Mathematical models of transdermal delivery systems

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Abstract

Stratum corneum is the remotest region of the skin and it is basically a multilayer lipid substrate pointed by corneocytes filled with proteins that compound the integrity of the membrane and drastically increase its tortuosity. Its hydrophobic nature, together with its natural tortuosity, insures that it nearly always provides the top hedge to the entrance of pharmaceutical molecules into the body. The only exceptions are represented by large hydrophobic compounds which can encounter problems at the interface between stratum corneum and viable epidermis where they are partitioned into an aqueous environment. Drug molecules can be administered either as liquid solutions or as suspensions and the final formulation can be more or less complex starting from gels or ointments multilayer transdermal patches. In this chapter we focus our attention on theoretical principles that can be used to describe transdermal release and we show that fairly simple models of membrane transport grounded on the applicable result to the second Fick's law of mass diffusion can explain drug release kinetics into this very complex biological environment.

Keywords: hydrogels, drug delivery, polymer, transderma, transport phenomena.

Contents

1. Introduction

Drug delivery through transdermal route (TDDS) is a feasible route of administration for high-potent, low-molecular weight therapeutic molecules that are subjected to considerable first-pass metabolism by the liver and/ or cannot repel the hostile terrain of the gastrointestinal tract [1, 2]. The proper selcetion of the active principle is governed by a huge number of factors including the physicochemical characteristics of the drugs, its pharmacokinetic property and its relations with the biological membrane [3, 4]. The delivery of drug molecules from a formulated device through the skin surface and its transport is a multistep process that involves:

(a) dissolution and then delivery from the device;

(b) partitioning into the external layer of the skin (stratum corneum, SC);

(c) transport through SC, via lipidic intercellular pathway, that represents the rate-limiting step of utmost compounds;

(d) partitioning from SC into the waterless feasible epidermis;

(e) diffusion into the upper dermis and through the epidermis;

(f) the capillary network uptake and then the systemic circulation (**Figure 1**) [5].

Thus, an ideal medicine candidate should have lipophilicity sufficient to partition into SC, but also proper hydrophilicity to guarantee the alternate step of partitioning into the feasible epidermis and ultimately into the systemic circulation. For utmost active molecules, except those enjoying very high lipophilicity, the step that determines the transport across the skin is the one across SC. However, from a release viewpoint, it is extremely better that the rate control is present in the delivery device to maintain invariant input rates and reduce variability from body to body. A TDDS is a medical device that can maintain the drug concentration in the blood within a specific therapeutic range ensuring that this level stays in between under and over dosing [6, 7]. It is indeed widely known that an underdosing condition corresponds to the absence of pharmacological activity of the active principle while an overdosing one is related to toxic level. In summary the proper design of an efficient TDDS should take into consideration many aspects starting from formulation to drug release performances. In this framework mathematical modelling can provide unique peculiarities, encouraging researchers to avoid trial-and-error approaches toward rational model-based methods [8-10].

In this chapter we discuss the most important mathematical models that can describe the transdermal release from a series of different medical devices. The models considered are built starting from second Fick's law of mass diffusion for mass transport across an homogeneous membrane with the applicable boundary conditions [11, 12].

[Insert Figure X.1 here]

2. Mathematical models in TDDS

As already said the rate of drug release from TDDS is controlled both by SC and the delivery device considered. So, the total transport phenomenon is the result of the combination of the device and the skin effects. Guy and coworker, for the first time, studied and identified the contribution of the medical device and the skin in TDDS [13].

They compared the amount of molecules released in a specific period of time from the device alone (M_{dev}) into aqueous solution with the amount obtained when the same device was in contact with the skin (M_{total}). The ratio between these two numbers reveals the relative contribution of the two effects:

$$F_D = fractional\ rate\ control\ by\ device = \frac{M_{total}}{M_{dev}} \quad (1)$$

If F_D=1 the release is controlled by the device, if F_D<1 the contribution of the skin is important. We can also consider that:

$$F_S = fractional\ rate\ control\ by\ the\ skin = (1 - F_D) = 1 - \frac{M_{total}}{M_{dev}} \quad (2)$$

Hadgraft and coworkers [14] investigated different transdermal systems considering different areas of contact with the skin and drug loading procedures. It was shown that the fractional rate control by the device is a number between 0.13 and 0.87. Among them they discovered that the most important parameter is represented by the surface area adherent to the skin. So, the most important parameter to be identified is the quantity of drug that is absorbed and then the relative contributions of the medical device and the skin.

2.1 Semi-solid dosage form

One of the simplest formulated devices is represented by the ones based on semi-solid forms [15, 16]. They consist on cream or ointment loaded with a finely divided drug suspension able to guarantee extremely high pharmacological activity. In this field Gao and coworkers developed a novel treatment for Estrogen Receptor-Positive (ER^+) breast tumor based on Formestane (4-OHA) cream that is able to overcome the drawbacks of traditional intramuscular administration [17]. In particular this novel formulation can retain the effects related to tumor shrinking. So, even if this research needs further confirmation studies it is possible to state that this formulation represents a better alternative, respect to classic administration routes, for the delivery of drug molecules (here Formestane) in ER^+ breast cancer (**Figure 2**).

[Insert Figure X.2 here]

Drug release is controlled by its formulation, as in the case of formulation with high viscosity that contains high lipophilic species or if the device is applied to a damaged skin. In other cases the rate-determining step is the transport through stratum corneum where the drug motion takes place quickly in the device. It then moves through the stratum corneum at a velocity obtained by the diffusivity determined within the membrane. The condition when the rate-determining step is represented by the transport within the device that contains a drug suspension was firstly analyzed by the work of Higuchi [18, 19]. In accordance with his theory, the quantity of drug molecules taken up by stratum corneum (per unit area) under quasi-steady state condition is:

$$Q = \sqrt{D \cdot t \cdot C_S \cdot (2C_o - C_S)} \quad (3)$$

Q: amount absorbed per unit area, C_o: initial drug concentration, C_s: solubility of drug within the system, D: diffusion coefficient through the device, t: time. By differentiating Equation 3 we can obtain the drug release rate at time t:

$$\frac{dQ}{dt} = \frac{1}{2} \cdot \sqrt{\frac{D \cdot C_S \cdot (2C_o - C_S)}{t}} \quad (4)$$

Considering that $C_o >> C_s$ Equations 3 and 4 can give:

$$Q = \sqrt{2 \cdot C_o.D \cdot t \cdot C_S} \quad (5)$$

$$\frac{dQ}{dt} = \sqrt{\frac{C_o \cdot D \cdot C_S}{2t}} \quad (6)$$

Bunge and coworkers [20] tested the approximation obtained by Higuchi and compared the results obtained with the mathematical solution of the equation that describes the system over the concentration range as discussed by Paul and coworkers [21]. The percentage released (M_t / M_o) can be obtained from a linear profile of concentration in the region where drug is dissolved. This can be done also considering the approximation of Higuchi:

$$\frac{M_t}{M_o} = \sqrt{\frac{2 \cdot D \cdot t \cdot R \cdot \left(1 - {}^{R}/_{2}\right)}{L^2}} \quad (7)$$

where the ratio C_s/C_o=R, L: device thickness. The exact solution obtained by Paul and coworkers [21] (no assumption of linear profile at the interface) is:

$$\frac{M_t}{M_o} = 2 \cdot \left(1 - R \cdot \beta \cdot e^{\beta^2} \cdot \sqrt{\frac{D \cdot t}{L^2}}\right) \quad (8)$$

Introducing the error function of β (erf(β)) β can be obtained by:

$$\sqrt{\pi} \cdot \beta \cdot e^{\beta^2} \cdot erf(\beta) = \frac{R}{1-R} \quad (9)$$

It is possible to state that both the exact solution and Higuchi approximation can predict the normalized percentage of drug released that presents an almost linear dependence on *R*. Higuchi equation presents a low underestimation of the drug released while exact solution is more precise. Bunge [20] discovered that this difference is related to the assumption of linear concentration in the region where drug is dissolved and so proposed a modification on Higuchi model that can compensate the underestimation related to that assumption:

$$\frac{M_t}{M_o} = \sqrt{\frac{2 \cdot D \cdot t \cdot R}{L^2} \cdot \left(1 - \frac{R \cdot (\pi - 2)}{\pi}\right)} \quad (10)$$

In TDDS field, the thickness of the gel, cream or ointment in contact with the skin, is not constant during time because of the presence of skin absorption, evaporation etc… In this field Guy and Hadgraft [22] optimized a model able to take into account device thickness and in particular its variation during time. Their assumption is that the limiting steps of mass transport are related to the motion within the device and across SC, while in the other skin layers is faster. So, drainage conditions are

present at the interface between SC and lower skin layers. The layer that control the release rate can be obtained considering the relative rates of transport in the device and in the stratum corneum. The drug amount (M_t) that moves across SC with thickness L_s ('s' = SC and 'o' = ointment) during time t is:

$$M_t = -D_s \cdot A \cdot \int_0^t \left(\frac{dC_s}{dx}\right)_{x=L_s} dt \tag{11}$$

To solve the equations the authors introduced some dimensionless numbers:

$$u = \frac{C}{C_\infty} \tag{12}$$

$$\lambda = \frac{D_s/L_s}{D_o/L_o} \tag{13}$$

$$p = \frac{D_o/L_o^2}{D_s/L_s^2} \tag{14}$$

$$\tau = \frac{D_s \cdot t}{L_s^2} \tag{15}$$

Assuming that the rate between the device and the stratum corneum is fast, the equations able to describe the mass transfer are:

$$\frac{\partial u_o}{\partial \tau} = p \cdot \left(\frac{\partial^2 u_o}{\partial \chi'^2}\right) \tag{16}$$

$$\frac{\partial u_s}{\partial \tau} = \lambda \cdot \left(\frac{\partial^2 u_s}{\partial \chi^2}\right) \tag{17}$$

where χ' (= x / L_o) and χ (= x / L_s) are normalized pathlength in the device and skin. The boundary condition at the interface of the SC and the device is:

$$\left(\frac{\partial u_o}{\partial \chi'}\right)_o = -\lambda \cdot \left(\frac{\partial u_s}{\partial \chi}\right) \tag{18}$$

Equation 11 with dimensionless numbers becomes:

$$M_t = A \cdot L_s \cdot C_o \cdot \int_0^\tau \left(\frac{du_s}{d\chi}\right) \cdot d\tau \tag{19}$$

The diffusion equations can be solved using the method of Laplace transforms:

$$M_t = A \cdot C_o \cdot L_s \cdot \Omega^{-1} \cdot \left\{\sqrt{s^3} \cdot cosh\sqrt{s} \cdot \left(K \cdot tanh\sqrt{s} + \lambda \cdot \sqrt{p} \cdot cotanh\left(\sqrt{\frac{s}{p}}\right)\right)\right\}^{-1} \tag{20}$$

K: the partition coefficient between the device of the membrane, Ω^{-1}: inverse Laplace transform. Equation 20 cannot be solved analytically so approximated approaches are needed and developed for long and short-time exposures [22].

At the short-time limit, the equation obtained from simplification is:

$$\frac{M_t}{M_\infty} = \frac{8\cdot\left(\frac{L_s}{L_o}\right)}{K+\sqrt{\frac{D_s}{D_o}}} \cdot \sqrt{\frac{1}{\pi}\cdot\left(\frac{D_s\cdot t}{L_s^2}\right)^3}\, exp\left(-\frac{L_s^2}{4\cdot D_s\cdot t}\right) \quad (21)$$

for short time the key parameters are drug diffusivity within the device and across the membrane, partition coefficient and the pathlengths ratio. According to Guy and coworkers if $D_s < D_o$ and K is small, considering that most devices favor the entrance of drug molecules into the stratum corneum, it is impossible to predict the dominant parameter [22]. **Figure 3** illustrates the percentage released as function of the dimensionless parameter $D\ t\ /L^2$ considering different partition coefficients at two values of $L_s\ /\ L_o$ ratio.

[Insert Figure X.3 here]

2.2 The slab

Hadgraft [23] optimized modeling strategies able to describe release phenomenon from medical devices applied to the skin. The model takes into consideration planar geometry and describes the fundamental characteristics of release from TDDS. He considered two models:

(i) sheet attached to the skin fully loaded with drug molecules (burst effect);

(ii) empty sheet supplied by a reservoir of drug (lag phase).

Hadgraft used the Laplace transforms method with boundary conditions to obtain a solution of the second Fick's law:

$$\frac{\partial C}{\partial t} = D\cdot\frac{\partial^2 C}{\partial x^2} \quad (22)$$

$$t = 0, C = C_o, \quad 0 < x < L \quad (23)$$

$$x = L, C = 0, \quad t \geq 0 \quad (24)$$

$$x = 0, \left(\frac{\partial C}{\partial x}\right)_o = 0, \quad t \geq 0 \tag{25}$$

First condition: at t = 0 the concentration of drug in the membrane is uniform

Second condition: skin is a perfect sink and the interface concentration is zero

Third condition: no reservoir at the inner patch face.

Solution of the equation with boundary conditions gives:

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2} \cdot \left(\sum_{n=1}^{\infty} \frac{1}{(2n-1)^2} \cdot exp\left(-\frac{(2n-1)^2 \cdot \pi^2 \cdot D \cdot t}{4 \cdot L^2}\right)\right) \tag{26}$$

For short times $D \cdot t / L^2 \ll 1$ equation 26 becomes:

$$\frac{M_t}{M_\infty} = 2 \cdot \sqrt{\frac{D \cdot t}{\pi \cdot L^2}} \tag{27}$$

In **Figure 4** the release profiles, obtained from complete and approximated solutions, are visible. For long times the layer disappears and the drug loaded is completely released into the skin: M_t tends to M_∞.

[Insert Figure X.4 here]

$$t = 0, C = C_o, \quad 0 < x < L \tag{28}$$

$$x = L, C = 0, \quad t \geq 0 \tag{29}$$

$$x = 0, C = C_o, \quad t \geq 0 \tag{30}$$

The equation that describes drug release [23]:

$$\frac{M_t}{M_\infty} = \frac{D \cdot t}{L^2} + \frac{1}{3} + \frac{2}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{n^2} \cdot exp\left(-\frac{D \cdot n^2 \cdot \pi^2 \cdot t}{L^2}\right) \tag{31}$$

This represents the standard form of an equation that describes mass transport through a rate-controlling device. An identical situation can be considered for diffusion across SC where the release of drug molecules from TDDS is very quick and the limiting-step is the motion across the stratum corneum then followed by an extremely fast entry into the epidermis. For long-time values the *exp* term tends to 0 and the equation obtained becomes:

$$\frac{M_t}{M_\infty} = \left(\frac{D \cdot t}{L^2} - \frac{1}{6}\right) \tag{32}$$

For short-times the result is:

$$\frac{M_t}{M_\infty} = 8 \cdot \sqrt{\frac{1}{\pi} \cdot \left(\frac{D \cdot t}{L^2}\right)^3}\, exp\left(-\frac{L^2}{4 \cdot D \cdot t}\right) \quad (33)$$

Hadgraft obtained the expressions discussed above considering a negligible role of the interfacial kinetics.

In some conditions this kinetics can be key point, for example when the drug is dissolved in an organic phase within the device and moves through the interface into a thin hydrophilic slab in contact with the first layer of the skin. Albery and coworkers investigated the existence of transport barriers (based on free energy) across liquid-liquid surface [24, 25]. In systems with multiple layers, if the kinetics at the interface is fast the release of drugs is equal to the one obtained with the monophasic system. If the interfacial kinetics is slower there is an impact on the release profile and its contribution depends on the rate of diffusion of drug in the layer considered and on the thickness of the organic sheet. Hadgraft studied different conditions using a dimensionless number:

$$\kappa = \frac{k_{int} \cdot L}{D} \quad (34)$$

k_{int} is the transfer rate across the interface, L the organic sheet thickness and *D* the diffusivity within the organic environment. If the transfer rate is fast respect to drug diffusion coefficient ($\kappa \gg 1$) the molecules of drug move into the water layer instantaneously and the kinetics at the interface plays no role (monophase). If the diffusion is fast respect to the transfer at the interface the drug molecules are present at the interface and there is a strong influence on the entire phenomenon. Considering that typical values for interfacial kinetics are of the order of 10^{-3} cm/s and diffusivities around 10^{-6} cm^2/s it is possible to state that only if the thickness of the organic sheet is lower than 100 micron the kinetics at the interface is not negligible.

2.3 Topical solutions and suspensions

Topical release profiles of drug molecules depend on the physical state of the drug and vary if it is present in solution or in suspension. Release from solution is more complex, from a mathematical point of view, because activity of the drug that changes should be considered as its concentration decreases in the formulation during time. In general, in this case, drug molecules move readily out of the film into the SC. Generally the skin does not provide any resistance to drug motion and works

as drainage, removing drug molecules when they enter. This happens in specific cases, like when the drug presents high lipophilicity and it is dissolved in a polar device or the opposite (polar drug in nonpolar device) then applied to a skin damaged region, where the uptake is almost instantaneous. In this situation the quantity of drug taken up is:

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2} \cdot \left(\sum_{n=0}^{\infty} \frac{1}{(2n+1)^2} \cdot exp\left(- \frac{D \cdot (2n+1)^2 \cdot \pi^2 \cdot t}{4 \cdot L^2} \right) \right) \quad (35)$$

M_t: amount of drug entered into the skin at time *t*, *D*: drug diffusivity into the slab with 2L thickness. As discussed above the assumption done does not happen often and so the skin usually creates resistance to the motion of drug molecules. Stratum corneum works as protective layer providing so resistance to the passage of molecules. Bigger the difference between the characteristic time of diffusion cross the device ($\frac{L_{dev}^2}{D_{dev}}$) and the skin ($\frac{L_{SC}^2}{K \cdot D_{SC}}$) bigger the control degree of the device. So, in systems where $\frac{L_{SC}^2}{K \cdot D_{SC}} \gg 10 \cdot \frac{L_{dev}^2}{D_{dev}}$ the percentage of drug released from a slab with L_{dev} thickness is [26, 27]:

$$\frac{M_t}{M_\infty} = \sum_{n=1}^{\infty} \frac{2K}{L_{dev}} \cdot \frac{\left(1 - exp\left(-D_{SC} \cdot t \cdot \alpha_n^2\right)\right)}{\left[L_{SC} \cdot \left(\alpha_n^2 + \left(\frac{K}{L_{dev}}\right)^2\right) + \left(\frac{K}{L_{dev}}\right)\right] \cdot cos\left(\alpha_n \cdot L_{SC}\right)} \quad (36)$$

The release scenario is complicated by the drug amount that decreases within the medical device before significant amount of drug have crossed SC. So, the driving force of the entire phenomenon decreases during the release phenomenon. Considering the release from a suspension we should divide the condition in two cases:

- release into a sink: Higuchi equation as described in section 2.1
- release into a resistant membrane: similar to the Equation 31. Here the lag phase is caused by SC.

The quantity of drug delivered per unit area through SC into the skin is:

$$\frac{M}{A} = (K \cdot C_{dev} \cdot L_{SC}) \cdot \left[\left(\frac{D_{SC} \cdot t}{L_{SC}^2} \right) - \frac{1}{6} - \frac{2}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{(-1)^n}{n^2} \cdot exp \cdot \left(- \frac{D_{SC} \cdot n^2 \cdot \pi^2 \cdot t}{L_{SC}^2} \right) \right] \quad (37)$$

K: partition coefficient between device and SC, C_{dev}: concentration of drug within the device, D_{SC}: drug diffusion coefficient in the device, L_{SC}: diffusion path within SC.

2.4 Transdermal patches

Patches used as TDDS is a medicated device able to deliver drugs through the skin [28, 29]. TDDS patches can be divided in four categories:

(i) semisolid like lotions, gels and ointments;

(ii) drug loaded in liquid state then sealed in a layer attached to the skin;

(iii) adherent structures with multiple sheets where the layer of drug is in contact with the skin that is separately surrounded by an adhesive layer;

(iv) solid forms;

(v) microneedles.

Classification can be also done in accordance with drug delivery mechanisms where drug molecules are dissolved in the formulated device or as solid powder.

Patches represent one of the most comfortable formulations due to the fact that they are non invasive, able to bypass the first pass metabolism and the gastro-intestinal tract. The skin where patches are applied should be clean, hairless and not oily.

The device consists on different layers:

(i) backing layer for the protection of formulation from the environment;

(ii) carrier (reservoir) of drug molecules to tune drug delivery;

(iii) adhesive to attach the patch to the skin;

(iv) liner to preserve patch and adhesive [30, 31].

Even if many patches are on the market this field remains very active in terms of research and development. The schematic representation of current status and long-lasting possibilities to have a patch suitable for long-acting drug delivery is visible in **Figure 5**.

[Insert Figure X.5 here]

Transdermal patches with drug present above the saturation concentration, in form of suspension, will give results that follow Higuchi model already discussed. During the delivery of drug molecules in a porous matrix from a suspension the Higuchi equation can be modified considering porosity (ε) and tortuosity (τ):

$$Q = \sqrt{\frac{2 \cdot C_0 \cdot D \cdot t \cdot C_s \cdot \varepsilon}{\tau}} \quad (38)$$

C_0: the initial drug concentration greater that C_s, the concentration that corresponds to the saturation. The corresponding release rate is:

$$\frac{dQ}{dt} = \sqrt{\frac{C_0 \cdot D \cdot C_s \cdot \varepsilon}{2 \cdot t \cdot \tau}} \quad (39)$$

if the drug is present below the concentration of saturation, the delivery profile is based on the membrane model developed by Hadgraft that studied a slab as discussed in section 2.2. The presence of a medical device with a membrane that controls the drug rate into the patch ensures that the device determines the input rate. If it is not true, the SC works as the real rate controlling membrane. An other interesting technology for patches is represented by the use of microneedles. In the last decades a lot of attention was dedicated to patches based on microneedles loaded with drugs [32-34]. They are produced using microelectromechanical-based technology using metals, polymers (synthetic or natural) or silicon. The main advantage of these devices resides in the possibility to overcome the SC that, as discussed, represents a very efficient barrier to the delivery of drug through the skin. This approach allows so to deliver high amount of drug for a longer period of time, in addition also bigger molecules can be released through the skin like peptides, insulin and antibodies [35-37]. Different types of microneedles were developed in the last years and the pros and cons of them are listed in **Table 1**.

Microneedle type	**Advantages**	**Disadvantages**
solid	- high mechanical strength - reasonable drug load	- poor accuracy - low biocompatibility
coated	- high mechanical strength - used for low doses drugs	- low drug loading - low biocompatibility
hollow	- precise dosage - high load - quick rate of release	- auxiliary devices required - low mechanical strength - low biocompatibility

dissolving	- easy production - sustained drug delivery	- low mechanical strength - low biocompatibility
hydrogel	- no residue in skin - easy production - sustained drug delivery	- low mechanical strength

Table 1. Advantages and disadvantages of different microneedle types.

Patches that use microneedle technology can be studied with a mathematical modeling starting from Fick's second law (Equation 22) as discussed in section 2.2 [38]. In particular the release of drug is driven by the formulation while SC is not present and drug is release directly into lower layers of the skin. Benslimane and coworkers modeled the unsteady diffusion of drugs delivered through a microneedle inserted into the skin [38]. They used a closed form of exact solution and also a numerical solution obtained using a finite difference method well-known. The results collected in this work underline the effects of the device length, the initial drug concentration and the drug diffusivity.

3. Future directions and conclusions

Current mathematical models used for TDDS generally consider that the diffusivity of drug in the device is constant during the motion and that the membrane is not affected by the formulated products. However, during the design of a TDDS device, different formulations are developed for the main aim to optimize drug release acting on the hydration of the skin or on drug penetration. So the function of the barrier (membrane) is influenced by the formulation designed. The main point is to understand if the different formulations is able to affect the assumption that the membrane stays unmodified during the release of drug molecules and so drug diffusivity is constant. Then a possible advance is represented by the incorporation of time-dependent diffusion coefficients that take into consideration the effects of formulation. In this chapter we focused our attention on mathematical solutions that have the main advantage that they are related to physical parameters present in the system. However this type of solutions present also disadvantages like the simple geometries

considered and the approximated boundary conditions that should be properly introduced to obtain reliable results.

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FIGURE AND TABLE CAPTIONS

Figure 1. *Release of drug molecules from a formulated device applied to the skin surface.*

Figure 2. The effects of 4-OHA cream on breast cancer growth. (A) Representative images of the tumors. (B) Expression of the proliferation marker Ki67 in tumor tissues was measured by immunohistochemistry. Scale bar, 20 mm. (C) Rat weight evolution during the experiment. The values are expressed as the mean. (D) Tumor growth curve. Average number of tumor nodules before and after treatment. (E) The data represent six sets of independent experiments and are shown as the means ± SD. *p < 0.05 vs. control group. The effects of 4-OHA on the growth of the cells. (F–I) Cells were cultured in 10% PRF-CT with E2 1 nM for 3 days before the experiment. (F, G) Cells were seeded in 96-well or six-well plates and 24 h later they were exposed to 1 mM of 4-OHA for 8 days. MTT (F) and Colony formation (G) assay were performed. Reprinted with permission from [17].

Figure 3. *Percentage of drug released, at short times, from a thin film of an ointment or a gel a function of the dimensionless parameter D t /L^2, for a series of values of K at two fixed values of L_s / L_o: 0.2 (a) and 0.02 (b).* **Reprinted with permission from [1].**

Figure 4. *Drug release profiles from a solution 'slab' under burst conditions (calculated using the complete solution and the short time approximation).* **Reprinted with permission from [1].**

Figure 5. *Current status and future prospects of long-acting transdermal formulations.* **Reprinted with permission from [28].**