Pseudo analytic approach to estimate drug transport and release in the annular section of human limbs

Saqib Mubarak
M. A. Khanday*
Ahsan Ul Haq
Department of Mathematics
University of Kashmir
Srinagar, 190006
India
khanday@uok.edu.in

Abstract. A mathematical model has been developed to estimate the concentration of transdermal drug transport in an annular section of the human forearm. The formulation of the model is based on the radial and angular diffusion equation together with appropriate boundary conditions. An analytic method has been employed to determine the steady-state concentration of the drug in the annular region of dermal system and the unsteady-state concentration of drug release and transport has been computed using finite difference explicit method. The proposed model may be useful for drug transport in human subjects especially for the application of drug through transdermal drug delivery system. The model has applications in biomedical sciences especially while dealing with the patients having oral and intravenous drug issues.

Keywords: transdermal drug diffusion, Dirichlet's problem, separation of variables method, finite difference method.

1. Introduction

The suitable administration route for strong and low molecular weight drugs is considered to be transdermal drug delivery. Its main advantage is that it is a substitute to tablets and injections. This delivery system is mainly concerned with the delivery device and anatomy of dermal region, which consists of uppermost stratum corneum and underlying layers of stratum germinativum, dermis and subcutaneous tissue[2]. The transdermal drug delivery system(TDDs) is a suitable format in which the drug is applied externally either through a reservoir in contact with the outermost layer or through periodic application. The drug and the delivery system are designed in such a way that the drug reaches the targeted area with prescribed concentration.

Over the last 50 years, mathematical modeling on the diffusional and release processes has been used to design a number of simple and complex drug delivery systems and devices to predict the overall release behaviour and diffusion of the

*. Corresponding author

drug. R.A. Gatenby and E.T. Gawlinski developed a reaction-diffusion model of cancer invasion[3]. They have developed a model encompassing the key components of their hypothesis predicting an acidic pH gradient extending into the peritumoral tissue, which they confirmed by reanalysis of extant experimental data. A two-layer reaction-diffusion-convection model for drug delivery in biological tissues was developed by S. McGinty and G. Pontrelli[11]. They have presented a general model of drug release from a drug delivery device(DDD) and the subsequent drug transport in biological tissue. Feizabadi *et al* have developed a two compartment interacting with the dynamic drugs[7]. They have combined the total cell evolution curve and a two compartment model interacting with dynamic anti-cancer agents. They have analytically obtained the evolution of subpopulations. N.A. Peppas and B.Narasimhan have developed mathematical models in drug delivery to predict how the new drug delivery systems can be designed[12].

Further Khanday and Rafiq have studied the absorption rate of drug at various compartments through TDD system[8]. Khanday *et al* have also developed some mathematical models for drug diffusion through the compartments of blood and tissue medium[6]. They have established mathematical models to understand the distribution of drug administration in human body through oral and intravenous routes. They formulated three models based on diffusion process using Fick's principle and law of mass action. Distribution of drug in a sample of five layers of human skin was also studied by A. Sharma and V.P. Saxena[13]. They have constructed a mathematical model to study the drug concentration in the different layers of skin through transdermal drug delivery system. They have used the finite element method with linear shape functions to obtain the solution of governing one dimensional partial differential equation for unsteady state case. Further, mathematical and computational models of drug transport in tumors were also developed by C.M. Groh *et al*[5]. They considered three different modelling approaches, each of which represented drug delivery from a central blood vessel to a surrounding tumor cord. Their models were based on the assumption of axial uniformity- the dependence of drug concentration on the distance from the central vessel does not vary along the vessel, to reduce the complexity of their models.

The mathematical models based on radial and angular diffusion were studied by various researchers. Heat and mass diffusions were extensively studied by Khanday and his co-workers[6, 8, 9, 10] however, the drug diffusion in an annular region of human forearm has not been studied so far. The transport of drug has been studied in the dermal and the muscular regions of the forearm. In the steady-state, we have taken the three regions of the dermal section viz: epidermis, dermis and hypodermis, while as in the unsteady-state case, epidermis, dermis and hypodermis have been collectively taken as the skin(dermal) region. Consider the boundary of the region with one end at the boundary of the bone and the other end at the skin surface. The formulation is based on the mass diffusion equation with appropriate boundary and initial conditions, and

the solutions have been established analytically and numerically respectively for the steady-state and unsteady-state cases. The proposed work can provide the details of drug transport in the annular region defined above.

2. Mathematical model

Consider the annular section of the human forearm with radii respectively as r_1 cm and r_2 cm such that $0 < r_1 < r_2$ as shown in Fig. 1 and Fig. 2.

Figure 1: Cylindrical sample section of human forearm.

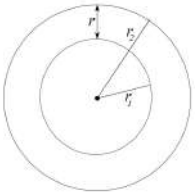

Figure 2: Annular Cross-section of the limb.

The drug is applied at the outer skin surface $r = r_2$ and the estimation of the drug transport in the ring shaped(annular) region(skin and muscle) can be established using suitable partial differential equation. The diffusion equation in plane polar coordinates for the transport and diffusion of a drug in the cross-section of the annular region of human forearm is given by Crank[1]

$$\frac{1}{D}\frac{\partial C}{\partial t} = \frac{\partial^2 C}{\partial r^2} + \frac{1}{r}\frac{\partial C}{\partial r} + \frac{1}{r^2}\frac{\partial^2 C}{\partial \theta^2} + R(r,\theta) \tag{1}$$

where $C(r,\theta,t)$ is the drug concentration in the annular dermal region $r_1 \leq r \leq r_2$, t denotes the time, θ determines the angular direction of drug, D is the diffusion coefficient and R is the rate of metabolic drug consumption.

It is imperative to see that the transport of the drug from the skin surface towards the deep core has a non-linear behaviour and at any radial distance, the oscillation of the drug flow has been assumed by using the following initial

and boundary conditions :

$$C(r_2,\theta,t) = c_0 \ at \ t = 0 \ and \ \forall \ 0 \leq \theta \leq \ 2\pi \tag{2}$$

$$C(r_2,\theta,t) = \sin(\theta - \frac{\pi}{2}t) \ \forall \ 0 \leq \theta \leq \ 2\pi \ and \ \forall \ t > 0 \tag{3}$$

$$C(r_1,\theta,t) = \cos(\theta - \frac{\pi}{2}t) \ \forall \ 0 \leq \theta \leq \ 2\pi \ and \ \forall \ t > 0 \tag{4}$$

2.1 Steady-state case

In this case, Eq. (1) reduces to

$$\frac{\partial^2 C}{\partial r^2} + \frac{1}{r}\frac{\partial C}{\partial r} + \frac{1}{r^2}\frac{\partial^2 C}{\partial \theta^2} = -R(r,\theta) \tag{5}$$

which is a non homogeneous partial differential equation.

The solution of Eq.(5) is sum of two terms, namely $C_1(r,\theta)$ which represents the complementary function corresponding to the solution of the homogeneous part of Eq.(5) and $C_2(r,\theta)$, which represents the particular integral corresponding to the non-homogeneous part of Eq.(5). Also, the boundary conditions in Eqs.(2) ,(3),(4) for the homogeneous part of Eq.(5), become respectively as :

$$C_1(r_2,\theta) = \sin(\theta) \ \forall \ 0 \leq \theta \leq \ 2\pi \tag{6}$$

$$C_1(r_1,\theta) = \cos(\theta) \ \forall \ 0 \leq \theta \leq \ 2\pi \tag{7}$$

Assume the periodicity condition as:

$$C_1(r,\theta + 2\pi) = C(r,\theta), \ r_1 \leq r \leq r_2 \tag{8}$$

The formulation part of the model is given by the boundary-value problem defined by Eqs.(5) - (8). The solution of the model can help us to estimate the steady-state drug concentration at various sections of the annular region given in Fig. (2).

2.1.1 Method

The model Eq. (5) is a non homogeneous equation in nature, its complete solution will be of the form

$$C(r,\theta) = C_1(r,\theta) + C_2(r,\theta) \tag{9}$$

where $C_1(r,\theta)$ and $C_2(r,\theta)$ respectively represent the solution of homogeneous part and the particular solution of Eq.(5).

Now considering the homogeneous part of Eq.(5) along with the conditions given by Eqs.(6) -(8), it becomes Dirichlet's boundary value problem for the annulus. The analytical solution of the problem is given as

$$C_1(r,\theta) = a_0 + \alpha_0 log(r) + \sum_{n=1}^{\infty} \big[(a_n r^n + \alpha_n r^{-n})\cos(n\theta) + (b_n r^n + \beta_n r^{-n})\sin(n\theta)\big] \tag{10}$$

where the coefficients a_0,α_0,a_n,α_n,b_n and β_n are determined and are given in Appendix.

Also the particular integral of Eq.(5) is

$$C_2(r,\theta) = \frac{1}{D_1^2 + D'^2} F(r,\theta) \tag{11}$$

where $D_1 = \frac{\partial}{\partial z}$, $z = log\ r$, $D' = \frac{\partial}{\partial \theta}$ and $F(r,\theta) = -r^2 R(r,\theta) = \frac{c_0}{r}\cos(\theta)$ (because the concentration decreases radially).

Now,

$$C_2(r,\theta) = \frac{1}{D_1^2 + D'^2}\frac{c_0}{r}\cos(\theta) = c_0 \frac{1}{D_1^2 + D'^2} e^{-z}\cos(\theta) = -\frac{c_0}{2r}\cos(\theta)$$

Therefore the complete solution of Eq.(5) is

$$C(r,\theta) = \left[(a_1 r + \alpha_1 r^{-1})\cos(\theta) + (b_1 r + \beta_1 r^{-1})\sin(\theta)\right] - \frac{c_0}{2r}\cos(\theta) \tag{12}$$

where the coefficients are defined in Appendix.

After finding the solution completely, we now assign different values to the physiological parameters used in the model depending on the sample of the annular section of the forearm under study. Some of the values of the parameters were taken from M.A. Khanday *et al*[10] in order to determine the drug concentrations in the mentioned regions using Eq. (12). Eq. (12) can help us in finding out the drug absorption and release in steady-state case by assigning values of the parameters.

2.1.2 Results

The drug concentration profiles in the annular region were computed taking the initial concentration $c_0 = 2.5 mg/cm^3$. The numerical values of the physiological parameters used and the results obtained are shown in Table 1. The computed values are given as follows: $C(r = 0.25) = C(0.25) = 0.42 mg/cm^3$, $C(r = 0.29) = C(0.29) = 0.21 mg/cm^3$, $C(r = 0.16) = C(0.16) = 0.43 mg/cm^3$, $C(r = 1.28) = C(1.28) = 0.02 mg/cm^3$.

For fixed $\theta = \pi/4$ and applying Lagranges's interpolation formula [4], the interpolation polynomial is given as

$$C(r) = 39.6r^3 - 67.3r^2 + 22.4r - 1.5 \tag{13}$$

The graph in Fig. 3 has been plotted between drug release/absorption versus radial distance of the annular region. The size of the ring was taken as $(1.02 \leq r \leq 3.0) cm$, where it was assumed that bone radius is 1.02 cm and the size of the limb is 3.0 cm.

Further the graphs given in Figs.[4] and [5] are plotted according to the equation(12).

Table 1: Physiological and Numerical values of parameters and Concentration in the different sections of the annular region[10].

Parameter	Epidermis	Dermis	Hypodermis	Muscle
r_1	$2.75\,cm$	$2.46\,cm$	$2.30\,cm$	$1.02\,cm$
r_2	$3.00\,cm$	$2.75\,cm$	$2.46\,cm$	$2.30\,cm$
r	$0.25\,cm$	$0.29\,cm$	$0.16\,cm$	$1.28\,cm$
Q	1.09	1.11	1.06	2.25
Q^{-1}	0.91	0.89	0.94	0.44
$Q - Q^{-1}$	0.18	0.22	0.12	1.81
a_1	$-1.85\ cm^{-1}$	$-1.65\ cm^{-1}$	$-3.38\ cm^{-1}$	$-0.24\ cm^{-1}$
α_1	$16.66\ cm$	$12.5\ cm$	$20.5\ cm$	$1.27\ cm$
b_1	$2.02\ cm^{-1}$	$1.84\ cm^{-1}$	$3.62\ cm^{-1}$	$0.54\ cm^{-1}$
β_1	$-15.27\ cm$	$-11.18\ cm$	$-19.16\ cm$	$-0.54\ cm$
C	$0.42\ mg/cm^3$	$0.21\ mg/cm^3$	$0.43\ mg/cm^3$	$0.02\ mg/cm^3$

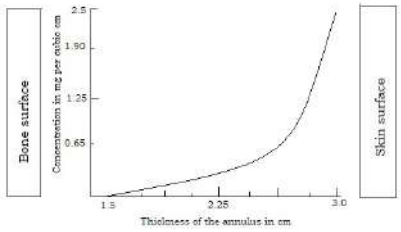

Figure 3: Drug Concentration in the annular section from the skin towards the core with $c_0 = 2.5mg/cm^3$

2.2 Un-steady state case

The unsteady-state diffusion equation in polar coordinates for the transport and diffusion of a drug is given in Eq.(1) along with the associated conditions given in Eqs.(2)-(4). In order to determine the time dependent drug distribution in the annular region of the human limb, the two subsections denoted by 1 and 2 in Fig. $6(a)$ were studied and the uniform treatment can be followed for other regions. The discretization of these regions is shown in Fig. $6(b)$, where nine nodal points are shown for bone, muscle and skin regions. The value of each of the nine nodal points has to be calculated for $k = 0, 1, 2$ time levels, so that we actually have twenty-seven nodal points. The subscripts d and m represent the parameters related to these regions respectively. The physiological and parametric behaviour of these regions is given below:

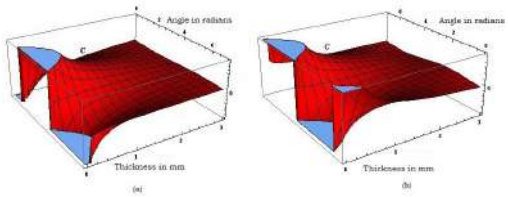

Figure 4: Drug flow in (a) epidermis and (b) dermis.

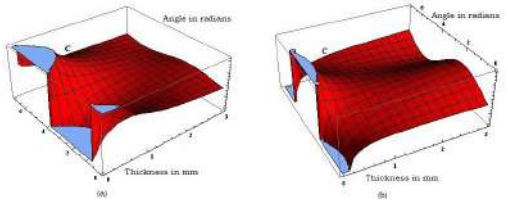

Figure 5: Drug flow in (a) hypodermis and (b) muscle.

Skin: In the uppermost layer of this region(epidermis), there are no blood vessels and hence almost negligible metabolic activity [9], thus we take $D_d = D_1 = constant = 0.002cm^2/min$ and $R_d = R_0 = 0$.

Muscular region: For this case, we take $D_m = D_2 = constant = 0.00204cm^2/min$ and $R_m = R_i = \frac{c_0}{(ih)^3}\cos(\pi/4)$ for $i = 1, 2$.

2.2.1 Method

On employing the explicit finite difference method to solve the boundary value problem given in Eqs.(1)-(4), we have

$$a_i C_{i,j,k+1} = \{a_i - d_i - 2(b_i + 1)\}C_{i,j,k} + (b_i + d_i)C_{i+1,j,k} + b_i C_{i-1,j,k} + C_{i,j+1,k} + C_{i,j-1,k} + e_i \tag{14}$$

$$C_{0,j,0} = c_0 = 2.5\ mg/cm^3\ \forall\ j \tag{15}$$

$$C_{0,j,k} = \sin(jk' - \frac{\pi}{2}kl)\ \forall\ k \neq 0\ and\ \forall\ j \tag{16}$$

$$C_{2,j,k} = \cos(jk' - \frac{\pi}{2}kl)\ \forall\ k \neq 0\ and\ \forall\ j \tag{17}$$

where the values of unknown parameters a_i, b_i, d_i and e_i are given in Appendix.

For $j = 0, 1, 2$ in Eq.(15), we obtain the values of $C_{0,0,0}, C_{0,1,0}$ and $C_{0,2,0}$, and are all found to be equal to $c_0 = 2.5\ mg/cm^3$. Also we obtained that $R_1 = 5.1mg/cm^6$, $R_2 = 0.6mg/cm^6$.

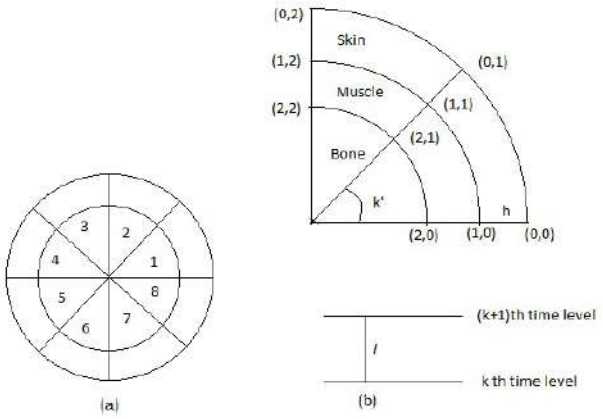

Figure 6: (a) Division of the annular cross-section into 8 sub-sections and (b) Layer-wise discretization of skin and muscle,$C_{i,j,k}$(i-space step parameter in cm, j-angular step parameter in radians and k-time step parameter in min based on finite difference method) is the nodal concentration at $(i, j, k)th$ place of the interface.

Now, using $j = 0, 1, 2$ and then $k = 1, 2$ in Eqs. (16) and (17), we obtain the nodal concentrations $C_{0,0,1}, C_{0,0,2}, , C_{0,1,1}, C_{0,1,2}, C_{0,2,1}, C_{0,2,2}, C_{2,0,1}, C_{2,0,2}, C_{2,1,1}$, $C_{2,1,2}, C_{2,2,1}$ and $C_{2,2,2}$.

Continuing in this way, we shall be able to compute the values of all nodal points of the sub-domains given by the symbols $C_{i,j,k}$, representing the nodal values of the drug concentration of the discretized region shown in Fig. 5 using Eq.(14).

2.2.2 Results

Assigning different values to the physiological parameters used in the model depending on the properties and the sample of the forearm(annular section) of skin and muscle under study, we have calculated the drug concentrations at various nodal points. The values have been calculated for $h = 0.70\ cm$ for skin, $h = 1.28\ cm$ for muscle,$l = 5\ min$ and $k' = \pi/4$, as given below in the following Tables $2 - 5$. Since,when the time has not started or when the drug has not been applied, there will be no diffusion of the drug inside the skin or muscle, so we choose $C_{1,0,0} = C_{1,1,0} = C_{1,2,0} = C_{2,0,0} = C_{2,1,0} = C_{2,2,0} = 0$.

3. Discussion

The mathematical model has been formulated to study the drug transport in an annular region of human forearm. The model has been solved for steady

Table 2: Numerical values of the coefficients appearing in Eq.(14).

Parameter	Value	Parameter	Value
a_0	0	d_0	0
a_1	30.1	d_1	0.6
a_2	120.7	d_2	1.2
b_0	0	e_0	0
b_1	0.6	e_1	$-1.5\ mg/cm^3$
b_2	2.4	e_2	$-0.6\ mg/cm^3$

Table 3: Concentration at nodal points corresponding to $i = 0$(i.e; at exposed skin surface).

Concentration-nodal points	Values in mg/cm^3
$C_{0,0,0}$	2.5
$C_{0,1,0}$	2.5
$C_{0,2,0}$	2.5
$C_{0,0,1}$	1
$C_{0,0,2}$	0
$C_{0,1,1}$	0.7
$C_{0,1,2}$	0.7
$C_{0,2,1}$	0
$C_{0,2,2}$	1

and unsteady-state cases using analytical and numerical methods respectively. For the steady-state case, the solution has been established using Dirichlet's boundary value problem and Lagrange's interpolation scheme, and the boundary conditions were constructed on the basis of drug/cream/ointment pasted on the skin surface. For the unsteady-state case, the solution was established using the explicit finite difference method where the domain is taken as the skin(dermal regions) and the muscular region. The transport of drug takes place through the dermal regions. The presence of pores on the skin surface and other biophysical and physiological parameters support the flow of drug towards the inner core. Since the formulation of the model has been carried out on a ring shaped annular region, both radial and angular variables play a key role to understand the mechanism of drug transport in this region. We assumed that the flux of drug at the skin surface satisfies sinusoidal pattern due the fact that drug transports in all directions and the rare presence of holes at the skin surface. The same argument is applicable at the bone surface which is infact the interior of the annulus. The partial differential equation (1) together with the appropriate boundary conditions were used to estimate the drug transport in the region $(0 <)r_1 < r < r_2$. The model equations were solved by using method of separation

Table 4: Concentration at nodal points corresponding to $i = 1$(i.e; at the interface between the skin and the muscle).

Concentration-nodal points	Values in mg/cm^3
$C_{1,0,1}$	0.08
$C_{1,0,2}$	0.04
$C_{1,1,1}$	0.00066
$C_{1,1,2}$	0.0046
$C_{1,2,1}$	0.00066
$C_{1,2,2}$	0.0093

Table 5: Concentration at nodal points corresponding to $i = 2$(i.e; at the interface between the bone and the muscle).

Concentration-nodal points	Values in mg/cm^3
$C_{2,0,1}$	0
$C_{2,0,2}$	1
$C_{2,1,1}$	0.7
$C_{2,1,2}$	0.7
$C_{2,2,1}$	1
$C_{2,2,2}$	0

of variables and Fourier expansions for the steady-state case and by the explicit finite difference method for the unsteady-state case. Our proposed model has an advantage that at any time we can find the value of the drug concentration inside the given region if the initial concentration is known.

4. Conclusion

It has been observed that the drug release and absorption in dermal and muscular regions has a continuous pattern from the outer surface towards the inner core through TDD route. The pattern of drug transport is shown in Fig. 3 with initial drug concentration of $c_0 = 2.5\ mg/cm^3$ while keeping one variable (θ) fixed. Also graphs given in Figs.[4] and [5] are plotted according to the Eqn.(12) which show the drug flow in the regions epidermis, dermis, hypodermis and muscle respectively, which describe that the concentration of the drug in each region is maximum near the boundaries of the regions and remains nearly uniform in the centre of each region in the steady state case.

The maximum drug absorption takes place in the papillary and reticular regions of human dermal system due to dense network of blood vessels. In the muscular region, the flow is comparatively steep as shown by the curve of the

graph in Fig. 3. The solution for the unsteady-state case as given by Eqn.(14) depicts that the drug concentration can be found at any time in any region of the domain. This study can help the medical scientists and allied researchers to understand the residual drug concentration and absorption at various tissues of the human forearm. Further, since the model does not possess an exact solution for the unsteady state case, this is a severe limitation of this model, hence this work can further be improved if an exact solution can be found.

Acknowledgements

The authors are highly thankful to National Board for Higher Mathematics, Department of Atomic Energy, Govt. of India for providing financial support under award no. 2/48(15)/2016NBHM(RP)-RND&II/16941 to carry out this work.

Appendix

$a_0 = 0;\ \alpha_0 = 0;\ a_1 = -\frac{r_2^{-1}}{Q-Q^{-1}};$

$\alpha_1 = \frac{r_2}{Q-Q^{-1}};\ b_1 = \frac{r_1^{-1}}{Q-Q^{-1}};\ \beta_1 = -\frac{r_1}{Q-Q^{-1}};\ a_n = \alpha_n = b_n = \beta_n = 0\ \forall\ n \neq 1\ ;$

$Q = \frac{r_2}{r_1}$

$a_i = \frac{i^2h^2k'^2}{Dl};\ b_i = i^2k'^2;\ d_i = ik'^2;\ e_i = -Ri^2h^2k'^2\ ;$

$i = 0,\ 1,\ 2.$

References

[1] J. Crank, *The mathematics of diffusion,* Clarendon Press, Oxford, Second Edition, 1975.

[2] B. Forslind, *The skin: upholder of physiological homeostasis a physiological and bio-physical study program,* Thrombosis Res., 80 (1995), 1-22.

[3] R.A. Gatenby, E.T. Gawlinski, *A reaction diffusion model of cancer invasion,* Cancer Research, 56 (1996), 5745-5753.

[4] B. S. Grewal, *Numerical methods in engineering and science,* Khanna Publishers Daryagang, New Delhi, Tenth Edition, (2014), 209-213.

[5] C.M. Groh *et al*, *Mathematical and computational models of drug transport in tumors*, J. R. Soc. Interface, 11:20131173.

[6] M.A. Khanday, Aasma Rafiq, Khalid Nazir, *Mathematical models for drug diffusion through the compartments of blood and tissue medium,* Alexandria Journal of Medicine, 53 (2017), 245-249.

[7] M.S. Feizabadi, C. Volk, S. Hirschbeck, *A two-compartment model interacting with dynamic drugs*, Applied Mathematics Letters, 22 (2009), 1205-1209.

[8] M.A. Khanday, Aasma Rafiq, *Variational finite element method to study the absorption rate of drug at various compartments through transdermal drug delivery system,* Alexandria Journal of Medicine, 51 (2015), 219-223.

[9] M.A. Khanday, Fida Hussain, *Explicit formula of finite difference method to estimate human peripheral tissue temperatures during exposure to severe cold stress,* Journal of Thermal Biology, 48 (2015), 51-55.

[10] M.A. Khanday *et al*, *A mathematical model for the estimation of thermal stress and development of cold injuries on the exposed organs of human body*, Journal of Mechanics in Medicine and Biology, 16 (2015), 1650062 1-16.

[11] S. McGinty, G. Pontrelli, *Drug delivery in biological tissues: a two-layer reaction-diffusion-convection model,* Progress in Industrial Mathematics, (2014), 355-363.

[12] N.A. Peppas, B. Narasimhan, *Mathematical models in drug delivery: how modelling has shaped the way we design new drug delivery systems*, Journal of Controlled Release, 190 (2014), 75-81.

[13] A. Sharma, V.P. Saxena, *Drug distribution in sample of five layers of human skin*, JIPBS, 4 (2017), 170-175.

Accepted: 25.03.2019