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A NEW METHOD FOR DETERMINING THE DIFFUSION COEFFICIENT OF DRUGS IN SEMISOLID VEHICLES FROM RELEASE DATA

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SUMMARY

Experimental data on release of benzocaine from a series of hydrophilic gels were used for the evaluation of a new method for determining the diffusion coefficient of drugs in semisolid vehicles. The values of D, the drug diffusivity in the vehicle, and of R, the diffusional resistance of the membrane interposed between releasing and receiving phase, resulted from a fit of the experimental release data to theoretical data generated by numerical analysis of a vehicle–membrane controlled diffusional model. Comparison of the computed D (and R) values with values obtained by different routes, or with literature data, showed the method to be conducive to rather accurate estimates of these parameters, in cases where the requirements of the theoretical model were fulfilled by the experimental system. The results are discussed in terms of validity, accuracy and applicability of the proposed method. Results obtained from systems not complying with the diffusional model are also discussed and evaluated. The computations were executed with the aid of an IBM 370/168 computer.

INTRODUCTION

The equations describing the 'in vitro' release of drugs from semisolid vehicles have in the past attracted the attention of the present Authors, as simple means for the assessment of some important physicochemical parameters relative to the drug–vehicle system. In particular, the said analytical relationships have been applied to the evaluation of the drug solubility in the vehicle (Bottari et al., 1974, 1977), and to the assessment of the diffusion coefficient in a variety of experimental systems (Bottari et al., 1974, 1977; Carelli et al., 1977). The latter parameter may play an important role in topical bioavailability when concentration gradients develop in the applied phase during release: in such cases, its knowledge may be of considerable utility either for selecting the most therapeutically valid vehicle and/or for predicting the pattern of drug release.

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Unfortunately, as was pointed out in the preceding papers, the application of analytical relationships often allows only an approximate evaluation of the diffusion coefficient, since most experimental systems do not adhere rigorously to the theoretical models, and/or the equations describing the release process are themselves approximated.

This paper presents a new method for determining the diffusion coefficient of a drug in a vehicle, based on a computation procedure providing a fit of the experimental release data to theoretical data, generated by numerical analysis of the diffusional model. Numerical methods of analysis do yield quite accurate solutions of the diffusion equations (Crank, 1967a). Furthermore, they possess the advantage of being applicable to diffusional models that cannot be treated analytically.

The validity, accuracy and applicability of the above method were evaluated by analyzing data on release of benzocaine from a series of hydrophilic gels.

COMPUTATION PROCEDURE

The theoretical diffusional model was derived from that treated by Koizumi and Higuchi (1968), with the following modifications: (a) the diffusivity in the vehicle is constant and (b) the receiving phase is a 'perfect sink'. The equations used in the computation are the following (Crank, 1967a; Koizumi and Higuchi, 1968):

at $x = h_v$,

$$S^+_{n-1} = (S^+_n - S_n) \cdot \frac{2(\Delta x)^2}{D(\Delta t)} + S^+_n + S_n - S_{n-1} \tag{1}$$

at $0 < x < h_v$,

$$S^+_{i-1} = (S^+_i - S_i) \cdot \frac{2(\Delta x)^2}{D(\Delta t)} + 2(S^+_i + S_i) - (S^+_{i+1} + S_{i+1}) - S_{i-1} \tag{2}$$

at $x = 0$,

$$\frac{-S_2 + 4S_1 - 3S_0}{2(\Delta x)} = \frac{S_0}{RD} \tag{3}$$

Here, the overall time of release, t_R, and the thickness of the vehicle layer, h_v, were divided, respectively, into m equal intervals of Δt, and n equal lengths of Δx. The variable S is defined by the ratio C/C_0 of drug concentration in the vehicle at time t and distance x from the releasing surface, to the initial concentration. S_{i-1}, S_1, S_{i+1} are the S values at $(i-1)\Delta x$, $i\Delta x$, $(i+1)\Delta x$, respectively, at $t = j\Delta t$; and $S^+_{i-1}, S^+_i, S^+_{i+1}$ are the corresponding values at $t = (j+1)\Delta t$. D represents the diffusion coefficient in the vehicle, while the diffusional resistance of the membrane, R, is defined by Eqn. 4 (Flynn et al., 1974):

$$R = \frac{h_m}{K_{m/v} D_m} \tag{4}$$

where h_m represents the thickness of the membrane; D_m, the diffusivity in the membrane; and $K_{m/v}$, the membrane–vehicle partition coefficient.

Eqns. 1, 2 and 3 enable calculation of theoretical release data by means of the compu-

tation procedure described below. These data are fitted to the experimental data by gradually adjusting the values of D and R. The procedure for computation is as follows [1].

(1) Divide the thickness of the vehicle layer, h_v, into n equal lengths of Δx and divide the overall release time, t_R, into m equal intervals of Δt.

(2) Fix a range of D values including the true value of the diffusion coefficient, and a range of R values including the true value of the membrane resistance. In the respective range, choose an arbitrary value of D and R.

(3) Set $S_i = 1$ (i = 0 to n) initial condition.

(4) Choose an arbitrary value of S_n^+.

(5) Calculate S_{n-1}^+ by Eqn. 1.

(6) Calculate S_{n-2}^+ by Eqn. 2.

(7) Repeat (6) until S_0^+ is calculated.

(8) Calculate separately the left-hand and the right-hand sides of Eqn. 3 and compare to verify if Eqn. 3 holds.

(9) If the calculated values of the left and the right sides of the equation are consistent within the range of error allowed, calculate the amount released per unit area, Q, at $t = \Delta t$ for the chosen values of D and R:

$$Q = \int_0^{h_v} (C_0 - C)\, dx \tag{5}$$

(10) If (9) is not the case, modify the value of S_n^+ depending on the results of (8). Then repeat steps (5) to (8), until (9) is the case.

(11) Replace all values of S_i by the new values of S_i^+ obtained, and repeat procedures (4) to (10) until the desired time ($t = m\Delta t$) is reached. Here m is the number of times step (11) is repeated.

(12) Calculate the area under the experimental Q vs t curve,

$$A_{ex} = \int_0^{t_R} Q_{ex}\, dt \tag{6}$$

and the area under the theoretical curve as computed by procedure (1) to (11),

$$A_{th} = \int_0^{t_R} Q\, dt \tag{7}$$

(13) If the values of A_{ex} and A_{th} calculated at (12) are consistent within the range of error allowed, calculate the area between the experimental and the theoretical Q vs t curve:

$$\Delta A = \int_0^{t_R} |(Q_{ex} - Q)|\, dt \tag{8}$$

[1] Since the computation procedure described in Koizumi and Higuchi (1968) was taken as the basis for deriving the theoretical release data, several steps are here rewritten as such.

(14) If (13) is not the case, modify the value of D depending on the results of (13). Then repeat steps from (3) to (12) until (13) is the case.

(15) If the condition at (13) is not satisfied by any of the D values included in the range fixed at (2), modify the value of R depending on the results of (13). Then repeat steps from (3) to (14) until the condition at (13) is satisfied.

(16) If the value of ΔA calculated by Eqn. 8 is negligibly small compared to A_{ex}, the most recent theoretical Q vs t curve will fit satisfactorily the experimental curve, and the correspondent D and R values will be the values of the effective diffusion coefficient in the vehicle and diffusional resistance of the membrane, respectively.

(17) If (16) is not the case, modify appropriately the value of R and repeat steps from (3) to (15) until (16) is the case.

Whether or not the obtained D and R represent true physical parameters will depend on the compliance of the experimental system with the requirements of the theoretical model, viz. (a) the drug is the only diffusing species; (b) the drug is completely and uniformly dissolved in the vehicle; (c) the diffusivity of drug in the vehicle and the diffusional resistance of the membrane are both constant; and (d) the release process is effectively vehicle–membrane controlled. In fact, as was previously reported (Carelli et al., 1977), experimental systems not obeying conditions (b) (c), or (d), can give the same release pattern as systems quite adherent to the model being discussed. This could be looked at as a source of error, since an accurate verification of conditions (b) to (d) is in some cases difficult to perform. In order to elucidate this point, the method was also applied to experimental release systems not complying with all of the above requirements.

MATERIALS AND METHODS

Materials

Glycerol [2], sorbitol [3], polysorbate 80 [4] and carboxyvinyl polymer [5], were used as received. The neutral sodium salt of carboxyvinyl polymer was prepared as described in the literature (Perotti, 1970). Ethyl-*p*-aminobenzoate (benzocaine)[2] was crystallized to a constant melting point of 91.5°C. Dimethyl polysiloxane (silicone rubber) [6] sheeting in a labeled thickness of approximately 127 μm was used as membrane material.

Vehicles, apparatus and procedures

Hydrophilic gels containing 1% w/v gelling agent were prepared, as previously described (Bottari et al., 1978), by dispersing the neutral carboxyvinyl polymer sodium salt into solutions of benzocaine in the following media:

a, water

b, water–glycerol (34 : 66 w/w)

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[2] Carlo Erba, Milano, Italy.

[3] I.C.I., Istituto Chemiotherapico Italiano, Milano, Italy

[4] Tween 80, Atlas Chemie GmbH, Essen, G.F.R.

[5] Carbopol 934, B.F. Goodrich Co., Cleveland, Ohio, U.S.A.

[6] Silastic, Dow Corning Corp., Medical Products Div., Midland, Mich., U.S.A.

c, water–sorbitol (45.5 : 54.5 w/w)

d, 1% w/v polysorbate 80 in water.

The apparatus and procedure used for the release experiments have already been described (Bottari et al., 1977). The depth of the polymethyl methacrylate [7] cell was varied, depending on the gel studied, by introducing in the cell the appropriate number of polymethyl methacrylate disks of the same diameter as the cavity (5 cm), and of 0.1 cm thickness. The cell was filled and assembled at room temperature, then equilibrated at 30°C prior to use. The release experiments were carried out according to the previously described procedure. At intervals, the receiving phase was analyzed spectrophotometrically [8] for benzocaine hydrochloride (227 nm). Each experiment was continued until more than 25% drug had been released. The overall release time was limited to 3 h in all cases, by appropriately adjusting the thickness of the vehicle layer, as indicated before.

Permeation experiments for determining the diffusional resistances of the silicone rubber membrane were performed using the previously described apparatus and technique (Bottari et al., 1977). The non-gelled solutions a, b, c and d, containing benzocaine at concentrations of 1.05, 3.05, 0.85 and 2.00 mg/ml, respectively (approximately 80% of saturation), were used as internal solutions (25 ml), while 0.1 N HCl was the receiving phase.

Either for the permeation and the release experiments, blank runs demonstrated the absence in the receiving phase of materials interfering with the spectrophotometric measurements. Impermeability of the membrane to glycerol and sorbitol was demonstrated by the periodic acid test (Shriner and Fuson, 1948). Each run was repeated at least three times and the results were averaged.

Computation of theoretical release data and their fit to the experimental data were executed by the IBM 370/168 computer. The simplified flow chart is shown in Fig. 8.

RESULTS AND DISCUSSION

Convergence of the iterative process and accuracy of results

Computer experimentation showed that subdivision of both the thickness of vehicle layer, h_v, and the overall time of release, t_R, into 30 intervals (i.e., $\Delta x = h_v/30$, $\Delta t = t_R/30$) was satisfactory from the standpoint either of convergence of the iterative process for computation of the S profiles, and of the accuracy of results. Indeed, subdivision into smaller intervals (a) did not produce appreciable variations of results, thus proving their accuracy (Crank, 1967b), and (b) it brought about the drawback of a greater precision required in the computation. This caused troubles with convergence, expecially for S lines corresponding to small amounts of released drug compared to the total amount initially contained in the vehicle. An overall released amount corresponding to approximately 25% of the initial content was in general sufficient to ensure convergence, if the indicated subdivision was used. This (or a greater) percentage of release was experimentally achieved within 3 h by appropriately adjusting the thickness of the vehicle layer.

[7] Plexiglas, Rohm and Haas Co., Philadelphia, Pa.

[8] Zeiss PMQ II spectrophotometer.

The latter in all cases largely exceeded the membrane thickness, so as to fulfill the condition of linear concentration gradients in the membrane, required by the theoretical model. For the sake of convergence, D and R values not excessively different from the true physical parameters should be checked in the fitting process. Application of Eqn. 9, previously used for obtaining estimates of diffusion coefficients from release data (Bottari

$$Q = 2Co\left(\frac{D}{\pi}t\right)^{1/2} \tag{9}$$

et al., 1974; Carelli et al., 1977; Davis and Khanderia, 1977), allowed us to restrict the D range within one order of magnitude. The R range was fixed consequently, since convergence of the iterative process required that $10^{-2} < DR < 1$ cm.

Systems complying with the diffusional model

The results of the described fitting process for gels a, b, and d (see Table 1 for solvent composition) are illustrated in Figs. 1, 2 and 3. The experimental data used in the computation were equispaced points lying on curves obtained by graphical interpolation of the experimental points. For each vehicle, two initial concentrations were investigated, in order to test the effect of varying Co on the computed D and R values. As it can be seen in the figures, the fit of calculated to experimental data is excellent in all cases. The computed values of parameters D and R are listed in Table 1. From the table it is clear that the values relative to gels a, b and d, respectively, are in effect independent of the ini-

TABLE 1

VALUES OF PARAMETERS D AND R CALCULATED BY THE NUMERICAL METHOD

Vehicle	Solvent composition w/w	Solubility in solvent [a] mg/ml	Initial concentration in vehicle Co, mg/ml (% of saturation)		D $cm^2\ sec^{-1} \cdot 10^6$	R $cm^{-1}\ sec \cdot 10^{-4}$
gel a	water	1.31	0.26	(20)	8.5	0.90
			0.52	(40)	8.7	0.83
gel b	water–glycerol (34 : 66)	3.77	0.75	(20)	0.79	2.5
			1.50	(40)	0.79	2.8
gel c	water–sorbitol (45.5 : 54.5)	1.05	0.52	(50)	0.60	0.91
			0.84	(80)	0.93	0.94
gel d	1% w/v polysorbate 80 in water	2.46	0.49	(20)	4.2	1.5
			0.98	(40)	4.3	1.6
Suspension-type gel [b]	water	1.31	2.59	(200)	6.2	1.5
			5.10	(390)	3.3	2.5

[a] Data from previous report (see Bottari et al., 1978).

[b] The experimental data on benzocaine release from this gel were drawn from a previous paper (see Bottari et al., 1977).

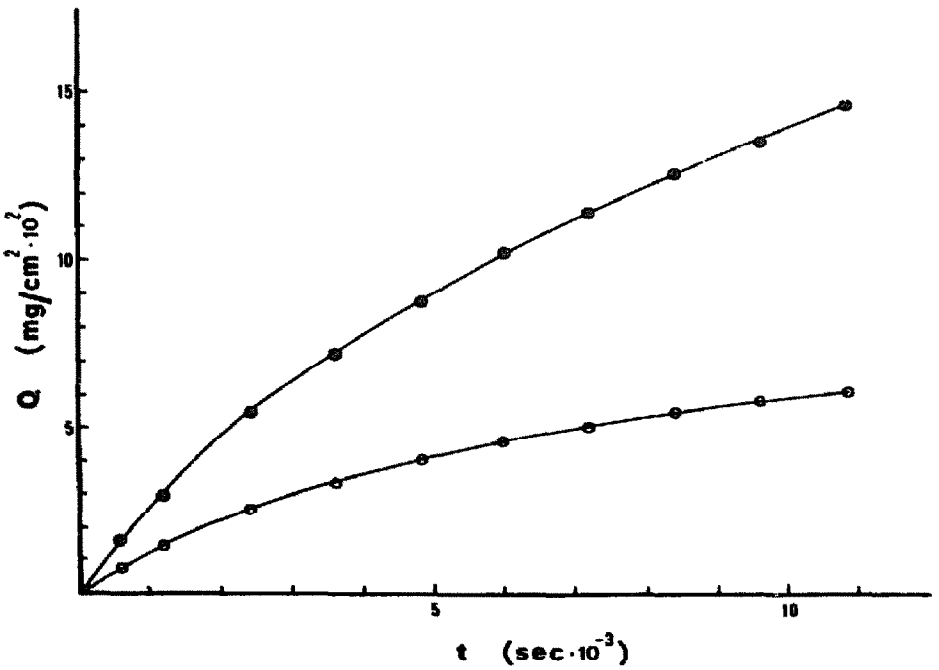


Fig. 1. Plots illustrating the fit of computed to experimental release data for gel a. Amount of benzocaine released per unit area vs time. Key: ○, Co = 0.26 mg/ml (20% of saturation); ●, Co = 0.52 mg/ml (40% of saturation); ———, theoretical values computed by the numerical method. h_v = 0.8 cm; Δx = 0.0266 cm; t_R = 3 h; Δt = 360 s.

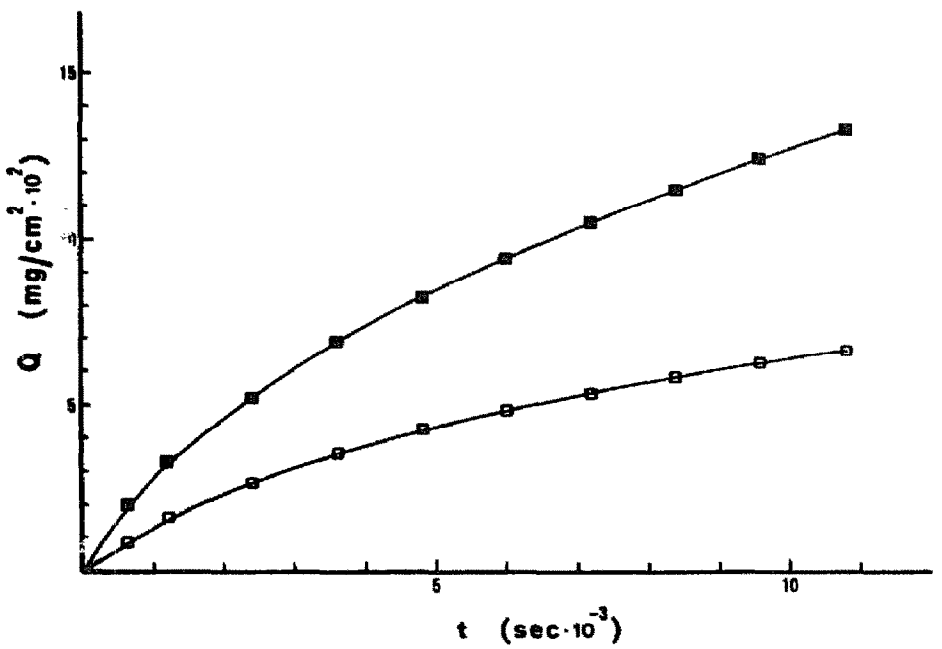


Fig. 2. Plots illustrating the fit of computed to experimental release data for gel b. Amount of benzocaine released per unit area vs time. Key: □, Co = 0.75 mg/ml (20% of saturation); ■, Co = 1.50 mg/ml (40% of saturation); ———, theoretical values computed by the numerical method. h_v = 0.3 cm; Δx = 0.01 cm; t_R = 3 h; Δt = 360 s.

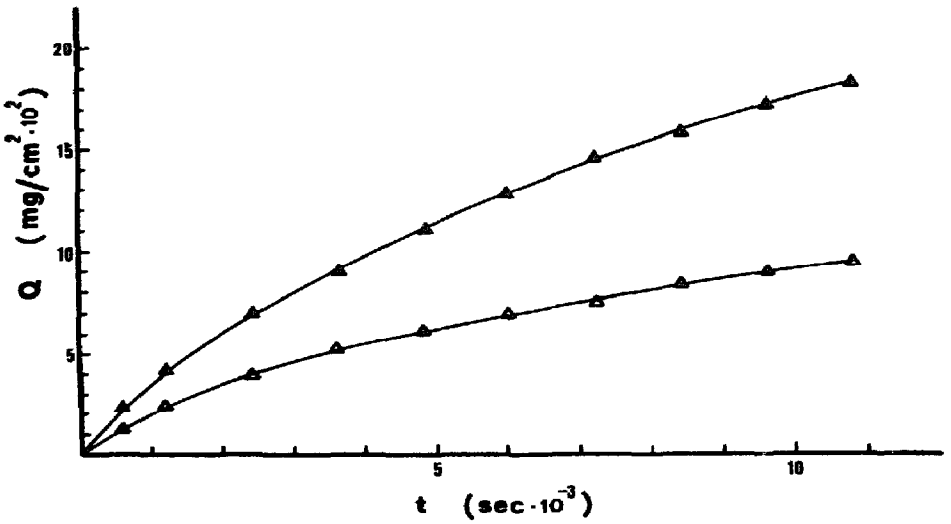


Fig. 3. Plots illustrating the fit of computed to experimental release data for gel d. Amount of benzocaine released per unit area vs time. Key: △, Co = 0.49 mg/ml (20% of saturation); ▲, Co = 0.98 mg/ml (40% of saturation); ———, theoretical values computed by the numerical method. h_v = 0.7 cm; Δx = 0.0233 cm; t_R = 3 h; Δt = 360 s.

tial drug concentration in the gels. The slight differences are ascribed to experimental errors and, to a lesser extent, to the errors allowed in the computation. Concentration-independence of the diffusion coefficient and of the membrane resistance is to be expected for gels a, b and d. Indeed, concentration-independence of the activity coefficient of benzocaine in these vehicles, a necessary condition for constancy of D and R

TABLE 2

VALUES OF DIFFUSION COEFFICIENT, MEMBRANE RESISTANCE AND GEL–WATER PARTITION COEFFICIENT, DETERMINED BY DIFFERENT ROUTES FOR GELS a, b, AND d

Vehicle	Diffusion coefficient $cm^2\ sec^{-1} \cdot 10^6$		Membrane resistance $cm^{-1}\ sec \cdot 10^{-4}$		Gel–water partition coefficient	
	Calculated by Eqn. 9	Computed by the numerical method [a]	Computed by the numerical method [a], R	Determined by permeation experiments, R′	Literature data [b]	Ratio of membrane resistances [c] $\frac{R}{R'_w}$
gel a	5.8	8.6	0.86 (5)	0.83	1.00	1.0
gel b	0.56	0.79	2.6 (5)	2.7	3.03	3.2
gel d	2.5	4.2 (5)	1.5 (5)	1.7	2.06	1.8

[a] Averaged data from Table 1.
[b] Averaged data from previous report (see Bottari et al., 1978).
[c] R'_w, is the R′ value relative to water as the donor phase ($0.83 \cdot 10^4\ cm^{-1}\ sec$).

(Flynn et al., 1974), was previously evidenced by Bottari et al. (1978), who showed that the gel–water partition coefficient was not influenced by concentration. The averaged values of D and R for the vehicles under discussion are listed in Table 2. In the same table are reported, for comparison, the values of the resistance, R′, of the silicone rubber membrane to permeation by benzocaine from the non-gelled solutions a, b and d, determined by permeation experiments under quasisteady-state conditions, using a previously described technique (Bottari et al., 1977). The corresponding first-order plots are represented in Fig. 4. Since an absence of chemical interactions between benzocaine and carboxyvinyl polymer sodium salt in gels a, b and d has been reported (Bottari et al., 1978), the R′ values are also representative of the diffusional resistances of the membrane in release from the respective gels. The agreement between the values of membrane resistance determined by the two different routes in quite satisfactory. Also noteworthy is the concordance between the values of the gel–water partition coefficient reported in the literature for gels a, b and d (Bottari et al., 1978) and those expressed as the ratio of membrane resistances, on the basis of Eqn. 4 (see Table 2).

The diffusion coefficient in gel a, $8.6 \cdot 10^{-6}$ cm^2 sec^{-1}, is in quite good agreement with the previous value, $9.1 \cdot 10^{-6}$ cm^2 sec^{-1}, obtained using different experimental conditions and analysis of data (Bottari et al., 1977). The diffusion coefficients in gels b and d cannot be compared with existing literature data. However, the validity of these values is substantiated by their self-consistency. Indeed, the value of the diffusion coefficient in gel d (1% polysorbate 80 as solvent), is consistent with the theory on contemporaneous

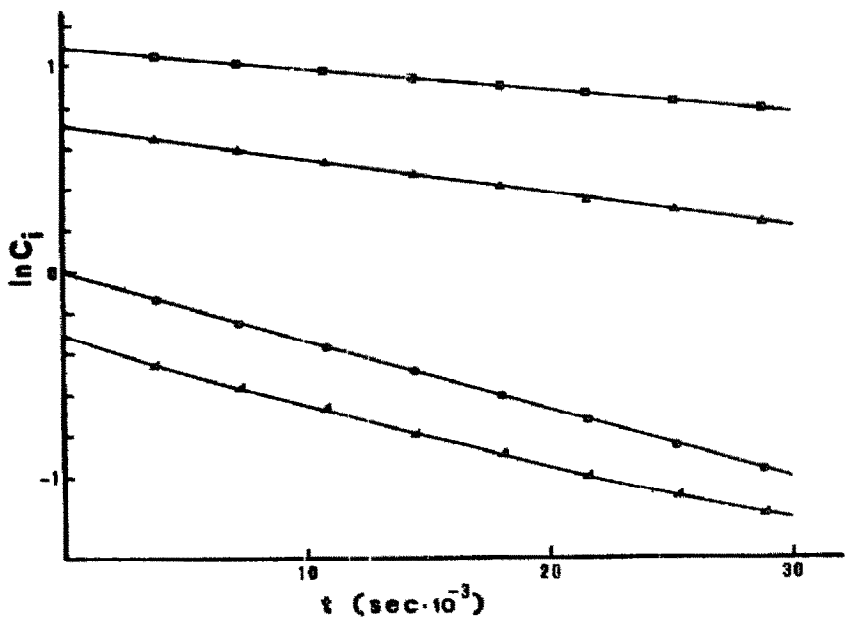


Fig. 4. Quasisteady-state permeation plots of benzocaine through a silicone rubber membrane from solutions a, b, c and d. Initial concentration, Cio = 80% of saturation. Key: ●, solution a, Cio = 1.05 mg/ml; ■, solution b, Cio = 3.05 mg/ml; ▲, solution c, Cio = 0.85 mg/ml; ▲, solution d, Cio = 2.00 ml.

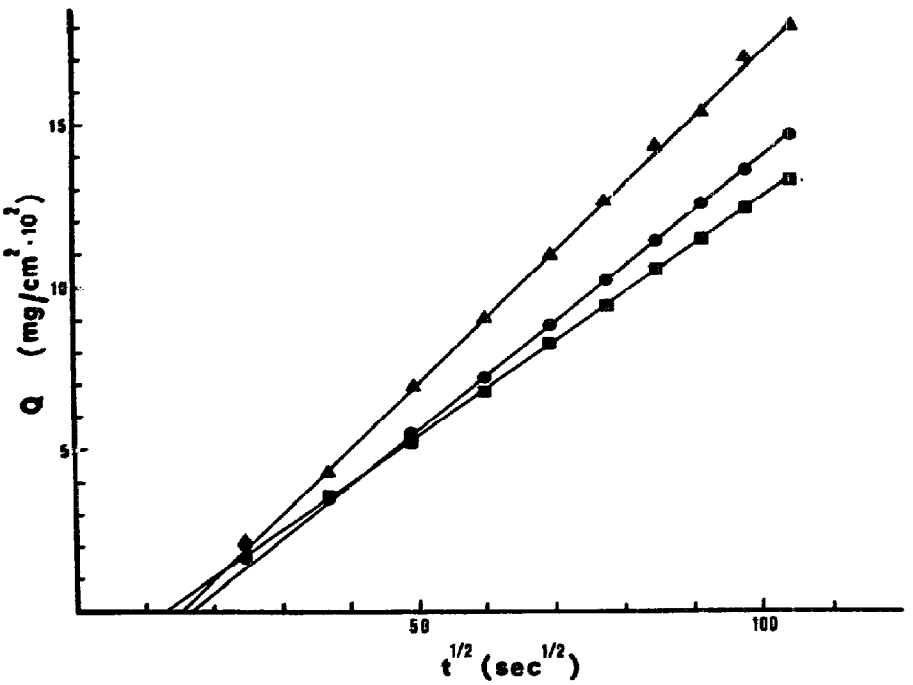


Fig. 5. Amount per unit area of benzocaine released from gels a, b and d, vs square root of time. Co = 40% saturation. Key: ●, gel a; ■, gel b; ▲, gel d.

diffusion and chemical reaction (Crank, 1967c), as shown by the fair correspondence of the ratio of this coefficient to that in gel a (water as solvent), 0.50, with the fraction of benzocaine non-interacting with the surfactant, 0.49, derived from previously published data (Bottari et al., 1978). As for the diffusion coefficient in gel b, the ratio of this coefficient to that in gel a, 0.091, is well included in the range from 1- to 2-fold the value of the ratio between the microscopic viscosity [9] of gel a and that of gel b, (0.067, and 0.134, respectively) [10] thus complying with the theory on diffusivity in homogeneous liquids (Flynn et al., 1974). The diffusion coefficients calculated from the averaged slopes of the Q vs $t^{1/2}$ plots according to Eqn. 9 (only the plots relative to Co = 40% of saturation are represented in Fig. 5), are compared in Table 2 with those obtained by the numerical method. Inspection of these data confirms the validity of the 'square root' plot and of Eqn. 9, as a reference for fixing the D range.

Systems not complying with the diffusional model

The results obtained for gels a, b and d apparently indicate that the release process is in these cases strictly adherent to the theoretical model. It should be recognized, in this

[9] The viscosity of the fluid entrapped in the gel network.

[10] These figures were derived using the tabulated value of 0.798 cP for water viscosity at 30°C (Weast, 1975–76), and the value of 11.82 cP, determined for 66% w/w glycerol at 30°C by means of a Rheomat-30 viscosimeter, Contraves, Zurich, Switzerland.

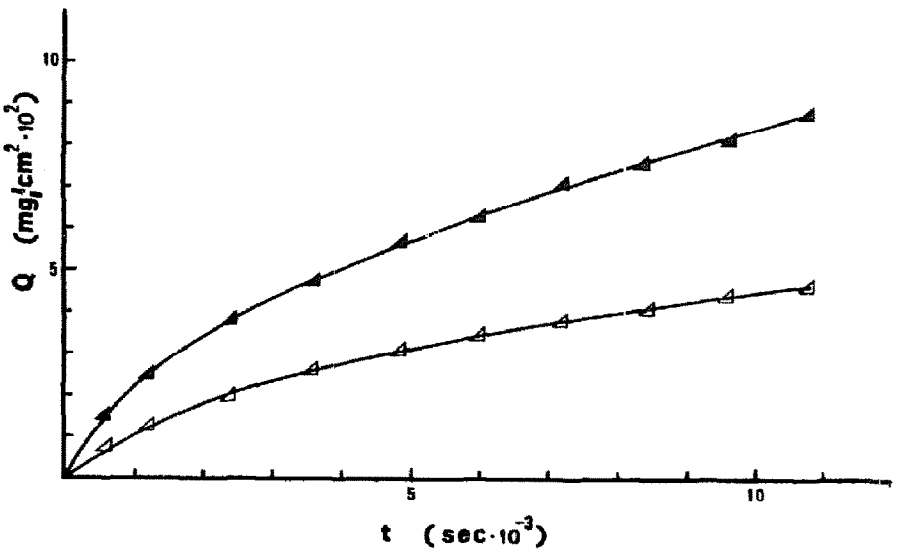


Fig. 6. Plots illustrating the fit of computed to experimental release data for gel c. Amount of benzocaine released per unit area vs time. Key: ◿, CO = 0.52 mg/ml (50% of saturation); ◿, Co = 0.84 mg/ml (80% of saturation); ———, theoretical values computed by the numerical method. h_V = 0.3 cm; Δx = 0.01 cm; t_R = 3 h; Δt = 360 s.

connection, that the fit of theoretical to experimental data is not sufficient, in itself, to prove such an adherence and, consequently, to substantiate the physical significance of the calculated parameters. Some examples intended to clarify this view are now being discussed.

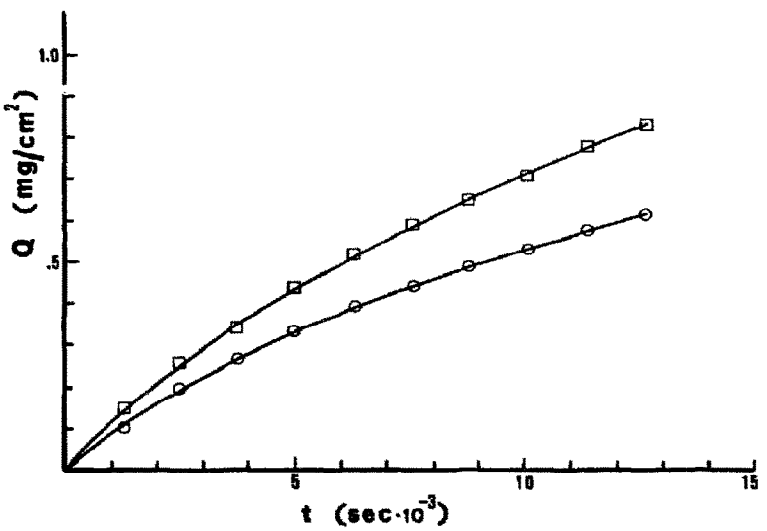


Fig. 7. Plots illustrating the fit of computed to experimental literature data on benzocaine release from a suspension-type aqueous gel (see Bottari et al., 1974). Amount released per unit area vs time. Key: ○, C_0 = 2.59 mg/ml (198% of saturation); □, C_0 = 5.10 mg/ml (389% of saturation); ———, theoretical values computed by the numerical method. h_V = 1 cm; Δx = 0.033 cm; t_R = 3.5 h; Δt = 420 s.

The apparent curvature of the first order plot in Fig. 4 relative to solution c, is indicative of concentration-dependence of the activity coefficient in this medium. The same indication comes from a previous work (Bottari et al., 1978) where an influence of concentration on the partition coefficient between gel c and water was evidenced. These findings suggest that the constancy of D and R, required by the theoretical model, is not observed in release from gel c. Nevertheless, the computed curve fits well the experimental release data for both values of the initial concentration (see Fig. 6). However, an inspection of the calculated parameters reveals their lack of physical meaning. Indeed, the significant difference between the D values relative to each Co (cf. Table 1) is not likely to be due to errors and should be considered indicative of deviation from the theoretical model. An even more evident inconsistency of the parameters obtained at different Co was observed where the deviation of the experimental system from the theoretical model was due to an initial concentration exceeding solubility (see data on suspension-type gel, Table 1 [11]). Then again, although a fit of data was possible (see Fig. 7), no physical meaning could be attributed to the parameters D and R. The data obtained from the permeation experiments, where the process was completely membrane-controlled, were also analyzed by the numerical method, but in no case could a theoretical curve fitting the experimental within the error allowed be generated.

CONCLUSIONS

In summary, the present method based on numerical analysis of 'in vitro' release data, has been shown to be conducive to rather accurate estimates of the diffusion coefficient of benzocaine in the vehicles investigated, in cases where the requirements of the theoretical model were fulfilled by the experimental system. In these cases, the derived values either of the diffusion coefficient and of the resistance of the diffusional barrier between releasing and receiving phase were essentially independent of the initial concentration in the vehicle. The method might be of wide applicability, as the vehicle–membrane controlled (or vehicle–boundary layer controlled) model is in fact operative in most cases of release from a rigid to a stirred liquid phase.

Simple criteria are to be followed for the fitting out and the performance of the release experiments. Since quasisteady-state conditions are wanted in the diffusional barrier between the phases, the amount of drug in the barrier should be at all times negligible with respect to that in the vehicle. Sink conditions in the receiving phase constitute another necessary requisite of the model. In cases, as the present one, of weakly acidic or basic drugs, this can easily be realized by converting the drug into its salt form in the receiving phase. For neutral drugs, an appropriate volume of this phase should be used and drug accumulation should be prevented, so that release would not be influenced by drug concentration in the stirred solution. The R value yielded by the present method in these cases would represent the sum of the individual resistances of the membrane and the adjacent hydrodynamic layer. The fit of theoretical to experi-

[11] The experimental data on benzocaine release from the suspension-type gel were drawn from the literature (Bottari et al., 1977).

mental data was shown not to guarantee, in itself, the validity of the computed D and R values. Indeed, a fit of data was obtained even for systems not complying with the theoretical model because of concentration dependence of D and R, or incomplete dis-

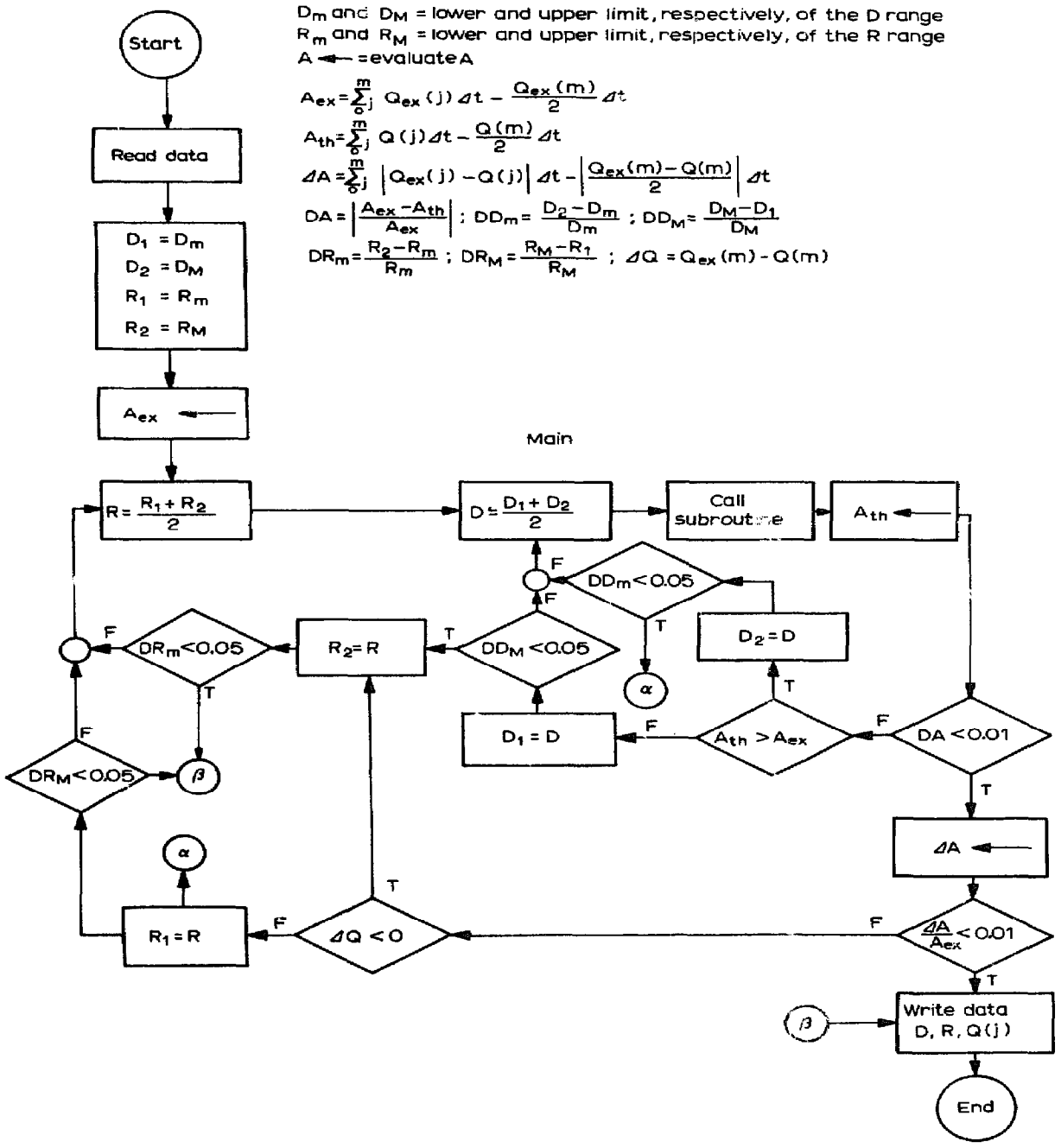
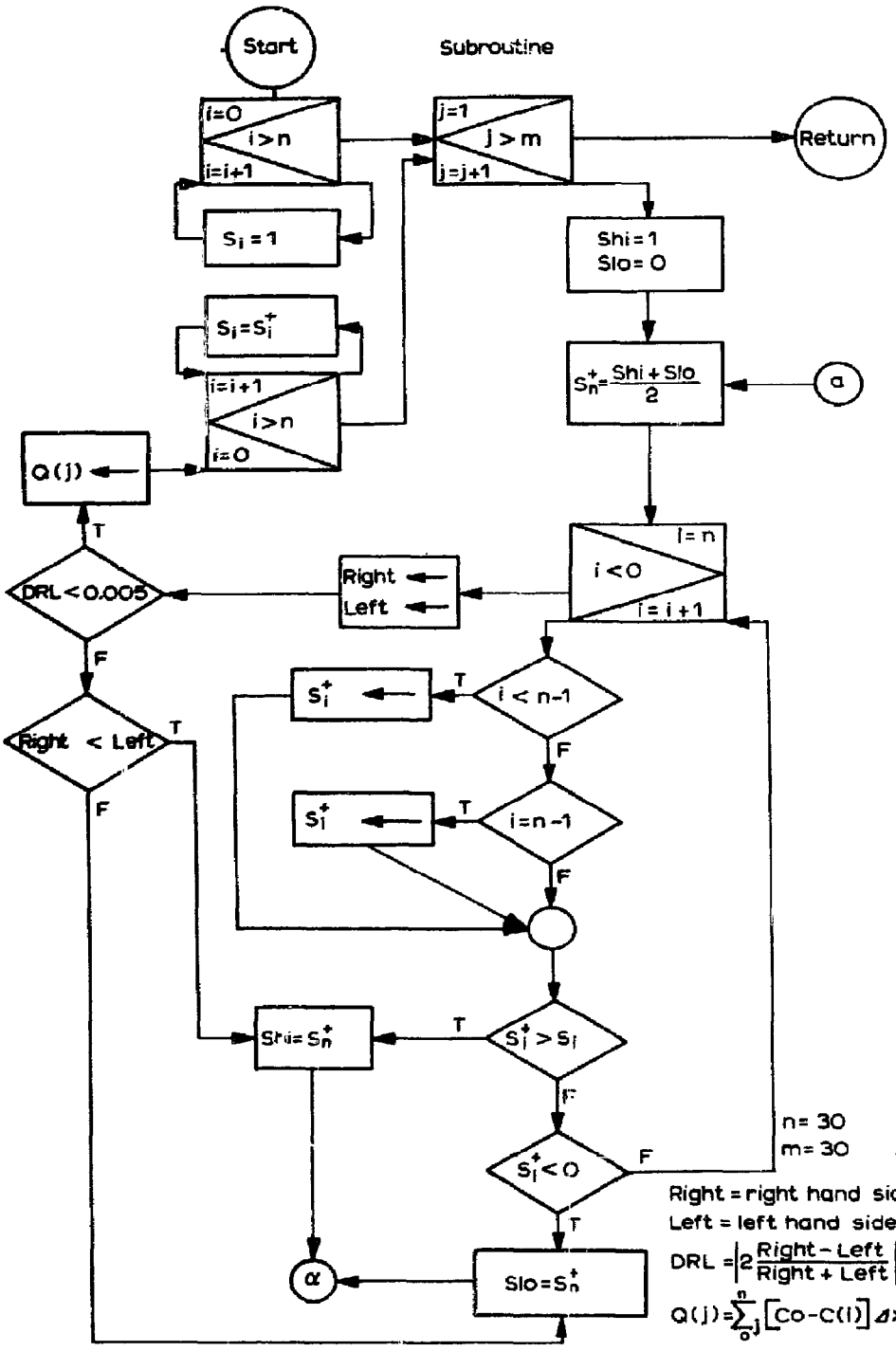


Fig. 8. Simplified flow diagram showing the procedure for computation of the D and R parameters.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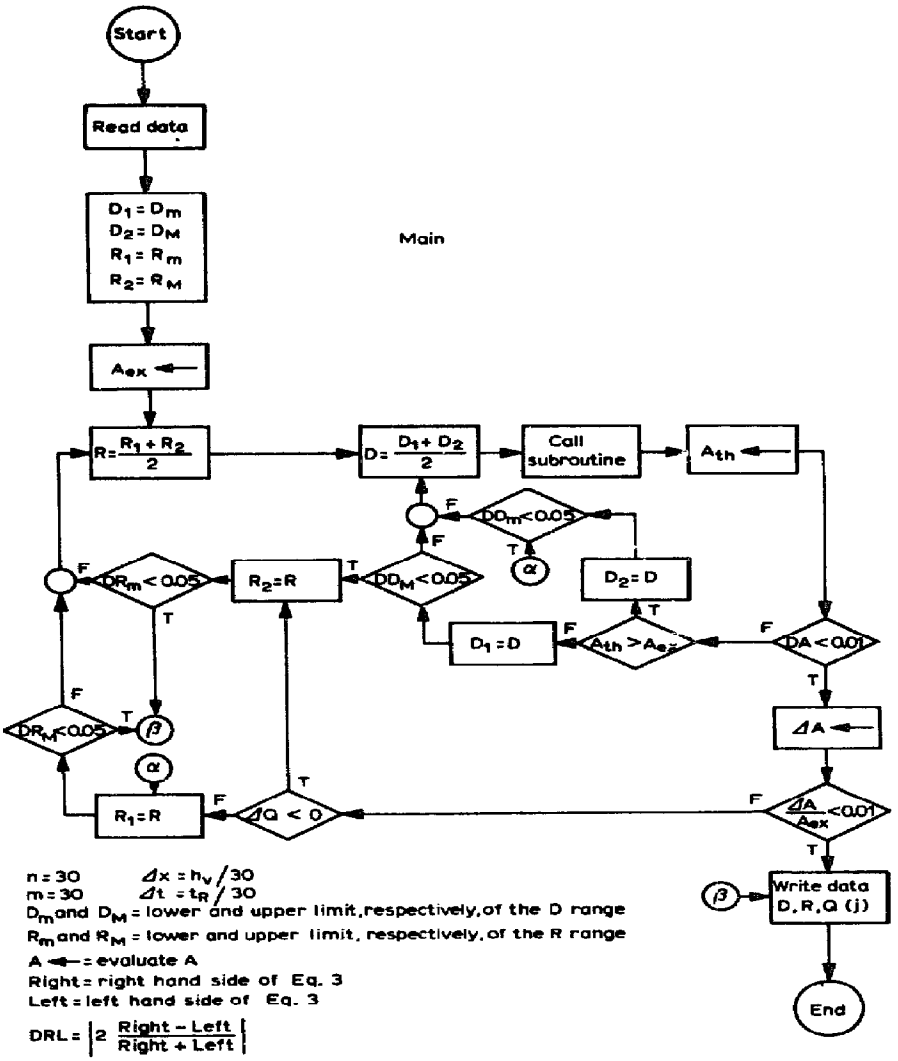
Subroutine
i=0
i > n
i=i+1
Si = 1
j=1
j > m
j=j+1
Return
Shi = 1
Slo = 0
Si = Si+
i=i+1
i > n
i=0
Q(j)
a
T
DRL < 0.005
Right
Left
i = n
i < 0
i = i + 1
F
Right < Left
Si+
i < n-1
i=n-1
Shi = Sn+
Si+ > Si
Si+ < 0
Slo = Sn+
n = 30
m = 30
Δx = hv/30
Δt = tR/30
Right = right hand side of Eq. 3
Left = left hand side of Eq. 3
DRL = |2 (Right − Left)/(Right + Left)|
Q(j) = Σ_0^n [Co − C(i)] Δx − [Co − (C(0) + C(n))/2] Δx



n = 30 $\quad \Delta x = h_v / 30$
m = 30 $\quad \Delta t = t_R / 30$
D_m and D_M = lower and upper limit, respectively, of the D range
R_m and R_M = lower and upper limit, respectively, of the R range
$A \leftarrow$ = evaluate A
Right = right hand side of Eq. 3
Left = left hand side of Eq. 3

$$DRL = \left| 2 \frac{\text{Right} - \text{Left}}{\text{Right} + \text{Left}} \right|$$

$$Q(j) = \sum_{i=0}^{n} (C_o - C(i)) \Delta x - \left(C_o - \frac{C(0) + C(n)}{2}\right) \Delta x$$

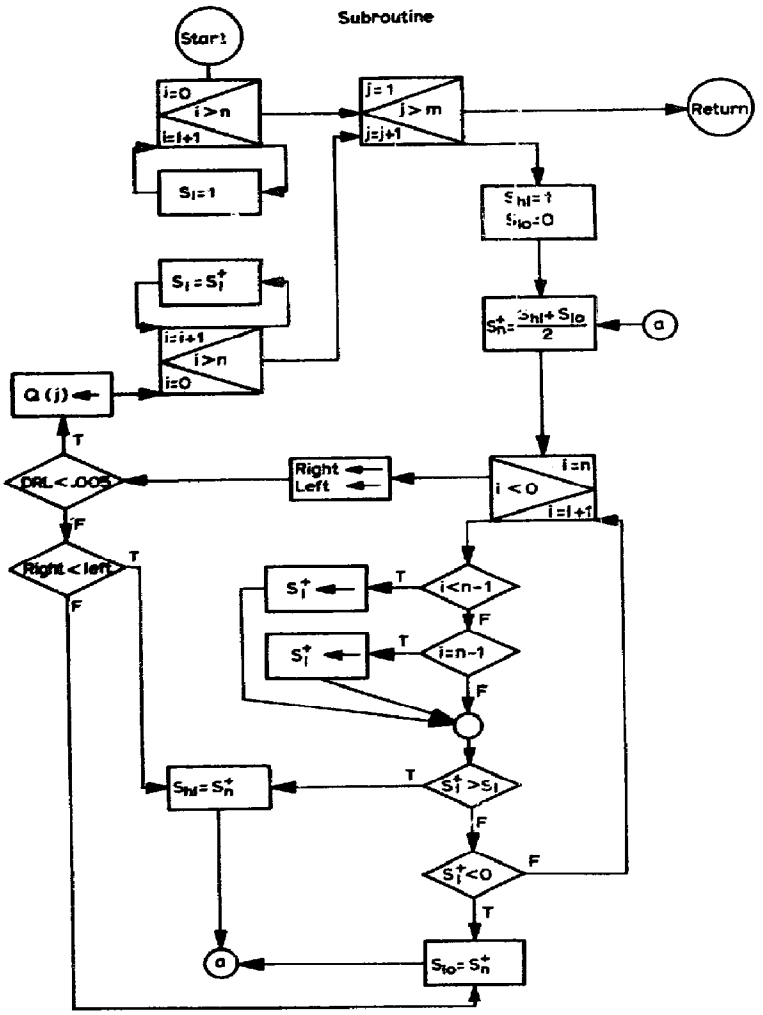
$$A_{ex} = \sum_{j=0}^{m} Q_{ex}(j) \Delta t - \frac{Q_{ex}(m)}{2} \Delta t$$

$$A_{th} = \sum_{j=0}^{m} Q(j) \Delta t - \frac{Q(m)}{2} \Delta t$$

$$\Delta A = \sum_{j=0}^{m} \left| Q_{ex}(j) - Q(j) \right| \Delta t - \left| \frac{Q_{ex}(m) - Q(m)}{2} \right| \Delta t$$

$$DA = \left| \frac{A_{ex} - A_{th}}{A_{ex}} \right| ; \quad DD_m = \frac{D_2 - D_m}{D_m} ; \quad DD_M = \frac{D_M - D_1}{D_M}$$

$$DR_m = \frac{R_2 - R_m}{R_m} ; \quad DR_M = \frac{R_M - R_1}{R_M} ; \quad \Delta Q = Q_{ex}(m) - Q(m)$$



solution of the drug in the vehicle. In these cases, the parameters derived from different initial concentrations in vehicle were in apparent disagreement. In general, independence of initial concentration in vehicle of both the D and the R values should be regarded as an important criterion for evaluating the validity of the obtained results.

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