Materials Today: Proceedings xxx (xxxx) xxx

Contents lists available at ScienceDirect

Materials Today: Proceedings

journal homepage: www.elsevier.com/locate/matpr

Mathematical modeling of transdermal drug delivery using microneedle

Abdelhakim Benslimane [a,b], Sofiane Fatmi [b,c,*], Lamia Taouzinet [b,c], Dalila Hammiche [d]

[a] Laboratoire Mécanique, Matériaux et Energétique, Faculté de Technologie, Université de Bejaia, Bejaia 06000, Algérie
[b] Technology Pharmaceutical Laboratory, Department of Processes Engineering, Faculty of Technology, Université de Bejaia, 06000 Bejaia, Algeria
[c] Associated Laboratory in Marine Ecosystems and Aquaculture, Faculty of Nature and Life Sciences, Université de Bejaia, 06000 Bejaia, Algeria
[d] LMPA, Department of Processes Engineering, Faculty of Technology, Université de Bejaia, 06000 Bejaia, Algeria

ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Mathematical
Modeling
Drug delivery systems
Microneedles

ABSTRACT

This work presents a closed-form analytical and numerical technique that is developed to investigate drug diffusion from sustained release systems (transdermal drug delivery using microneedle). Diffusion is known as predominant transport phenomenon in drug delivery systems. Therefore, parameter optimization in relation to diffusional mass transport, such as diffusion coefficient, initial concentration and device length were the essential keys to achieve perfect drug control. A closed form analytical solution was derived from Fick's second law and a numerical solution is presented using finite difference method in order to compute the concentration distribution. Furthermore, the effect of the diffusion coefficient, initial concentration and device length on the concentration diffusion is investigated. Results reveal the influence of the different parameters studied on diffusion and concentration over time and space.

Selection and peer-review under responsibility of the scientific committee of the Polymer & Mediterranean Fiber International Conference2021.

1. Introduction

A drug delivery system (DDS) is a generic term for a set of physicochemical technologies that can manage the distribution and release of pharmacologically active compounds into cells, tissues, and organs, allowing them to exert optimal effects [1,2]. Also, DDS refers to the administration modes and drug formulations that effectively transport the drug in order to optimize therapeutic efficacy and reducing side effects [3–5]. There are many different types of administration modalities depending on the delivery mechanism, such as oral administration, transdermal administration, lung inhalation, mucosal administration, and intravenous injection. Due to several advantages over oral and intravenous techniques, transdermal drug delivery (TDD) is considered one of the most appealing ways for administration of pharmaceutics and cosmetic actives components [6–7]. Microneedles (MNs) are needles with a micron-scale that are used in TDD systems [8–9]. Microneedle (MN) technology holds a lot of promise for regulated drug delivery, and it's getting a lot of attention from researchers and clinics [10]. MNs can puncture through the skin stratum corneum layer and into the epidermis, avoiding nerve fiber contact [11]. Microneedle concept of is well established and the related experimental validation has already been extensively investigated in the literature.

Given the importance of such products in therapy, they have already been widely studied both theoretically and experimentally. Microneedles systems mathematical modeling is an area of growing research. The detailed review paper published by Anissimov et al. [12] presented different examples of epidermal and dermal transport processes and summarized various mathematical models that have been developed forward to describe the phenomenon. Mathematical models of epidermal and dermal transport are essential for optimization and development of products for percutaneous drug delivery. The mathematical modeling is also helpful to analyze experimental data which could reduce considerably the number of *in vitro* and *in vivo* studies.

Lindstrom and Ayres [13] were among the first to use mathematical methods to predict drug transport through the skin. Recently, a mathematical model was developed by Qaliaf et al. [14] to investigate dermal drug delivery. The authors carried out numerical simulations also to describe the pharmoco-kinetics of drug penetration into the skin from microneedle array. Missel

* Corresponding author at: Technology Pharmaceutical Laboratory, Department of Processes Engineering, Faculty of Technology, Université de Bejaia, 06000 Bejaia, Algeria.
E-mail address: sofiane.fatmi@univ-bejaia.dz (S. Fatmi).

https://doi.org/10.1016/j.matpr.2022.01.028
2214-7853/
Selection and peer-review under responsibility of the scientific committee of the Polymer & Mediterranean Fiber International Conference2021.

[15] investigates diffusion and partitioning in biological systems using finite element method. Sharma and Saxena [16] used the same method (FEM) to analyze the steady state drug distribution in transdermal drug delivery systems. Khanday and Rafq [17] and deMonte et al. [18] further studied the numerical estimation of drug diffusion in the transdermal drug delivery system.

From analytical point of view, Nazir et al. [19] developed mathematical model for the transport of drug in normal and cancerous tumors. The model was solved analytically using separation of variables and eigenvalue approach. Recently, Madhihah et al. [20] used separation of variables to investigate the release rate of drug from hollow microneedles and the effect of microneedles length and diffusion coefficient on drug release rate.

Another approach of solving the diffusion equation with appropriate initial and boundary conditions is using Laplace transform [21]. In the context of the percutaneous penetration this technique was pioneered by Hadgraft [22–23].

The purpose of this work is to investigate the transdermal drug delivery using microneedles inserted in skin. Herein, the unsteady one-dimensional diffusion model is considered. Fick's second law differential equation is solved numerically using the well-known finite difference method and a closed-form of exact solution is obtained to lead to concentration field. The analytical and numerical results obtained have been validated with the literature result available. The effects of different parameters were investigated then various analytical and numerical results obtained have been presented and discussed.

2. Mathematical formulation of the problem

The schematization of the microneedles array transdermal drug delivery is shown in Fig. 1.

2.1. Analytical model

A model of transdermal drug delivery was constructed to explain the transport of drug molecules through the skin. The fundamental equation that defines transient drug diffusion across the skin tissue is given by Fick's second law as:

$$\frac{\partial C(x,t)}{\partial t} = D\left(\frac{\partial^2 C(x,t)}{\partial x^2}\right) \tag{1}$$

where $C(x,t)$ is the concentration of the drug at the point $\times$ and time t and D is its diffusion coefficient in the matrix. Diffusion coefficient shows how fast drug penetrates the skin.

The initial concentration of the active pharmaceutical ingredient (API) is:

$$C(x,0) = C_0,\ 0 \prec x \prec L \tag{2}$$

where L is the length of the microneedle and C_0 Drug solution is available along the microneedle and in the patch even before application on the skin.

A symmetry condition is imposed at $x = 0$ as a first boundary condition:

$$\frac{\partial C(0,t)}{\partial x} = 0,\ t \succ 0 \tag{3}$$

The second boundary condition is applied at $x = L$:

$$C(L,t) = 0,\ t \succ 0 \tag{4}$$

The Laplace transform of Eq. (1) is given by:

$$sC(x) - C_0 = D\frac{d^2C(x)}{dx^2} \tag{5}$$

where

$$C(x) = \int_0^\infty C(x,t)e^{-st}dt \tag{6}$$

The general solution of Eq (5) is given by:

$$C(x) = Ae^{x\sqrt{\frac{s}{D}}} + Be^{-x\sqrt{\frac{s}{D}}} + \frac{C_0}{s} \tag{7}$$

where A and B are constants to be determined using boundary conditions. This step is particularly simple and leads to a linear system of two equations with two unknowns A and B to be solved. So, applying Laplace transform of the boundary condition Eqs. (3 and 4) to Eq (7) we obtain:

$$\begin{cases} A\sqrt{\frac{s}{D}} - B\sqrt{\frac{s}{D}} = 0 \\ Ae^{L\sqrt{\frac{s}{D}}} + Be^{-L\sqrt{\frac{s}{D}}} + \frac{C_0}{s} = 0 \end{cases} \tag{8}$$

which gives:

$$A = -\frac{C_0}{2\cdot s\cdot\cosh\left(\sqrt{\frac{s}{D}}L\right)};\ B = -\frac{C_0}{2\cdot s\cdot\cosh\left(\sqrt{\frac{s}{D}}L\right)} \tag{9}$$

By virtue of Eqs. (7 and 9), the expressions concentration of the active pharmaceutical ingredient is derived as follows:

$$C(x) = -\frac{C_0}{2\cdot s\cdot\cosh\left(\sqrt{\frac{s}{D}}L\right)}\left(e^{x\sqrt{\frac{s}{D}}} + e^{-x\sqrt{\frac{s}{D}}}\right) + \frac{C_0}{s} \tag{10}$$

The inverse Laplace transform of $C(x)$ is computed using the following Bromwich integral:

$$C(x,t) = \frac{1}{2\pi i} \times \int\left[-\frac{C_0}{2\cdot s\cdot\cosh\left(\sqrt{\frac{s}{D}}L\right)}\left(e^{x\sqrt{\frac{s}{D}}} + e^{-x\sqrt{\frac{s}{D}}}\right) + \frac{C_0}{s}\right]e^{st}ds \tag{11}$$

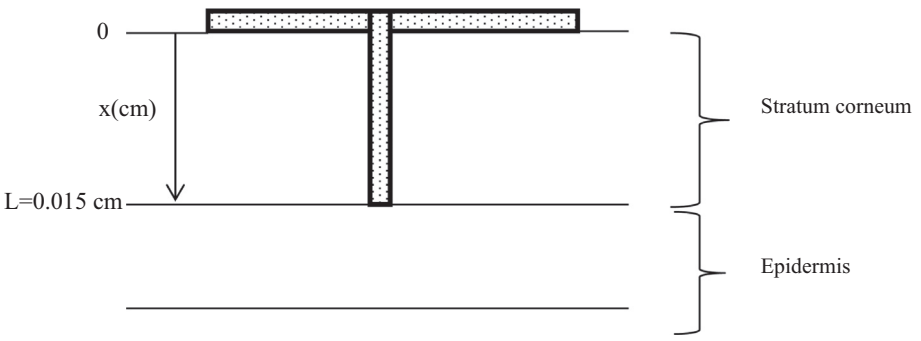

Fig. 1. Model of drug delivery with a microneedle.

and the Bromwich integral is computed using the residue theorem as:

$$C(x,t)=\sum_{pole} Residue\left(\left[-\frac{C_0}{2\cdot s\cdot\cosh\left(\sqrt{\frac{s}{D}}L\right)}\left(e^{x\sqrt{\frac{s}{D}}}+e^{-x\sqrt{\frac{s}{D}}}\right)+\frac{C_0}{s}\right]e^{st}\right)_{pole} \tag{12}$$

The residue at the pole $s = 0$ is 0. The other poles are determined by the equation:

$$\cosh\left(\sqrt{\frac{s}{D}}L\right)=0 \tag{13}$$

which yields:

$$s=-\frac{(2n+1)^2\pi^2 D}{4L^2} \tag{14}$$

where n is an integer ranging from 0 to ∞. The residue at the pole takes the form:

$$\mathrm{R}=\frac{2(-1)^{2+n}C_0\left(e^{\frac{i(2n+1)\pi x}{2L}}+e^{-\frac{i(2n+1)\pi x}{2L}}\right)e^{-D\frac{(2n+1)^2\pi^2}{4L^2}t}}{(2n+1)\pi} \tag{15}$$

As a result, the concentration in the time domain is:

$$C(x,t)=\sum_{0}^{\infty}\frac{2(-1)^{2+n}C_0\left(e^{\frac{i(2n+1)\pi x}{2L}}+e^{-\frac{i(2n+1)\pi x}{2L}}\right)e^{-D\frac{(2n+1)^2\pi^2}{4L^2}t}}{(2n+1)\pi} \tag{16}$$

2.2. Numerical solution

In this work, the standard finite difference method (FDM) is used to numerically solve the above differential equation with its initial and boundary conditions. Equation (1) subjected to the boundary and initial conditions given in Eqs. (2–4) have been integrated numerically using a finite difference method which is forward in time and central in space. The implementation of the numerical method was made using MATLAB software and all simulations are computed with this program.

Let us denote $C(x_i,t_i)=C_i^j$ and approximate various partial derivatives as:

$$\frac{\partial^2 C(x,t)}{\partial x^2}\cong\frac{C_{i+1}^j-2C_i^j+C_{i-1}^j}{\Delta x^2} \tag{17}$$

Similarly, for the time derivative we define the approximation:

$$\frac{\partial C(x,t)}{\partial x}\cong\frac{C_i^{j+1}-C_i^j}{\Delta t} \tag{18}$$

Using Eqs. (17) and (18), Eq. (1) may be transformedto the following difference equation:

$$C_i^{j+1}=C_i^j+\frac{D\Delta t}{\Delta x^2}\left(C_{i+1}^j-2C_i^j+C_{i-1}^j\right) \tag{19}$$

For the solution of the present problem we have discretized the microneedles length by using the formula $x_i=(i-1)\Delta x$, $(i=1,2,.....,N+1)$ such that $x_{N+1}=L$. Similarly for discretization of time, we have used the following discretization formula $t_j=(j-1)\Delta t$, $(i=1,2,.....)$ for the entire microneedles length segment under study with Δx and Δt are the increments in space and time, respectively.

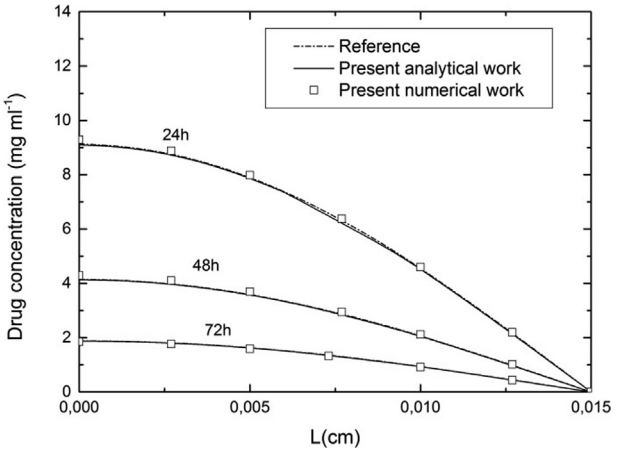

Fig. 2. Comparison between current work and results of Madhihah et al. [20].

3. Results and discussions

3.1. Verification

In Fig. 2, the analytical and numerical results of current work are compared with those obtained from Ref. [20] where authors studied the transdermal drug delivery assisted with microneedles. The authors in their model applied a finite drug supply and the problem has been solved analytically.

In this case, to achieve the results, a microneedle with length L is considered. The model is solved by using the input parameters as shown in Table 1.

As expected, drug concentration inside the patch, for specific locations, decreases with time due to drug absorption through skin.

3.2. Current results

The effects of diffusion coefficient (D), initial concentration (C_0) and the length (L) on the drug concentration inside the delivery device are investigated and results were presented and discussed.

Figs. 3–5 show the drug concentration inside the delivery device function of microneedle length where the effects of different parameters were investigated.

Fig. 3 shows drug concentration inside the microneedle function of microneedle length for various values of diffusion coefficient (D = 5 10^{-9}, 1 10^{-9}, 5 10^{-8} and 1 10^{-7}) in order to quantify the effect of this parameter on the kinetics of drug delivery, while, time, length and initial concentration was fixed. The effect of diffusion coefficient (D) is evident in this figure. Indeed, increases in diffusion coefficient (D) leads to a decrease in remaining amount of drug at a fixed position.

In Fig. 4 drug concentration distributions inside the microneedle, corresponding to a fixed time (t = 24 h) are presented for four initial concentrations. Fig. 4 reveals that drug concentration increases when the initial concentration (C_0) increases. Indeed, increases in initial concentration leads to an increase in remaining amount of drug at a fixed position.

Table 1
Parameters of solved model.

Parameters	Value
Duration of application, t (h)	24, 48 and 72
Diffusion coefficient, D (cm^2mn^{-1})	5 10^{-8}
Device drug concentration, C_0 (mg ml^{-1})	15.8
Microneedles length, L (cm)	0.015

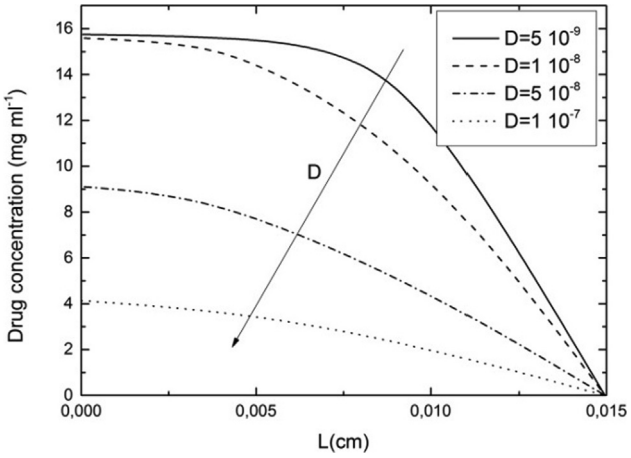

Fig. 3. Prediction of drug concentration inside the delivery device for t = 24 h, L = 0.015 cm, C_0 = 15.8 mg/ml and for D = 5 10^{-9}, 1 10^{-9}, 5 10^{-8} and 1 10^{-7} cm^2/mn.

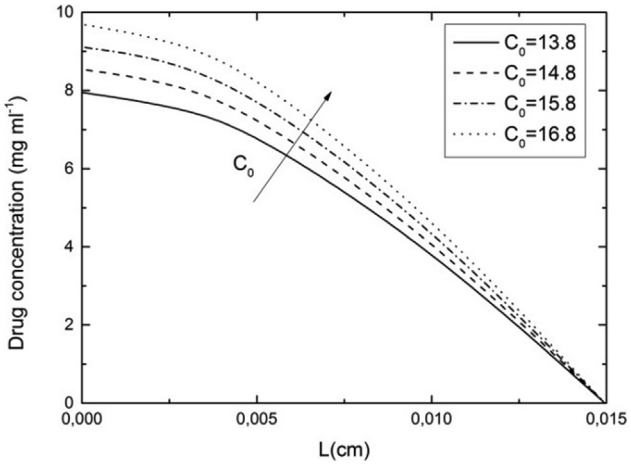

Fig. 4. Prediction of drug concentration inside the delivery device for t = 24 h, L = 0.015 cm, D = 5 10^{-8} cm^2/mn and for C_0 = 13.8, 14.8, 15.8 and 16.8 mg/ml.

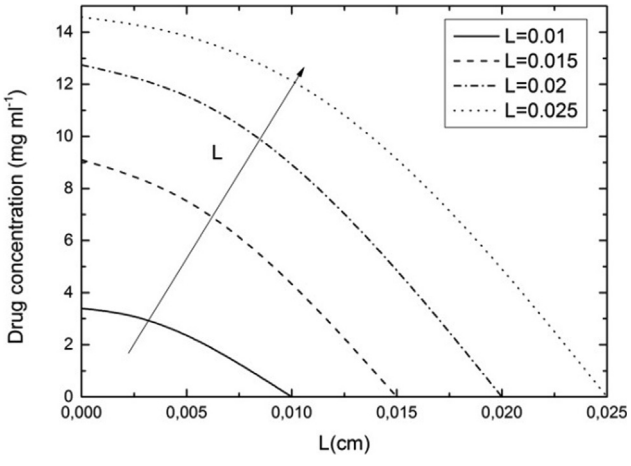

Fig. 5. Prediction of drug concentration inside the delivery device for t = 24 h, D = 5 10^{-8} cm^2 /mn and for C_0 = 15.8 mg/ml and L = 0.01, 0.015, 002 and 0.025 cm.

In Fig. 5 drug concentration distributions inside the microneedle, corresponding to a fixed time (t = 24 h) are presented for four different length. In this figure, one can observe that drug concentration increases when the length increases. However, it can be noticed that a small length increase leads to an important increase in remaining amount of drug at a fixed position. Indicating a better potential drug sustained release.

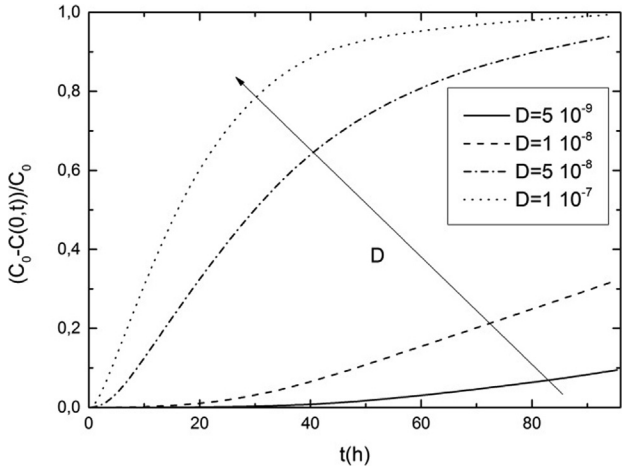

Fig. 6. Prediction of delivery profile for x = 0 cm, C_0 = 15.8 mg/ml and for D = 5 10^{-9}, 1 10^{-9}, 5 10^{-8} and 1 10^{-7} cm^2/mn.

In Fig. 6 drug delivery profiles are presented for four different diffusion coefficients. All simulated curves present a sustained delivery profiles. Also, one can notice that the effect of drug diffusion coefficient is inversely proportional to the prolongation of drug release.

4. Conclusion

In this paper, unsteady diffusion of transdermal drug delivery using a microneedle inserted in the skin is modeled. A closed-form of exact solution is derived from Fick's second law differential equation. This equation is also solved numerically using the well-known finite difference method. Furthermore, the effect of the diffusion coefficient, initial concentration and device length on the concentration profiles is studied.

Results show the parameters influences on diffusion and concentration over time and space of transdermal drug sustained delivery. In fact, the effect of diffusion coefficient (D), initial concentration (C0) and the length (L) on the drug concentration inside the delivery device leads to prolongation of drug release, known as 'sustained drug delivery'.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank the General Directorate of Scientific Research and Technological Development (DGRSDT/MESRS-Algeria) for their financial support.

References

[1] P. Vega-Vásquez, N.S. Mosier, J. Irudayaraj, Nanoscale drug delivery systems: from medicine to agriculture, Front. Bioeng. Biotechnol. 8 (2020) 79.
[2] A.M. Vargason, A.C. Anselmo, S. Mitragotri, The evolution of commercial drug delivery technologies, Nat Biomed. Eng. 5 (9) (2021) 951–967.
[3] A.D. Mali, R. Bathe, M. Patil, An updated review on transdermal drug delivery systems, Int. J. Adv. Sci. Res. 1 (6) (2015) 244–254.

[4] C. Li, J. Wang, Y. Wang, H. Gao, G. Wei, Y. Huang, H. Yu, Y. Gan, Y. Wang, L. Mei, H. Chen, H. Hu, Z. Zhang, Y. Jin, Recent progress in drug delivery, Acta Pharm. Sin. B. 9 (6) (2019) 1145–1162.
[5] J.A. Kumar, N. Pullakandam, S.L. Prabu, V. Gopal, Transdermal drug delivery system: An overview, Int. J. Pharm. Sci. Rev. Res. 3 (2) (2010) 49–54.
[6] M. Roohnikan, E. Laszlo, S. Babity, D.A. Brambilla, Snapshot of transdermal and tropical drug delivery research in Canada, Pharmaceutics. 11 (6) (2019) 256.
[7] L.i. Yan, M. Alba, N. Tabassum, N.H. Voelcker, Micro- and Nanosystems for Advanced Transdermal Delivery, Adv. Therapeutics. 2 (12) (2019) 1900141, https://doi.org/10.1002/adtp.v2.1210.1002/adtp.201900141.
[8] M.R. Prausnitz, R. Langer, Transdermal drug delivery, Nat. Biotechnol. 26 (11) (2008) 1261–1268.
[9] X. Jin, D.D. Zhu, B.Z. Chen, M. Ashfaq, X.D. Guo, Insulin delivery systems combined with microneedle technology, Adv. Drug Deliv. Rev. 127 (2018) 119–137.
[10] T. Moniz, S.A. Costa Lima, S. Reis, Marine polymeric microneedles for transdermal drug delivery, Carbohydr. Polym. 266 (2021) 118098, https://doi.org/10.1016/j.carbpol.2021.118098.
[11] N. Elahpour, F. Pahlevanzadeh, M. Kharaziha, H.R. Bakhsheshi-Rad, S. Ramakrishna, F. Berto, F.3D printed microneedles for transdermal drug delivery: A brief review of two decades, Int. J. Pharm. 597 (2021) 120301, https://doi.org/10.1016/j.ijpharm.2021.120301.
[12] Y.G. Anissimov, O.G. Jepps, Y. Dancik, M.S. Roberts, Mathematical and pharmacokinetic modelling of epidermal and dermal transport processes, Adv. Drug Deliv. Rev. 65 (2013) 169–190.
[13] F.T. Lindstrom, J.W. Ayres, Diffusion model for drug release from suspensions II: release to a perfect sink, J. Pharm. Sci. 66 (1977) 662–668.
[14] B.A. Qaliaf, D.B. Das, D. Mori, Z. Cui, Modeling transdermal delivery of high molecular weight drugs from microneedle systems, Philos. Trans. R Soc. A 365 (2007) 2951–2967.
[15] P.J. Missel, Finite element modeling of diffusion and partitioning in biological systems: The infinite composite medium problem, Ann. Biomed. Eng. 28 (11) (2000) 1307–1317.
[16] Sharma A, Saxena VP, Finite element modeling of drug distribution in transdermal drug delivery system, Ind J Bio-Mech, NCBM-2009, ISSN 0974-0783.
[17] M.A. Khanday, A. Rafq, Numerical estimation of drug difusion at dermal regions of human body intransdermal drug delivery system, J. Mech. Med. Biol. (2016).
[18] F. de Monte, G. Pontrelli, S. Becker, Transdermal drug delivery and percutaneous absorption: Mathematical modelling perspective. Chap 10, heat transfer and fluid flow in biological processes, Elsevier, New York, 2014, pp. 3658–3669.
[19] K. Nazir, S. Mubarak, A.H. Lone, R. Bhat, F.A. Zargar, M.A. Khanday, Compartment modelling and eigenvalue expansion to study the drug concentration in capillary and tissue regions surrounding the malignant tumour.Network Modeling Analysis in Health Informatics and, Bioinformatics 10 (1) (2021).
[20] S. Madhihah, A. Malik, I. Abdullah, S.M. Mahali, Analytic solution for hollow microneedles assisted transdermal drug delivery model, Int. J. Appl. Eng. Res. 13 (1) (2018) 737–742.
[21] J. Crank, The Mathematics of Diffusion, second ed., Clarendon Press, Oxford, 1975.
[22] J. Hadgraft, Calculations of drug release from controlled release devices. The slab, Int. J. Pharm. 2 (1979) 177–194.
[23] J. Hadgraft, The epidermal reservoir: a theoretical approach, Int. J. Pharm. 2 (1979) 265–274.