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ORIGINAL ARTICLE

Design of optimized diffusion-controlled transdermal drug delivery systems

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Abstract

Background: We describe a systematic approach to designing multilayer transdermal patches based on therapeutically relevant specifications of the drug. *Method*: Random search optimization techniques are used to optimize maximum drug release from the patch subject to the therapeutic specifications. Barrier layer thickness and relative concentrations of the drug in the drug-containing layers are used as key design parameters. *Results*: A patch made of two drug-containing layers of equal thicknesses and relative drug concentrations of 20% and 80%, and a barrier layer with thickness of 14% compared to the total thickness of drug-containing layers was found to be the most optimum design. *Conclusion*: The proposed design is almost universally applicable and satisfies therapeutically relevant specifications while maximizing drug utilization.

Key words: Controlled release, diffusion, multilayer patch, optimization, skin, transdermal delivery

Introduction

Injections and oral dosage forms have traditionally been the dominant drug delivery systems. Pills are the easiest and most convenient way of delivering drugs, especially when routine administration is required for chronic therapy[1]. This advantage, however, is offset for sensitive drugs due to enzymatic degradation in the gastrointestinal tract. Injections comprise the second most commonly used method for delivering therapeutics. However, needle phobia is a significant issue in both adults and children making needle administration stressful[2]. Furthermore, hepatic metabolism results in rapid clearance of active drug from the blood plasma making repeated administration inevitable. Patient compliance, noninvasive and sustained delivery, and the ability to accommodate sensitive drugs are key features desirable of future drug delivery systems. Transdermal drug delivery is a promising candidate in this search. This technique makes use of the skin as a port of entry for systemic delivery of drug molecules[3–6]. Transdermal drug delivery relies on the absorption of a topically applied drug into the subcutaneous vasculature for systemic effects. Typically, the transport of drug from the skin surface into the underlying dermal capillaries occurs through diffusion or diffusion facilitated by physical or chemical permeation enhancers[7]. Transdermal administration eliminates hepatic first-pass metabolism and can significantly improve the bioavailability and half-life of a sensitive drug. This mode of administration is noninvasive and painless, thereby improving patient compliance. In its simplest form, a transdermal delivery device is an adhesive patch that is easy to apply on skin and provides patients the ability to self-administer the drug outside of a clinical setting. A typical transdermal patch contains a drug reservoir that contacts the skin on one side and is sealed by a backing membrane on the other. The reservoir may contain the active drug in a liquid formulation or dispersed in a polymeric matrix. To date, there are 19 marketed transdermal products (not counting generics) based on 17 drugs and it is estimated that more than 1 billion patches are manufactured annually[7].

The major thrust in transdermal drug delivery research today is on the formulations or devices that permeabilize the skin. In contrast, the patches still maintain a rudimentary design. The first generation of transdermal patches was designed for low-molecular-weight lipophilic drugs that are rapidly absorbed across the skin by diffusive transport. Topical application of these drugs from a reservoir

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placed on the skin is sufficient to produce therapeutically relevant systemic concentrations. However, the release profile obtained from a reservoir containing uniformly distributed drug shows a burst effect. After a lag period during which the skin is saturated with the drug, concentration of the drug in systemic circulation increases rapidly before declining to a steady value. The initial burst effect may cause the blood concentration of the drug to increase above its toxicity limits and is therefore clearly undesirable. The burst effect is of special concern for drugs that have a narrow therapeutic index (also termed therapeutic ratio). The therapeutic index is defined as the ratio of toxic dose (TD_{50}) to effective dose (ED_{50}). A low therapeutic index implies a narrow operating window between effective and toxic dosages. A large fraction of drugs used in transdermal patches today have a narrow therapeutic index. For example, fentanyl, a narcotic analgesic, which is increasingly prescribed in the form of a transdermal patch for pain management, has a narrow therapeutic index. A fentanyl overdose can cause difficulty in breathing, unconsciousness, and even death. Transdermal patches containing fentanyl, therefore, require rigorous control of the drug release rates to avoid complications arising from an overdose. Another example is a transdermal patch containing ethinyl estradiol and norelgestromin that has gained popularity as a contraceptive. Complications due to overdoses have been reported, including 60% higher serum levels of estrogen for users of the Ortho Evra patch as compared to oral contraceptives containing the same active drugs. This exposed patients to higher risks of heart attack, stroke, hypertension, venous thrombosis, and embolism[8]. Nicotine[9], cyclosporine[10], lidocaine[11], digoxin[12], clonidine[13], and insulin[13] are similar examples of narrow therapeutic index drugs that are in clinical use or under clinical trials for use in transdermal patches. Diffusion-controlled transdermal drug delivery patch systems incorporating these drugs need to be designed with great precaution to avoid any undesired burst effect. Various methods such as modification of the geometries of the device[14,15], use of rate-controlling barrier[16,17], judicious design of the polymer matrix encapsulating the drug[18–20], and use of organosilicate nanocomposites[21] have been proposed to overcome an undesired burst effect.

In this study, we propose an elegant yet practically easy and feasible method to obtain desired drug release profiles from a transdermal patch that consists of multiple layers of a polymer with nonuniform drug concentrations. We describe a systematic approach for designing transdermal delivery systems based on the therapeutically relevant specifications of maximum allowable dose rate, minimum effective dose rate, time to achieve the effective dose rate, and the design life of the patch. These therapeutically relevant specifications can be considered as constraints for optimization. The objective function of the optimization is depletion of the drug, where depletion is defined as the fraction of the drug initially charged to the delivery device that is actually delivered to the patient. It is generally possible to satisfy even demanding values of the therapeutically relevant specification if the depletion is low, that is, if much of the drug is wasted. The design approach presented here, however, satisfies therapeutic constraints while maximizing depletion and thus minimizing loss of a potentially high-value therapeutic. The approach is broadly applicable and can be applied to transdermal patches as well as implantable drug delivery systems. In this study, we will focus on the use of this device for transdermal drug delivery.

Methods

Patch geometry and design

The transdermal patch considered in this study is a multilayered, planar, drug-in-polymer adhesive patch that is directly applied to the skin. Each layer contains a different concentration of drug encapsulated in the polymer matrix. The patch is provided with a release liner which is removed immediately prior to use. Impermeable release films can be used to separate the layers during storage. An impermeable membrane, farthest from the skin, remains in place throughout the application life of the patch. Skin penetration enhancers and other expedients can also be incorporated in the polymer layers but are not explicitly considered in this study. Figure 1a shows the design considered in this study. The particular design illustrated in Figure 1a contains three distinct layers. All parameters of the patch are represented in a nondimensional form to allow a generalization of the results that has led to a nearly universal design. The first layer that contacts the skin, called the barrier layer, has zero initial concentration of the drug. The two successive layers have initial concentrations c_1 (Layer 1) and c_2 (Layer 2). The values of c_1 and c_2 are adjusted so that their average concentration is 1 and their sum is always equal to 2. The drug concentrations are initially uniform within a layer, and there is a sharp interface between the layers. The drug-containing layers have a total dimensionless thickness of 1.0. In the schematic shown in Figure 1a, the two layers have equal thickness of 0.5. The thickness of the barrier layer is expressed as a fraction, b, of the combined thicknesses of the drug-containing layers so that the total thickness of the patch including the barrier layer is $L = 1 + b$.

Mathematical formulation

A Fickian diffusion model is used to study the type of the patch discussed here. An analytical solution for the cases of interest in this study has been available for decades[22,23], although numerical solutions are easy to implement. The system is modeled as a one-dimensional transient diffusion system according to Fick's second law

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left(D \frac{\partial c}{\partial x} \right), \tag{1}$$

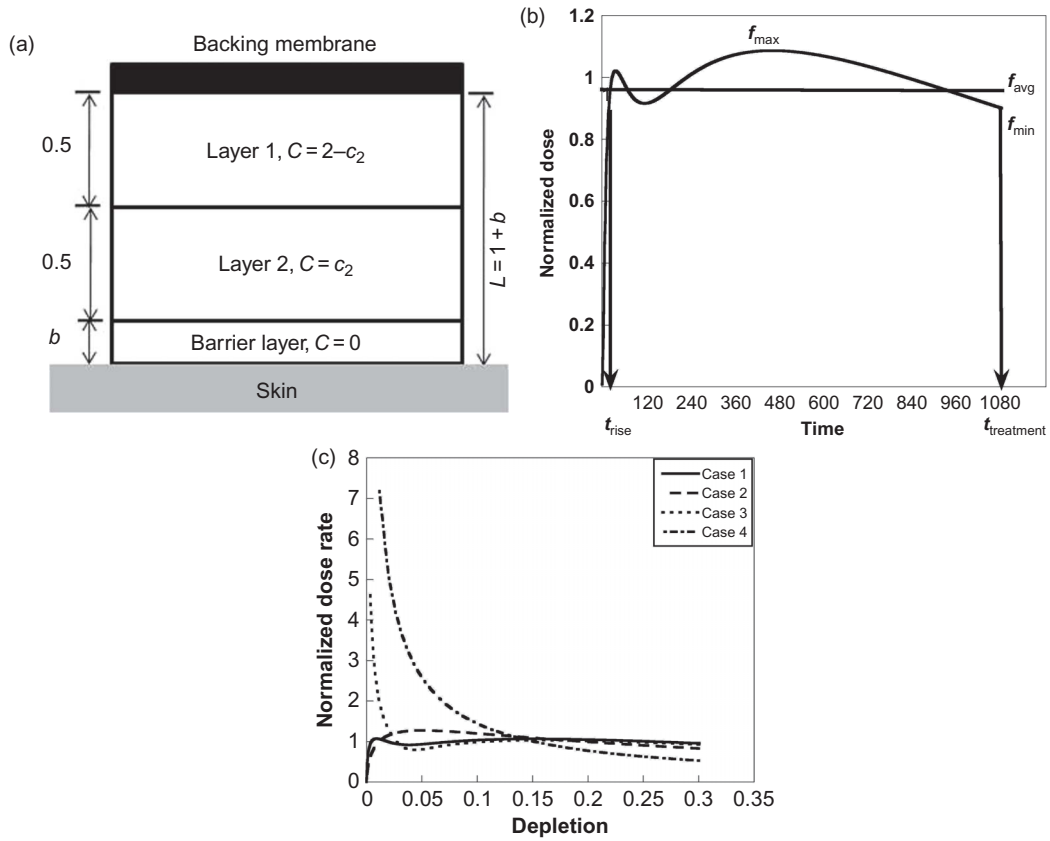

Figure 1. (a) Schematic of a typical patch considered in this study. The patch contains two layers of an adhesive polymer encapsulating an active drug along with a barrier layer. (b) Drug release profile desired from a patch. f_{avg}, f_{min}, and f_{max} represent the average, minimum, and maximum dose rates, respectively. t_{rise} and $t_{treatment}$ represent the time required to reach the minimum dose rate and total application time of the patch, respectively. (c) Drug release profile from conventional patch designs. Cases 1 and 2 show drug release profiles obtained from a patch with two and one drug-containing layer(s), respectively, with a barrier layer. Cases 3 and 4 show drug release profiles obtained from a patch with two and one drug-containing layer(s), respectively, without a barrier layer.

where x is a dimensionless variable, scaled by the combined thicknesses of the two layers that initially contain the chemical. The boundary conditions are

$$c = 0 \text{ at } x = 1 + b, \quad t > 0, \tag{2}$$

$$\frac{\partial c}{\partial x} = 0 \text{ at } x = 0, \quad t > 0. \tag{3}$$

Here, b is the scaled thickness of the barrier layer. The initial conditions for the two-layer case are

$$\begin{aligned} c(0,x) &= c_1 = f(x) \text{ at } t = 0, \quad 0 < x < x_1, \\ c(0,x) &= c_2 = f(x) \text{ at } t = 0, \quad x_1 < x < 1, \\ c(0,x) &= 0 = f(x) \text{ at } t = 0, \quad 1 < x < 1 + b. \end{aligned} \tag{4}$$

The solution to this partial differential equation, with constant diffusivity D, is available in the literature[22,23]:

$$C(t,x) = \left(\frac{2}{1+b}\right)\sum_{n=0}^{\infty} \exp\left(\frac{-D(2n+1)^2 n^2 t}{4(1+b)^2}\right) \times \cos\frac{(2n+1)\pi x}{2(1+b)} \int_0^{1+b} C_0(x') \cos\frac{(2n+1)\pi x'}{2(1+b)}\, dx'. \tag{5}$$

As the barrier layer is initially free of the chemical, the effective upper limit of the integral in Equation (5) is 1. For the case of two chemical-containing layers,

$$C(t,x) = \left(\frac{2}{1+b}\right)\sum_{n=0}^{\infty} \exp\left(\frac{-D(2n+1)^2 n^2 t}{4(1+b)^2}\right) \cos\frac{(2n+1)\pi x}{2(1+b)} \times \left[\int_0^{x_1} c_1 \left(\cos\frac{(2n+1)\pi x}{2(1+b)}\right) dx + \int_{x_1}^{1} c_2 \left(\cos\frac{(2n+1)\pi x}{2(1+b)}\right) dx\right]. \tag{6}$$

The flux or release of the drug is determined by differentiation of Equation (6) with respect to x and setting $x = L = (1 + b)$:

$$J(t,L) = -D\left(\frac{\partial c}{\partial x}\right)_{x=L}, \tag{7}$$

$$J = \frac{2D}{1+b}\sum_{n=0}^{\infty} (-1)^n \exp\left(\frac{-D(2n+1)^2 \pi^2 t}{4(1+b)^2}\right) \times \left\{(c_1 - c_2)\left[\sin\frac{(2n+1)\pi x_1}{2(1+b)}\right] + c_2\left[\sin\frac{(2n+1)2\pi x_2}{2(1+b)}\right]\right\}. \tag{8}$$

Equation (8) provides the flux for a patch with two layers that initially contain the drug and a barrier layer that is initially free of the drug. In this result, the total scaled thickness of the device is $1 + b$. The relative thicknesses of the various layers can be adjusted by appropriately selecting x_1 and b.

Specifications for drug and patch

We assume that the following therapeutically relevant parameters are known and specified for the drug based on its pharmacokinetic profile: (1) the desired treatment time, $t_{\text{treatment}}$ (week or month); (2) the desired amount of drug to be delivered over the duration of treatment, d (mg or g); (3) the desired average dose rate, $f_{\text{avg}} = d/t_{\text{treatment}}$ (mg/day); (4) the minimum effective dose rate, $f_{\text{min}} < f_{\text{avg}}$ (mg/day); (5) the maximum allowable dose rate, $f_{\text{max}} > f_{\text{avg}}$ (mg/day); and (6) the maximum allowable time, t_{rise}, to achieve the minimum effective dose rate (minutes or hours after the patch is applied to the skin). In addition to the therapeutically relevant specifications for the drug, the patch designer needs to specify the following parameters for the patch itself: (1) patch size (contact area) and (2) total thickness of the drug-containing layers. These parameters are mostly determined based on practical considerations of use of the patch by the end user.

Once all specifications for the drug and the patch are available the optimizations will determine the relative amounts of drug in each of the drug-containing layers, the thickness of the barrier layer relative to the combined thicknesses of the drug-containing layers, and the total charge of drug consistent with the optimized maximum depletion. Empirical cross-linking experiments can be used to set the drug diffusivity in the patch to achieve the desired, maximum depletion in the treatment time. All specifications are converted to dimensionless numbers. Distances are scaled by the combined thicknesses of the drug-containing layers, and dose rates are scaled by the average dose rate. The rise time is scaled by total treatment time. Figure 1b shows a response curve desired from an optimal patch design and illustrates the various specifications for the drug. Note that all dose rates have been normalized by the average dose rate, $f_{\text{avg}} = d/t_{\text{treatment}}$.

Following assumptions are made about the drug encapsulated in the polymer matrix:

1. The drug-containing layers as well as the barrier layer are made of a cross-linkable polymer and the diffusivity of the drug in the polymer matrix can be adjusted empirically through the degree of cross-linking.
2. The maximum drug loading is low enough so that the diffusivity of the drug is independent of its concentration.
3. The skin behaves as a perfect sink. This assumption holds true for low-molecular-weight lipophilic solutes that show high partition coefficients and consequently high absorption rates across the skin. Almost all transdermal drugs marketed in the form of a patch fall under this category. This assumption can be modified for solutes for which skin behaves as a transport barrier, but this situation is beyond the scope of this study.

Optimization objective and strategy

The desired outcome of the proposed patch design is to rapidly attain the minimum effective dose rate and to maintain the instantaneous dose rate above the minimum effective value but below the maximum allowable dose rate throughout the remainder of the treatment time. The optimization process can be used to determine the relative amounts of drug in each of the drug-containing layers, and the total charge of drug consistent with the desired outcome. Maximum possible drug depletion, subject to therapeutically relevant specifications of f_{min}, f_{max}, and t_{rise}, is defined as the goal for the optimization process. Depletion is defined as d/M_0, where d is the total amount of drug delivered from the patch over the entire application time and M_0 is the initial loading of the drug summed over all layers. We assume that the average dose rate and values for the three constraints are medically prescribed. There obviously must be some latitude, that is $f_{\text{min}} < 1$, because an absolutely flat delivery profile by diffusion from a patch is impossible. Note that f_{min} and f_{max} have been scaled by the average dose rate. The fractional depletion must also be less than 1. Patch design parameters, other than the empirically determined extent of cross-linking needed to achieve the desired average dose rate, are independent of the desired average dose rate. A maximum value for the fractional depletion of the initial drug loading will be determined by optimization. The absolute value for M_0 can be calculated from the desired dose rate in absolute units such as mg/day and the optimized, fractional depletion. For optimization purposes, it is sufficient to set $M_0 = 1$ in arbitrary units. There are two design parameters, c_2 and b, that are chosen to maximize depletion, while satisfying the constraints on f_{min}, f_{max}, and t_{rise}. Note that c_1 is not independently adjustable. For the case where the two drug-containing layers have equal thickness, that is, $x_1 = 0.5$, c_1 is constrained by the overall material balance: $c_1 = 2 - c_2$

The objective of the current optimization problem is to determine the best values for the parameters c_2 and b. Best values are those that will maximize depletion while satisfying the constraint on f_{min}, f_{max}, and t_{rise}. Random search optimization technique was used in this study. This technique can be applied to constrained or unconstrained optimization problems and nonlinearities are easily accommodated. It can be used with any number of adjustable parameters, and it has been used for a 99-parameter estimation of an optimal function[24]. The solution starts with initial guesses of c_2 and b that satisfy the constraints. A small random change is made in these parameter values to create a new set. If this new set satisfies all the constraints and gives a better value of the depletion, it is accepted

and becomes the starting point for another set of random changes. Otherwise, the old parameters are retained as the starting point for the next attempt. The key step is the random variation that simultaneously changes the new trial values for the parameters. For this study, the following steps are used:

$$c_2 = c_{2\text{best}} + 0.01(\text{Rnd} - 0.5),$$
$$b = b_{\text{best}} + 0.01(\text{Rnd} - 0.5).$$

Here, Rnd is a random number uniformly distributed over the range 0–1. Repeated numerical experiments with different initial values can be used to search the optimal values of c_2 and b to get the maximum depletion. Note that $0 < c_2 < 2$ and that $b > 0$.

The random search technique is computationally inefficient but robust and easy to implement. The computational expense for the studies reported here was insignificant when using the analytical solution for flux. The same calculations have been performed numerically for more complicated cases but remain simple and fast to implement[25].

Results

Drug release profile from conventional patch designs

A conventional patch system where a drug is dissolved in a single polymer matrix shows an undersired burst effect. The barrier layer plays an important role in controlling this burst. Figure 1c shows normalized dose rates plotted against depletion for several design strategies with and without the barrier layer. Cases 1 and 2 illustrate the use of barrier layer that causes zero flux at the time of initial contact, $t = 0$. Case 1 shows a response curve obtained from a design with a barrier layer and two drug-containing layers. The response in Case 2 is obtained from a design utilizing a barrier layer and a single drug-containing layer. Cases 3 and 4 show flux profiles obtained from a design with two and one drug-containing layer(s), respectively, without a barrier layer. These designs theoretically give infinite flux at $t = 0$. The profiles in Figure 1c are plotted until the instantaneous dose rate reaches a depletion of 30%, suggesting the patch must be discarded after 30% of the initial mass has diffused out of the patch. This limit is chosen somewhat arbitrarily and can be changed depending on the specific drug. In general, maximum depletion is preferred for economical reasons. It should be noted that curves in Figure 3 are not optimized results. The optimization results are discussed subsequently and describe a patch design with two drug-containing layers along with a barrier layer.

Drug release profile from optimized patch designs

The optimization problem was solved for different values of f_{min}. Figure 2 shows (a) maximized depletion, (b) maximum dose rate, and (c) rise time plotted as a function of dimensionless f_{min}. Note that c_1 is not independently adjustable and is subject to constraint $c_1 + c_2 = 2$. From Figure 2a and b, if $f_{\text{min}} = 0.5$, the depletion is about 75% and f_{max} is 1.54, respectively. If this f_{max} is not acceptable, then f_{min} is increased with a consequent reduction in the depletion and f_{max}. For example, for $f_{\text{min}} = 0.85$, the depletion and f_{max} reduces to 42% and 1.12, respectively. Therefore, there is a clear trade-off between the depletion and f_{min}. In Figure 2a, the smooth line is an approximation that uses $c_2 = 0.4$ and $b = 0.14$ for different values of f_{min} while filled diamonds represent the optimized depletion. Although the depletion values of f_{min} while filled diamonds represent the optimized depletion. Although the depletion values are marginally lower for the approximation than for the optimized results, a patch with $c_2 = 0.4$ and $b = 0.14$ has the strong merit of near universality. It provides drug delivery with the limits of $0 < f_{\text{min}} < 0.9$ at near optimal utilization of the drug. The results in Figure 2a are based on maximizing the depletion subject to the specified values of f_{min} and f_{max}. Corresponding values of f_{max} are plotted in Figure 2b. The optimized results shown in Figure 2a also reflect a constraint, $t_{\text{rise}} < 0.02$. The approximation using $c_2 = 0.4$ and $b = 0.14$ gives shorter rise times than the optimized results because for a fixed patch design, higher depletions over time $t_{\text{treatment}}$ require higher diffusivities. From Figure 2c, if $f_{\text{min}} = 0.9$, the rise time is about 0.02 or just over 3 hours for a patch designed for 1 week application. If f_{min} can be relaxed to 0.8, the rise time drops to approximately 2 hours for a 1-week patch. As an example, to design a patch from results shown in Figure 2a–c, suppose the medically prescribed value of f_{min} is 0.6. Either optimal values or approximations of c_2 and b can be chosen. According to Figure 2a–c, the corresponding values of depletion, f_{max}, and t_{rise} are approximately 70%, 1.4, and 0.005, respectively, for approximated values of c_2 and b. If this f_{max} or overdose is acceptable, then the optimization is complete. If f_{max} is too high, then f_{min} must be increased with a consequent reduction in depletion and an increment in t_{rise}. Figure 2d shows flux profiles as a function of depletion for different values of minimum dose. For example, in the profile for $f_{\text{min}} = 0.75$, the corresponding values of depletion and f_{max} are approximately 55% and 1.2.

Effect of drug layer thickness and nonuniform diffusivity on patch performance

The optimization results in the previous section assume equal thickness of two drug-containing layers and equal diffusivities in the entire patch. It is also possible to treat the relative thicknesses of the two drug-containing layers as optimization variables. However, Figure 3a indicates that there is little improvement to be gained in patch performance by varying the thickness of drug-containing layers. This is in agreement with published literature[26]. In the optimized results discussed

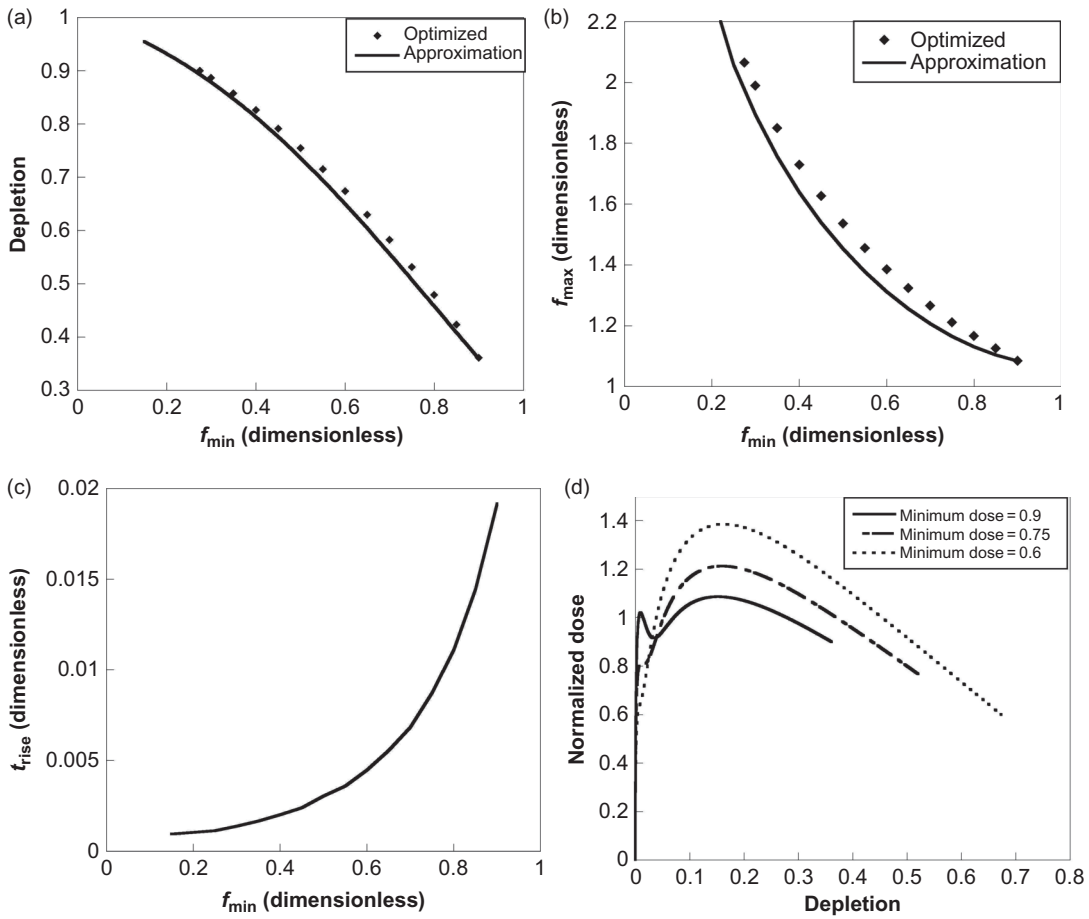

Figure 2. (a) Maximum depletion obtained from an optimized patch as a function of minimum dose rate. (b) Maximum dose rate obtained from an optimized patch as a function of minimum dose rate. Approximation represents a patch design with $c_2 = 0.4$ and $b = 0.14$. (c) Rise time as a function of minimum dose rate in an optimized patch design. (d) Drug release from an optimized patch for different specified minimum doses.

previously, the diffusivities were assumed to be uniform in all three layers, that is, two drug-containing layers and the barrier layer. The combined effects of nonuniform initial concentration profile and nonuniform diffusivities were examined. The objective is to determine optimum initial concentrations and barrier thickness to maximize the depletion while satisfying the constraints on f_{min}, f_{max}, and t_{rise}. Two situations were examined: (a) uniform diffusivity, $D = 1$, in all three layers and (b) the diffusivity of barrier layer, $D = 1.25$, higher than the diffusivity, $D = 1$, in the drug-containing layers. Figure 3b indicates that the small difference in the diffusivity of the barrier layer has an insignificant effect on the depletion. As the diffusivity in the barrier layer increases, the optimal barrier thickness also increases (Figure 3c) but the optimal initial concentration profile remains more or less the same (Figure 3d). The barrier layer thickness is an independent parameter that is varied by the optimization technique to compensate for the higher diffusivity.

Effect of number of drug-containing layers on patch performance

Variable thickness of the drug layers and variable diffusivities in the patch have little or no improvement in the depletion. It is desirable to see if the patch comprising of three or more drug-containing zones of equal thickness has any significant improvement in the depletion. A patch containing three layers each of thickness 1/3 (Figure 4a) and a patch containing five layers each of thickness 1/5 (Figure 4b) were designed and results compared with the design of a patch with two layers, each of thickness 1/2. The maximized depletion profiles for 2-, 3-, and 5-layer patches as a function of f_{min} are shown in Figure 4c. The depletion for $f_{min} = 0.9$ is approximately 35%, 37%, and 40% for 2, 3, and 5 layers, respectively. The depletion did not increase beyond 40% for a 7-layer patch (data not shown). This is expected considering the design approach and the optimization problem which has to satisfy the constraints of f_{min}, f_{max}, and t_{rise}.

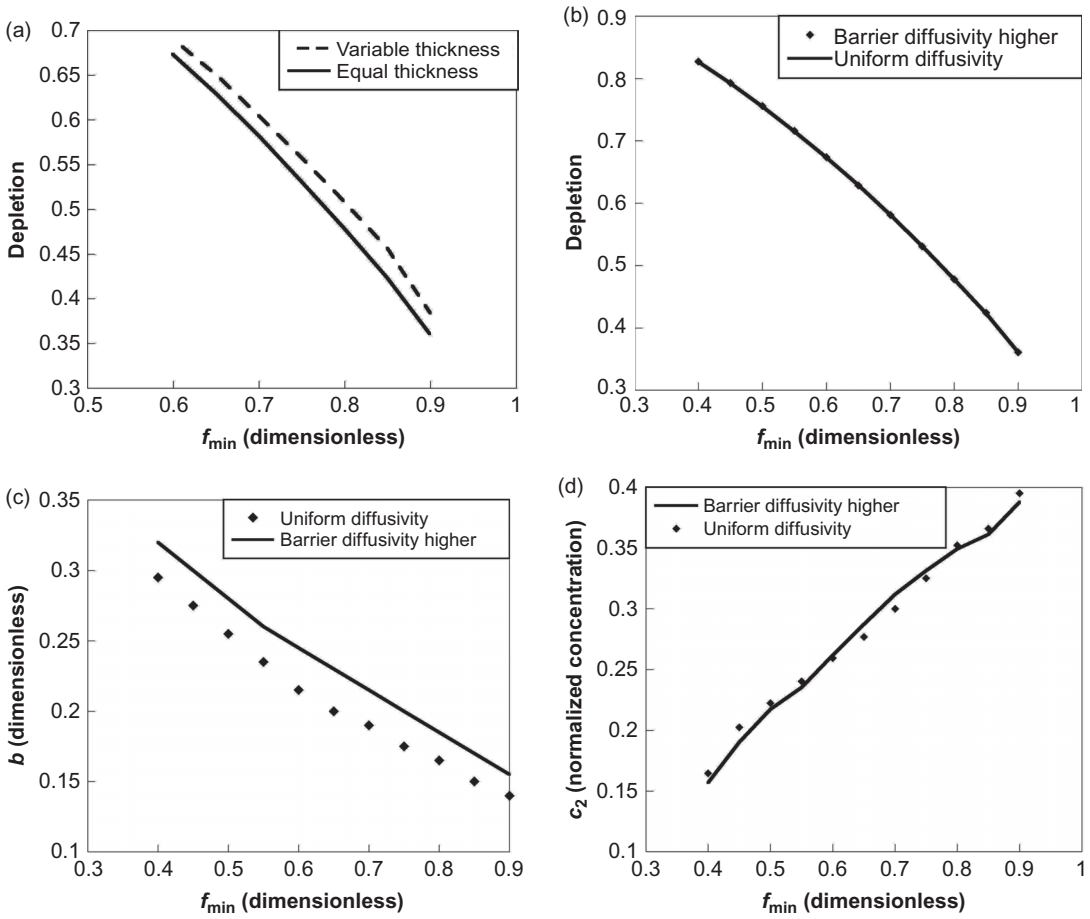

Figure 3. (a) Drug depletion from a patch containing drug-incorporating layers of equal thickness and variable thicknesses. (b) Drug depletion from a patch with uniform and nonuniform drug diffusivity in the barrier layer and the drug-containing layers. (c) Barrier layer thickness for a patch with uniform and nonuniform drug diffusivity in the various layers. (d) Initial drug concentration profile in a patch with uniform and nonuniform drug diffusivity in the various layers.

Discussion

Transdermal drug delivery presents an attractive alternative to systemic delivery of active therepeutics that have low bioavailability due to high degradation in the gastrointestinal tract or significant hepatic metabolism when delivered by the parenteral route. Transdermal delivery overcomes the hepatic first-pass metabolism and avoids degradation problems associated with the enteral route of drug administration. Besides, the noninvasive and painless delivery characteristics improve patient compliance, especially for chronic therapy. A transdermal patch using a single layer with an initially uniform drug concentration gives an initial burst that can lead to complications for drugs with a narrow therapeutic index. One way to eliminate the undesired burst effect is through the use of a rate-controlling barrier membrane. In this study, we present the theory of an alternative approach based on the use of multiple layers containing different initial drug concentrations to obtain highly sustained drug delivery rates while maximizing drug utilization from the patch. Maximum drug utilization is important for economical reasons in case of high-value therapeutics. Considerable efforts have been made to model diffusion-controlled release from a single-layered system containing a dispersed, particulate drug[27–29]. Rather, less effort has been spent on simulating diffusion of a drug when its concentration is nonuniform and below its saturation solubility in a multilayer polymer device. Lee[30] has examined the effect of nonuniform initial concentrations on the release kinetics from diffusion-controlled and surface erosion-controlled matrix systems containing a dissolved drug. Lu et al.[31] and Georgiadis and Kostoglou[26] contributed further by determining the initial drug concentration in the layers to provide a system that exhibits a substantially constant drug flux. They chose to minimize the standard deviation between the instantaneous and desired drug release rate. However, the use of standard deviation provides little insight from a therapeutic viewpoint and a low value of standard deviation may mask a large, short-term excursion. Also, the necessary trade-off between the various therapeutically relevant specifications and effective utilization of the drug has not been fully explored.

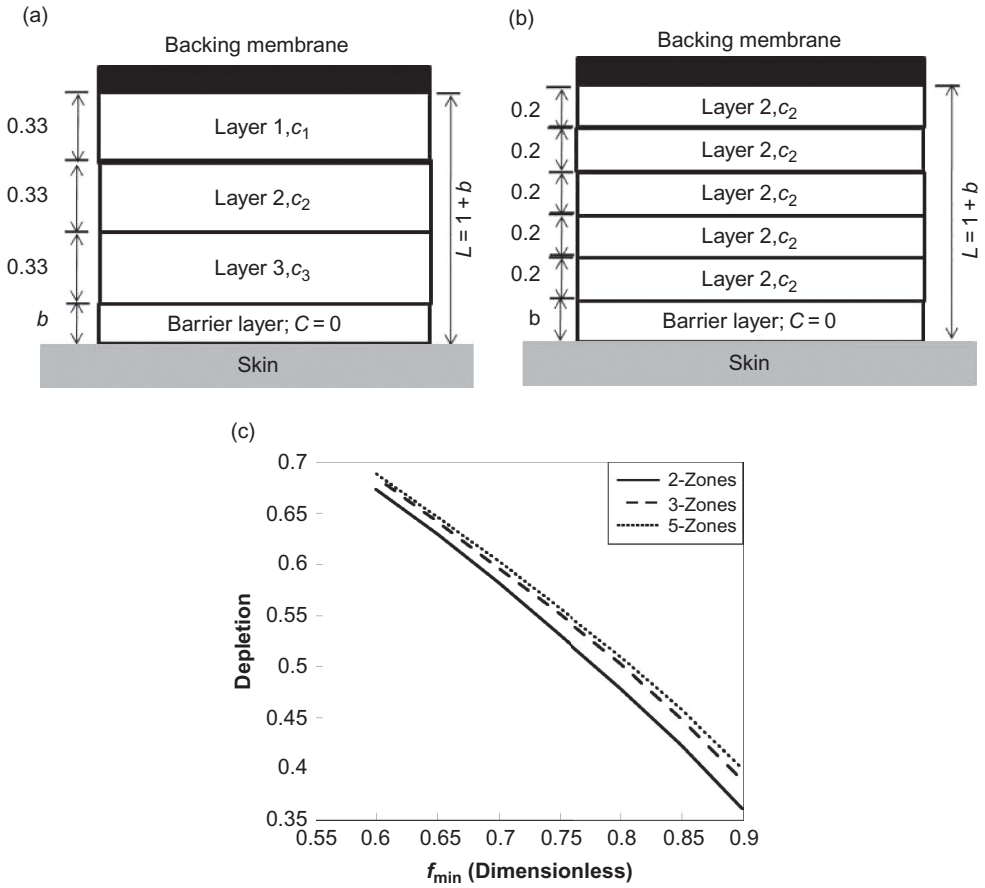

Figure 4. (a) Patch configuration comprising of three drug-containing layers and a barrier layer. (b) Patch configuration comprising of five drug-containing layers and a barrier layer. (c) Drug depletion obtained from a patch containing 2, 3, and 5 drug-incorporating layers.

The current study provides a systematic approach to the design of transdermal patches based on the therapeutically relevant specifications of maximum allowable dose rate, minimum effective dose rate, time to achieve the effective dose rate, and the application life of the patch. An optimal patch would attain the minimum effective systemic concentration of the drug in a short time and maintain the dose rate at a steady value above the minimum effective concentration but below the toxic dose for the entire time the patch is applied (Figure 1b). Conventional patch designs utilizing a uniform drug reservoir exhibit infinite flux at time t = 0 (Figure 1c: Cases 3 and 4). Addition of a barrier layer significantly reduces this initial burst (Figure 1c: Cases 1 and 2). Figure 2 shows further optimization of the patch design by incorporating a barrier layer along with two drug-containing layers with uniformly distributed drug at different concentrations. A clear trade-off is observed between depletion and minimum desired dose rate (Figure 2a). As the minimum desired dose rate approaches the average dose rate, the amount of drug available for therapeutic benefit drops significantly. A similar inverse relation is observed between the minimum dose rate and maximum allowed dose rate (Figure 2b). Maintaining the maximum allowable dose rate below the toxic limit and closer to the average dose rate necessitates a higher minimum dose rate and consequently lower drug utilization from the patch. The time required to attain therapeutically minimum systemic concentrations of the drug depends exponentially on minimum prescribed dose rate (Figure 2c). Transdermal patches incorporating analgesics or pain relievers would favor short rise times. The minimum dose rate for such patches needs to be optimized to provide a safe upper limit on the maximum dose rate while still maximizing depletion from the drug reservoir. Optimized profiles such as those shown in Figure 2d along with data in Figure 2a–c can be employed for selecting the operational parameters of rise time, dose rates, and depletion. Data shown in Figure 2 also provides an almost universal set of patch parameters for optimized performance. A two-layer patch with initial drug loading of 20% and 80% in the two drug-containing layers along with a barrier layer that has thickness of 14% relative to the total patch thickness performs quantitatively similar to an optimized patch. This result has important consequences in design of a patch for virtually any therapeutic that maximizes drug utilization while still adhering to specified dose rates as

well as total dosage. In further optimizing the patch design obtained in Figure 2, we observed that varying the thicknesses of drug-containing layers or the diffusivity of drug in the barrier layer has only marginal effect on performance of the patch (Figure 3). We also assessed the improvement in patch performance by adding multiple drug-containing layers. Again, only marginal improvements were observed when increasing the number of drug-containing layers from 2 to 5 (Figure 4). Results described in Figures 2–4 indicate that we have arrived at an optimized patch design that contains two drug-incorporating layers along with a barrier layer. Also, this optimized performance can be mimicked through the use of a universal combination of (1) drug loading in the drug-incorporating layers and (2) barrier layer thickness for any drug subject to its therapeutically relevant constraints.

Practically, nonuniform initial concentration profiles can be achieved through the use of multilaminates prepared by solvent casting[16] and photopolymerization techniques[31,32]. The individual drug-containing laminates need to be isolated from each other prior to application. If the device is fully assembled prior to its application to the patient, diffusion will occur during normal storage, eliminating the desired concentration differences between the layers. To avoid this scenario, the device should be assembled immediately prior to use. One approach is to insert impermeable slip films between the layers and to remove them when the patch is applied to the skin. Alternately, the patch assembly can be frozen and maintained at a suitably low temperature prior to use.

Conclusion

A drug delivery device comprising two drug-containing layers and a barrier layer was designed to satisfy therapeutically relevant specifications while maximizing utilization of the drug. The novel and broadly applicable approach produced a design of almost universal applicability. The mathematical analysis showed that the burst effect could be controlled by varying the concentration distribution of drug in the two zones and mainly by an addition of the barrier layer. The random search optimization technique was successfully used to search systematically the initial concentration distribution in the two zones and the thickness of the barrier to maximize the depletion of drug from the patch while satisfying all the operational characteristics. A study using nonuniform diffusivities in the patch showed an insignificant improvement in the depletion, little advantage of using different thicknesses for the two drug-containing layers or using more than two drug-containing layers. Therefore, we can conclude that the specified design using two drug-containing layers and a barrier layer is a practical optimum that satisfies the therapeutic constraints while being practical in terms of manufacturing and application.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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