A fourth-order accurate numerical solution to the problem of unsteady diffusion of chemicals through human skin

Samir F. Radwan
Mathematics Eng. Dept., Faculty of Eng., Alexandria University, Alexandria, Egypt
E-mail : RadwanSamirfarid@hotmail.com

The present paper is devoted mainly to present a higher-order accurate numerical solution to the problem of the unsteady diffusion of a chemical substance, such as pesticides or aerosols, through the human skin.A mathematical model is used to simulate the different processes by which a substance can penetrate the multi-layered skin structure to blood vessels. The resulting unsteady governing equations are solved using a fourth order accurate explicit finite difference scheme and the Du-Fort Frankel scheme. The question of numerical stability and convergence of the present schemes is addressed. The accuracy and the computational efficiency of the above schemes have been checked. This shows that the fourth-order accurate explicit scheme is stable and efficient for solving the unsteady skin diffusion type-problems, especially with large computation time.

يقدم هذا البحث حلا عدديا ذا دقة من الدرجة الرابعة لحل مشكلة الحالة غير المستقرة لنفاذية الجلد عند تعرضه لمواد كيميائية مثل المبيدات أو عند تعرضه لتلوث كيميائي جوي؛ بغرض معرفة التوزيعات الزمنية لنفاذية هذه المادة الكيميائية خلال طبقات الجلد المختلفة ومقدار تركيزها فيها وتطبيقاتها في مجال العلوم البيئية وخصوصا التلوث البيئي. وقد تم وضع نموذج رياضي لتمثيل الجلد وما يحتويه من طبقات وكذلك تمثيل العمليات الحيوية التي يمكن بواسطتها أن تنفذ أي مادة كيميائية في طبقات الجلد المختلفة ومنها الي الشرايين الدموية. وتم استنتاج خوارزم محدد صريح ذي دقة من الدرجة الرابعة لحل المعادلات الناتجة من هذا النموذج الرياضي. وقد درست مشكلة استقرار وثبات خوارزم الحل والقيود اللازمة لذلك. وتم اختبار هذا الخوارزم في حل مشكلة النفاذية غير المستقرة لمادة كيميائية خلال جلد إنسان. وقد أوضحت النتائج التي تم الحصول عليها في البحث الحالي مدي كفاءة واستقرار الخوارزم الذي تم تطويره وإمكانية استخدامه في العلوم البيئية وخصوصا علي المدي الزمني الطويل.

Keywords: Unsteady skin diffusion, Percutaneous absorption modelling, Fourth-order accurate finite-Difference method

1. Introduction

The interest in understanding the human skin permeability has increased recently, especially with the increase in industrialization of our life, and with the increase in the risks of aerosols and war gases. In recent studies about the skin permeability of different species including man, when they are exposed to several pesticides, Bartek and La Budde [6], and Wester and Noonan [18] have indicated that human skin is the least permeable skin to chemical substances. Even so, we are living in an age where we are constantly exposed to active substances in our environment which are capable of penetrating the healthy human skin in a sufficient degree of concentration to produce harmful effects. Often such exposure is intentional, mainly in the field of dermatology, where potent compounds are applied to skin for their local therapeutic effect. They are either anti-inflammatory agents that are used widely in treating skin diseases, or cosmetics such, as Scopolamine that can block the innervation of the eccrine sweat glands, thus preventing sweating, as indicated by Higuchi [9]. Also, the processes of penetration of medicinal substances from outside into the skin and through the skin layers into the blood streams, which are known as percutaneous absorption, have wide applications in the fields of pharmacy and dermatology [1-3,5,8,9]. For example, intelligent formulation of dermatological preparations depends on a thorough understanding of percutaneous absorption. On the other hand, the exposure to harmful substances, such as pesticides and aerosols, is sometimes unavoidable and they can damage or even destroy the skin structure, thus allowing much greater quantities of material to penetrate in a nonselective manner. This defines

the scope of the problem, and also points to the need for better understanding of skin permeability and how it is changed by exposure to various chemical substances.

It is appropriate to consider briefly the anatomical skin structure. The skin consists of two main parts: (a) the epidermis with multilayered structure, and a thickness of 1 to 2 mm, as shown in fig. 1, and (b) the dermis with dense irregularly arranged connective tissues, and a thickness of 0.2 to 4 mm. There are also appendages and blood vessels which traverse the skin structure such as hair follicles, sweat gland ducts, and sebaceous glands, for more details, see Kelly et al. [11].

Penetration of a chemical substance through the skin has been studied in detail especially in the field of pharmacy. Barr [5] has reviewed the subject and concluded that the main avenue of penetration is through the epidermis layers, rather than through hair follicles or sweat gland ducts, simply because the epidermis presents a surface area 100-1000 times greater than the other routes. Albery and Hadgraft [2] developed a theoretical model for the transport of a drug through the epidermis with interfacial barriers between its layers. However, their model is simple and approximate since the epidermis is simulated by only two layers (corneum and granular layers) and the internal barrier between them. Albery et al. [3] presented a mathematical model for the percutaneous absorption of 3 different esters of nicotinic acid through the epidermis and the dermis layers. Again, the model is simple and approximate because it neglects the diffusion through the various unequally permeable layers of epidermis, and considers them one layer. Hadgraft [8] reviewed the absorption of drug through the skin, and discussed the different possible routes of drug penetrations. From his review, one can conclude that the most accepted routes for penetration of a chemical substance through skin are due to the following two processes. The first process is the intracellular diffusion, in which the active substance diffuses through the various unequally permeable layers of the epidermis until it reaches the viable epidermis zone with small diffusion coefficient (10^{-7} cm^2 s^{-1}) and finally the epidermal-dermal interface where blood

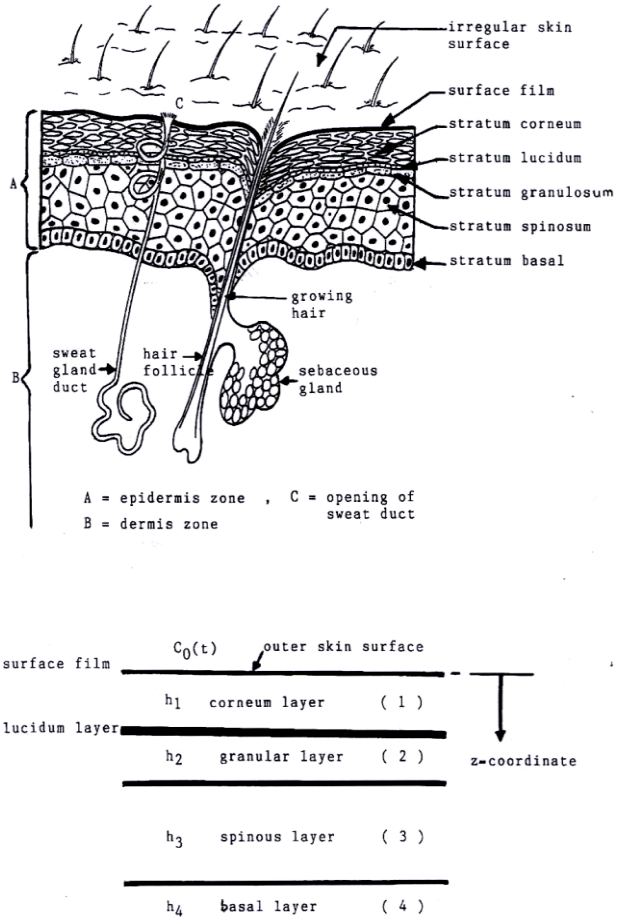

Fig. 1. The multi-layered skin structure and its present model.

vessels are situated. In most circumstances, the viable epidermis zone will not provide much of a diffusional resistance, and the blood vessels in the interface region remove the diffused substance efficiently. The second process is flow through the appendages on the surface, such as hair follicles and sweat gland ducts, with subsequent absorption of the substance through their membrane-like boundaries into the various layers of the epidermis and then diffusion as in the first process.

Murdoch et al. [12] have presented a theoretical model to simulate the diffusion of a product through the skin using the above-mentioned two popular mechanisms of penetration. The model simulates intracellular diffusion in each layer of epidermis by applying Fick's second law of diffusion, while the second process of penetration is

incorporated in the model by adding a source term to the governing equation in each layer. Moreover, the model also, incorporated the process of continuous cell creation in the innermost layer of the epidermis (viable epidermis) that slows down absorption from the outer layer. The resulting governing equations are a system of partial differential -algebraic equations with mixed interface conditions, that are solved by using SPRINT package [7]. The package is based on the implementation of Gear's method of Hindmarsh [10], and the Blended linear multistep method of Skeel and Hong [17]. Inspite of the accuracy of SPRINT package, they had to solve a system of ordinary differential-algebraic equations at each time step, which makes the package highly expensive and inefficient, especially for unsteady skin diffusion problems with long computation time. However, no much work has been done in the area of numerical modelling of the unsteady diffusion of a chemical substance through the skin, especially the application of the higher order accurate schemes. As such, the present study aims at studying the feasibility of extending the fourth-order accurate scheme to solve the unsteady diffusion of a chemical substance through the skin.

Therefore, our goal is to develop a simple efficient higher-order accurate numerical method for solving the problem of unsteady diffusion of a chemical substance through the skin, when the outer surface of the skin is exposed to chemical hazards, using a fourth -order accurate finite difference explicit scheme, and also to determine the feasibility of its use as well as to verify the high-order of accuracy claimed.

2. Mathematical formulation

In the present study, a theoretical model similar to the model used by Murdoch et al [12], has been used. It simulates the three different processes by which a chemical substance can penetrate the skin structure to blood vessels. It simulates intracellular diffusion through the various layers of epidermis by applying Fick's second law of diffusion [14], while the second process of penetration is incorporated in the model by adding a source term to the governing equation in each layer. Moreover, the model also incorporates the process of continuous cell creation in the innermost layer of the epidermis (viable epidermis) that slows down absorption from the outer layer. The model of the multilayered epidermis is shown in fig. 1. Each of the surface film and lucidum layer is very thin and its thickness can be neglected. However, their functions as barrier zones are incorporated by assigning them as partition coefficients (α_0 , α_1 ,...). The governing equation of the concentration C_j (z,t) in the j-th layer takes the following form :

$$\frac{\partial C_j}{\partial t} = L\left(C_j\right), \qquad j = 1,2,3,4 \cdot$$

$$L(C_j) = \frac{\partial}{\partial z}\left(D_j \frac{\partial C_j}{\partial z} \right) + v_j \frac{\partial C_j}{\partial z} - \mu_j C_j + \lambda_j (C_o - \beta_j), \tag{1}$$

where D_j (z) is the diffusion coefficient in the j-th layer, v is the advection rate representing cell creation and μ is the reaction or neutralization rate. The last term in the equation above represents the additional diffusion through the appendage ducts where the λ and β are related to the permeability of the duct membrane. Defining,

$$\tilde{\mu}_j = \mu_j + \lambda_j \beta_j ,$$

and dropping the ~ yields

$$\frac{\partial C_j}{\partial t} = L(C_j), \qquad j = 1,2,3,4$$

$$L(C_j) = \frac{\partial}{\partial z}\left(D_j \frac{\partial}{\partial z} \right) + v_j \frac{\partial C_j}{\partial z} - \mu_j C_j + \lambda_j C_o . \tag{2}$$

At the interface between the layers the concentrations $C(z, t)$ may be discontinuous, but the flux is continuous, which takes the following two imposed conditions:

$$C_{j+1} = \alpha_j C_j \ , \ j = 0, 1, 2, 3$$

$$D_j \frac{\partial C_j}{\partial z} + v_j C_j = D_{j+1} \frac{\partial C_{j+1}}{\partial z} + v_{j+1} C_{j+1}, \qquad j = 1,2,3 \ . \tag{3}$$

Initially, the concentration is zero everywhere except on the exterior skin surface, where it is equal to C_o (t), the concentration of the substance on the outer surface. Therefor, the initial and boundary conditions are:

$$C_j(z,0) = 0, \quad j = 1, \ldots 4. \tag{4}$$

$$C_1(0,t) = C_0(t)\, a_0 \qquad C_4(\sum h_j, t) = 0, \tag{5}$$

where the initial concentration, C_o (t), and the partition coefficients, a_j, are given. The second boundary condition implies that the blood vessel flushes away any substance that permeates through the boundary of last layer. The governing equations, eq. (2) and eq. (3), are then non-dimensionalised using a scale appropriate for the given problem, which will depend upon the substance used. For the present data listed in Appendix A., the following non-dimensionalised variables are used:

$$\xi = \frac{D_2}{h_2^2} t, \qquad x = \frac{z}{h_2}, \tag{6}$$

then, define

$$\frac{\partial}{\partial t} = \frac{\partial \xi}{\partial t} \frac{\partial}{\partial \xi} = \frac{D_2}{h_2^2} \frac{\partial}{\partial \xi} \qquad \frac{\partial}{\partial z} = \frac{\partial x}{\partial z} \frac{\partial}{\partial x} = \frac{1}{h_2} \frac{\partial}{\partial x}, \tag{7}$$

the resulting governing equations are:

$$\frac{\partial C_j}{\partial \xi} = a_{3j} \frac{\partial^2}{\partial x^2} C_j + a_{2j} \frac{\partial C_j}{\partial x} + a_{1j} C_j + a_{oj}, \tag{8}$$

where the coefficients a_{mj} (m =0, 1, 2, 3) are function of the skin parameters, and they take the following forms:

$$a_{oj} = \frac{\lambda_j C_o h_2^2}{D_2}, \qquad a_{1j} = -\frac{\mu_j h_2^2}{D_2}$$
$$a_{2j} = \frac{1}{D_2} \frac{\partial D_j}{\partial x} + \frac{v_j h_2}{D_2}, \quad a_{3j} = \frac{D_j}{D_2}. \tag{9}$$

3. The numerical schemes

In the present study, higher order accurate finite difference schemes, namely the fourth -order accurate explicit finite difference scheme and the Du-Fort Frankel scheme, are used to solve the unsteady diffusion eqs. (8) and the interface conditions eqs. (3) together with the initial and the boundary conditions eq. (4) and eq. (5). The present numerical schemes are done explicitly to overcome the difficulties associated with the imposed jump conditions at the interface boundaries.

3.1. The fourth-order accurate explicit scheme

Let the interval [x_o, x_N] be discretized into N grid steps of size Δx where $\Delta x = (x_i - x_{i-1})$, i is an index of any grid-point in x direction. and n is an index for the temporal grid point. The fourth-order accurate finite difference approximations for the first-order derivative and for the second-order derivative can take the following forms [13]:

$$\frac{\partial C_i}{\partial x} = D_x \left[1 - \frac{\Delta x^2}{6} \delta_x^2 \right] C_i + O(\Delta x^4), \tag{10}$$

$$\frac{\partial^2 C_i}{\partial x^2} = \delta_x^2 \left[1 - \frac{\Delta x^2}{12} \delta_x^2 \right] C_i + O(\Delta x^4), \tag{11}$$

where,

$$D_x C_i = \frac{1}{2\Delta x} (C_{i+1} - C_{i-1}),$$
$$\delta_x^2 C_i = \frac{1}{\Delta x^2} (C_{i+1} - 2C_i + C_{i-1}). \tag{12}$$

The explicit form of the present fourth-order accurate scheme for the time-dependent diffusion eq. (8) in each layer, using the previous approximations, takes the following form:

$$\left[\frac{C_i^{n+1}-C_i^n}{\Delta\xi}\right]=a_3\,\delta_x^2\left[1-\frac{\Delta x^2}{12}\,\delta_x^2\right]$$
$$C_i^n+a_2 D_x\left[1-\frac{\Delta x^2}{6}\delta_x^2\right]C_i^n$$
$$+a_1 C_i^n+a_0+O\left(\Delta t^2+\Delta x^4\right), \qquad (13)$$

and the final form of the present fourth-order accurate explicit scheme for the unsteady diffusion equation, eq. (8), in each layer of the model becomes :

$$C_i^{n+1} = A_1 C_{i+2}^n + A_2 C_{i+1}^n + A_3 C_i^n + A_4 C_{i-1}^n + A_5 C_{i-2}^n + A_6 . \qquad (14)$$

Where

$$A_1 = (-a_3 d - a_2 c)/12,$$
$$A_2 = (16a_3 d + 8a_2 c)/12$$
$$A_3 = 1 - 2.5\, a_3 d + a_1 \Delta\xi,$$
$$A_4 = (16a_3 d - 8a_2 c)/12$$
$$A_5 = (-a_3 d + a_2 c)/12,$$
$$A_6 = a_0 \Delta\xi$$

$$c = \frac{\Delta\xi}{\Delta x}, \quad d = \frac{\Delta\xi}{\Delta x^2}. \qquad (15)$$

3.2. The Du-Fort Frankel scheme

The Du-Fort Frankel scheme for the time-dependent diffusion eq. (8), in each layer, can be obtained by using second-order accurate central finite-difference approximations for both temporal and spatial derivatives. It takes the following form:

$$\left[\frac{C_i^{n+1}-C_i^{n-1}}{2\Delta\xi}\right]=a_3\left[\delta_x^2\right]C_i^n$$
$$+a_2[D_x]C_i^n+a_1 C_i^n+a_0$$
$$+O\left(\Delta\xi^2(\Delta\xi/\Delta x)^2+\Delta x^2\right), \qquad (16)$$

Where

$$D_x C_i = \frac{1}{2\Delta x}\left(C_{i+1}-C_{i-1}\right),$$

$$\delta_x^2 C_i = \frac{1}{\Delta x^2}\left(C_{i+1} - 2C_i + C_{i-1}\right). \qquad (17)$$

Define, $c=\frac{\Delta\xi}{\Delta x}$, $d=\frac{\Delta\xi}{\Delta x^2}$, and in order to obtain the final form of the explicit Du Fort Frankel scheme for the unsteady Diffusion equation, eq. (8), the center node value (C_i) in the diffusion terms in eq. (16) are replaced by their average value at time levels (n-1) and (n+1). The final form of the explicit Du-Fort Frankel scheme for the unsteady Diffusion equation becomes:

$$C_i^{n+1} = A_1 C_i^{n-1} + A_2 C_{i+1}^n + A_3 C_i^n + A_4 C_{i-1}^n + A_5, \qquad (18)$$

where

$$A_1=(1-2a_3 d)/G,\ A_2=(2a_3 d+a_2 c)/G$$
$$A_3=(2a_1\Delta\xi)/G,\ A_4=(2a_3 d-a_2 c)/G$$
$$A_5=(2a_0\Delta\xi)/G,\ G=(1+2a_3 d)$$

3.3. The computation procedure

The calculations start from the initial values of $C(x, 0) = 0$, and then, using the above-mentioned numerical schemes, the solution at the interior points in each layer at new time level can be obtained. While the solution at the interface nodes (C_{BL} and C_{BR}) are obtained by solving the interface-condition equations, eq. (3), using three- point second-order accurate finite differences.. The final discretized interface -conditions are:

$$C_{BL}^{n+1}=q_1 C_{BL-1}^{n+1}+q_2 C_{BL-2}^{n+1}$$
$$+q_3 C_{BR+1}^{n+1}+q_4 C_{BR+2}^{n+1}, \qquad (19)$$

$$C_{BR}^{n+1} = \alpha\, C_{BL}^{n+1}, \qquad (20)$$

where the subscripts *BL* and *BR* denote to the nodes to the above and under sides of the interface respectively. The coefficients q_m (m = 1, 2, 3, 4) take the following forms:

$$q_1=\frac{4D_{BL}}{Q},\ q_2=-\frac{D_{BL}}{Q},$$

$$q_3 = \frac{4D_{BR}}{Q},\ q_4 = -\frac{D_{BR}}{Q},$$

$$Q = 3\,(D_{BL} + \alpha\, D_{BR}) + 2h_2 \Delta x\,(v_{BL} - \alpha v_{BR}). \quad (21)$$

3.4. Stability limits and convergence

The present fourth-order explicit scheme allows us to use considerably fewer discretized points, in comparison with the second-order schemes, to achieve a comparable accuracy. But because it is an explicit scheme, it is necessary to use Von Neumann linear stability analysis [15] to define the numerical stability limit of the present fourth-order explicit scheme. Let numerical solution $C(x, \xi)$ be represented by a finite Fourier series, and for linear stability we can examine the behavior of a single term of the series as follows:

$$C(i\Delta x, n\Delta\xi) = G(\xi)e^{I\,[\,k\,i\,\Delta x\,]}, \quad (22)$$

where $G(\xi)$ is the amplitude function at time-level n of this term whose wave number in the x direction is k, and $I = \sqrt{-1}$. Defining the x phase angle as $\theta = k\Delta x$, then, eq. (22) becomes:

$$C_i^n = G^n\ e^{I\,[\,i\theta]}, \quad (23)$$

and then substituting (23) into eq. (14), we obtain the following equation for the amplification factor ζ:

$$\zeta = G^{n+1} / G^n, \quad (24)$$

which takes the following form:

$$\zeta = \left(\begin{array}{l} (1 - a_1\Delta\xi) + a_3 d \\ (\,2.5 + 2.67\cos\theta - 0.17\cos 2\theta\,) \end{array} \right)$$

$$+ \quad I\,(\,a_2 c\,(\,1.33\sin\theta - 0.17\sin 2\theta\,)\,). \quad (25)$$

For stable numerical solution, Von Neumann stability requires:

$$|\zeta| \le 1 \quad \text{for all} \quad |\theta| \le \pi. \quad (26)$$

This condition is satisfied for the present data if:

$$|\,d = \frac{\Delta\xi}{\Delta x^2}\,| \le 0.15, \quad (27)$$

which is not the same condition for the second order accurate explicit scheme [4], ($|d| \le 0.5$). Fig. 2. shows the polar diagram of the amplification factor λ for different values of d, for the present fourth-order accurate explicit scheme. Concerning the Du-Fort Frankel scheme for the present unsteady diffusion equation, it has the unusual property of being unconditionally stable [16]. Concerning the consistency of the present schemes, both of the schemes are consistent with the original differential eq. (8). The finite difference equations for the present schemes, eq. (14) and eq. (18), are consistent in the sense that the local truncation error tends to be zero as $\Delta\xi$ and Δx approach zero. This concludes that each of the finite-difference schemes to the unsteady skin diffusion equation, the f ourth-order explicit scheme and Du-Fort Frankel, satisfies the consistency condition. Then, the stability condition will be the sufficient condition for convergence [15].

4. Numerical results

The present numerical modelling for solving the unsteady skin diffusion problem has been tested using a set of data which represents "average" human skin. They are listed in Appendix A. The present fourth-order accurate explicit scheme calculations are carried out using space and time step sizes of Δx = 0.25 and $\Delta\xi$= 0.006, in comparison with Δx = 0.05 and $\Delta\xi$= 0.0012 used in the Du-Fort Frankel

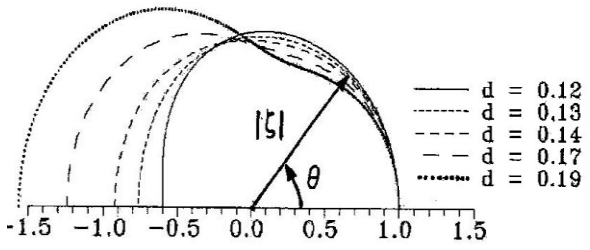

Fig. 2. The computed amplification factors of the numerical solution of the unsteady diffusion eq. (8), using the fourth-order accurate explicit finite difference scheme for different values of d.

calculations to achieve a comparable accuracy. The time step was the maximum allowable from the stability limit and corresponds to a real time of 75 seconds this makes the present higher-order accurate scheme an efficient method of solution, especially if long time computations are required. The present scheme is capable of computing the concentration in the various skin layers at various times ranging from one hour to 28 days, as shown in fig. 3 and fig. 4. Once the substance penetrates into the skin, the concentrations evolve in a smooth way. The concentrations change linearly with space coordinate x, in strata granulosum and basal. While the change is nonlinear in strata corneum and spinosum. Moreover, the flux across the last boundary in basal layer has been computed successfully by the present schemes, and it approaches asymptotically to a steady state after about 14 days, as shown in fig. 5. It is clear that the present fourth-order accurate explicit scheme is capable of predicting the solution of the unsteady skin diffusion problem without any numerical instability or oscillations, and even with a less grid points (80 points) across the skin layers, in comparison with Du-Fort Frankel scheme and the second-order accurate explicit scheme that each requires 200 grid points to achieve a comparable accuracy, as shown in figs. 3, 4 and 8. This
verifies the high order of accuracy of the present fourth order accurate explicit scheme.

The numerical results of the present fourth-order accurate scheme are checked by comparing them with the results obtained by Murdoch et al. [12], using SPRINT package based on the method of lines, and with 200 grid points. The comparison shows that they are in good agreement, as shown in fig. 5 and fig. 6. However, the present fourth-order accurate method is more efficient and economical than SPRINT package because it computes the solution by using a simple algebraic finite difference equation, and with a few discretized points. While for the SPRINT package, a system of ordinary differential -algebraic equations has to be solved, at each time step to obtain the solution.

A remark about the computational efficiency of the present fourth-order accurate explicit scheme is appropriate. The present higher-order scheme can produce the solutions with a few grid points (80 points), and with an accuracy identical to the one obtained with 200 grid points, as shown in fig. 7 and fig. 8, for the concentrations after 28 days. This verifies the efficiency of the present fourth-order accurate scheme. The computational efficiency of the present two schemes has also been checked. The execution times, using personal computer necessary to obtain stable solutions at real time =24 hours and 28 days and with comparable accuracy for the present two schemes, are listed in table 1.

The fourth-order accurate explicit scheme computations with $\Delta\xi_{max}$ = 0.01 required about 3 seconds of execution time, after 24 hours, in comparison with 14 seconds of execution time needed by the Du-Fort Frankel scheme computations with $\Delta\xi_{max}$= 0.005. Similarly after 28 days, the fourth-order accurate explicit scheme is five times more economical than the Du-Fort Frankel scheme. This indicates that the present fourth-order accurate explicit scheme is efficient and economical for solving the unsteady skin diffusion-type problems, especially with large computation time.

5. Conclusions

In conclusion, the fourth-order accurate explicit scheme and the Du-Fort Frankel scheme are used to solve the unsteady diffusion of a chemical substance, like pesticides and aerosols, through the human skin layers. The computed results indicate that the present fourth-order accurate numerical method is suitable for solving the unsteady skin diffusion type problems with interface jump conditions and it is found to be efficient and economical when, compared with the other methods. It has the following features.

1. It results in an explicit finite difference equations with a fourth-order accuracy on all grid point.
2. The boundary conditions and the interface -condition are easily applied without any difficulty.
3. It is stable and efficient in comparison with the other methods. So, it can be used in solving the unsteady skin diffusion problems with long computation time.

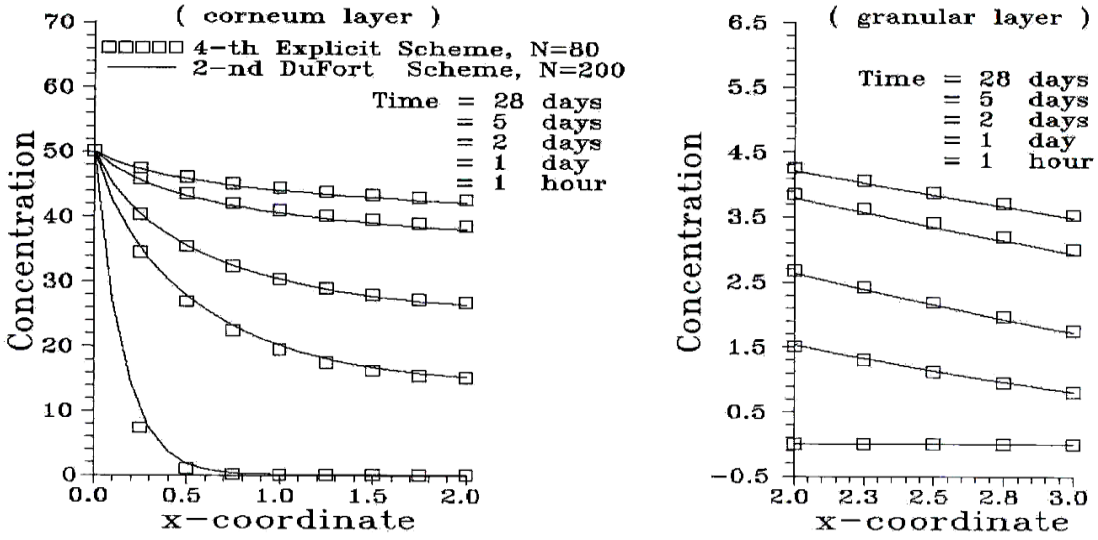

Fig. 3. The computed concentration curves in the corneum and granular layers of the skin model, at various times, ranging from 1 hour to 28 days, using the present fourth-order accurate explicit scheme, and their comparison with the Du Fort Frankel scheme solutions.

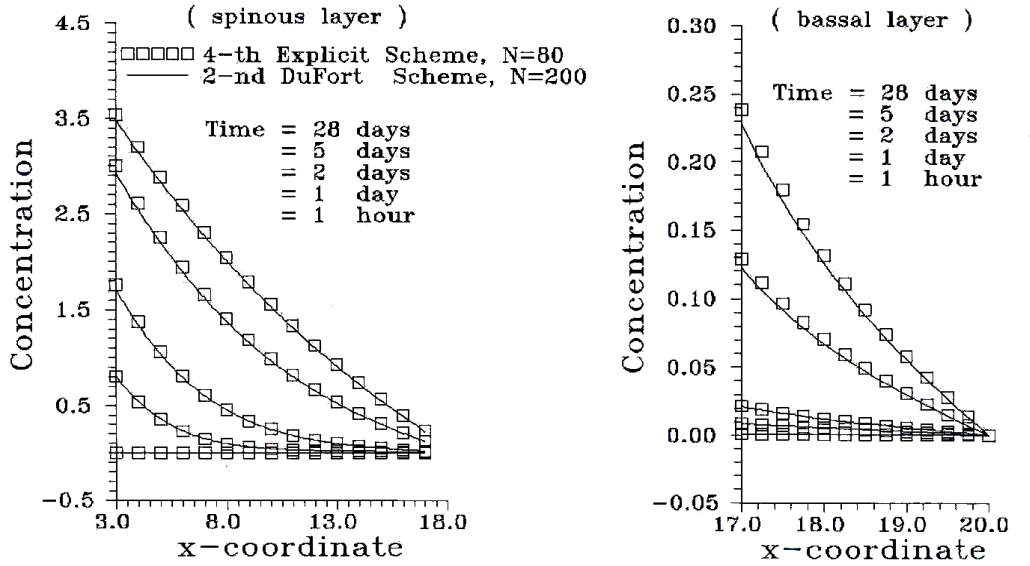

Fig. 4. The computed concentration curves in the spinous and basal layers of the skin model, at various times, ranging from 1 hour to 28 days, using the present fourth-order accurate explicit scheme, and their comparison with the Du Fort Frankel scheme solutions.

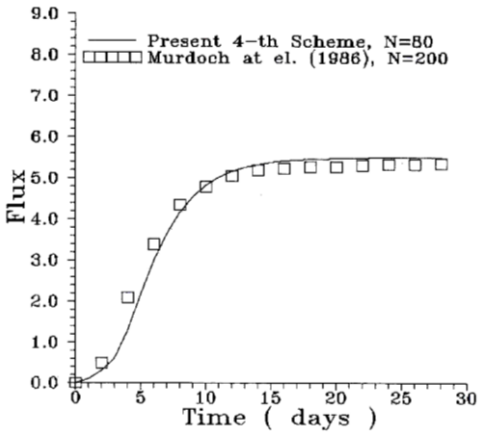

Fig. 5. The computed flux across the last boundary, using the present fourth-order explicit scheme, and their comparison with Murdoch et al. solutions [12].

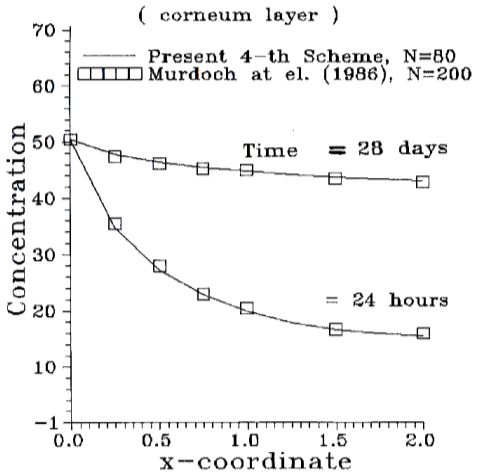

Fig. 6. The computed concentration curves in the corneum layer, at times = 24 hours and 28 days, using the present fourth-order accurate explicit scheme and their comparison with Murdoch et al. solutions [12].

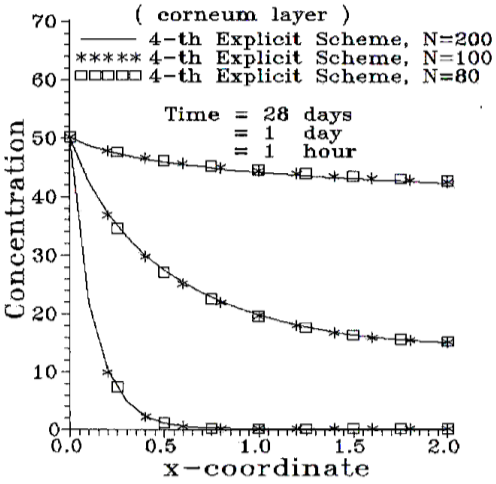

Fig. 7. The computed concentrations in the corneum layer, using the present fourth-order accurate explicit scheme for different grid sizes.

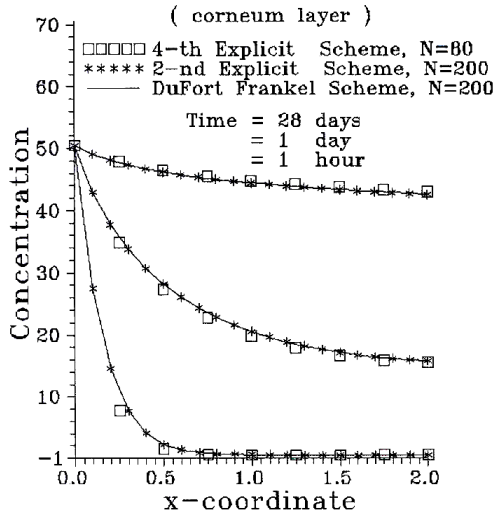

Fig. 8. The computed concentrations in the corneum layer, using the present fourth-order accurate explicit scheme, and their comparison with the Du-Fort Frankel scheme solutions and the second-order accurate explicit scheme solutions.

Table 1
Comparison of execution times for computed solutions of unsteady Skin diffusion eq. (9), at real times equal to 24 hours and 28 days.

Time of computations	Fourth-order accurate explicit scheme	Du fort frankel scheme
after 24 hours	Δt = 0 .25 and $\Delta\xi$ = 0.01 Ex. time = 3 sec.	Δt = 0 .1 and $\Delta\xi$ = 0.005 Ex. time = 14 sec.
after 28 days	Δt = 0 .25 and $\Delta\xi$ = 0.006 Ex. time = 100 sec.	Δt = 0 .2 and $\Delta\xi$ = 0.0012 Ex. time = 680 sec.

Appendix A

The following data represents the average human skin, and they take the following values for skin parameters [12]:

Layer name	h_j	D_j	v_j	μ_j	λ_i
Corneum	10	$10^{-4}(1+z)$	5×10^{-6}	5×10^{-8}	2.7×10^{-7}
Granulosum	5	2×10^{-3}	5×10^{-5}	5×10^{-8}	2.5×10^{-7}
Spinosum	70	4×10^{-3}	5×10^{-5}	5×10^{-8}	2.7×10^{-7}
Basal	15	5×10^{-3}	5×10^{-5}	4.5×10^{-5}	2.5×10^{-7}

where, h_j is the thickness of j-th layer in (μm) , j = 1, 2, 3, 4, D is the diffusion coefficient in ($\mu m^2\ s^{-1}$), v is the advection rate representing cell creation in ($\mu m\ s^{-1}$), μ is the modified reaction rate in (s^{-1}), and λ is a constant related to the permeability rate of the duct membrane in (s^{-1}). The concentration of the substance on the outer skin surface, $C_o(t)$, is equal to 1, and the partition coefficients (a_0 , a_1, a_2, a_3) have the values of (50 , 0.1 , 1 , 1), respectively.

References

[1] W.J Albery and J. Hadgraft, "Percutaneous Absorption: Interfacial Transfer Kinetics", J. Pharm. Pharamacol, Vol. 3, pp. 65-68 (1979).

[2] W.J. Albery and J. Hadgraft, "Percutaneous Absorption: Theoretical Description", J. Pharm. Pharamacol., Vol. 31, pp. 129-139 (1979).

[3] W.J. Albery, Guy R.H. and Hadgraft J. "Percutaneous Absorption: Transport in the dermis", Int. J. Pharm., Vol. 15, pp. 125-148 (1983).

[4] D.A. Anderson, J. C. Tannehill and R. H Pletcher, Computational Fluid Mechanics and Heat Transfer, McGraw-Hill Book Camp., New York (1984).

[5] M. Barr, Percutaneous Absorption, J. Pharm. Sciences, 51 (5), pp. 395-409 (1962).

[6] M.J. Bartek and J.A. La Budde, "Percutaneous Absorption in Vitro", In H. Maibach (Ed.), Animal Models in Dermatology, Churchill Livingstone, New York, pp. 103-120 (1975).

[7] M. Berzins and R.M. Furzeland, A User's Manual for SPRINT- A Versatile Software Package for Solving Systems of Algebraic Ordinary and Partial Differential Equations, Parts I and II, Dept. of Computer Studies, Univ. of Leeds, Leeds (1985).

[8] J. Hadgraft, "Percutaneous Absorption: Possibilities and Problems", Int. J. Pharm., Vol. 16, pp. 255-270 (1983).

[9] T. Higuchi, "Physical Chemical Analysis of Percutaneous Absorption Process from Creams and Ointments", J. Soc. Cosmet. Chem., Vol. 11, pp. 85-97 (1960).

[10] A.C. Hindmarch, "LSODE and LSODI, Two New Initial Value Ordinary Differential Equation Solvers", ACM SIGNUM Newsletter Dec. Issue, pp. 10-11 (1980).

[11] D.E. Kelly, R.L. Wood and A.C. Enders Microscopic Anatomy, Williams and Wilkings Comp., Baltimore (1984).

[12] T. Murdoch, M. Rees and W.L. Seward "The Numerical Solution of a Model of Skin Diffusion Using SPRINT", Report No. 8610, Oxford Univ., Computing Laboratory, Oxford, UK., September (1986).

[13] S.A. Orszag and M. Israeli, "Numerical Simulation of Viscous Flows", Annual Rev. of Fluid Mech., Vol. 6, pp. 1281–3182 (1974).

[14] A.J. Raudkivi and R.A. Callander Advanced Fluid Mechanics Arnold Publishers London (1975).

[15] R.D. Richtmyer and K.W. Morton Difference Methods For Initial-Value Problems, Interscience Publishers, New York (1967).

[16] P.J. Roache, Computational Fluid Dynamics Hermosa Publishers Albuquerque, New Mexico (1976).
[17] R.D. Steel and A.K. Kong "Blended Linear Multistep Methods", ACM Trans. Math. Software, Vol. 3, pp. 326-345 (1974).
[18] R.C. Wester and P.K., Noonan "Relevance of Animal Models for Percutaneous Absorption", Int. J. Pharm., Vol. 7, pp. 99-110 (1980).

Received July 16, 2005
Accepted September 27, 2005