Drug Release From Drug Delivery Devices: Derivation and Applications of a Multi-region Finite Element Model

Kristinn Guðnason

Industrial Engineering, Mechanical Engineering and Computer Science
School of Engineering and Natural Sciences
University of Iceland
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DRUG RELEASE FROM DRUG DELIVERY DEVICES: DERIVATION AND APPLICATIONS OF A MULTI-REGION FINITE ELEMENT MODEL

Kristinn Guðnason

180 ECTS thesis submitted in partial fulfillment of a
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Ph.D. Supervisor:
Prof. Fjóla Jónsdóttir

Ph.D. Committee:
Prof. Fjóla Jónsdóttir
Prof. Sven Þ. Sigurðsson
Prof. Már Másson

Opponents:
Prof. Anuj Chauhan
Colorado School of Mines, USA
Prof. Sean McGinty
University of Glasgow, Scotland

Industrial Engineering, Mechanical Engineering and Computer Science
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Industrial Engineering, Mechanical Engineering and Computer Science
School of Engineering and Natural Sciences
University of Iceland
Hjarðarhagi 2–6
107 Reykjavík
Iceland

Telephone: +354 525 4700

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Abstract

The effectiveness of a drug treatment regimen relies on the efficient delivery to afflicted target areas. Drug delivery devices aim to achieve a sustained release and maintain a steady drug concentration level that falls within a therapeutic range. Polymeric delivery systems are widely studied for the local treatment of brain tumors, vascular diseases, ocular diseases, reproductive health, and wound healing. Controlled release systems are developed to control drug exposure over time, to facilitate drug penetration of physiological barriers, to minimize drug loss from premature elimination, and to target the desired site of action while decreasing drug exposure elsewhere. It is decisive to know which device properties are crucial to provide the desired system performance, especially considering that challenges encountered during production can more efficiently be addressed if there is a thorough understanding of how drug release is controlled.

This thesis describes the derivation of a finite element drug transport model that provides a framework for simulating drug release from drug delivery devices. The combined effects of different drug solute mechanisms affecting transport, including diffusion, dissolution, binding, mass transfer resistance and partitioning between phases were incorporated. The framework was verified with purpose built models to compare against data from experiments and to deduce physical parameter values. Simulations of Franz diffusion cell experiments were conducted using one dimensional multi-layer models but simulations of release experiments involving lenses relied on three dimensional models with rotational symmetry, which resulted in two dimensional multi-region models. The numerical model maintains important aspects of the mathematical model regarding mass conservation and distribution of eigenvalues. In the case of hydrogels, it was shown how polymer-solute interactions, which influence partitioning, affect the interface driving force, emphasising the necessity of properly modelling interface mass transfer.

Árangur lyfjameðferðar er háður því að skilvirkur lyfjaflutningur verði til þeirra líkamshluta sem lyfjunum er ætlað að verka á. Markmið lyfjagjafarbúnaðar er að ná fram viðvarandi lyfjalosun til að viðhalda þeim styrkleika sem fellur innan meðferðarramma. Rannsóknir hafa verið gerðar á fjölliðalyfjagjafakerfum til meðferðar við heilaæxli, æðaskjúkdómum, augnsjúkdómum og við sáragræðslu. Stýrð losunarkerfi eru þróuð til að halda langtíma neikveiðum áhrifum í skefjum, að greiða fyrir flutningi í gegnum líffeðlisfræðilegar hindranir, að lágmarka lyfjatap vegna ótímabærs brottfalls og til að flytja lyf á tilætlaðan stað meðan skaðleg áhrif annars staðar eru lágmörkuð. Það skiptir sköpum að þekkja hvaða eðliseiginleikar kerfis hafa mest áhrif á flutning til að losunarkerfi nái tilætluðum árangri, en einnig til að takast á við áskoranir á framleiðslustigi með skilvirkari hætti.

Ritgerðin lýsir útleiðslu á almennu lyfjaflutningsbútalíkani til að herma lyfjalosun frá lyfjagjafarbúnaði. Tekið er tillit til samverkandi áhrifa mismunandi þátta sem hafa áhrif á flutning lyfs sem uppleysts efnis, þar á meðal sveimis, upplausnar fastra efna, efnabindingar, skiptingar og mótstöðuáhrifa efna milli fasa. Almenna líkanið var sannreynt með smíði sértækra líkana af tilraunum, þá sérstaklega til að bera saman við tilraunagögn og til að stika líkanabreytur. Hermun Franz flæðisellu tilrauna var byggð á einvíðum marglaga líkönum en hermun losunartilrauna með linsum bygðist á þrívíðum líkönum með snúningssamhverfu, sem verða þá í reynd tvívið margsvæða líkön, þar sem sýnt er fram á að tölulega líkanið viðhaldi mikilvæga eiginleika stærðfæðilíkansins eins og massavarðveislu og dreifingu eigingilda. Sérstakt tillit var tekið til fjölliðukerfa, sýnt var framm á hvernig víxlverkandi áhrif lyfs við fjölliðu, þar á meðal skiptistuðulsáhrif, höfðu áhrif á efnaflutning yfir jaðar.

List of Publications

Publications included in the thesis

I **Numerical simulation of Franz diffusion experiment: application to drug loaded soft contact lenses**
Kristinn Gudnason, Svetlana Solodova, Anna Vilardell, Mar Masson, Sven Sigurdsson, Fjola Jonsdottir
Journal of Drug Delivery Science and Technology ***38****, (2017): pp. 18-27.*

II **A numerical framework for drug transport in a multi-layer system with discontinuous interlayer condition**
Kristinn Gudnason, Sven Sigurdsson, Bergthora S. Snorradottir, Mar Masson, Fjola Jonsdottir
Mathematical biosciences ***295****, (2018): pp. 11-23.*

III **A Numerical Framework for Diffusive Transport Rotational Symmetric Systems with Discontinuous Interlayer Discontinuous Interlayer Conditions**
Kristinn Gudnason, Sven Sigurdsson, Fjola Jonsdottir
IFAC-PapersOnLine ***51****(2), (2018): pp. 643-648.*

IV **Modelling the Release of Moxifloxacin from Plasma Grafted Intraocular Lenses with Rotational Symmetric Numerical Framework**
Kristinn Gudnason , Sven Sigurdsson, Fjola Jonsdottir, A. J. Guiomar, A. P. Vieira, P. Alves, P. Coimbra, M. H. Gil
International Conference on Bioinformatics and Biomedical Engineering (2018): pp. 329-339. Springer, Cham.

V **Multi-region finite element modelling of drug release from hydrogel based ophthalmic lenses**
Kristinn Gudnason, Sven Sigurdsson, Fjola Jonsdottir
Mathematical biosciences ***331****, (2021): 108497.*

Contents

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1 Introduction

1.1 Backround

A deciding factor for the success of drug development is the efficient delivery of a therapeutic agent to a target site [1–4]. Although systemic drugs, such as conventional oral pills and injections, represent the most common mode of administering drugs today, they are unable to meet many advanced therapeutic needs [5]. Access to the intended site of action can be limited, as is the case with ophthalmic delivery through systemic means where large doses are required to achieve therapeutic drug concentrations in the retina [6]. Such cases can result in both inadequate drug concentrations in the diseased site as well as causing off-target toxicity in healthy tissue [7]. Local drug release, when feasible, allows for delivery of the largest fraction of drug molecules at the site of action, which reduces drug toxicity [8]. Controlled release systems are developed to control drug exposure over time, to facilitate drug penetration of physiological barriers, to minimize drug loss from premature elimination, and to target the desired site of action while decreasing drug exposure elsewhere [9]. Such systems open up the possibility for optimized drug administration and improved patient compliance [7]. The aim is then to achieve a local sustained release and to maintain steady drug concentration levels that falls within a therapeutic range, for the required amount of time [9]. This means controlled release systems should sustain effective drug levels, as depicted by the dot-dash curve in Figure 1.1, bounded between a minimum toxic concentration (MTC) from above, and a maximum effective concentration (MEC) from below. This should be contrasted with the the more conventional multiple dose regimen, depicted by the dotted curve, where therapeutic levels are achieved through carefully timed doses.

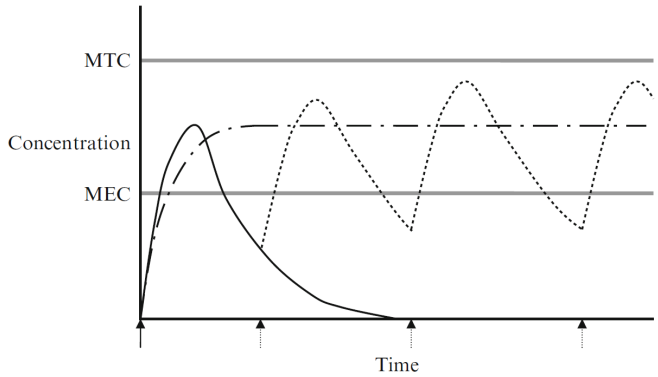

Figure 1.1. Curves show drug concentration of different treatment regimens of a rapidly absorbed and rapidly eliminated drug [9]. The therapeutic range, where drug is effective without displaying toxicity, is bounded between the minimum toxic concentration (MTC) from above, and the maximum effective concentration (MEC) from below. Arrows show time of intake of a single dose in dosing regimen. Solid curve: Single dose. Dotted curve: Multiple dosing. Dot-dash curve: Sustained relase.

In the case of ophthalmic delivery, a cataract, which is a clouding of the lens in the eye which leads to impaired vision, is commonly treated by surgically removing the natural eye lens and replacing it with an artificial intraocular lens (IOL). Complications in cataract surgery can lead to endophthalmitis which is an inflammation of the aqueous and vitreous humors caused by bacteria or fungi [10], and can lead to vision loss if left untreated. More than 90% of drugs are currently being delivered in the form of solutions or suspensions [11]. The efficiency of such formulations is influenced by several factors, including low bioavailability, poor compliance, and rapid clearence by tear drainage. Low ocular bioavailability requires high drug concentrations in the eye drops, which can result in toxicity in the corneal tissues [12, 13]. Hydrogel based IOLs have been considered as drug delivery devices for the sustained release of antibiotics and anti-inflammatories [14–20]. Hydrophilic acrylic IOLs have been shown to be safe and effective drug-delivery system for fourth-generation fluoroquinolones [21], in particular for moxifloxacin, which has favourable ocular penetration and pharmacokinetics [22] and is commonly used in the treatment of conjunctivitis, keratitis, keratoconjunctivitis, and bacterial endophthalmitis [23, 24]. When utilized as drug delivery systems, IOLs replace the need for patient compliance reducing post-surgery complicatations [25].

Novel drug delivery devices are developed to make up for the shortcomings of traditional administration. As we learn more about the dynamics of drug transport in tissues, safe and effective local drug delivery systems can be designed based on these principles for a wider range of clinical applications [26]. Hydrogel-based polymers have been considered as devices for the controlled release of drugs for transdermal, oral, nasal and parenteral administration routes [27]. Additionaly, implantable or injectable polymeric delivery systems are widely studied for the local treatment of brain tumors, vascular diseases, ocular diseases, reproductive health, and wound healing [26]. The potential for the growth of polymer based drug delivery systems is limitless, and newer polymers would serve the purpose of controlled and sustained delivery for treating vision-threatening diseases [28]. Close cooperation between researchers in basic sciences, clinical researchers, IOL manufacturers and the pharmaceutical industry is an important prerequisite for further development [29].

Permeation studies through membranes have long been carrier out to infer solute-diffusive properties of the membrane [30]. Samples are taken from a receptor medium forming a characteristic release curve. Assuming transport to be solely governed by diffusion, an algebraic expression can be obtained for the diffusion coefficient depending on the time-lag [30], which is determined by finding the intercept of the steepest tangent of the release curve. For closed systems, after a gradual build-up within the membrane, the release curve is at its steepest only for a brief moment after which it gradually tapers off making time-lag estimation sensitive to sample timings and interpretation. Practical consideration aside, where boundary layer resistance is encountered, a situation which appears to be quite common, time-lag is significantly increased [31].

The mathematical modelling of drug delivery is an important tool in identifying key parameters and mechanisms of drug release [32, 33] and has the potential to facilitate product development and optimize complex dosage forms. It is decisive to know which device properties are crucial to provide the desired system performance, especially considering that challenges encountered during production can more efficiently be addressed if there is a thorough understanding of how drug release is controlled [34]. Furthermore, such an understanding can aid in the development of new delivery strategies to afflicted areas. The effort associated with modelling drug release systems largely depends on the mechanisms explicitly incorporated, which often require more complex methods for solving the associated mathematical equations. Nevertheless, in the cases that a particular mechanism

may be safely ignored, simplified models, solvable using well known conventional methods, are often employed. Of the many concurrent mechanisms which can come into play during drug release, diffusion often takes the primary role [32]. Recent diffusion based models have been applied to screen for prospective in vivo efficacy of hydrogels as drug carriers, to determine diffusion of drug solutes, and to predict release profiles [35–39].

Partitioning and resistance effects can have a substantial effect on interface mass transfer. These effects are challenging [40], largely due to the associated discontinuities in concentration and thus require more involved solution methods [41, 42]. The effects are phenomenologically challenging, as mass transfer conditions have been applied to model partitioning [43, 44]. However, mass transfer conditions can only describe negative jumps in concentration in the direction of the flux and cannot describe jumps when a system is in equilibrium. This means that naturally occuring discontinuities cannot be adequately modelled without explicitly incorporating partitioning. Hickson *et al.* [45] developed a finite difference scheme suitable for multilayered diffusion with a mass transfer coefficient describing resistance to mass transfer across layer interfaces. Later, this method was applied by McGinty and Pontrelli [46] to solve for mass transfer interface conditions between drug delivery device and skin in a general model which also incorporates dissolution and solubility, coupled with diffusion, as well as convection and reaction in the biological tissue. Rim *et al.* [42] modelled transdermal drug delivery explicitly incorporating partitioning between layers applying a mixed finite element method where cross boundary flux is modelled as independent variables, in addition to the concentrations at each side of the boundary. March and Carr [41] presented a finite volume scheme, incorporating both partition and mass transfer boundary conditions for layered diffusion problems. They proved that the eigenvalues of their scheme remained real and non-positive. Gupta *et al.* described trans-corneal penetration of the lipophilic compound Rhodamine B [47] using a realistic multilayered model, accounting for effective diffusion in the water based stroma layer and both paracellular diffusion and reversible lipid bilayer partitioning within epithelium and endothelium cellular layers. A similar study was conducted, with the more hydrophilic fluorescein [48], along with a customized model thereof. Good model parameter estimation was achieved in both cases by comparing transient concentration profiles to data obtained using a confocal fluorescence microscope and would not have been possible without including appropriate interface effects.

1.2 Research objectives

The research presented in this thesis arose from participation in the European MEra-Net project SurfLenses [49]. The purpose of the project was to develop new efficient systems with controllable drug-elution rate for the treatment or prophylaxis of ocular diseases and post-surgical infections. For the success of the project, which started in 2014 and finished in 2017, it included collaboration of industry, clinicians and academic groups from Belgium, Iceland and Portugal. Systems studied included transdermal and ophthalmic drug delivery devices. A particular emphasis was on characterizing drug transport from hydrogel systems. The work on constructing models for pharmaceutical systems and evaluating relevant mechanisms then developed into a study of how to construct a general multiregion finite element framework that would explicitly account for all the relevant mechanisms that may play in drug release from drug delivery systems.

Research questions

1 How can the combined effects of different drug mechanisms affecting transport, including the associated discontinuities, be accurately accounted for by a mathematical model in the most direct way?

2 How can a flexible finite element approach be developed so that it realistically reflects the geometry to be modelled, while preserving the properties of the mathematical model?

3 How can such an approach be applied to interpret the effect that different mechanisms have on measurement results?

1.3 Scientific contribution

A main contribution of this thesis is to derive a multiregion Galerkin finite element model that deals with the combined effects of different drug solute mechanisms affecting transport, including diffusion, dissolution and binding, as well as mass transfer resistance and partitioning between phases resulting in discontinuities across interior and exterior boundaries. By deriving such a model directly from the weak formulation of the underlying mathematical model, based on partial differential equations, it is easier to demonstrate that all these relevant effects are modelled accurately and that the numerical model maintains important aspects of the mathematical model regarding e.g. mass conservation and distribution of eigenvalues. While numerous accounts of numerical model results on drug transport are to be found in the literature, such issues are rarely considered. Furthermore, lack of flexibility in the numerical methods applied sometimes result in unnecessary or misleading simplifications. Both general one- and two-dimensional models are derived in the papers of this thesis, the latter using triangular elements which allows fitting the model to irregular geometries. Special attention is given to the case of three-dimensional models with rotational symmetry, such as models involving lenses.

Models of experiments were constructed to compare against data and deduce physical parameter values. Modelled devices include hydrogel based intraocular and soft-contact lenses, as well as a silicone matrix transdermal system. Interface conditions, describing flux between adjacent phases, were characterized as the product of a mass transfer coefficient, parametrizing flux resistance, and a driving force induced by a difference in concentration, which deviates from equilibrium. The equilibrium state itself is prescribed by partition conditions. In the case of hydrogels, it was shown how polymer-solute interactions, which influence partitioning, affect the interface driving force, further emphasising the necessity of properly modelling interface mass transfer.

1.4 Outline of the dissertation

An overview of the the transport processes involved in drug release will be laid out in Chapter 2. In Chapter 3, the methodology applied in the presented research will be briefly explained which is followed by discussion and conclusions in Chapter 5 which also includes a discussion on future work. In Chapter 4, a summary of the five following publications, on which the dissertation is based, will be given:

I Kristinn Gudnason, Svetlana Solodova, Anna Vilardell, Mar Masson, Sven Sigurdsson, Fjola Jonsdottir, 2017. Numerical simulation of Franz diffusion experiment: Application to drug loaded soft contact lenses. Journal of Drug Delivery Science and Technology.
doi: 10.1016/j.jddst.2016.12.011

II Kristinn Gudnason, Sven Sigurdsson, Bergthora S. Snorradottir, Mar Masson, Fjola Jonsdottir, 2018. A numerical framework for drug transport in a multi-layer system with discontinuous interlayer condition. Mathematical Biosciences
doi: 10.1016/j.mbs.2017.10.012

III Kristinn Gudnason, Sven Sigurdsson, Fjola Jonsdottir, 2018. A Numerical Framework for Diffusive Transport in Rotational Symmetric Systems with Discontinuous Interlayer Conditions. IFAC-PapersOnLine.
doi: 10.1016/j.ifacol.2018.03.109

IV Kristinn Gudnason, Sven Sigurdsson, Fjola Jonsdottir, A. J. Guiomar, A. P. Vieira, P. Alves, P. Coimbra, M. H. Gil, 2018. Modelling the Release of Moxifloxacin from Plasma Grafted Intraocular Lenses with Rotational Symmetric Numerical Framework. International Conference on Bioinformatics and Biomedical Engineering.
doi: 10.1007/978-3-319-78723-7_28

V Kristinn Gudnason, Sven Sigurdsson, Fjola Jonsdottir, 2021. Multi-region finite element modelling of drug release from hydrogel based ophthalmic lenses Mathematical Biosciences.
doi: 10.1016/j.mbs.2020.108497

2 Transport processes in drug delivery devices

Several interplaying mechanisms are going on during drug release and need to be understood for the design of effective drug delivery devices. In this chapter, an overview is given of different processes at play during drug transport from drug delivery devices presented in this thesis. Effects contributing to solute diffusion are described, followed by a characterization of partitioning. Then, the nature of mass transfer between adjacent phases is laid out. First, a brief outline of the physiological obstacles faced by drug delivery is given for the cases of transdermal and ocular delivery.

2.1 Physiological obstacles

To elicit its pharmacological and therapeutic effects, a drug has to cross various cellular barriers by passive or transporter-mediated uptake. Membrane permeability is a key determinant in pharmacokinetic behavior determining absorption, distribution, metabolism and excretion (ADME) [1]. Release from drug delivery devices must be tailored to the presented physiological obstacles for it to be effective.

Eye

The eye is composed of two regions, the anterior and the posterior segments; see Figure 2.2. The anterior segment, situated at the front, contains the cornea, iris, ciliary body, and lens. The cornea is the transparent outer layer of the eye and consists of three sublayers, the epithelium, stroma, and the endothelium. Ocular drug delivery presents a challenge due to the

presence of various anatomic and physiologic barriers. Inimitable static and dynamic ocular barriers not only exclude the entry of xenobiotics but also discourage the active absorption of therapeutic agents [50] which results in a short duration of therapeutic effect in target tissues [51]. The application of intraocular lenses as drug delivery devices for the sustained release of antibiotics and anti-inflammatories to prevent endophthalmitis has been the focus of recent studies [14–21].

Obstacles to topical administration of eye drops, include blinking, lacrimation, flow through the nasolacrimal duct, rapid absorption into the bloodstream as well as poor corneal penetration lead to low bioavailability. Less than 5% of the drug administered through eye drops enters the eye [52], making it hard to reach therapeutic levels. Intracameral antibiotic administration, which bypasses these obstacles, places higher concentrations at the target site than topical administration [53]. Fluorescence profiles, pictured in Figure 2.1, show distinct discontinuities in concentration at the boundaries between epithelium, stroma and endothelium, highlighting the need to accurately account for individual properties of the cornea sublayer and the adequacy of modelling the cornea as three layers [47, 54].

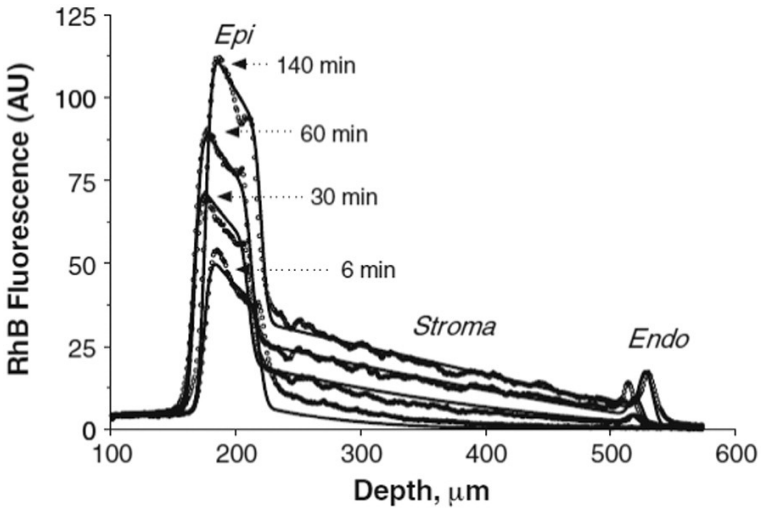

Figure 2.1. Time evolution of concentration profiles of rhodamine versus along the depth through a rabbit cornea [47]. Due to the high lipophilicity of rhodamine, there is a gradual accumulation of in the epithelium and endothelium lipid sub-layers.

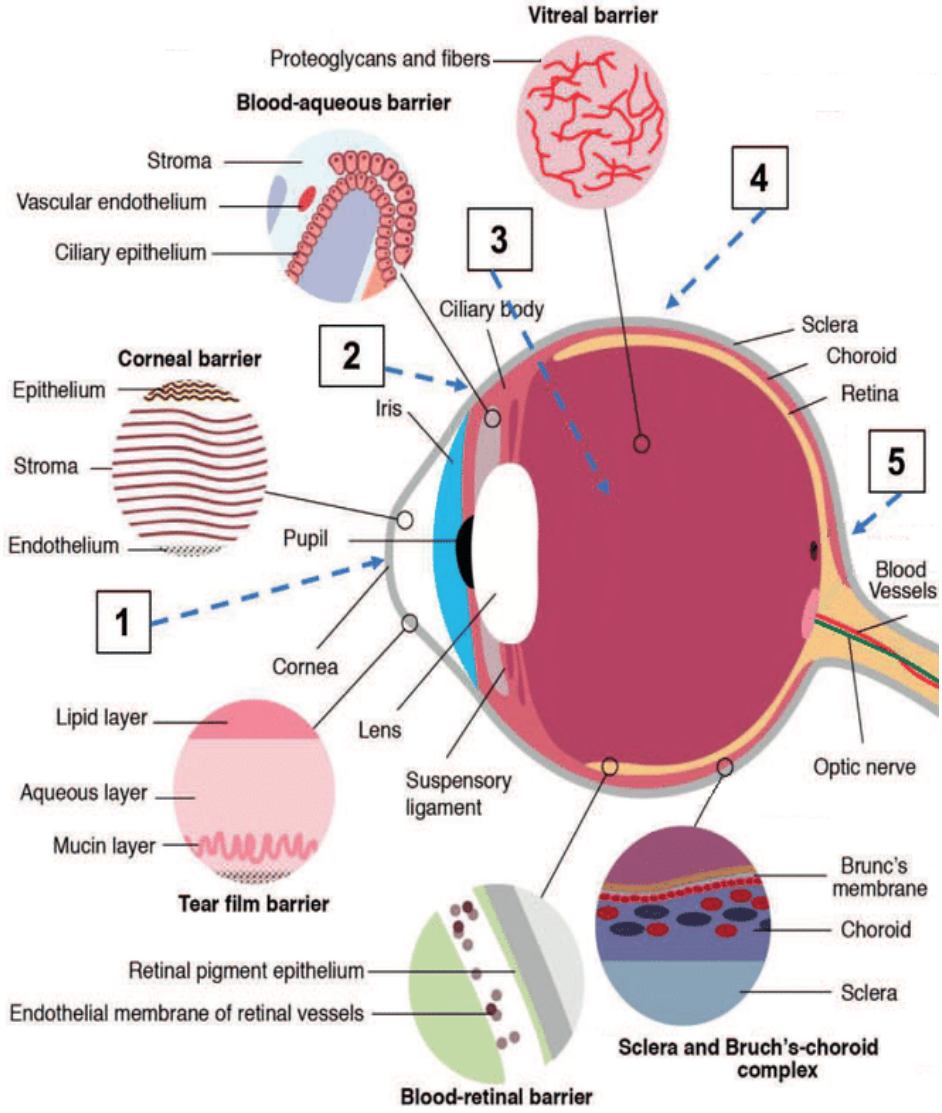

Figure 2.2. A cross section of the eye, adapted from [55], showing barriers and possible numbered routes for different routes of ocular drug delivery, which are as follows: 1) topical, 2) subconjunctival/subtenon, 3) intravitreal, 4) peribulbar, 5) retrobulbar.

Skin

The transdermal route has some advantages for systemic drug delivery. These include the ease of use (and withdrawal in the advent of side-effects), improved patient compliance and avoidance of first-pass metabolism preventing gastrointestinal degradation [56]. However the transdermal permeation rate of most drugs is limited by the stratum corneum [57].

The primary transport pathway for most drugs passively traversing the stratum corneum is the intercellular lipid region [1]; see Figure 2.3. While small and lipophilic drugs have been successfully delivered using transdermal delivery systems, this approach fails to deliver therapeutic macromolecules due to size-limited transport across the stratum corneum, the outermost layer of the epidermis. The low permeability of the stratum corneum to water-soluble drugs as well as macromolecules poses important challenges to transdermal administration [58].

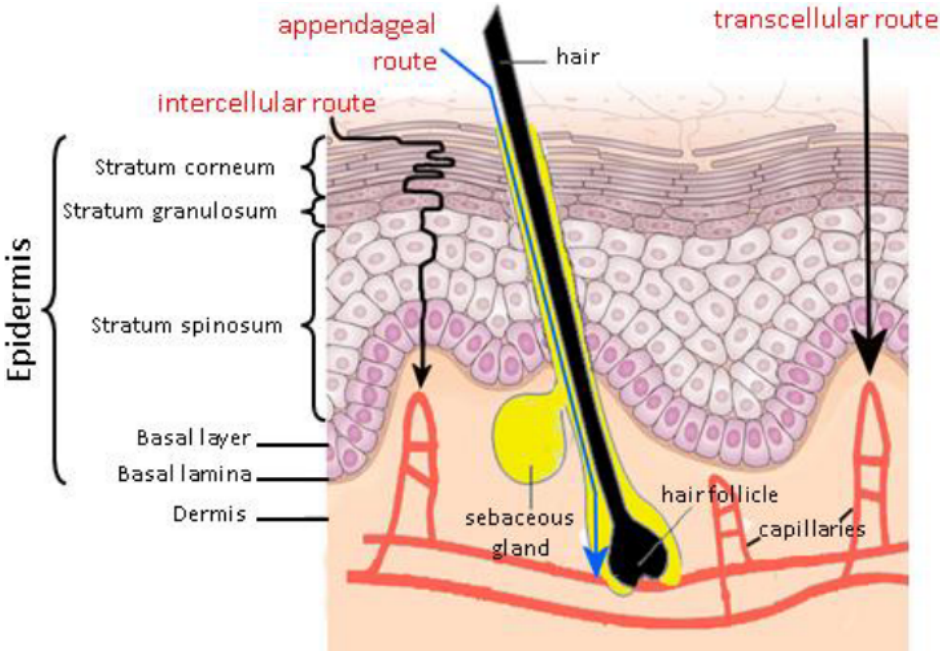

Figure 2.3. A cross section of the outer most layer of the skin, the epidermis, showing the sublayer cell structure as well as possible routes of absorption, presented in [59].

2.2 Hydrogels

A hydrogel can be described as a three-dimensional cross-linked polymeric chain mesh network that readily absorbs and holds water in spaces between the chains [60–62]. Recent studies show the potential of hydrogel based ophthalmic lenses as a viable platform for the controlled release ophthalmic drug delivery [18–20, 63].

Drug solute transport occurs within the aqueous volume and is characterized by diffusion [64, 65] and can be expressed as a product of a hydrodynamic-resistance factor and a steric or obstruction factor [66]. Additionally, solute-polymer interactions affect aqueous volume transport as well as hydrogel equilibrium partitioning. This was demonstrated by Dursch *et. al.* [67], by varying hydrogel compositions of 2-hydroxyethylmethacrylate (HEMA) and 2-acrylamido-2-methylpropane sulfonic acid (AMPS), see in Figure 2.4.

For copolymer hydrogels, varying polymer composition can modify the degree to which solute-polymer interactions affect release [67, 68]. Copolymerization of monomers containing ionic or hydrophobic groups has been shown to increase in hydrogel drug loading capacity and release time [69]. Additionally, surface modifications and coatings have been applied to further increase the release times [70–72]. Lenses loaded with vitamin E were found to increase tortuosity thereby prolonging the release duration of both hydrophobic and hydrophilic drugs [73–75].

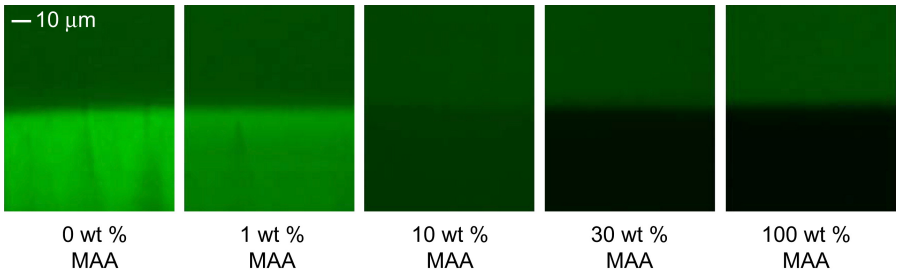

Figure 2.4. Images of five copolymer hydrogels with differing proportions of HEMA and MAA equilibrated with sodium fluorescein aqueous solution, results from [67]. Top half of the images show equilibrated solutions whereas the bottom half show concentration in hydrogels exhibiting the different partition coefficients.

2.3 Diffusion

One of the most important modes of transport through local tissue and within delivery devices alike is diffusion [26]. Diffusive transfer is driven by differences in chemical potential which, for dilute solutions, can be reasonably approximated by molar concentration [76]. Mass transfer occurs as a result of a concentration difference as described by Fick's law, which relates the diffusive flux to the gradient of the concentration [77, 78], i.e. from regions of higher concentration to regions of lower concentration.

Diffusional mass transport is almost always involved in the control of drug release out of a drug delivery systems [32, 33]. In vitro experiments are commonly carried out to infer the diffusion coefficient [79], giving insight into permeation of biological barriers [47, 80] or the release from potential drug carriers [68]. In addition to passive diffusional para- and trans-cellular processes, biological membrane permeation can also be affected by carrier-mediated transport [81].

In the context of solute transport, the main feature of hydrogels, which numerous applications capitalize upon, is the ability of the hydrogel to restrict the diffusive movement [82]. Solute transport as characterized by diffusion within a hydrogel occurs within the aqueous volume [64, 65] and may be hindered by specific adsorption to polymer chains [66]. In a formulation first attributed to Brady [83], the relative diffusivity of the hydrogel and bulk diffusion can be expressed as a product of a hydrodynamic-resistance factor and a steric or obstruction factor [66].

2.4 Partitioning

The partition coefficient is defined as the ratio of concentrations at equilibrium of a solute distributed between two immiscible phases [84, 85]. As such, it dictates the equilibrium state which a solute concentration distribution tends to. In some cases, analytical expressions of the partition coefficient can be derived from chemical potential equilibrium considerations based on thermodynamic relations [67, 86]. It can also be applied as a measure of the difference in solubility of the solute in these two phases [87–89]. For nonlinear reaction-diffusion systems it may depend on concentration [90, 91] however a constant partition coefficient can be assumed for dilute solutes [67] or when saturable binding does not occur on a timescale much quicker than diffusion [92]. A related concept, the distribution coefficient, also takes the equilibrium of ionized compounds into account and is ph-

dependent [93]. The octanol-water partition coefficient is widely used in pharmacology as a measure of the lipophilicity [93], or the conversely related hydrophilicity, of a solute which predicts protein binding, metabolism, and absorption [94, 95]. For cell membrane permeability, octanol-water partitioning indicates whether a solute permeates cellular barriers via the paracellular or transcellular routes [94].

Solubilities of aqueous solutes in hydrogels determine their effectiveness as drug delivery vehicles [67]. A hydrogel partition coefficient can be defined as the ratio of the drug concentration in the gel and the surrounding aqueous phase concentration at equilibrium [67, 96]. Various solute-polymer interactions dictate the solubilities of aqueous solutes in hydrogels [67]. More specifically, specific adsorption, nonspecific electrostatic and size exclusion effects have been shown to enhance, or decrease, the hydrogel partition coefficient [35, 66–68, 97].

2.5 Interface mass transfer

All applications of drug delivery devices require careful consideration of mass transfer between the adjacent phases involved. Diffusive mass transfer between two adjacent phases can be defined by interface resistance and a driving force [98, 99]. The driving force is induced by a difference in solute concentration between the adjacent phases which deviates from equilibrium, partitioning consequently plays a major role in its characterization.

In vitro membrane diffusional permeability experiments typically include a stirred bulk aqueous release phase where solute accumulation is measured. Despite stirring, a stagnant unstirred water layer (UWL) may form at the membrane interface that acts as an additional rate-limiting diffusion barrier [100]. In particular for lipophilic permeants which experience significant diffusive resistance in aqueous layers, this can lead to erroneously low permeation [101]. To determine the true permeability of the membrane, the contribution of the UWL to the observed permeability has to be considered [102].

The relative contribution of these barriers to drug disposition may vary significantly between different experimental setups [103]. Commonly applied when estimating diffusion, sink boundary conditions approximate the receptor to be empty of solute. However this represents the fastest release condition with the highest possible driving force and, for this reason, it is not consistent with the physiological conditions [104].

Franz cell permeation studies are often conducted on membranes having higher permeability than intact human skin, rodent skin, tape-stripped skin or skin treated with chemical or physical permeation enhancers. In such cases it is wise to consider the possible impact of the unstirred layer on the results [101].

2.6 Dissolution

For drug delivery systems containing solid drug, dissolution describes the transition from solid to aqueous phase. The main driver of the dissolution of drug in a solid state is via thermal agitation by surrounding solvent molecules [105, 106]. The drug dissolution rate encompasses a series of processes, one of which may be rate-limiting, meaning more rapid processes may be safely neglected for the quantification of the overall rate [105]. These steps include surface wetting, breakdown of solid state bonds, solvation, diffusion across the surrounding liquid unstirred boundary layer, and eventually, convection within the well-stirred bulk fluid. Various mechanistic and semi-empirical models exist, emphasizing different steps.

Emphasising the effects of the liquid, unstirred boundary layer, Noyes and Whitney regarded the dissolution phenomenon to be controlled by diffusion [107]. Applying Ficks first law, the dissolution rate was considered to be a factor of the concentration difference across the layer and a constant, depending on available surface area and bulk diffusion coefficient. The concentration profile across the layer was thus described by a linear approximation depending on the bulk concentration and the concentration at the dissolving surface, equal to the drug's solubility. Nernst and Brunner [108, 109] expanded this approach, and further characterized the constant factor in terms of the layer thickness, also noting that the convection becomes more important with increasing distance from the dissolving surface. This approach was adapted by Hixson and Crowell [110] to develop a cube-root law, emphasizing the changing surface of the dissolving solid but assuming solid to be non disintegrating and spherical. Additionally, it is assumed that the dissolved solute in the bulk does not change with time. Dissolution and release from a planar matrix systems was carried out using these principles by Frenning [111]. For inert matrix systems, it was found that if drug loading exceeded drug solubility in the matrix, Higuchi-type moving-boundary descriptions [112] tend to be useful for obtaining approximate analytical solutions [113].

2.7 Binding

In the case of ocular drug delivery, diffusion coupled with binding kinetics, play a role in describing the heterogeneous transport across the cornea. Slow accumulation of lipohilic solute within epithelium and endothelium sublayers was accounted for by modelling transport through the cytoplasm to putative intracellular lipophilic domains as reversible non-saturable linear binding [47]. The intracellular binding represented a partitioning process and is characterized by a net driving force, given by the equilibrium weighted difference of bilayer and intracellular concentrations, as well as a rate constant. For the stroma, binding-unbinding reactions to collagen fibrils and glycosaminoglycans occur at a faster time scale compared to that of diffusion and so sublayer transport was approximated by effective diffusivity for both lipophilic and hydrophilic solutes [47, 48, 54].

As mentioned above, solute diffusion within hydrogel may be hindered by specific adsorption to polymer chains [66] and can partly account for partitioning [67]. Increased capacity can in some cases be engineered by altering adsorption properties through the crosslinking process [114].

3 Methods

This chapter gives an overview of the methodology applied in the research presented in this thesis. In 3.1, the various experimental setups modelled in this thesis are described. In 3.2, the mathematical equations required to model drug transport systems are presented.

3.1 Experiments

In publications of this thesis, models of experiments are constructed to reflect underlying transport mechanisms. To demonstrate the developed numerical approach, model simulations are compared to experiment data to deduce physical parameter values. Data is gathered from drug release studies where samples are extracted from a release medium to determine the concentration through either high-performance liquid chromatography or UV-visible spectrophotometry. The time ordered collection of such measurements form a release curve, which model simulations can be compared against. Extracted samples are replaced with fresh phosphate buffered saline (PBS) to maintain the receptor volume. This has the side-effect of proportionally diluting the receptor of drug solute. For receptor volume V_r by and sample volume V_s, solute concentration would drop proportionally by V_s/V_r. A stirbar induces dispersion of the drug throughout the release medium with the aim of ensuring uniformly distributed concentration [115], which is vital for consistent sampling [80].

Franz-diffusion cell

In its conventional setup, the Franz-diffusion cell (FDC) contains a membrane to be studied, held in place between a donor chamber and a receptor chamber. Initially, a solution containing dissolved drug is loaded into the donor and pure PBS is loaded into the receptor. Drug permeates the membrane and into the receptor where samples are extracted via sampling port. Both a conventional FDC donor loaded setup as well as a pre-loaded setup were considered in publication I to investigate the delivery properties of hydrogel Etaficon A, a material used in soft contact lenses, with diclofenac. In the pre-loaded setup, the donor chamber is replaced by a plexiglass plate and the membrane is soaked in drug solution before insertion onto the cell. In publication II the conventional setup was applied, both to study the properties of moxifloxacin with the IOL material CI26Y, as well as ibuprofen, with skin in conjunction with a silicone matrix skin setup in publication II, extending results presented in Snorradottir *et al.* [116]. The silicone matrix skin setup is similar to the pre-loaded setup in that the drug emitting donor chamber is replaced by other means. The various setups are depicted in Figure 3.1. The release curves generated by the conventional FDC donor loaded setup typically follow a characteristic S shaped curve with 3 distinct stages. A flat lag stage which gives way to slow growth as concentration levels rise within the membrane. Once a steady state is reached, the release curve has attained its maximum slope and very gradually tapers off, approaching a flat ceiling, as it approaches equilibrium.

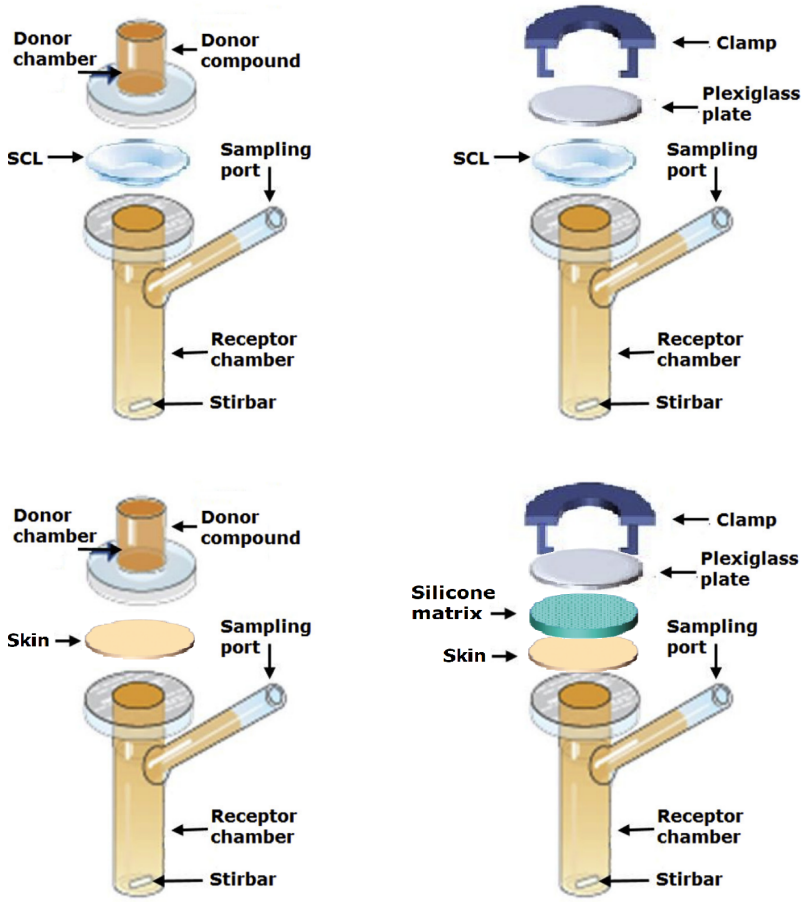

Figure 3.1. Top: Franz Diffusion cell experiments as presented in publication I. Bottom: Transdermal Franz-diffusion experiments. Top left: Conventional donor-loaded setup. Top right: Pre-loaded setup. Bottom right: Conventional donor-loaded setup with skin. Bottom left: Silicone matrix skin setup.

Load and release

Load and release studies were conducted to study the release properties of intraocular lens hydrogel material. This was done by soaking the material in drug solution before immersion into fresh PBS solution, where samples were taken over time. Contrasted with the one dimensional nature of the Franz-diffusion cell, solute can pass through multiple sides, emphasizing the need to accurately account for geometry. Publication IV considers the release of moxifloxacin from intraocular lens, which had been plasma-grafted with polyacrylate coating to act as resistance barriers for drug release. Two types of polyacrylates were considered along with an unmodified lens resulting in differing release profiles, attributed to the varying resistance. Publication V revisits the release study conducted in publication IV and considers drug loading and release from disc shaped intraocular lens material, as presented in [117]. The disc studies were carried out with different loading times and different temperatures during load and release stages. Increased drug loading duration generally increased both the rate and the amount of drug released, indicating that for lower durations, loading equilibrium had not been achieved. A schematic depiction of loading and release can be seen in Figure 3.2.

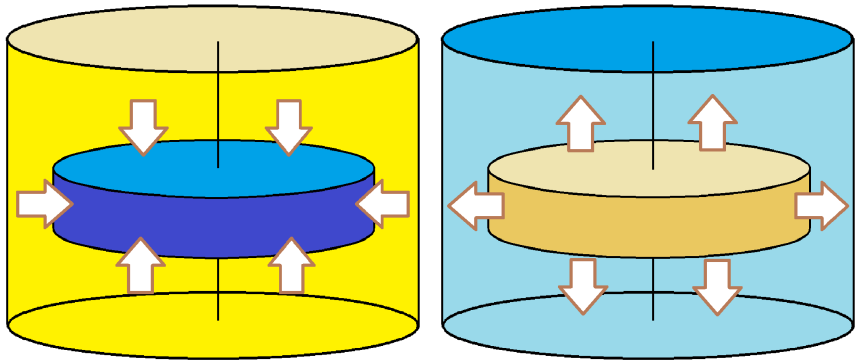

Figure 3.2. A schematic depiction of disc shaped material immersed in drug solution during loading (left) before being put into fresh PBS (right) to measure release.

3.2 Mathematical model

Here, the mathematical equations encapsulating the mechanisms considered in this thesis are introduced. Appropriate equations are chosen to model different parts of a drug transport system which together comprise a system of partial differential equations (PDEs). A more detailed account of these equations is given in publications II-V, along with derivations of the finite element numerical framework and discussion of it properties.

Solute transport in hydrogels

Expressed as Fick's second law, diffusion often takes the primary role during drug release [32]. Extending Fick's second law to account for adsorption, the following modified equation has been applied as the basis for solute hydrogel transport [35, 66, 68]

$$\varphi_1 \frac{\partial C_{aq}}{\partial t} + \sum_j \varphi_{2,j} \frac{\partial C_{ad,j}}{\partial t} = \varphi_1 \, \nabla \cdot (D \, \nabla C_{aq}) \tag{3.1}$$

where D is the hydrogel diffusion coefficient, accounting for hydrodynamic and steric factors, C_{aq} and φ_1 are aqueous solute concentration and volume fraction, respectively, and $C_{ad,j}$ and $\varphi_{2,j}$ are adsorbed solute concentration and volume fraction of polymer component j. The total adsorbed solute concentration is given by $\varphi_2 = \sum_j \varphi_{2,j}$, which sums to one with φ_1. Note that (3.1) reduces to Fick's second law

$$\frac{\partial C_{gel}}{\partial t} = \nabla \cdot (D_{gel} \, \nabla C_{gel}), \qquad D_{gel} = \frac{D}{1 + \sum_j H_j \varphi_{2,j} / \varphi_1} \tag{3.2}$$

by considering the combined gel concentration of solute in aqueous and different adsorbed phases, C_{gel}, and assuming linear adsorption as defined by Henry's law

$$C_{gel} = \varphi_1 \, C_{aq} + \sum_j \varphi_{2,j} \, C_{ad,j}, \qquad C_{ad,j} = H_j \, C_{aq}, \quad \forall j \tag{3.3}$$

respectively. Here H_j is the solute adsorption constant for polymer component j. D_{gel} is often referred to as effective diffusion [35, 66, 68] and accounts for the slowing of adsorption in addition to hydrodynamic and steric factors. By considering the aqueous solute phase concentration C_{aq} as the primary variable, adsorption effects can be incorporated through the application of a specific storage coefficient γ. This leads to an alternative

transport model within hydrogels derived from (3.1)

$$\gamma \frac{\partial C_{aq}}{\partial t} = \nabla \cdot (D \nabla C_{aq}), \qquad \gamma = 1 + \sum_j H_j \varphi_{2,j} / \varphi_1 \tag{3.4}$$

Dissolution

In order to model the drug release from solid form, Noyes-Whitney's equation can be applied to describe dissolution

$$\begin{aligned} \frac{\partial C_\alpha(x,t)}{\partial t} &= \frac{\partial}{\partial x}\left(D_\alpha \frac{\partial C_\alpha(x,t)}{\partial x}\right) - A_{0,\alpha} k_\alpha \left(\frac{S_\alpha(x,t)}{S_\alpha(x,0)}\right)^{2/3} (c_{s,\alpha} - C_\alpha(x,t)) \\ \frac{\partial S_\alpha(x,t)}{\partial t} &= -A_{0,\alpha} k_\alpha \left(\frac{S_\alpha(x,t)}{S_\alpha(x,0)}\right)^{2/3} (c_{s,\alpha} - C_\alpha(x,t)) \end{aligned} \tag{3.5}$$

where $k_{d,\alpha}$ is the dissolution rate coefficient of solid drug $(\mathrm{cm/h})$, $c_{s,\alpha}$ is the solubility of the drug $(\mathrm{mg/cm^3})$, $A_{0,\alpha}$ is the initial surface area of the solid drug per unit volume $(\mathrm{cm^2/cm^3})$, where the drug particles are assumed implicitly by the model to retain their shape as the drug dissolves such that the surface area is proportional to the volume to the power of $2/3$ [118]. Initial concentrations of bound drug $S_\alpha(x,0)$ and unbound drug $C_\alpha(x,0)$ must be specified in each layer.

Two phases

The binding and unbinding process can be in the form of a two-phase equation

$$\begin{aligned} \frac{\partial C_\alpha(x,t)}{\partial t} &= \frac{\partial}{\partial x}\left(D_\alpha \frac{\partial C_\alpha(x,t)}{\partial x}\right) - k_1 S_\alpha(x,t) + k_2 C_\alpha(x,t) \\ \frac{\partial S_\alpha(x,t)}{\partial t} &= -k_1 S_\alpha(x,t) + k_2 C_\alpha(x,t) \end{aligned} \tag{3.6}$$

where k_1 and k_2 are unbinding and binding rate coefficients $(1/\mathrm{h})$, respectively. In some applications it is appropriate to assume a conservation condition for binding by replacing the k_2 coefficient with $k_2'(S_{max,\alpha} - S_\alpha(x,t))$, where $S_{max,\alpha}$ denotes the density of binding sites [46]. In this case the model is non-linear and the present finite element method has to be modified by linearizing the equation in an appropriate way.

Interface mass transfer

The flux between adjacent phases, i and j, can be expressed as a product of a mass transfer coefficient K_{ij} and a driving force $\triangle C_{ij}$ [99]

$$N_{ij} = K_{ij} \triangle C_{ij} \tag{3.7}$$

Here, $1/K_{ij}$ can be understood to be the sum of weighted resistances of either side of the interface, representing the overall resistance to mass transfer. For an equilibrium partition coefficient P_{ij}, the driving force is induced by a difference in concentration, which deviates from equilibrium

$$\triangle C = C_i - P_{ij}\, C_j \tag{3.8}$$

With the addition of flux continuity, interface conditions can then be stated as

$$-D_i(\nabla C_i \cdot \mathbf{n}) = D_j(\nabla C_j \cdot \mathbf{n}) = K_{ij}(C_i - P_{ij}C_j) \tag{3.9}$$

where the unit normal vector $\mathbf{n}$ is considered to be on the boundary pointing outwards of its respective domain. Partition conditions can be achieved by setting K_{ij} high and continuity across an interface is achieved by setting K_{ij} high and $P_{ij} = 1$.

The effect of partitioning and mass transfer resistance manifest itself as discontinuities in concentration across interfaces. To demonstrate these effects, the time evolution concentration profiles across membranes are presented in Figure 3.3 with different boundary properties during loading (left) as well as release (right). The boundary was simulated using (3.9) for 3 different pairs of K and P values, chosen to show the effects of (A) continuity, (B) partitioning, and (C) mixed partitioning and interface mass transfer resistance. Membrane transport was simulated by diffusion (3.4), with the same D value chosen for all cases. Analogous to the experiment shown in 3.2 (neglecting the curved surface), the membrane is surrounded by bulk. In the load cases, membranes accumulate solute from a non-zero initial bulk concentration. The same homogeneous concentration distribution is assumed across the membranes for the release cases which diffuses and gradually accumulates in the bulk. Note the effect of resistance in case (C), where concentration changes close the boundary are more dampened when compared to the other cases.

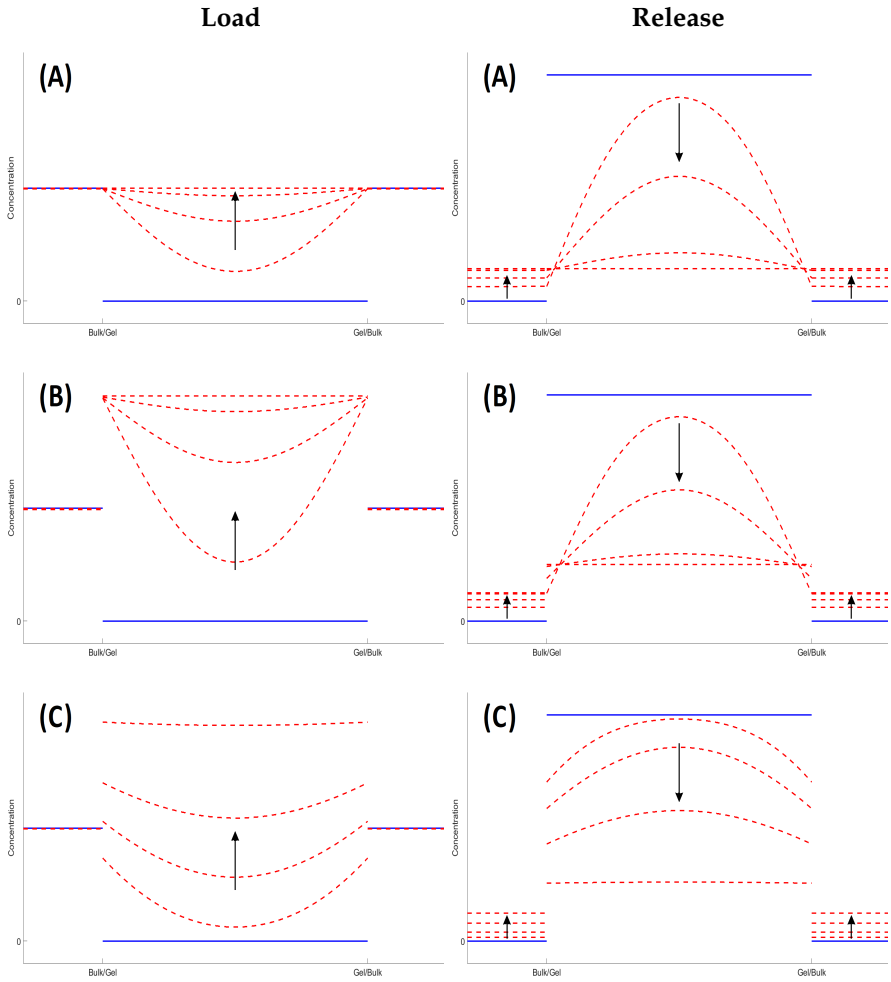

Figure 3.3. Solute concentration profiles within a membrane with fixed diffusion value surrounded by faster diffusing bulk medium on both sides, showing loading (left column) and release (right column). Interface conditions are varied to show the effects of concentration (A) continuity in the top row, (B) partitioning in middle row and (C) partitioning and interface mass transfer resistance effects bottom row. Initial concentration is shown in blue and subsequent profiles are shown in dashed red curves with black arrows indicating time evolution.

Finite element formulation

In order to construct models of drug delivery systems, a finite element numerical formulation, incorporating mechanisms presented above, was developed. Systems are broken down into subregions over which different mechanisms are prescribed to reflect the local transport characteristics. Initially, the finite element scheme is constructed separately on discretized subregions with arbitrary flux conditions at each boundary. Equations over all subregions are subsequently assembled into a global system that ensures continuous flux between subregions while at the same time satisfying the interface mass transfer conditions presented above. The resulting time dependant ordinary differential equation can then be solved using numerical integration.

A one dimensional multi-layer approach is demonstrated in publication I with the modelling of Franz-diffusion experiments. The one dimensional approach is further developed and presented in publication II. In publication III, the approach is extended to a three-dimensional rotational symmetric setting making it possible to model more complex geometries, e.g. general three-dimensional lens geometries. In paper IV, drug release from the optical lens component of an intraocular lens, as depicted in Figure 3.4 is modelled. In paper V, it is shown that the global system is similar to a symmetric negative semidefinite system, ensuring the validity of the finite element formulation. Additionally, a load and release model from disc shaped material as well as an expansion of the intraocular lens release model including haptics is presented.

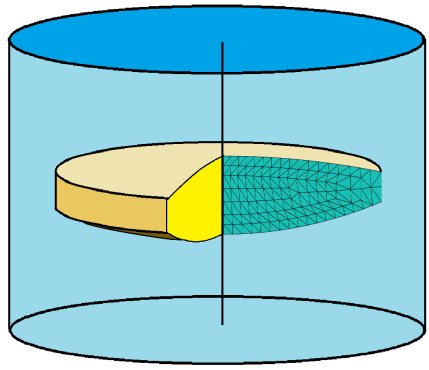

Figure 3.4. Cross-section and discretization of the optical lens component of an intraocular lens.

4 Summary of publications

A summary of the publications which this thesis is based on is given, preceded by a statement on the candidates contribution.

Candidates contribution

The candidate is the main contributor to the research of this thesis and production of the presented publications. The experiments were carried out by co-authors, but discussed and analyzed jointly.

4.1 Publication I - Numerical simulation of Franz diffusion experiment: Application to drug loaded soft contact lenses

Kristinn Gudnason, Svetlana Solodova, Anna Vilardell, Mar Masson, Sven Sigurdsson, and Fjola Jonsdottir. (2017), *Journal of Drug Delivery Science and Technology*, **38**, 18-27.

This publication describes the modelling of diclofenac solute permeation experiments of diclofenac through etafilcon A hydrogel in the form of soft contact lenses (SCLs). Two configurations of Franz diffusion cell experiments were set up to study release profiles in the receptor chamber. In the donor-loaded case, the donor compartment was initially loaded diclofenac solution. In the pre-loaded case, the donor compartment is discarded and SCLs were set on top of the release compartment after a being soaked in drug solution. Both configurations were carried out under different temperatures and varying initial drug loading concentrations. Specifically designed mathematical models of the experiment were developed from a general multi-layer finite element model, accounting for the effects of diffusion, interface mass transfer resistance and partitioning between hydrogel and bulk solution. A study of the model parameters was carried out to give insight into the influence different mechanisms have on the drug release. It was found that partitioning played a large role in explaining release curve data while the large value chosen for mass tranfer indicated little resistance to interface penetration.

4.2 Publication II - A numerical framework for drug transport in a multi-layer system with discontinuous interlayer condition

Kristinn Gudnason, Sven Sigurdsson, Bergthora S. Snorradottir, Mar Masson, and Fjola Jonsdottir. (2018), *Mathematical biosciences*, **295**, 11-23.

A multi-layer finite element framework is laid out for the modelling of drug delivery systems. The framework accounts for solute partitioning and resistance between material layers as well as diffusion, two phase reversible binding and dissolution within layers. A detailed account is given into the finite element scheme following a two step construction. Specific models are constructed to demonstrate the capabilities of the framework. A FDC experiment model simulating moxifloxacin permeation through the intraocular lens material CI26Y composed of 2-hydroxyethyl methacrylate and methylmethacrylate with experiments carried out on three different thicknesses of the material. A two-layer two phase transdermal drug delivery model is reproduced to compare against results obtained with a semi-analytical approach. Dual FDC experiment models simulating ibuprofen permeation through skin involving different donor setups. One with solid ibuprofen dissolving within an impregnated silicone matrix and one with a standard donor chamber containing ibuprofen solution. Good agreement with experiments was achieved applying the same parameter values, for all thicknesses of the CI26Y material and for the different donor setups of the skin permeation experiments, respectively. Results of the transdermal drug delivery model agree with the the referenced semi-analytical approach, validating the presented numerical framework.

4.3 Publication III - A numerical framework for diffusive transport in rotational symmetric systems with discontinous interlayer conditions

Kristinn Gudnason, Sven Sigurdsson, and Fjola Jonsdottir. (2018), *IFAC-PapersOnLine*, **51**(2), 643-648.

A rotational symmetric finite element approach is presented, extending the the multi-layer framework developed in publication II. The approach is demonstrated with a the biconvex lens system using parameter values deduced in previous publications.

4.4 Publication IV - Modelling the release of moxioxacin from plasma grafted IOLs

Kristinn Gudnason, Sven Sigurdsson, Fjola Jonsdottir, A. J. Guiomar, A. P. Vieira, Patrícia Alves, Patrícia Coimbra, and M. H. Gil. (2018), *Bioinformatics and Biomedical Engineering. IWBBIO 2018. Lecture Notes in Computer Science*, **10813**, 329-339.

The rotational symmetric finite element approach is applied to model the release of moxifloxacin from different types of plasma-grafted intraocular lenses. The shape of the optical part of the intraocular lens is fully taken into account. Two types of polyacrylates were plasma-grafted to the intraocular lens to act as barriers for release, accounted for with different values of mass tranfer coefficient.

4.5 Publication V - Multi-region finite element modelling of drug release from hydrogel based ophthalmic lenses

Kristinn Gudnason, Sven Sigurdsson, and Fjola Jonsdottir. (2021), *Mathematical Biosciences*, **331**, 108497.

A Galerkin finite element framework for solute transport in hydrogels is presented. It accounts for diffusion within the gel, storage effects due to polymersolute interaction, as well as partitioning and mass transfer resistance effects at the interface. While the derived global system is not symmetric in the case of partitioning, it is similar to a symmetric negative semidefinite system, ensuring the validity of the finite element formulation as well as the numerical stability of the implicit backward Euler time integration method employed. A rotational symmetric approach is adopted to account for realistic geometry. The theoretical basis is given for hydrogel-bulk partitioning, effective diffusion and specific storage in terms of solute-polymer interactions. Likewise, it is shown how surface modifications, coatings and unstirred diffusion boundary layers may be formulated as resistance to mass transfer across the hydrogel interface. Two specific hydrogel models are presented and verified with release experimental data. The first is the release of moxifloxacin from intraocular lenses (IOLs) plasma grafted with different polyacrylates. The second accounts for both loading as well as the release of diclofenac from disc shaped IOL material loaded for varied time periods and different temperatures during loading and release.

5 Discussion and Conclusions

A Galerkin finite element numerical method was developed for solving mathematical models, based on partial differential equations describing solute transport, for the purpose of modelling release from drug delivery devices. Modelled devices include hydrogel based intraocular and soft-contact lenses as well as a silicone matrix transdermal system. In regards to research question 1, the combined effects of different drug solute mechanisms affecting transport were composed into a mathematical multi-compartmental model. The effects of solute diffusion, dissolution and binding were included to describe transport within compartments whereas mass transfer resistance and partitioning dictate solute flux between adjacent phases at compartment interfaces. Particular emphasis was put on the use of interface conditions which give rise to discontinuities, which prove difficult for conventional solution methods, which employ instead perfect sink conditions [32]. The importance of interface conditions was further highlighted as a key characteristic of many drug transport systems which often goes overlooked or misinterpreted by recent studies [43, 44].

Regarding research question 2, the presented finite element formulation was derived from the equivalent weak form of the proposed mathematical model in publication II. This involved following a two step construction by first applying the finite element scheme separately for each given subregion with arbitrary flux conditions at the outer boundaries of the subregion. Subregion equations are sequentially assembled into a global system such that continuous flux between subregions is ensured. In this latter step, subregion flux is accounted for by a local flow matrix at each interior and exterior

boundary edge into the assembly of a global stiffness matrix. Due to the interface conditions encoded in the local flow matrices, the resultant assembled global stiffness matrix is non-symmetric. It was however, found to be similar to a symmetric positive semidefinite matrix, ensuring non-negative real eigenvalues. Furthermore, it was shown that the associated bilinear form is coercive, confirming the validity of the finite element approach. The approach was initially developed into a one dimensional multi-layer model and later expanded into a three-dimensional multi-compartment rotational symmetric setting in publications III-V, allowing e.g. for general three dimensional lens-geometries to be accurately modelled. The modelling of experiments gave insight into the different mechanisms at work. Using the developed numerical framework, purpose built models were constructed to simulate release curves of different configurations of Franz diffusion cells as well as load and release experiments.

The release of diclofenac from commercial soft contact hydrogel lenses, consisting of Etaficon A, was studied in publication I. Conventional donor-loaded, as well as pre-loaded Franz diffusion cell setups were modelled, incorporating solute diffusivity within the hydrogel, hydrogel-bulk partitioning and interface mass transfer resistance between compartments. Regarding research question 3, physical parameter values were varied to study the release curve of both configurations to understand drug accumulation in release chambers. The characteristic *S* shaped release curve was recreated by model simulations of the donor-loaded setup. The effects of diffusion and interface mass transfer resistance were found to be hard to disentagle. Simulations were compared to data to deduce possible release mechanisms. Donor-loaded experiments were found to be more consistent than the pre-loaded, as the same set of estimated parameters could consistently explain varied initial concentrations. Experiments carried out at a higher temperature could be explained by an increase in solute diffusivity. Instead of applying a corrective procedure, which can mischaracterize solute accumulation in the receptors, sample extraction was incorporated explicitly and found to explain drops in the release curve.

The conventional donor-loaded model was also used to study the release of moxifloxacin from different thicknesses of the intraocular lens material CI26Y in publication II. Good agreement with experiments was achieved applying the same parameter values to all thicknesses. This proved difficult without the combined effects of the partitioning and mass transfer parameters. Low mass transfer parameter value obtained indicates high interface resistance and explains the total lack of drug penetration for the

thickest lens. Previously modelled FDC configurations involving release from skin with both conventional donor chamber as well as a drug eluting silicone matrix was revisited with updated interface conditions, extending results presented in Snorradottir *et al.* [116]. The Noyes-Whitney equation was employed to model dissolution of solid drug in the silicone matrix as a secondary state. The added mass transfer parameter in the updated model reflects the natural drug resistance of the skin sublayers and allowed for a significantly better fit for the donor-skin system and a similar fit for the matrix skin system. A two-layer transdermal drug delivery model was constructed to compare against a semi-analytical approach as presented in Pontrelli and de Monte [119]. Along with solute diffusion, a secondary state two-phase equation was employed to simulate binding dynamics of drug delivery device and skin layers. A mass transfer equation was employed both to simulate solute transfer between layers as well as at the outer skin boundary. A good agreement was achieved using the same physical parameter values, verifying the presented numerical approach. Similarly, a rotational symmetric model, based on the same principles as presented in papers III, IV and V, was constructed for comparison with results from [120]. Both model simulations were in good agreement verifying the rotational symmetric implementation although the results are not published.

In publication IV, a three-dimensional rotational symmetric model was constructed to simulate the release of moxiloxacin from different types of plasma-grafted intraocular lenses in an effort to more accurately assess release characteristics, allowing for the biconvex optical component of the intraocular lens to be fully taken into account. A one dimensional approach would neglect 21% of the total surface area compared to the presented optical lens model. Two types of polyacrylates were plasma-grafted to seperate batches of intraocular lenses to act as barriers for the release of the loaded drug, namely 2-hydroxyethylmethacrylate (HEMA) and 2-acrylamido-2-methylpropane sulfonic acid (AMPS) Plasma-grafted and unmodified lenses were soaked in moxifloxacin solution, sterilized and then stored. The subsequent release process was simulated by assuming that equilibrium had been reached during loading. Mass transfer resistance parameter values were allowed to vary depending on surface modification whereas diffusion and partitioning values were kept the same for all cases. The low deduced mass transfer value of the AMPS system indicates more resistance at the surface than the unmodified IOL system, as opposed to the HEMA system which showed lower resistance. The model was revisited to account for the drug release from the lens haptics, resulting in a better fit. In publications I and II the receptor and donor medium were modelled explicitly with a high dif-

fusion value to enforce mixed concentration throughout bulk fluid. In publications IV and V, the corresponding outer medium was modelled in terms of diffusive flux at the gel-medium boundary, reducing computational load.

Experiments conducted by Topete *et al.* [117], involving the loading and release diclofenac from CI26Y discs at different temperatures, were modelled in publication V. The geometry of the discs was fully captured by rotational symmetry as opposed to a one dimensional analog which would neglect 17% of the total surface area. As was done in the experiments, loading was simulated for 5 different time periods, resulting in different concentration distributions throughout the discs, serving as the initial conditions for subsequent release simulations. Different parameter values were chosen for the release stage to reflect the higher release temperature. A fairly good match was achieved for the three longest loading durations whereas a relatively large difference between the simulated results and experiments for the two shorter time durations remains to be explained.

This work highlights the incorporation of relevant mechanisms into an accurate finite element modelling framework for solute transport, in particular that of interface conditions whereby partitioning and mass transfer resistance can be accurately accounted for. Recent advances in the understanding of drug partitioning in hydrogels have quantified the phenomenon in terms of various polymer-solute interactions [35, 66–68, 97]. Interface transport, as characterized by the product of a mass transfer coefficient and driving force, is thus directly affected by polymer-solute interactions as the driving force is induced by a deviation from equilibrium. Drug release modelling demonstrated the limitations of the often used perfect sink conditions [35, 68] as bulk solute concentration gradually approaches equilibrated levels and modulates interface flux through a decrease in driving force. Perfect sink conditions assume bulk concentration to be negligible [32] and represent the fastest possible release with the highest possible driving force, not consistent with the physiological conditions [104].

The data fitting approach applied in this work relied mainly on trial and error, varying physical parameter values slightly until a fit was achieved. Additionally, a rudimentary gradient based approach was adopted to minimize the mean squared error (MSE) to obtain the single set of parameter values for the three different thicknesses of IOL materials, presented in paper II. An exploration of the MSE for this case indicated a reduced set of viable parameter values due to the difference in lens thickness, although this exploration has yet to be published. A similar point was alluded to in

the parameter analysis of paper I where it was suggested that experiments repeated with a different membrane thickness could help to distinguish between parameter effects.

Dilution of the receptor medium which occurs when a sample is removed and replaced with fresh medium was modelled as a proportional drop in receptor concentration rather than to correct measured release data as is commonly done, see for example [121]. Replacement creates a sudden imbalance in receptor concentration which itself leads to increased release rate which normally goes unaccounted for. While correcting data may be appropriate for some applications, it is unadvisable for data fitting with simulations as this would artificially increase concentration levels which could lead to a bias in deduced physical parameter values.

Future work

To further validate modelling results, additional experiments need to be carried out and modelled, involving the same drug, material and environmental conditions but differing in thickness, initial concentration or experimental setup. A difference in outcomes may expose discrepancies in theory and practice. The effect of hydrogel partitioning on interface driving force can be further investigated by modelling experiments involving hydrogels with polymer components that have varied specific adsorption properties. Specifically, the inclusion of solute polymer adsorption as a storage coefficient with altered interface driving force characteristics warrants further study. Additionally, comparing the applicability of the framework to that of available finite element or finite volume packages could highlight possible discrepancies between different numerical implementations as well as differing approximations of transport phenomena.

For individual release curves multiple sets of parameter values can adequately explain the same experimental data. Insight gained by analysing the model parameter space can be used to make adjustments to experimental conditions that will determine the unique set. An alternative to deducing transport characteristics of drug device materials from release curves, model simulations may be compared directly against measured transient concentration profiles as measured by fluorescence confocal microscopy. This was accomplished by [47, 48, 54] to study rhodamine and fluorescence transport, compounds which differ in lipophilicity, through the different sublayers of the cornea with good results. Fluorescence confocal microscopy was also used to complement back-extraction data of fluorescein and Oregon Green

to estimate equilibrium partition coefficients of hydrogels of varying HEMA and MAA composition [67] and could be further applied to shed light on binding characteristics with the appropriate modelling approach. Furthermore, the developed framework lends itself to to drug transport within a more complex geometry e.g. a cross-section of an eye with rotational symmetry. Presented derivations can be easily extended to more general three-dimensional settings as making the framework applicable to irregular geometries. Furhtermore, models can be expanded to include the cornea and aqueous humor and predict drug dispersion in vivo.

Mechanisms for interface resistance due to unstirred diffusive boundary layers can be further characterized in terms of a Sherwood number, which is proportional to the boundary layer mass transfer coefficient, and relates convective mass transfer with the diffusion rate across the unstirred boundary [122]. The Sherwood number itself can be further defined as a function of the Reynolds and Schmidt numbers, which can help determine mass transfer resistance if these numbers are readily available.

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