Mathematical Modeling 41**
3.1 “In-vitro” modeling 42

3.1.1 Mass balance of urea in the vessel 42
3.1.2 Mass balance of urea in the fluid phase of the column 44
3.1.3 Mass balance of urea bound to the polymeric phase 45
3.1.4 Modeling of urea adsorption 46
3.1.5 The kinetic constant 50
3.1.6. Coefficient of Determination $R2$ 51
3.2 "In-vivo" modeling 52
3.2.1 Mass balance of urea in an open loop configuration 53
3.2.2 Mass balance of urea in a closed loop configuration 55
3.3 COMSOL implementation 57
3.3.1 Implementation in COMSOL for "in vitro" simulations. 57
3.3.2 Implementation in COMSOL for "in vivo" simulations. 63
3.3.3 Domain Point probe 70
3.3.4 Boundary conditions 71

**Results and Discussion ..... 73**

4.1 Results from dynamic experiments 74
4.1.1 Single unit dynamic experiment parametric study 76
4.1.2 Multiple unit dynamic experiment parametric study 79
4.2 Results from Binding Capacity tests 84
4.3 Results from in-vitro model 88
4.3.1. First order kinetic with UBC fixed 88
4.3.2 Pseudo-2nd order with UBC as a function of free urea concentration 91
4.3.4 Results from parallel and series configuration 100
4.4 Results from in-vivo model 103
4.4.1 Estimation of kinetic constant kA from literature data 103
4.4.2 Parametric study for in vivo model 106

**Conclusions ..... 119**

5.1 Conclusions 120
5.1.1 Introduction 120

5.1.2 Conclusions of the project 120

**References ..... 123**

# Table of Figures

Figure 1. Kidney anatomy .....2
Figure 2. Stages of ESKD .....4
Figure 3. WAK system for Hemodialysis and Peritoneal dialysis.....5
Figure 4. Hemodialysis scheme.....7
Figure 5. Peritoneal dialysis scheme .....8
Figure 6. Structure of the most known uremic toxins: Urea (1) - Uric Acid (2) - Creatinine (3) - p-Cresyl Sulfate (4) - Indoxyl Sulfate (5) .....9
Figure 7. Chemical structure of urea molecule.....9
Figure 8. Scheme of body urea cycle steps.....10
Figure 9. Chemical structure of a urea sorbent.....13
Figure 10. Chemical structure of ninhydrin and PGA sorbents.....14
Figure 11. Types of Isotherms of Absorption to describe equilibrium[21] .....16
Figure 12. Roadmap of artificial kidneys development.....20
Figure 13. Styrene structure .....26
Figure 14. Poly(methacrylic acid) sodium salt structure .....27
Figure 15. DVB structure .....27
Figure 16. 50% benzoyl peroxide blend with cyclohexyl structure.....27
Figure 17. Aluminum Chloride structure.....28
Figure 18 Glass reactor.....29
Figure 19. Oil bath.....30
Figura 20. Vacuum drying oven .....31
Figure 21. Second polymerization step: Acetilation of polystyrene .....33
Figure 22. Third polymerization step: Oxidation of acetylated polystyrene into PGA.....34
Figure 23. Small scale set-up for dynamic experiment .....36
Figure 24. Simple scheme of dynamic experiment set-up.....36
Figure 25. A scheme of the dynamic experiment set-up .....42

Figure 26. Mass balance in the vessel ..... 43

Figure 27. Mass balance of fluid phase in the column ..... 44

Figure 28. Mass balance of polymeric phase in the column ..... 45

Figure 29. Freundlich isotherm ..... 48

Figure 30. Langmuir isotherm ..... 49

Figure 31. Fitting of pseudo-kinetic constant k as a linear function of lateral flow velocity $v_{avg}$ ..... 51

Figure 32. Diffusion of small-molecular-weight solute from blood to dialysate through a membrane ..... 53

Figure 33. Scheme of a single pass open loop configuration dialysis process ... 55

Figure 34. Scheme of a closed loop configuration dialysis process ..... 56

Figure 35. Screenshot of in vitro parameters on Comsol software ..... 61

Figure 36. Implementation of Global ODEs and DAEs for the vessel in vitro.. 62

Figure 37. Implementation of Transport of Diluted Species for the fluid phase in the column in vitro. ..... 62

Figure 38. Implementation of Coefficient Form PDE for polymeric phase in the column in vitro ..... 63

Figure 39. Screenshot of in vivo parameters on Comsol software ..... 66

Figure 40. Implementation of Global ODEs and DAEs for the vessel (filter) in vivo. ..... 67

Figure 41. Implementation of Transport of Diluted Species for the fluid phase in the column in vivo. ..... 68

Figure 42. Implementation of Coefficient Form PDE for polymeric phase in the column in vivo. ..... 69

Figure 43. Implementation of Global ODEs and DAEs 2 for the body compartment in vivo. ..... 69

Figure 44.The Domain Point Probe at the beginning of the adsorption unit ..... 70

Figure 45. The Domain Point Probe at the end of the column in the case of dynamic experiment simulation ..... 71

Figure 46. Scheme of dynamic experiment set-up ..... 76

Figure 47. Single column experiment Cv/Cv0 along the time at Cv0=15mM, $m_p$=8g and varying flowrate at 12 - 25 - 40 mL/min ..... 77

Figure 48. Single column experiment Cv/Cv0 along the time at Cv0=30mM $m_p$=8g and varying flowrate at 12 - 25 - 40 mL/min ..... 78

Figure 49. Scheme of parallel configuration set-up ..... 79

Figure 50. Scheme of series configuration set-up ..... 80

Figure 51. Parallel experiment Cv/Cv0 along the time at Cv0=30mM $m_p$=16g and varying flowrate at 20 - 40 mL/min ..... 81

Figure 52. Single column and parallel experiments Cv/Cv0 along the time at Cv0=30mM, flowrate 40 mL/min varying $m_p$ at 8g or 16g ..... 82

Figure 53. Series and parallel experiments Cv/Cv0 along the time at Cv0=30mM, flowrate 40 mL/min and 16g of polymer ..... 83

Figure 54. Series experiment Cv/Cv0 along the time at Cv0=30mM flowrate at 40 mL/min and varying $m_p$=16g – 8g – 4g ..... 84

Figure 55.UBC in mmol/g along incubation time for different initial urea concentrations at 15 - 20 - 30 mM and 30 – 50 mM with respectively $m_p$ at 15.7 mg and $m_p$ at 32.4 mg ..... 85

Figure 56. Urea concentration along incubation time for different batch of polymer with $m_p$ at 15.7 mg or 32.4 mg and different initial urea concentration. ..... 86

Figure 57. Bound urea concentration along free urea concentration from binding capacity test compared with Freundlich and Langmuir isotherm of equilibrium ..... 87

Figure 58. Simulation of experimental results from single column at 30 mM varying flowrate at 12 - 25 - 40 mL/min and pseudo-first order kinetic model.. 89

Figure 59. Comparison between experimental results from single column at 30 mM varying flowrate at 12 - 25 - 40 mL/min and pseudo-second order kinetic model (n=2) and fixed UBC. ..... 90

Figure 60. Fitting of Freundlich isotherm on experimental data of UBC in order to optimize Keq and n ..... 92

Figure 61. Cv/Cv0 along the time using Freundlich model with two different pseudo-2$^{nd}$ order kinetics on experimental result at 30 mM in a single unit configuration with 40 mL/min ..... 93

Figure 62. Fitting of kinetic constant k using Freundlich isotherm and kinetic equation 4.7 ..... 94

Figure 63. Prediction of experimental results at 15 mM in a single unit configuration varying flowrate, using Freundlich model and kinetic equation 4.7. ..... 95

**Figure 64. Fitting of Langmuir isotherm on experimental data of UBC on order to optimize $Q_{max}$ and $k_L$.** ..... 96

Figure 65. Cv/Cv0 along the time using Langmuir model with two different pseudo-2$^{nd}$ order kinetics on experimental result at 30 mM in a single unit configuration with 40 mL/min ..... 97

Figura 66. Fitting of kinetic constant k using Langmuir isotherm and kinetic equation 4.7. ..... 98

Figure 67. Simulation of experimental results on a single unit configuration, 30 mM and varying flowrate at 12 – 25 – 40 mL/min using Langmuir isotherm and equation 4.7. ..... 99

Figure 68. Prediction of experimental results on a single unit configuration, 15mM and varying flowrate at 12 – 25 – 40 mL/min using Langmuir isotherm and equation 4.7. ..... 100

Figure 69. Prediction of experimental results from parallel configuration at 30 mM, 16g of polymer, and total flowrate of 40 mL/min or 80 mL/min ..... 101

Figure 70. Prediction of experimental results from series configuration at 30 mM, 16g of polymer, flowrate of 40 mL/min, varying the length L of the polymeric bed at 2.5 – 5 – 10 cm. ..... 102

Figure 71. Decrease in log urea concentration during a short hemodiafiltration ..... 104

Figure 72. Urea concentration in the blood along the time during a short hemodiafiltration session compared with urea concentration described by the model with optimized kinetic constant kA=0.367 L/min ..... 105

**Figure 73. Simple scheme of a closed loop dialysis** ..... 106

Figure 74. plot of urea concentration in the filter and in the blood varying $\boldsymbol{vavg}$ at 2.4 – 4 – 8 cm/min, with $\boldsymbol{mp}$=1kg, $\boldsymbol{V}$=300mL/min and $\boldsymbol{UBC}$=1.8 mmol/g. ..... 110

Figure 75. Plot of urea concentration in the filter and in the blood varying $\boldsymbol{mp}$ at 1kg – 2kg – 3kg, with $\boldsymbol{vavg}$=8 cm/min, $\boldsymbol{V}$=300mL/min and $\boldsymbol{UBC}$=1.8 mmol/g ..... 112

Figure 76. Plot of urea concentration in the filter and in the blood varying $\boldsymbol{V}$ at 300 mL/min – 600 mL/min – 1000 mL/min, with $\boldsymbol{vavg}$=8 cm/min, $\boldsymbol{mp}$=1kg and $\boldsymbol{UBC}$=1.8 mmol/g ..... 114

Figure 77. plot of urea concentration in the filter and in the blood varying $\boldsymbol{UBC}$ at 1.8 mmol/g – 3.75 mmol/g – 6.25 mmol/g, with $\boldsymbol{vavg}$=8 cm/min, $\boldsymbol{mp}$=1kg and $\boldsymbol{V}$=300 mL/min). ..... 117

# Table of Tables

Table 1. Human scale background information for small scale set-up .....37

Table 2. Small scale information to set-up dynamic experiments .....38

Table 3. Values of polymer mass and column length for dynamic experiments 58

Table 4. Values of Langmuir parameter $Q_{max}$ and UBC for the parametric study in the in vivo simulations .....64

Table 5. Starting parameters for dynamic experiments set-up geometry .....74

Table 6. Dynamic experiments performed .....75

Table 7. Parametric study of single column dynamic experiments .....76

Table 8 . Parametric study of parallel set-up dynamic experiments .....80

Table 9. Parametric study of series set-up dynamic experiments .....82

Table 10. Optimized kinetic constant k with $R^2$ function for different flowrate 12 – 25 – 40 mL/min using Freundlich isotherm.....94

Table 11. Optimized kinetic constant k with $R^2$ function for different flowrate 12 – 25 – 40 mL/min using Langmuir isotherm .....97

Table 12. Starting parameters related to vessel, column and body in the in vivo modeling implementation .....107

Table 13. Values of Qmax and UBC to be varied in the parametric study of the in vivo simulation .....108

Table 14. Values for each parameter to be varied in the parametric study of the in vivo simulation. .....109

Table 15. Modeling results varying lateral flow velocity in the parametric study for in vivo simulation. .....110

Table 16. Modeling results varying mass of polymer in the parametric study for in vivo simulation. .....113

Table 17. Modeling results varying dialysate flowrate in the parametric study for in vivo simulation. .....115

# Abstract

This thesis was carried out as part of a joint project between the University of Salerno, Utrecht University and University Medical Center Utrecht. In particular, the aim of this thesis was the laboratory synthesis and characterization of a polymer capable of adsorbing urea and the mathematical modelling of the urea adsorption process in an artificial kidney to be used in a dialysis process related to End Stage Kidney Disease (ESKD). Through binding capacity tests performed at various urea concentrations, a static urea binding capacity (UBC) of 1.6 mmol/g was obtained at 37°C, at a urea concentration of 30 mM per 8 g polymer. Successively, UBC measurements revealed that urea binding depends on free urea during uptake. Two different equilibrium relationships were indeed studied to describe the mechanism: Langmuir and Freundlich. They were optimized using the available UBC test results. The polymer was used in small-scale dynamic experiments simulating a dialysis session under different operating conditions and different configurations. A descriptive mathematical model was implemented using Comsol Multiphysics software. The initial aim was to describe the experimental results and optimize the kinetic constant. The mechanism was described via pseudo-second-order kinetics, driven by the urea bound to the polymer and considering the UBC as a function of free urea concentration, using the Langmuir equilibrium isotherm. The model was found to be descriptive and predictive for different plant configurations. An in-vivo mathematical model was then implemented, related to a closed loop 'single pool' dialysis process. From a parametric study, the effect on column's geometry and on the amount of total dialysate required was analyzed, obtaining that the polymer mass has a strong influence on the amount of dialysate and consequently on the final characteristics of the device.

# Abstract (Italian)

La tesi è stata svolta nell'ambito di un progetto congiunto, tra l'Università di Salerno, Utrecht University e University Medical Center Utrecht. In particolare, l'obiettivo di questa tesi è stato la sintesi in laboratorio e la caratterizzazione di un polimero in grado di adsorbire l'urea e la modellazione matematica del processo di adsorbimento dell'urea che caratterizza un rene artificiale da utilizzare in un processo dialitico relativo alla End Stage Kidney Disease (ESKD). Tramite prove di capacità di legame eseguite a varie concentrazioni di urea, si è ottenuta una urea binding capacity (UBC) statica di 1.6 mmol/g a 37°C, ad una concentrazione di urea di 30 mM per 8 g di polimero. Successivamente, le misure di UBC hanno permesso di capire che il legame dell'urea dipende dall'urea libera durante l'assorbimento. Sono state quindi studiate due diverse relazioni di equilibrio per descrivere il meccanismo: Langmuir e Freundlich. Queste sono state ottimizzate utilizzando i risultati dei test sulla UBC disponibili. Il polimero è stato impiegato in esperimenti dinamici su piccola scala, in grado di simulare una sessione di dialisi in diverse condizioni operative e differenti configurazioni. È stato implementato un modello matematico descrittivo utilizzando il software Comsol Multiphysics. L'obiettivo iniziale è stato quello di descrivere i risultati sperimentali e ottimizzare la constante cinetica. Il meccanismo è stato descritto tramite una cinetica di pseudo-secondo ordine, guidata dall'urea legata al polimero e considerando l'UBC come funzione della concentrazione di urea libera, utilizzando l'isoterma di equilibrio di Langmuir. Il modello è risultato descrittivo e predittivo per diverse configurazioni impiantistiche. È stato quindi implementato un modello matematico in-vivo, relativo a un processo di dialisi a circuito chiuso "single pool". Da uno studio parametrico si è analizzato l'effetto sulla geometria della colonna e sulla quantità di dializzato totale necessario, risultando che la massa di polimero ha una forte influenza sulla quantità di dializzato e di conseguenza sulle caratteristiche finali del dispositivo.

# References


1. Jong, J.A.W., *Bottom-up Development of Urea Sorbents for Dialysate Regeneration*, 2019. Utrecht University.
2. Monica S.Y. Ng, Vivek Charu, David W. Johnson, Michelle M. O'Shaughnessy, A. J. Mallett, *National and international kidney failure registries: characteristics, commonalities, and contrasts*. Kidney International, 2022. 101: p. 23–35.
3. M.K. van Geldera, Jong J.A.W, L. Folkertsmaa, Yong Guob, Christian Blücheld, M. C. Verhaara , Mathieu Odijkc, C.F. Van Nostrum , W.E. Hennink, K.G.F. Gerritsen *Urea removal strategies for dialysate regeneration in a wearable artificial kidney*. Elsivier, 2020.
4. Scarano C., *Urea adsorption for artificial kidneys: synthesis of polyphenylglyoxaldehyde and mathematical modeling of its applications*, 2020, University of Salerno.
5. Johnson C.A., Levey A. S., Coresh J., Levin A., Lau J., Eknoyan G., *Clinical Practice Guidelines for Chronic Kidney Disease in Adults: Part I. Definition, Disease Stages, Evaluation, Treatment, and Risk Factors.* Am Fam Physician, 2004, 70(5): p.869-76.
6. S. L. White, A. Cass, R. C. Atkins, and S. J. Chadban, *Chronic Kidney Disease in the General Population,* Adv Chronic Kidney Dis., 2005, 12(1): p.5-13.
7. Megha Salani, Shuvo Roy, and William H. Fissell, *Innovations in Wearable and Implantable Artificial Kidneys*, Am J Kidney Dis., 2018, 72(5): p.745-751.
8. Sana Daneshamouz, Ubong Eduok, Amira Abdelrasoul, Ahmed Shoker, *Protein-bound uremic toxins (PBUTs) in chronic kidney disease (CKD) patients: Production pathway, challenges and recent advances in renal PBUTs clearance*, Elsivier, 2021.
9. Raymond Vanholder, Tessa Gryp, Griet Glorieux, *Urea and chronic kidney disease: the comeback of the century*, Ghent University Hospital, Belgium, Nephrol Dial Transplant, 2018 33: p. 4–12.
10. Jane Y. Yeun, M.D. Thomas A. Depner, M.D. C, *Principles of Hemodialysis*

11. Prescribing hemodialysis: A Guide to Urea Modeling Thomas A. Depner, M.D. University of California, Davis, Kluwer Academic Publishers BostonlDordrechtILondon

12. Section 18 / Continuous Renal Replacement Therapies CHAPTER 260 Continuous Ultrafi ltration and Dialysis with a Wearable Artifi cial Kidney Victor Gura and Claudio Ronco

13. How to interpret protein binding capacity: chromatography resins By Marianne Carlsson, Product Specialist protein purification GE Healthcare

14. Adsorption, chemisorption, and catalysis a,bMilan Králik* aVUCHT a.s., Areál Duslo a.s., 927 03 Šaľa, Slovakia bFaculty of Chemical and Food Technology, Slovak University of Technology in Bratislava, Radlinského 9, 812 37 Bratislava, Slovakia Received 16 January 2014; Revised 14 June 2014; Accepted 25 June 2014

15. Thermodynamical and analytical evidence of lead ions chemisorption onto Pimenta dioica J. Cruz-Olivares a, C. Pérez-Alonsoa, C. Barrera-Díaz b,∗, R. Natividadb, M.C. Chaparro-Mercadoc a Universidad Autónoma del Estado de México, Facultad de Química, Paseo Colón intersección Paseo Tollocan S/N, C.P. 50120, Toluca, Estado de México, Mexico b Centro Conjunto de Investigación en Química Sustentable UAEM – UNAM, Carretera Toluca-Atlacomulco, km 14.5, Unidad El Rosedal, C.P. 50200, Toluca, Estado de México, Mexico c Departamento de Ingenierías, Universidad Iberoamericana, Prol. Paseo de la Reforma 880, Lomas de Santa Fe, Álvaro Obregón, D.F. 01219, Mexico

16. Removal of cadmium from aqueous solutions by adsorption onto orange waste A.B. Perez-Mar ´ ´ın, V. Meseguer Zapata ∗, J.F. Ortuno, ˜ M. Aguilar, J. Saez, M. Llor ´ ens ´ Department of Chemical Engineering, University of Murcia, 30071 Murcia, Spain Received 26 July 2005; received in revised form 24 April 2006; accepted 6 June 2006

17. A Statistical Approach to Determine Optimal Models for IUPAC-Classified Adsorption Isotherms Md. Matiar Rahman 1,2,3, Mahbubul Muttakin 2 , Animesh Pal 2,4 , Abu Zar Shafiullah 5 and Bidyut Baran Saha 1,2,* 1 Mechanical Engineering Department, Kyushu University, 744 Motooka, Nishi-ku, Fukuoka 819-0395, Japan

18. Chapter (12) Single Pool Urea Kinetic Modeling Alicja E. Grzegorzewska; Ahmad Taher Azar; Laura M. Roa; J. Sergio Oliva; José A. Milán; Alfonso Palma.

19. «A Revised Pseudo-Second-Order Kinetic Model for Adsorption, Sensitive to Changes in Adsorbate and Adsorbent Concentrations» Jay C. Bullen,* Sarawud Saleesongsom, Kerry Gallagher, and Dominik J. Weiss

20. The post-hemodialysis rebound: Predicting and quantifying itseffect on Kt/V JAMES E. TATTERSALL, DOMINIC DETAKATS, PAUL CHAMNEY, ROGER N. GREENWOOD, and KEN FARRINGTON Lister Hospital, Stevenage, Herts, England, United Kingdom, Kidney International, Vol. 50 (1996), pp. 2094—2102.

21. https://www.enea.it/it/Ricerca_sviluppo/documenti/ricerca-di-sistema-elettrico/adp-mise-enea-2015-2017/processi-e-macchinari-industriali/rds_par2015-057.pdf