Published in final edited form as:

J Control Release. 2014 September 28; 190: 664–673. doi:10.1016/j.jconrel.2014.04.048.

Controlled Release for Local Delivery of Drugs: Barriers and Models

Jennifer R. Weiser^a and W. Mark Saltzman^{a,*}

Jennifer R. Weiser: jennifer.weiser@yale.edu; W. Mark Saltzman: mark.saltzman@yale.edu

^aDepartment of Biomedical Engineering, Yale University, New Haven, Connecticut, 06511, USA

Abstract

Controlled release systems are an effective means for local drug delivery. In local drug delivery, the major goal is to supply therapeutic levels of a drug agent at a physical site in the body for a prolonged period. A second goal is to reduce systemic toxicities, by avoiding the delivery of agents to non-target tissues remote from the site. Understanding the dynamics of drug transport in the vicinity of a local drug delivery device is helpful in achieving both of these goals. Here, we provide an overview of controlled release systems for local delivery and we review mathematical models of drug transport in tissue, which describe the local penetration of drugs into tissue and illustrate the factors—such as diffusion, convection, and elimination—that control drug dispersion and its ultimate fate. This review highlights the important role of controlled release science in development of reliable methods for local delivery, as well as the barriers to accomplishing effective delivery in the brain, blood vessels, mucosal epithelia, and the skin.

Keywords

Controlled release; pharmacokinetics; polymer systems; local delivery; wound healing

1. Introduction

Some of the earliest and most successful controlled release systems were designed for sustained release of agents at a local site. Ocusert® provides 7 days of continuous local release of pilocarpine in the cul-de-sac of the eye for treatment of glaucoma [1, 2]; Progestasert® and Mirena® release progestins in the uterus for several years, producing long-term inhibition of sperm motility and fertilization, and control of menstrual bleeding [3–6]. In fact, many of the controlled release systems described over the past 30 years can provide effective delivery of agents for local action in the tissue where the system is deployed. Articles published in earliest volumes of the *Journal of Controlled Release* demonstrate how these systems can be used for local drug delivery in the eye [7, 8], to teeth

© 2014 Elsevier B.V. All rights reserved.

*To whom correspondence should be addressed. Department of Biomedical Engineering, MEC 414, Yale University, 55 Prospect Street, New Haven, Connecticut, 06511 USA. Tel.: +1 (203) 432-4262. Fax: +1 (203) 432-0030. mark.saltzman@yale.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

[9], in the female reproductive tract [10, 11], and on prosthetic heart valves [12]. Other articles described the local penetration of drugs through tissues, particularly the skin [13–16].

Our laboratory has been interested for many years in the design of controlled release systems for local delivery in tissues. The *Journal of Controlled Release* has been an excellent forum for this work, which included an implantable system for controlled delivery of steroids in the brain [17], a delivery system for nerve growth factor (NGF) that produces a predictable spatial distribution of NGF activity [18], a delivery system for controlled release of antibodies [19], protein antigens [20] or DNA vaccines [21] in the vagina, a dual-release system for creating sharp, localized boundaries of biological activity [22], a model for drug release from polymer-coated vascular stents [23], microfluidic probes for convection-enhanced delivery in the brain [24], and nanoparticulate systems for vaginal delivery of siRNA [25, 26].

Local release, when feasible, allows for delivery of the largest fraction of drug molecules at or near the site of action, which reduces drug toxicity. Local delivery is, therefore, an attractive alternative to systemic delivery, which can produce inadequate doses of the agent in target tissue, as well as toxicity in healthy tissue [27–32]. As a result, 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 [33–42]. These delivery systems face the interesting challenge of creating a sustained release of the agent locally, without negatively impacting the healthy surrounding area. The ability to control dose and spatial penetration of the therapeutic agent increases the effectiveness of the therapeutic agent locally, while minimizing toxicity to other tissues.

We now understand many of the features that contribute to effective local controlled release. The dispersion of drug locally is governed by physiological transport principles, which are particular to the anatomic site and which can influence both the rate of release of the agent from the controlled release device and its fate in the local tissue [43, 44]. Local anatomy and microenvironment are, therefore, potential barriers to local delivery: understanding these barriers is critically important in the design of the controlled release device in these settings. Here, we review the principles of controlled drug delivery from local devices. We present these principles in the form of mathematical models, which can be used to quantify the barriers to local delivery and also to guide the design of devices for optimal local therapies.

Mathematical models are tremendously powerful tools in the development of drugs and drug delivery systems. Pharmacokinetic modeling has played a major role in the advancement of every kind of drug therapy [45, 46]. Likewise, models have long been used by controlled release scientists to understand their new systems [47–56]. These models generally attempt to explain mechanisms of controlled release, such as diffusion of the agent within the device, or degradation of a polymer carrier, or osmotic pumping, swelling, hydrolysis, or disintegration within a device [47–51, 57]. Until relatively recently, few models examined the local transport of the agent once it was released from the controlled release device and migrating through the local tissue. This element is essential for understanding the barriers to local delivery.

In one approach to developing an integrated understanding of the relationship between agent release from a device and penetration into the local tissue, a mathematical model was used to describe the transport of drugs into and through the tissue near a controlled release device [43]. Mechanisms of transport of the agent through the local tissue can be similar to the mechanisms of transport within the device: for example, diffusion of agents due to concentration gradients is usually an important mode of transport in both devices and tissues. But transport within the tissue often involves additional transport mechanisms, due to the anatomy of the tissue extracellular space (ECS) and the opportunity for interaction between the agent and the molecular and cellular components of the tissue. For example, after an agent is released from the delivery system, the agent diffuses away from the implant through the surrounding tissue where it is potentially internalized by cells, metabolized by extra- or intracellular enzymes, or swept away from the site after permeation into a local capillary (Figure 1). In this modeling approach, which was applied to the release of agents from polymer devices implanted into the brain, both diffusion of drug within the device and diffusion and reaction of drug in the tissue outside the device were considered [43]. This work demonstrated that, regardless of the design of the delivery system, the dynamics of local transport govern the spatial pattern of drug distribution after release from the implant. Local transport mechanisms determine the volume over which an agent is distributed; thus understanding these mechanisms is essential for optimizing the effectiveness of local delivery. In the remainder of this review, we present general models of local transport, describe how these models can be used to describe local delivery in brain, blood vessels, mucosal epithelia, and skin, and discuss the use of these models in the design of effective controlled release systems for use in these settings.

2. Mathematical models of local penetration after controlled release from a device

Consider a controlled release device implanted into or in contact with a tissue, where the tissue consists of three phases: an intracellular space (ICS), a cellular membrane (CM), and an extracellular space (ECS). This multiphase approach to modeling diffusion in tissues was first developed by Nicholson for the transport of agents in the brain [58], and has been adapted to local controlled release from implants in the brain [43, 59]. The molar concentration of the drug per total tissue volume, C , is expressed by the equation:

$$C = \alpha \cdot C_{ECS}^0 + \beta \cdot C_{ICS}^0 + (1 - \alpha - \beta) \cdot C_{CM}^0 \quad (1)$$

Where α represents the volume fraction of the ECS, β represents the volume fraction of the ICS, and the moles of drug volume per phase are represented by C_{ECS}^0 , C_{ICS}^0 , and C_{CM}^0 . Assuming that the tissue is isotropic, the local concentration of the drug agent is modeled by the following equation, which accounts for the transport and elimination in the local tissue environment:

$$\frac{\partial c}{\partial t} = -\nabla \cdot (-\alpha \cdot D_{ECS} \nabla C_{ECS}^0 + \alpha \cdot \bar{v}_r C_{ECS}^0) - (\alpha \cdot k_{ECS} \cdot C_{ECS}^0 + \beta \cdot k_{ICS} \cdot C_{ICS}^0 + (1 - \alpha - \beta) \cdot k_{CM} \cdot C_{CM}^0) - \frac{\partial B}{\partial t} \quad (2)$$

In Eq. (2), t is the time post-device implantation, D_{ECS} is the diffusion coefficient of the drug in the ECS, $\bar{v}_r$ is a vector representing the fluid velocity. The three coefficients-, k_{ECS} , k_{ICS} , and k_m –are first-order rate constants representing drug elimination in each of the three tissue phases: ECS, ICS, and CM. Many drugs bind reversibly to components of the tissue, and when bound are no longer subject to diffusion and convection: this fact is acknowledged in Eq. (2) in the final term, where B represents the total concentration of bound drug per volume of tissue. Therefore, it is appropriate to describe the total concentration of the bound agent in an analogous equation to Eq. (1):

$$B = \alpha \cdot B_{ECS}^0 + \beta \cdot B_{ICS}^0 + (1 - \alpha - \beta) \cdot B_{CM}^0 \quad (3)$$

where B represents the total concentration of the bound therapeutic agent, and the moles of bound drug in each tissue phase are represented by B_{ECS}^0 , B_{ICS}^0 , and B_{CM}^0 .

These equations are combined to create a general model for drug dispersion in the region surrounding the delivery device:

$$\underbrace{\frac{\partial C_{ECS}^0}{\partial t}}_{\text{transient}} + \underbrace{\frac{\alpha}{\alpha^*} \bar{v}_r \cdot \nabla C_{ECS}^0}_{\text{convection}} = \underbrace{\frac{\alpha}{\alpha^*} D_{ECS} \nabla^2 C_{ECS}^0}_{\text{diffusion}} - \underbrace{\frac{\alpha \cdot k_{ECS} + \beta \cdot k_{ICS} \cdot P_{ICS:ECS}}{\alpha^*} C_{ECS}^0}_{\text{elimination}} \quad (4)$$

The new variables introduced in Eq. (4) are defined as:

$$\alpha^* = \alpha \cdot (1 + K_{ECS}) + \beta \cdot P_{ICS:ECS} \cdot (1 + K_{ICS}) + (1 - \alpha - \beta) \cdot P_{CM:ECS} \quad (5)$$

$$K_{ECS} = \frac{B_{ECS}^0}{C_{ECS}^0}, \quad K_{ICS} = \frac{B_{ICS}^0}{C_{ICS}^0}, \quad P_{ICS:ECS} = \frac{C_{ICS}^0}{C_{ECS}^0}, \quad P_{CS:ECS} = \frac{C_{cm}^0}{C_{ECS}^0}$$

where K_{ECS} represents the binding constant between bound and free drug in the ECS, represents the binding constant between bound and free drug in the ICS, $P_{ICS:ECS}$ is the partition coefficient between the ICS and the ECS, and $P_{CM:ECS}$ is the partition coefficient between the CM and the ECS.

Combining the definitions of total concentration (C) in Eq. (1) and the partition coefficients, $P_{ICS:ECS}$ and $P_{CM:ECS}$, Eq. (4) can be expressed:

$$\frac{\partial C}{\partial t} + v \cdot \nabla C = D \nabla^2 C - k \cdot C \quad (6)$$

with

$$v = \frac{\alpha}{\alpha^*} \cdot v_r, \quad D = \frac{\alpha}{\alpha^*} \cdot D_{ECS}, \quad k = \frac{\alpha \cdot K_{ECS} + \beta \cdot k_{ICS} \cdot P_{ICS:ECS}}{\alpha^*}$$

where v is the apparent velocity in the ECS, D is the apparent diffusion coefficient of the agent in the surrounding tissue, and k is the apparent first-order elimination constant.

While presented above in the context of agent transport in the brain, Eq. (6) can be applied to any tissue microenvironment. But each tissue has a unique set of characteristics that must be considered. For example, rates of agent diffusion vary from tissue to tissue, due to the particular features of each tissue. Water-soluble drugs, which do not readily penetrate plasma membranes, diffuse primarily through the ECS. The volume fraction of the ECS in the brain is approximately 20% ECS, which imparts a particular tortuosity, or geometrical hindrance, on diffusion [60]. In contrast, the volume fraction of ECS is 13% in kidney and 7% in muscle [61]. Tissue characteristics also can vary throughout a tissue: the volume fraction of ECS is low in the epidermis—preventing diffusion of water-soluble drugs—and is substantially higher in the dermis. In some tissues, agent diffusion is not isotropic. The most well-characterized example is the anisotropic diffusion of water and water-soluble agents in white matter tracts in the brain [62], but diffusional anisotropy can occur in various tissues including other parts of the nervous system [63] and temporomandibular joint discs [64].

Taking into account the tissue environment, these local transport models can be applied in the context of local controlled release from implanted devices in a tissue. Table 1 shows solutions to Eq. (6) in a few typical situations. A simple, but instructive, case occurs when bulk fluid movement (i.e. convection) in the tissue is negligible and the transport is assumed to be at steady-state. Eq. (6) then reduces to (in rectangular coordinates):

$$0 = D \frac{d^2 c}{dx^2} - k \cdot C \quad (7)$$

which can be solved subject to two boundary conditions. Assuming that the concentration of released agent is $C = C_i$ at the interface between the device and the tissue and that $C=0$ far from the device, Eq. (7) can be solved to give Eq. (9), shown in Table 1. Non-dimensionalization of this solution reveals a single parameter, $\emptyset$, a diffusion/elimination modulus, that determines the steepness of the drug concentration profile in the vicinity of the implant [43]:

$$\emptyset = L \sqrt{\frac{k}{D}} \quad (8)$$

where L is the linear dimension of the tissue volume. Briefly, the larger the diffusion/elimination modulus is for a known geometry, the steeper the predicted concentration gradient. As the value of $\emptyset$ decreases, the distance that the drug penetrates into the surrounding tissue increases (Figure 2). In other words, the volume of tissue that is effectively treated by diffusive transport is determined by the ratio of the rate of elimination and the rate of diffusion.

Three other solutions to Eq. (6) are shown in Table 1, each one relaxing one or more of the major assumptions used to derive Eq. (7): Eq. (10) was obtained by relaxing the assumption of steady-state; Eq. (11) was obtained by relaxing the assumption that convection is negligible; and Eq. (12) was obtained by relaxing the assumption of steady-state, and also omitting elimination.

3. Local drug delivery to the brain

How do these mathematical models compare to real situations of local drug delivery from implants? This question has been explored extensively for implants that release drugs into the brain [65–67]. Mathematical modeling contributed to the development and FDA approval of the first clinical system for local drug delivery in the brain, Gliadel®, which was approved for treatment of glioblastoma multiforme in 1996 [34].

It is well accepted that—under most conditions—convective transport in the brain is negligible, particularly through grey matter regions that are far from ventricular surfaces and subarachnoid spaces. In the earliest comparisons with experimental data, the solution to Eq. (6) in spherical coordinates was integrated to yield a prediction for the total amount of drug in the brain as a function of time after implantation of a dexamethasone-releasing implant [17]: the prediction agreed well with experimental data [43]. But a better test of the value of the model requires measurement of concentration gradients in the tissue, to see if the model successfully predicts the pattern of spatial distribution of the agent. Quantitative autoradiography allows for measurement of spatial patterns of concentration in cut sections from tissues, provided that the agent is radiolabeled. This approach was used to measure concentrations of chemotherapy drugs [67] and the protein nerve growth factor [68] during controlled release from an implant in the brain. Solutions to Eq. (6) accurately predict these measured concentrations, as shown in Figure 3, in which measured concentrations of tritiated bis-chloroethylnitrosourea (BCNU) released from an implanted polymer matrix in the brains of adult male rats are compared to the mathematical model [59, 67]. Similar approaches were used to measure concentration profiles in rabbits [65] and non-human primates [67].

In the context of agent delivery to the brain, the mathematical models suggest a more general way for thinking about the relationship between penetration into the local tissue and effectiveness of local drug delivery. We can define an effectiveness of local distribution of a drug, η , which is the ratio of the average drug concentration within a particular volume of tissue to drug concentration at the device/tissue interface:

$$\eta = \frac{\int_0^L C(x) \cdot A dx}{C(x=0)} \quad (12)$$

Substituting Eq. (9) for $C(x)$ and $C(x=0)$ into Eq. (12) yields:

$$\eta = \frac{1}{\phi} [1 - \exp(-\phi)] \quad (13)$$

For drug delivery throughout this region of tissue to be effective, the drug concentration must be nearly uniform throughout the volume: in this case, since the average concentration is close to the maximum concentration, η approaches unity. When drug distribution is ineffective, the concentration of agent at the implant/tissue interface is much higher than the average concentration (i.e. there are steep concentration gradients within the tissue volume) and η approaches zero. Defined in this way, the parameter η provides a quantitative measure of the effectiveness of drug penetration or distribution throughout a region of interest

(Figure 4). From this analysis, it is clear that a major barrier to penetration of agents locally in the brain is their relatively rapid elimination from the local site. This observation has been used to design drugs that are more effective at local penetration, by making modifications that stabilize the agents in the tissue, thereby allowing for enhanced penetration [69, 70].

The previous examples used simplifying assumptions and corresponding solutions to the transport equation, Eq. (6), in order to extract principles that could guide the design of local controlled release devices in the brain. In some situations—especially in convection-enhanced delivery, where controlled fluid flows are introduced through catheters and used to transport agents through a desired volume of the brain—fluid convection contributes substantially to drug movement [71]. In one approach to modeling these more complex situations, the brain is modeled as a porous medium and flows are accounted for by solution of the continuity equation, Darcy's law, and Eq. (6) [72, 73]. Directionality of fluid transport and diffusion also can be relevant in the brain due to the different diffusional resistances of gray and white matter [74] and to perivascular transport [75]. Inclusion of convection, or geometric complexity, or anisotropic transport generally requires numerical approaches for solving the transport equations. A recent article reviews some of the issues important in developing numerical simulations of drug distribution as a means of improving on the design of delivery systems for BCNU [76].

New approaches to local delivery in the brain take advantage of drug-loaded nanoparticles. For example, locally administered nanoparticles, infused into the brain by convection-enhanced delivery (CED), can provide controlled release locally after convection-mediated delivery to a desired volume of tissue [77]. In addition, it may be possible to deliver systemically-administered nanoparticles to defined regions of the brain by the combined use of magnetic targeting and focused ultrasound [78].

4. Local drug delivery in blood vessels

Local drug delivery is a useful approach for treatment of vascular disease. In an early study demonstrating the potential of local delivery, a hollow cylindrical device, consisting of an ethylene-vinyl acetate copolymer (EVAc) matrix loaded with heparin, was placed on the adventitial surface of the rat carotid artery [79]. To determine heparin levels in the tissue, models derived from Eq. (6) were used to describe the penetration of heparin in the arterial wall during delivery from a perivascular device. The concentration of heparin within the vascular tissue was predicted with these models (Figure 5). This work demonstrated the value of understanding the barriers to local transport in interpreting heparin action after local delivery to the vessel wall [80].

Drug-eluting stents are arguably the most important local controlled release devices developed to date, in terms of the number of devices that have been used clinically. Percutaneous intervention via stents, envisioned in 1964, was first tested in human clinical trials in 1986 [81]. The first drug-eluting stents were placed into human patients in 2002 [82] and approval of the first stents by the US FDA came in 2003 (Cypher®, releasing everolimus) and 2004 (Taxus®, releasing paclitaxel).

Mathematical models of local drug transport are important tools in drug-eluting stent design because they allow for the integration of the multiple barriers to local transport of agents that determine stent effectiveness (Figure 6). Unlike Gliadel® implants for the brain, which are flat discs or wafers, drug-eluting stents are typically thin, latticed cylindrical devices with drug-loaded polymer coatings [82, 83]. This difference in geometry can be accounted for in mathematical models, by writing the equations in an appropriate coordinate system and using boundary conditions to define the sites of drug release [44, 84, 85]. For stents, which frequently have complex geometries, these equations may not have analytical solutions, so numerical methods are often used. Eq. (6) still applies to describe local transport in the tissue, but usually convection cannot be ignored. In addition, rates of diffusion and convection can be directionally dependent and agents binding to tissue components can play a significant role. Furthermore, while the release of drug from the struts of each stent produces high localized concentrations of the agent in the tissue directly adjacent to the strut, concentrations may be much lower in the tissue at the midpoint between struts [44, 80, 84, 86–88]. As in the brain, local penetration of agents after release from the drug-eluting stent depends on a significant number of features of the local tissue (Figure 6).

A variety of mathematical models have been used to describe local drug delivery by stents and other vascular devices; they range in complexity from simplified one-dimensional [80] or two-dimensional [44, 89] geometries, up to three-dimensional multidomain simulations that account for anisotropic diffusion, porosity, drug–protein binding, presence of plaque, and local hemodynamics [85]. Because of the geometrical complexity of many vascular devices, and the physiological complexity of the tissue, models of local delivery by drug-eluting stents are often solved numerically, by either mapping the tissue space encompassing many struts into a grid (Figure 7a) or focusing on a single characteristic element of the device, such as a stent strut (Figure 7b). Recent work using these approaches has defined the importance of drug properties (particularly extent of binding to proteins in tissue), polymer coating properties, degree of embedding of struts into the tissue, inter-strut spacing, and local blood flow within the vessel. Each of these factors can influence the spatial and temporal pattern of drug concentration in arterial tissue [85, 90–93].

5. Local drug delivery to mucosal epithelia

Mucosal epithelia in the eye, lung, gastrointestinal, and reproductive tissues represent important targets for drug delivery. The gastrointestinal tract is a common site for systemic drug delivery, due to the convenience of oral administration. The ocular mucosa and the female reproductive tract are established sites for local controlled release, as exemplified by Ocusert® and Progestasert®. Vaginal rings have emerged as safe and effective methods for sustained delivery of agents to the vaginal mucosa: for example, Nuvaring® releases low doses of progestins and estrogen for sustained contraception.

The epithelial surfaces of the gastrointestinal, reproductive, respiratory, and ocular tissues are coated with a layer of mucus—sometimes called a mucus blanket, particularly within the respiratory system—that lubricates these surfaces and protects them from invasion by pathogens. Mucus is a tough and dynamic barrier, constantly being renewed by secretion from cells within the epithelium and constantly being digested or shed. Continuous secretion

of mucus creates a flow away from the epithelium, which must be overcome by diffusion if molecules delivered into the mucus are to reach the epithelial cells [95]. Fortunately, although the properties of mucus vary among tissues, most molecules—even large molecules such as antibodies—can diffuse as rapidly in mucus as they do in water [96]. Further, the shear-thinning behavior of mucus creates unstirred layers that persist even in the presence of vigorous stirring actions, presenting a diffusional barrier to drug penetration (an excellent description of the barrier properties of mucus is provided by Cone [95]). To create a successful controlled release system that works in this setting, these obstacles to drug movement must be overcome.

Our understanding of the molecular structure of mucus—and the relationship of mucus composition to its barrier function—is due in large measure to mathematical models, beginning with the seminal work of Peppas [97]. These models of transport through mucus are based on principles from polymer physics and incorporate the properties of the mucus gel, its constituents, and the diffusing agent of interest. A recent paper reviews models of molecular diffusion in mucus, including the techniques most often used to measure rates of diffusion in mucus [96]. As a result of this work, our understanding of the barrier properties of mucus, and its impact on the performance of controlled release systems that must perform in the presence of mucus, is advanced. As one example of this, a compartmental model—incorporating controlled release from a device into mucus—was used to describe the behavior of vaginal rings that slowly release antibodies [39]. This model (Figure 8a) accurately predicted antibody accumulation in mucus and blood after insertion of an antibody-loaded vaginal ring; it also provided insight into aspects of vaginal ring design that are most important for achieving local versus systemic antibody concentrations (Figure 8b).

The autoradiographic methods that were used to study concentration profiles of agents during local controlled release in the brain (Figure 3) also can be used to measure concentrations produced by controlled release at a mucosal surface. Figure 9 shows concentration gradients measured in mice during controlled delivery of radiolabelled antibodies from a vaginal ring. The experimentally measured gradients were compared to Eq. (9), revealing that diffusion of antibodies through the epithelium and simultaneous uptake into capillaries resulted in antibody transport from the mucus, through the epithelial tissue, and into the blood [98].

An alternate approach, which is likely to be expanded in the future, is to deliver drugs to the mucosal surface in particulates that provide controlled release. If the particles are appropriately designed, they can deliver agents as well as become internalized in cells within the epithelium. For example, nanoparticulate delivery systems (NPs) have been shown to have certain valuable properties: drugs can be loaded into certain biodegradable NPs at high levels [99, 100], slowly released from NPs – sometimes for several weeks [99, 100]; NPs can be designed to penetrate through mucus [96, 101], such that they become well-distributed throughout the reproductive epithelium [25, 101]. The limitations of this approach for achieving controlled release are not yet clear: mucus-penetrating NPs persist for ~24 hr after intravaginal administration [25, 101], although their effects can persist for longer [40]. But vaginally administered NPs can be effective: topically administered NPs loaded with chemotherapy agents are effective against local tumors in mice [100, 102], and

NPs loaded with an siRNA that blocked herpes virus entry into cells [26] or an antiviral agent [101] reduced genital herpes infections in mice.

6. Local drug delivery to skin

Lotions, creams, and ointments have been used for local treatment of skin for many centuries. Controlled release technologies have broadened the role of local delivery to skin; transdermal delivery systems often use a polymer membrane to control the rate of diffusion of agents from a reservoir through the surface of the skin and into the systemic circulation. Transdermal patches allow for systemic delivery of potent, lipid-soluble agents such as scopolamine for motion sickness [103], nicotine to aid in cessation of smoking [104], steroids for hormone replacement therapy or birth control [105–107], nitroglycerin for angina [108], and fentanyl for chronic pain [109]. Transdermal delivery has many advantages: it is minimally painful, offers controlled release, has a lower rate of infection and higher rate of compliance compared to injections, and avoids first-pass metabolism seen in oral drug delivery [110–112]. When transdermal delivery is used to provide systemic therapy, administration of the right dose depends on understanding the rate of drug penetration through the epidermis to the capillaries in the dermis (Figure 10).

Mathematical models of drug permeation through skin—which can be derived from Eq. (6)—provide information on the rate of drug penetration, which directly correlates to the concentration of the drug available systemically. For example, the stratum corneum barrier can be modeled using a simplification of Eq. (6), in which convection and elimination are both ignored ($v=0$ and $k=0$):

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} \quad (13)$$

which can be solved subject to appropriate initial and boundary conditions to yield Eq. (12) (see Table 1). The amount of agent penetrating the skin, Q , can be found by calculating the flux of the agent through the stratum corneum, multiplying by the surface area (A), and integrating over time:

$$Q = \int_0^t \left[-AD \frac{\partial c}{\partial x} \Big|_{x=H} \right] dt \quad (14)$$

Using Eq. (12) for C yields:

$$Q = C_0 A H \left(\frac{D}{H^2} t - \frac{1}{6} - \frac{2}{\pi} \sum_{n=1}^{\infty} \frac{(-1)^n}{n^2} \exp \left(-t \frac{D}{H^2} \pi^2 n^2 \right) \right) \quad (15)$$

which can be simplified at sufficiently long times (when $t > H^2/D$):

$$Q = \frac{C_0 A D}{H} \left(t - \frac{H^2}{6D} \right) \quad (16)$$

In the case of skin, the concentration on the outside boundary, C_0 , is equal to the concentration in a donor solution in contact with the skin (C_d , for example, may be the concentration in an aqueous reservoir in contact with the skin) multiplied by a partition coefficient, K , which defines the equilibrium partitioning between skin and the donor solution. For long times of exposure to a constant donor solution ($t \gg H^2/6D$), the flux of agent through the skin is:

$$Flux = \frac{1}{A} \frac{dQ}{dt} = \frac{KD}{H} C_d \quad (17)$$

In this case, the permeability coefficient k_p can be defined as:

$$k_p = \frac{KD}{H} \quad (18)$$

The contributions of these solutions to Eq. (6) in enhancing our understanding of agent transport through skin and designing transdermal delivery systems is well-described in the literature (see [56, 112, 113] for some recent reviews).

Comprehensive models of skin permeation take into account more than the stratum corneum, as all three layers of the skin—epidermis, dermis, and subcutaneous tissue (Figure 10)—can contribute to drug transport. The stratum corneum is usually the rate-limiting barrier, and it also can serve as a reservoir for some drugs administered to the skin due to its high lipid content [114]. Models of permeation of skin can take forms different than Eq. (6) by treating each layer as a discrete environment or compartment [112–115]. These layers are then assembled in series to describe transport through skin. In all of these models, it is important to consider accessory elements in skin—hair follicles and glands—that also contribute substantially to drug transport.

Importantly, much of the work done to define the barrier properties of skin can be used to define quantitative structure-permeation relationships (QSPR) [113]. One goal of a QSPR is to provide a means to predict the rate of permeability of an unknown compound, by reference to a large set of similar compounds for which the permeability is known. A popular QSPR was developed by Potts and Guy [116]:

$$\log(k_p) = -6.3 + 0.71 \log P - 0.0061 MW \quad (19)$$

where k_p is expressed in units of cm/sec, P is the octanol:water partition coefficient for an agent of interest, and MW is the agent's molecular weight. This relationship allows for prediction of permeability of the skin to a wide range of compounds. More accurate predictions for agents with a wide range of properties can be achieved by using modeling approaches that account for the different physical pathways available for transport of hydrophilic and hydrophobic agents [117].

Although transdermal delivery systems are applied to a local region of skin, the goal is often to achieve systemic distribution of the drug. But there are medical indications for local controlled release to the skin, particularly to enhance wound healing. Controlled release materials can be used to deliver antimicrobial agents [118], growth factors [119, 120], and

genes [121] directly to wounds. Despite the development of controlled release systems that might work in this setting, the dynamics of local delivery to wounds have yet to be described. Drug penetration through wounds is no doubt dramatically different than drug penetration through skin, because the normal architecture of skin (Figure 10) is lost in wounds. In addition, the altered physiological state and cellular composition of wounds will likely change the patterns of drug metabolism. For the future, defining drug transport in the wound microenvironment is essential for the rational design of effective controlled release systems tailored to this altered tissue state.

7. Conclusion

Controlled release scientists have made major contributions to medicine through the design, fabrication, and testing of drug delivery systems aimed to work locally. While targeted drug therapies that are administered systemically remain elusive, local drug delivery systems provide a proven solution to achieving highly targeted therapy. 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.

References

1. Armaly MF, Rao KR. Effect of pilocarpine Ocusert with different release rates on ocular pressure. *Investigative Ophthalmology*. 1973; 12:491–496. [PubMed: 4742991]
2. Quigley HA, Pollack IP, Harbin TS. Pilocarpine Ocuserts – Long-term clinical trials and selected pharmacodynamics. *Archives of Ophthalmology*. 1975; 93:771–775. [PubMed: 1235481]
3. Zador G, Nilsson BA, Nilsson B, Sjoberg NO, Westrom L, Wiese J. Clinical experience with the uterine progesterone system (Progestasert®). *Contraception*. 1976; 13:559–569. [PubMed: 1261259]
4. Andersson K, Odland V, Rybo G. Levonorgestrel-releasing and copper-releasing (Nova T) IUDs during five years of use: A randomized comparative trial. *Contraception*. 1994; 49:56–72. [PubMed: 8137626]
5. Lethaby AE, Cooke I, Rees M. Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. *Cochrane Database Syst Rev*. 2005
6. Hidalgo M, Bahamondes L, Perrotti M, Diaz J, Dantas-Monteiro C, Petta C. Bleeding patterns and clinical performance of the levonorgestrel-releasing intrauterine system (Mirena) up to two years. *Contraception*. 2002; 65:129–132. [PubMed: 11927115]
7. Gurny R, Boye T, Ibrahim H. Ocular therapy with nanoparticulate systems for controlled drug delivery. *Journal of Controlled Release*. 1985; 2:353–362.
8. Langer R, Lund D, Leong K, Folkman J. Controlled release of macromolecules: Biological studies. *Journal of Controlled Release*. 1985; 2:331–341.
9. Friedman M, Brayer L, Golomb G, Hiller H. Prevention of plaque accumulation by local application of a sustained release delivery system of chlorhexidine. *Journal of Controlled Release*. 1984; 1:157–160.
10. McNeill ME, Graham NB. Vaginal pessaries from crystalline/rubbery hydrogels for the delivery of prostaglandin E2. *Journal of Controlled Release*. 1984; 1:99–117.
11. Sanders LM, McRae GI, Vitale KM, Kell BA. Controlled delivery of an LHRH analogue from biodegradable injectable microspheres. *Journal of Controlled Release*. 1985; 2:187–195.
12. Golomb G, Langer R, Schoen FJ, Smith MS, Yong Mi C, Levy RJ. Controlled release of diphosphonate to inhibit bioprosthetic heart valve calcification: Dose-response and mechanistic studies. *Journal of Controlled Release*. 1986; 4:181–194.
13. Merritt EW, Cooper ER. Diffusion apparatus for skin penetration. *Journal of Controlled Release*. 1984; 1:161–162.

14. Merkle HP, Knoch A, Gienger G. Release kinetics of polymeric laminates for transdermal delivery: Experimental evaluation and physical modelling. *Journal of Controlled Release*. 1985; 2:99–110.
15. Hoelgaard A, Mollgaard B. Dermal drug delivery — Improvement by choice of vehicle or drug derivative. *Journal of Controlled Release*. 1985; 2:111–120.
16. Nagai T. Adhesive topical drug delivery system. *Journal of Controlled Release*. 1985; 2:121–134.
17. Reinhard CS, Radomsky ML, Saltzman WM, Hilton J, Brem H. Polymeric controlled release of dexamethasone in normal rat brain. *Journal of Controlled Release*. 1991; 16:331–339.
18. Beaty CE, Saltzman WM. Controlled growth factor delivery induces differential neurite outgrowth in three-dimensional cell cultures. *Journal of Controlled Release*. 1993; 24:15–23.
19. Parkhurst MR, Saltzman WM. Controlled delivery of antibodies against leukocyte adhesion molecules from polymer matrices. *Journal of Controlled Release*. 1996; 42:273–288.
20. Wyatt TL, Whaley KJ, Cone RA, Saltzman WM. Antigen-releasing polymer rings and microspheres stimulate mucosal immunity in the vagina. *Journal of Controlled Release*. 1998; 50:93–102. [PubMed: 9685876]
21. Shen H, Goldberg E, Saltzman WM. Gene expression and mucosal immune responses after vaginal DNA immunization in mice using a controlled delivery matrix. *Journal of Controlled Release*. 2003; 86:339–348. [PubMed: 12526829]
22. Fleming AB, Saltzman WM. Simultaneous delivery of an active protein and neutralizing antibody: creation of separated regions of biological activity. *Journal of Controlled Release*. 2001; 70:29–36. [PubMed: 11166405]
23. Sirianni RW, Jang EH, Miller KM, Saltzman WM. Parameter estimation methodology in a model of hydrophobic drug release from a polymer coating. *Journal of Controlled Release*. 2010; 142:474–482. [PubMed: 19958804]
24. Neeves KB, Lo CT, Foley CP, Saltzman WM, Olbricht WL. Fabrication and characterization of microfluidic probes for convection enhanced drug delivery. *Journal of Controlled Release*. 2006; 111:252–262. [PubMed: 16476500]
25. Cu Y, Booth CJ, Saltzman WM. In vivo distribution of surface-modified PLGA nanoparticles following intravaginal delivery. *Journal of Controlled Release*. 2011; 156:258–264. [PubMed: 21763739]
26. Steinbach JM, Weller CE, Booth CJ, Saltzman WM. Polymer nanoparticles encapsulating siRNA for treatment of HSV-2 genital infection. *Journal of Controlled Release*. 2012; 162:102–110. [PubMed: 22705461]
27. Pitt CG. The controlled parenteral delivery of polypeptides and proteins, *International. Journal of Pharmaceutics*. 1990; 59:173–196.
28. Heller J. Polymers for controlled parenteral delivery of peptides and proteins. *Advanced Drug Delivery Reviews*. 1993; 10:163–204.
29. Cleland, JL.; Langer, R. Formulation and delivery of proteins and peptides – design and development strategies. In: Cleland, JL.; Langer, R., editors. *Formulation and Delivery of Proteins and Peptides*. Amer Chemical Soc; Washington: 1994. p. 1-19.
30. Domb AJ. Polymeric carriers for regional drug-therapy. *Mol Med Today*. 1995; 1:134–139. [PubMed: 9415149]
31. Albertsson AC, Varma IK. Recent developments in ring opening polymerization of lactones for biomedical applications. *Biomacromolecules*. 2003; 4:1466–1486. [PubMed: 14606869]
32. Uhrich KE, Cannizzaro SM, Langer RS, Shakesheff KM. Polymeric systems for controlled drug release. *Chem Rev*. 1999; 99:3181–3198. [PubMed: 11749514]
33. During MJ, Freese A, Sabel BA, Saltzman WM, Deutch A, Roth RH, Langer R. Controlled release of dopamine from a polymeric brain implant – in vivo characterization. *Annals of Neurology*. 1989; 25:351–356. [PubMed: 2634975]
34. Fleming AB, Saltzman WM. Pharmacokinetics of the carmustine implant. *Clin Pharmacokinet*. 2002; 41:403–419. [PubMed: 12074689]
35. Ludwig A. The use of mucoadhesive polymers in ocular drug delivery. *Advanced Drug Delivery Reviews*. 2005; 57:1595–1639. [PubMed: 16198021]

36. Andrews GP, Lavery TP, Jones DS. Mucoadhesive polymeric platforms for controlled drug delivery. *European Journal of Pharmaceutics and Biopharmaceutics*. 2009; 71:505–518. [PubMed: 18984051]
37. Putnam D. Drug delivery – The heart of the matter. *Nature Materials*. 2008; 7:836–837.
38. Orloff LA, Domb AJ, Teomim D, Fishbein I, Golomb G. Biodegradable implant strategies for inhibition of restenosis. *Advanced Drug Delivery Reviews*. 1997; 24:3–9.
39. Saltzman WM, Sherwood JK, Adams DR, Haller P. Long-term vaginal antibody delivery: Delivery systems and biodistribution. *Biotechnology and Bioengineering*. 2000; 67:253–264. [PubMed: 10620255]
40. Woodrow KA, Cu Y, Booth CJ, Saucier-Sawyer JK, Wood MJ, Saltzman WM. Intravaginal gene silencing using biodegradable polymer nanoparticles densely loaded with small-interfering RNA. *Nature Materials*. 2009; 8:526–533.
41. Boateng JS, Matthews KH, Stevens HNE, Eccleston GM. Wound healing dressings and drug delivery systems: A review. *Journal of Pharmaceutical Sciences*. 2008; 97:2892–2923. [PubMed: 17963217]
42. Meinel AJ, Gernershaus O, Luhmann T, Merkle HP, Meinel L. Electrospun matrices for localized drug delivery: Current technologies and selected biomedical applications. *European Journal of Pharmaceutics and Biopharmaceutics*. 2012; 81:1–13. [PubMed: 22342778]
43. Saltzman WM, Radomsky ML. Drugs released from polymers – diffusion and elimination in brain-tissue. *Chem Eng Sci*. 1991; 46:2429–2444.
44. Hwang CW, Wu D, Edelman ER. Physiological transport forces govern drug distribution for stent-based delivery. *Circulation*. 2001; 104:600–605. [PubMed: 11479260]
45. Brunton, L.; Chabner, B.; Knollman, B. Goodman & Gilman's The Pharmacological Basis of Therapeutics. In: Buxton, ILO.; Benet, LZ., editors. *Pharmacokinetics: The dynamics of drug absorption, distribution, metabolism, and elimination*. McGraw-Hill; 2010. p. 17-40.
46. Saltzman, WM. *Drug Delivery: Engineering Principles for Drug Therapy*. Oxford University Press; USA: 2001.
47. Langer RS, Peppas NA. Present and future applications of biomaterials in controlled drug delivery systems. *Biomaterials*. 1981; 2:201–214. [PubMed: 7034798]
48. Saltzman WM, Langer R. Transport rates of proteins in porous materials with known microgeometry. *Biophys J*. 1989; 55:163–171. [PubMed: 2467696]
49. Siepmann J, Gopferich A. Mathematical modeling of bioerodible, polymeric drug delivery systems. *Advanced Drug Delivery Reviews*. 2001; 48:229–247. [PubMed: 11369084]
50. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. *Acta Pol Pharm*. 2010; 67:217–223. [PubMed: 20524422]
51. Fredenberg S, Wahlgren M, Reslow M, Axelsson A. The mechanisms of drug release in poly(lactic-co-glycolic acid)-based drug delivery systems-A review. *International Journal of Pharmaceutics*. 2011; 415:34–52. [PubMed: 21640806]
52. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. *International Journal of Pharmaceutics*. 1983; 15:25–35.
53. Korsmeyer RW, Lustig SR, Peppas NA. Solute and penetrant diffusion in swellable polymers. I. Mathematical modeling. *J Polym Sci Pt B-Polym Phys*. 1986; 24:395–408.
54. Korsmeyer RW, Vonmeerwall E, Peppas NA. Solute and penetrant diffusion in swellable polymers. II. Verification of theoretical models. *J Polym Sci Pt B-Polym Phys*. 1986; 24:409–434.
55. Peppas NA, Sahlin JJ. A simple equation for the description of solute release. III. Coupling of diffusion and relaxation. *International Journal of Pharmaceutics*. 1989; 57:169–172.
56. Grassi M, Lamberti G, Cascone S, Grassi G. Mathematical modeling of simultaneous drug release and in vivo absorption. *International Journal of Pharmaceutics*. 2011; 418:130–141. [PubMed: 21237258]
57. Peppas NA, Brannonpeppas L. Water diffusion and sorption in amorphous macromolecular systems and foods. *J Food Eng*. 1994; 22:189–210.
58. Nicholson C. Interaction between Diffusion and Michaelis-Menten Uptake of Dopamine after Iontophoresis. *Biophys J*. 1995; 68:1699–1715. [PubMed: 7612814]

59. Fung LK, Saltzman WM. Polymeric implants for cancer chemotherapy. *Advanced Drug Delivery Reviews*. 1997; 26:209–230. [PubMed: 10837544]
60. Nicholson C, Sykova E. Extracellular space structure revealed by diffusion analysis. *Trends Neurosci*. 1998; 21:207–215. [PubMed: 9610885]
61. Magzoub M, Zhang H, Dix JA, Verkman AS. Extracellular Space Volume Measured by Two-Color Pulsed Dye Infusion with Microfiberoptic Fluorescence Photodetection. *Biophys J*. 2009; 96:2382–2390. [PubMed: 19289063]
62. Beaulieu C. The basis of anisotropic water diffusion in the nervous system – a technical review. *NMR Biomed*. 2002; 15:435–455. [PubMed: 12489094]
63. Beaulieu C, Allen PS. Determinants of anisotropic water diffusion in nerves. *Magn Reson Med*. 1994; 31:394–400. [PubMed: 8208115]
64. Shi C, Wright GJ, Ex-Lubeskie CL, Bradshaw AD, Yao H. Relationship between anisotropic diffusion properties and tissue morphology in porcine TMJ disc. *Osteoarthritis Cartilage*. 2013; 21:625–633. [PubMed: 23353670]
65. Strasser JF, Fung LK, Eller S, Grossman SA, Saltzman WM. Distribution of 1,3-bis(2-chloroethyl)-1-nitrosourea and tracers in the rabbit brain after interstitial delivery by biodegradable polymer implants. *J Pharmacol Exp Ther*. 1995; 275:1647–1655. [PubMed: 8531140]
66. Fung LK, Shin M, Tyler B, Brem H, Saltzman WM. Chemotherapeutic drugs released from polymers: distribution of 1,3-bis(2-chloroethyl)-1-nitrosourea in the rat brain. *Pharmaceutical Research*. 1996; 13:671–682. [PubMed: 8860421]
67. Fung LK, Ewend MG, Sills A, Sipos EP, Thompson R, Watts M, Colvin OM, Brem H, Saltzman WM. Pharmacokinetics of interstitial delivery of carmustine, 4-hydroperoxycyclophosphamide, and paclitaxel from a biodegradable polymer implant in the monkey brain. *Cancer Research*. 1998; 58:672–684. [PubMed: 9485020]
68. Krewson CE, Klarman ML, Saltzman WM. Distribution of nerve growth factor following direct delivery to brain interstitium. *Brain Res*. 1995; 680:196–206. [PubMed: 7663977]
69. Fleming AB, Haverstick K, Saltzman WM. In vitro cytotoxicity and in vivo distribution after direct delivery of PEG-camptothecin conjugates to the rat brain. *Bioconjugate Chemistry*. 2004; 15:1364–1375. [PubMed: 15546204]
70. Haverstick K, Fleming A, Saltzman WM. Conjugation to increase treatment volume during local therapy: a case study with PEGylated camptothecin. *Bioconjugate Chemistry*. 2007; 18:2115–2121. [PubMed: 17935287]
71. Bobo RH, Laske DW, Akbasak A, Morrison PF, Dedrick RL, Oldfield EH. Convection-enhanced delivery of macromolecules in the brain. *Proc Natl Acad Sci U S A*. 1994; 91:2076–2080. [PubMed: 8134351]
72. Kim JH, Astarly GW, Kantorovich S, Mareci TH, Carney PR, Sarntinoranont M. Voxelized Computational Model for Convection-Enhanced Delivery in the Rat Ventral Hippocampus: Comparison with In Vivo MR Experimental Studies. *Ann Biomed Eng*. 2012; 40:2043–2058. [PubMed: 22532321]
73. Kalyanasundaram S, Calhoun VD, Leong KW. A finite element model for predicting the distribution of drugs delivered intracranially to the brain. *Am J Physiol-Regul Integr Comp Physiol*. 1997; 273:R1810–R1821.
74. Tao L, Nicholson C. Diffusion of albumins in rat cortical slices and relevance to volume transmission. *Neuroscience*. 1996; 75:839–847. [PubMed: 8951877]
75. Foley CP, Nishimura N, Neeves KB, Schaffer CB, Olbricht WL. Real-Time Imaging of Perivascular Transport of Nanoparticles During Convection-Enhanced Delivery in the Rat Cortex. *Ann Biomed Eng*. 2012; 40:292–303. [PubMed: 22009318]
76. Pereira DY, Yip AT, Lee BS, Kamei DT. Modeling Mass Transfer from Carmustine-Loaded Polymeric Implants for Malignant Gliomas. *Journal of Laboratory Automation*. 2014; 19:19–34. [PubMed: 23975389]
77. Zhou JB, Patel TR, Sirianni RW, Strohbehn G, Zheng MQ, Duong N, Schafbauer T, Huttner AJ, Huang YY, Carson RE, Zhang Y, Sullivan DJ, Piepmeyer JM, Saltzman WM. Highly penetrative, drug-loaded nanocarriers improve treatment of glioblastoma. *Proc Natl Acad Sci U S A*. 2013; 110:11751–11756. [PubMed: 23818631]

78. Liu HL, Hua MY, Yang HW, Huang CY, Chu PC, Wu JS, Tseng IC, Wang JJ, Yen TC, Chen PY, Wei KC. Magnetic resonance monitoring of focused ultrasound/magnetic nanoparticle targeting delivery of therapeutic agents to the brain. *Proc Natl Acad Sci U S A*. 2010; 107:15205–15210. [PubMed: 20696897]
79. Lovich MA, Edelman ER. Tissue concentration of heparin, not administered dose, correlates with the biological response of injured arteries in vivo. *Proc Natl Acad Sci U S A*. 1999; 96:11111–11116. [PubMed: 10500138]
80. Lovich MA, Edelman ER. Computational simulations of local vascular heparin deposition and distribution. *Am J Physiol-Heart Circul Physiol*. 1996; 271:H2014–H2024.
81. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular Stents to Prevent Occlusion and Re-Stenosis after Transluminal Angioplasty. *New England Journal of Medicine*. 1987; 316:701–706. [PubMed: 2950322]
82. Serruys PW, Kutryk MJB, Ong ATL. Drug therapy – Coronary-artery stents. *New England Journal of Medicine*. 2006; 354:483–495. [PubMed: 16452560]
83. Rogers JH, Laird JR. Overview of new technologies for lower extremity revascularization. *Circulation*. 2007; 116:2072–2085. [PubMed: 17967988]
84. Lambert TL, Dev V, Rechavia E, Forrester JS, Litvack F, Eigler NL. Localized arterial-wall drug-delivery from a polymer-coated removable metallic stent – kinetics, distribution, and bioactivity of forskolin. *Circulation*. 1994; 90:1003–1011. [PubMed: 8044913]
85. Vairo G, Cioffi M, Cottone R, Dubini G, Migliavacca F. Drug release from coronary eluting stents: A multidomain approach. *J Biomech*. 2010; 43:1580–1589. [PubMed: 20185137]
86. Dev V, Eigler N, Sheth S, Lambert T, Forrester J, Litvack F. Kinetics of drug-delivery to the arterial-wall via polyurethane-coated removable nitinol stent – comparative-study of 2 drugs. *Catheter Cardiovasc Diagn*. 1995; 34:272–278.
87. Lovich MA, Edelman ER. Mechanisms of transmural heparin transport in the rat abdominal-aorta after local vascular delivery. *Circ Res*. 1995; 77:1143–1150. [PubMed: 7586227]
88. Sakharov DV, Kalachev LV, Rijken DC. Numerical simulation of local pharmacokinetics of a drug after intravascular delivery with an eluting stent. *Journal of Drug Targeting*. 2002; 10:507–513. [PubMed: 12575741]
89. Zunino P. Multidimensional Pharmacokinetic Models Applied to the Design of Drug-Eluting Stents. *Cardiovascular Engineering*. 2004; 4:181–191.
90. Mongrain R, Faik I, Leask RL, Rodes-Cabau J, Larose E, Bertrand OF. Effects of diffusion coefficients and struts apposition using numerical simulations for drug eluting coronary stents. *J Biomech Eng-Trans ASME*. 2007; 129:733–742.
91. Zhu XX, Pack DW, Braatz RD. Modelling intravascular delivery from drug-eluting stents with biodegradable coating: investigation of anisotropic vascular drug diffusivity and arterial drug distribution. *Comput Methods Biomech Biomed Eng*. 2012; 17:187–198.
92. Borghi A, Foa E, Balossino R, Migliavacca F, Dubini G. Modelling drug elution from stents: effects of reversible binding in the vascular wall and degradable polymeric matrix. *Comput Methods Biomech Biomed Eng*. 2008; 11:367–377.
93. Balakrishnan B, Tzafiriri AR, Seifert P, Groothuis A, Rogers C, Edelman ER. Strut position, blood flow, and drug deposition – Implications for single and overlapping drug-eluting stents. *Circulation*. 2005; 111:2958–2965. [PubMed: 15927969]
94. Davia L, Grassi G, Pontrelli G, Lapasin R, Perin D, Grassi M. Mathematical modelling of NABD release from endoluminal gel paved stent. *Comput Biol Chem*. 2009; 33:33–40. [PubMed: 18799356]
95. Cone RA. Barrier properties of mucus. *Advanced Drug Delivery Reviews*. 2009; 61:75–85. [PubMed: 19135107]
96. Cu Y, Saltzman WM. Mathematical modeling of molecular diffusion through mucus. *Advanced Drug Delivery Reviews*. 2009; 61:101–114. [PubMed: 19135488]
97. Peppas NA, Hansen PJ, Buri PA. A theory of molecular diffusion in the intestinal mucus. *International Journal of Pharmaceutics*. 1984; 20:107–118.
98. Kuo PY, Sherwood JK, Saltzman WM. Topical antibody delivery systems produce sustained levels in mucosal tissue and blood. *Nature Biotechnology*. 1998; 16:163–167.

99. Sawyer A, Saucier-Sawyer J, Booth C, Liu J, Patel T, Piepmeier J, Saltzman WM. Convection-enhanced delivery of camptothecin-loaded polymer nanoparticles for treatment of intracranial tumors. *Drug Deliv and Transl Res.* 2011; 1:34–42. [PubMed: 21691426]
100. Blum J, Weller C, Booth C, Babar I, Liang X, Slack F, Saltzman WM. Prevention of K-Ras- and Pten-mediated intravaginal tumors by treatment with camptothecin-loaded PLGA nanoparticles. *Drug Deliv and Transl Res.* 2011; 1:383–394.
101. Ensign LM, Tang BC, Wang YY, Tse TA, Hoen T, Cone R, Hanes J. Mucus-Penetrating Nanoparticles for Vaginal Drug Delivery Protect Against Herpes Simplex Virus. *Sci Transl Med.* 2012; 4
102. Yang M, Yu T, Wang YY, Lai SK, Zeng Q, Miao B, Tang BC, Simons BW, Ensign LM, Liu G, Chan K W Y, Juang C Y, Mert O, Wood J, Fu J, McMahon MT, Wu T C, Hung C F, Hanes J. Vaginal Delivery of Paclitaxel via Nanoparticles with Non-Mucoadhesive Surfaces Suppresses Cervical Tumor Growth. *Advanced Healthcare Materials.* 2013 n/a-n/a.
103. McCauley ME, Royal JW, Shaw JE, Schmitt LG. Effect of transdermally administered scopolamine in preventing motion sickness. *Aviat Space Environ Med.* 1979; 50:1108–1111. [PubMed: 393242]
104. Rennard S, Christen A, Beiswanger B, Mau M, Walker C, Hatsukami D, Allen S, Huber M, Jensen J, Daughton D, Cheney R, Hatlelid K, Thompson A, Lichtenstein E, Biglan A, Ochs L, Heatley S, Repsher L, Schones W, Stillman D, Casey C, Poole B, Leitch J, Fortmann S, Killen J, Hansen M, Douss LR, Hughes J, Valliere W, Solomon L, Wadland W, Glover E, Glover P, Causey D, Knowles M, Vossroberts K, Prather D, Trunnell N, Moos D, Rolf C, Nowak R, Ackerman P, Malone N. Transdermal nicotine for smoking cessation – 6-month results from 2 multicenter controlled clinical-trials. *JAMA-J Am Med Assoc.* 1991; 266:3133–3138.
105. Chetkowski RJ, Meldrum DR, Steingold KA, Randle D, Lu JK, Eggena P, Hershman JM, Alkjaersig NK, Fletcher AP, Judd HL. Biologic Effects of Transdermal Estradiol. *New England Journal of Medicine.* 1986; 314:1615–1620. [PubMed: 3012339]
106. Place, VA.; Nichols, KC. Transdermal delivery of testosterone with testoderm to provide a normal circadian pattern of testosterone. *New York Acad Sciences; New York:* 1991.
107. Audet MC, Moreau M, Koltun WD, Waldbaum AS, Shangold G, Fisher AC, Creasy GW, Grp OEES. Evaluation of contraceptive efficacy and cycle control of a transdermal contraceptive patch vs an oral contraceptive – A randomized controlled trial. *JAMA-J Am Med Assoc.* 2001; 285:2347–2354.
108. Good WR. Transder®-Nitro Controlled Delivery of Nitroglycerin via the Transdermal Route. *Drug Development and Industrial Pharmacy.* 1983; 9:647–670.
109. Lehmann KA, Zech D. Transdermal fentanyl – Clinical pharmacology. *J Pain Symptom Manage.* 1992; 7:S8–S16. [PubMed: 1517637]
110. Prausnitz MR, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery. *Nat Rev Drug Discov.* 2004; 3:115–124. [PubMed: 15040576]
111. Prausnitz MR, Langer R. Transdermal drug delivery. *Nature Biotechnology.* 2008; 26:1261–1268.
112. Jepps OG, Dancik Y, Anissimov YG, Roberts MS. Modeling the human skin barrier -Towards a better understanding of dermal absorption. *Advanced Drug Delivery Reviews.* 2013; 65:152–168. [PubMed: 22525516]
113. Mitragotri S, Anissimov YG, Bunge AL, Frasch HF, Guy RH, Hadgraft J, Kasting GB, Lane ME, Roberts MS. Mathematical models of skin permeability: An overview. *International Journal of Pharmaceutics.* 2011; 418:115–129. [PubMed: 21356301]
114. Anissimov YG, Jepps OG, Dancik Y, Roberts MS. Mathematical and pharmacokinetic modelling of epidermal and dermal transport processes. *Advanced Drug Delivery Reviews.* 2013; 65:169–190. [PubMed: 22575500]
115. Holz M, Fahr A. Compartment modeling. *Advanced Drug Delivery Reviews.* 2001; 48:249–264. [PubMed: 11369085]
116. Potts RO, Guy RH. Predicting skin permeability. *Pharmaceutical Research.* 1992; 9:663–669. [PubMed: 1608900]

117. Mitragotri S. Modeling skin permeability to hydrophilic and hydrophobic solutes based on four permeation pathways. *Journal of Controlled Release*. 2003; 86:69–92. [PubMed: 12490374]
118. Herron M, Agarwal A, Kierski PR, Calderon DF, Teixeira LBC, Schurr MJ, Murphy CJ, Czuprynski CJ, McAnulty JF, Abbott NL. Reduction in Wound Bioburden using a Silver-Loaded Dissolvable Microfilm Construct. *Advanced Healthcare Materials*. 2014 n/a-n/a.
119. Lao GJ, Yan L, Yang C, Zhang LM, Zhang SL, Zhou YJ. Controlled Release of Epidermal Growth Factor from Hydrogels Accelerates Wound Healing in Diabetic Rats. *J Am Podiatr Med Assoc*. 2012; 102:89–98. [PubMed: 22461265]
120. Johnson NR, Wang YD. Controlled delivery of heparin-binding EGF-like growth factor yields fast and comprehensive wound healing. *Journal of Controlled Release*. 2013; 166:124–129. [PubMed: 23154193]
121. Kobsa S, Kristofik NJ, Sawyer AJ, Bothwell ALM, Kyriakides TR, Saltzman WM. An electrospun scaffold integrating nucleic acid delivery for treatment of full-thickness wounds. *Biomaterials*. 2013; 34:3891–3901. [PubMed: 23453058]

Figure 1.

Mechanisms of transport and elimination of an agent during controlled release from a polymeric device into a local region of tissue. The solid circles represent the therapeutic agent and the arrows represent the modes of transport and reactions that occur after release from the device (top). Release from a controlled release device to the extracellular space (ECS) (arrow a), diffusion through the tortuous ECS due to concentration gradients (b), convective movement in the interstitial fluid within the ECS (c), internalization by a cell via passive, active, or facilitated transport to the intracellular space (ICS), which involves crossing through the cellular membrane (CM) (d), metabolism within the ECS (e), metabolism within a cell (f), diffusion across the semipermeable capillary walls (g), and the subsequent systemic transport or elimination via the capillary blood flow (h).

Figure 2.

Concentration of an agent as a function of distance from the controlled release device, where transport of the agent depends on diffusion only with first-order elimination under steady state conditions. Each curve represents a different value of the modulus θ , from 0 to 30: if $L = 1$ cm and D is 10^{-7} cm²/s, a typical diffusion coefficient for an agent in tissue (see Chapter 4 of [46]) these modulus values correspond to k values of 0 (no elimination), 10^{-8} , 10^{-6} , and 10^{-4} s⁻¹.

Figure 3.

Concentration profiles in the vicinity of a BCNU-releasing polymer implant.

Autoradiographic techniques were used to obtain the experimental results (open circles).

These experimental data were compared to model predictions, represented by the solid lines, obtained from steady-state diffusion/elimination or transient diffusion/convection models.

Adapted from Saltzman [46].

Figure 4.

The extent of agent penetration into a tissue as a function of the agent's properties. This prediction is based on a one-dimensional model in a rectangular coordinate system, but can be extended to other geometries [43].

Figure 5.

Predicted heparin penetration through an arterial wall after release from a perivascular controlled release device. The device is on the adventitial side of the artery. Here, Eq. (6) was used to simulate heparin concentrations assuming no convection ($v = 0$) and no elimination ($k = 0$). Appropriate boundary conditions allowed the investigators to predict heparin concentrations in the tissue as a function of time, and interpret experimental data on the biological response of the tissue to heparin delivery. Adapted from Lovich and Edelman [79], with permission.

Figure 6.

Mechanisms of transport and elimination of an agent during controlled release from a drug-eluting stent implanted in an artery. The solid circles represent the therapeutic agent and the arrows represent the modes of transport and reactions that occur after release from the device's struts. Release from a controlled release device to the extracellular space (ECS), either the intima, media, or lumen (arrow a), diffusion through the ECS due to concentration gradients or convective transport (b), partition from intima to media (c), metabolism within a cell (d), drug may be bound by protein binding in vessel wall (e) partition from media to adventitia (f), and the subsequent systemic transport or elimination from the adventitia (g).

Figure 7.

a) An example of numerical modeling of local drug release from the struts of a drug-eluting stent. Each of the white circular regions in the main image represents a stent strut, which is surrounded by vascular tissue. The lines indicate the mesh structure that is generated for numerical modeling of transport in the tissue surrounding the struts. The top image shows the global mesh and the zoomed image below shows more detail of the mesh resulting from the tighter spatial mapping adjacent to each strut. Adapted from Mongrain et al. [90], with permission. b) Geometry of a polymer-coated strut, partially embedded in an idealized arterial wall. Adapted from Zhu et al. and Davia et al. [91, 94].

Figure 8.

a) Schematic of compartmental model for antibody biodistribution after local controlled release from a vaginal ring. b) Predicted concentrations for antibody in the vaginal mucus (top) and blood (bottom) as a function of rate of release from the vaginal ring (the diffusion coefficient for antibody diffusion in vaginal ring—the controlling parameter for antibody release—varied from 0.3 to $30 \times 10^{-9} \text{ cm}^2/\text{sec}$). Adapted from Saltzman et al. [39]

Figure 9.

Antibody penetration through the vaginal epithelium depends on diffusion. These plots compare local antibody concentrations, measured by autoradiography, to steady-state solutions of the transport equations, as in Eq. (9), which are shown as solid lines. Concentrations measured in tissues from the nine mouse experiment at 16, 24, or 48 hr after insertion of an antibody-loaded vaginal ring are shown as open squares. Distance into tissue was measured relative to the tissue/mucus interface. Redrawn from original data presented in Kuo et al. [98].

Figure 10.

Mechanisms of drug transport and elimination during controlled release from a topical device on the skin. The solid circles represent the therapeutic agent and the arrows represent the modes of transport and reactions that occur after release from the device. Release and subsequent diffusion via transcellular, intercellular, or follicular routes (arrow a) to the extracellular space (ECS), drug may be reversibly bound by protein binding (b), diffusion through the ECS due to concentration gradients or convective transport (c), metabolism within a cell (d), partition through tissue layers (e), and the subsequent systemic transport or elimination (f). The thickness of the stratum corneum is represented by H.

Table 1

Analytical solutions for the drug transport equation (Eq. (6))

	Initial and Boundary Conditions	Analytical Solutions in Rectangular Coordinates
Steady-state solution (omitting convection)	$C = C_i$ for $x = 0$ $C = 0$ for $x \rightarrow \infty$	$C = C_i \exp\left(-\frac{x}{L}\phi\right) \quad \text{Eq. (9)}$
Transient solution (omitting convection)	$C = 0$ for $t = 0; x > 0$ $C = C_i$ for $t > 0; x = 0$ $C = 0$ for $t > 0; x \rightarrow \infty$	$C = C_i \left[\exp\left\{-x \sqrt{\frac{k}{D}}\right\} \cdot \operatorname{erfc}\left\{\frac{x}{2\sqrt{D \cdot t}} - \sqrt{k \cdot t}\right\} + \exp\left\{x \sqrt{\frac{k}{D}}\right\} \cdot \operatorname{erfc}\left\{\frac{x}{2\sqrt{D \cdot t}} - \sqrt{k \cdot t}\right\} \right] \quad \text{Eq. (10)}$
Transient solution (convection included)	$C = 0$ for $t = 0; x > 0$ $C = C_0$ for $t > 0; x = 0$ $C = 0$ for $t > 0; x \rightarrow \infty$	$C = C_0 \left\{ \operatorname{erfc}\left(\frac{x - v \cdot t}{2\sqrt{D \cdot t}}\right) + \exp\left(\frac{x \cdot v}{D}\right) \cdot \operatorname{erfc}\left(\frac{x + v \cdot t}{2\sqrt{D \cdot t}}\right) \right\} \cdot \exp(-k \cdot t) \quad \text{Eq. (11)}$
Transient solution (no convection or elimination)	$C = 0$ for $t = 0; x > 0$ $C = C_0$ for $t > 0; x = 0$ $C = 0$ for $t > 0; x = H$	$C = C_0 \left(1 - \frac{x}{H}\right) + \frac{2}{\pi} \sum_{n=1}^{\infty} \left(\frac{-c_0}{n}\right) \sin \frac{n\pi x}{H} \exp\left(-D \frac{n^2 \pi^2 t}{H^2}\right) \quad \text{Eq. (12)}$

 C_i = concentration at the polymer/tissue interface

L = half-thickness of the implant

$$\phi = L \sqrt{\frac{k}{D}} = \text{diffusion/elimination modulus}$$