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A new mathematical model describing the release data of the active substance from tablets using the flow-through cell apparatus

Nowy matematyczny model opisujący wyniki uwalniania substancji aktywnej z tabletek w aparacie przepływowym

Nowadays the basic criteria of the interpretation of release process, described in the pharmacopoeial monograph, is the Q ratio expressed as the amount of the released substances at the time in percentage [7]. However, performing the mechanism of releasing the substance and describing the process is a problem.

As shown in the review of reports [6] for interpretation of the kinetics release of the active substances from the solid dosage forms, the scientists usually use the models of Hixon and Crowell (1931), Higuchi (1961), Weibull (1972), Peppas (1985) based on the amount of the released substances at the time and which calculated the dissolution constant rates describing the process until the release of 60 % of drug. However, Monte Carlo simulations based on the statistics evaluation and probability calculus have limited practical application [18].

A lot of papers and reports [1, 2, 8, 10, 17] proposed for the description of release kinetics are not sufficient because these expressions do not entirely explain the complexity of the dissolution process of the solid dosage forms at different hydrodynamic flows of the dissolution medium and also physical or chemical changes during the dissolution process under given temperature conditions. Scientists [6, 22] have for one hundred years tried to explain the process of penetration of the mass to the solvent through the thin solution layer on the solid-liquid boundary.

Among many studies, the chemical engineering knowledge establishes the dissolution processes of solids. Scientists [22] use the model of solid-liquid barrier which assumed that at the moment of contact between the solid and liquid on the solid surface a thin diffusion layer is formed of the saturated solution of the soluble substance in the adhesive layer of liquid. The dissolution process is caused by the concentration of the gradient at the boundary of solid-liquid. The fundamental physicochemical parameters describing the dissolution process can be calculated from Nernst-Brunner (1904) [6] as follows: $dC/dt = [D \cdot S/V \cdot h] \cdot (C_s - C_1)$ (Eq.1), where dC/dt is concentration gradient, D is the diffusion coefficient, S is the actual solid surface area, V is the volume of the dissolution medium, h is the thickness of the diffusion layer, C_S is the concentration of the saturated solution, C_1 is the substance concentration dissolved at defined volume of the solution.

The rate of the dissolution process depends on the diffusion coefficient, the surface area of the solid, the thickness of the diffusion layer and the concentration gradient [9,12, 20]. However, measurement of the change of solid area surfaces is not easy. During the studies of release of the active substance, for example from tablets with fast disintegration, its surface is changed from the

initial area corresponding to the area surface of grains of the active substance dispersed at the upper surface of the tablet to the maximum area surface formed as a result of the mass disintegration and better moistening of the surface. In this period of time the grains have a normal granulometric schedule with the equality range more or less of the average diameter [19, 25]. During the dissolution process the size all of the grains is decreased. The small grains dissolved and the diameter of the large grains became smaller so in this case the number of grains started in the dissolution process is systematically decreasing but their average diameter values is constant almost to the end of the process.

However, the initial and the middle phases of the simultaneous disintegration and dissolution processes usually run with considerable interruptions caused by temporary disorders with destruction of the mass. At the end of the phase, the dissolution process runs with repeatable results until the release of almost all declared drug dose, because it does not additionally complicate through the disintegration process and moving the mass. These observations show that the dissolution rate of the active substance from the tablet depends on changing of the actual dissolution surface of grains. However, the calculation of the actual surface of dissolution at each moment during the process which should be directly proportional to the actual concentrations of the gradient and the quantity of the dissolved substance in a period of time is a problem.

The biopharmaceutical studies reported that the change of solubility of the active substance is caused by changing the solvent or pH of the solution, the addition of the solubilizers, cosolvants, tenzydes, complexion agents and others [16, 23]. The rate of the dissolution process and also the concentration gradient at the time is slowed by increasing viscosity and density of the dissolution medium. However, determination of the hypothetic concentration of the saturated solution in the diffusion layer and the thickness of this layer is not easy. A few reports [3, 24] described a relationship between the thickness of interphase diffusion layer and the solid dissolution rate, so when the layer was thin the dissolution is faster. The thickness of the diffusion layer is decreased when the rate of the flow liquid around the dissolving grains increased. The paper [22] shows that this thickness can be within the range from 5 to 100 μm and even on 0.1 μm distance around the solid surface the liquid is moved.

Dependences between physicochemical parameters on the solid-liquid boundary describe the dimensionless equation proposed by [3, 4, 22, 24]: $Sh = \varphi \cdot Sc^a \cdot Re^b \cdot B^c$ (Eq.2), where Sh is the Sherwood number, Sc is the Schmidt number, Re is the Reynolds number, B is the apparatus parameter describing the dispersion of grains in the dissolution medium formed from desintegration of the tablet mass in the dissolution cell, φ is proportional ratio, a, b and c are exponents. These parameters can be determined from the following expressions:

$$Sh = K \cdot dz/D \cdot \rho \text{ (Eq.3)}, \quad Sc = \mu/D \cdot \rho \text{ (Eq.4)}, \quad Re = \rho \cdot dz \cdot v/\mu \text{ (Eq.5)}, \quad B = V_{sg}/V_c \text{ (Eq.6)},$$

where K is the mass transfer coefficient, dz is the average diameter of grains, D is the diffusion coefficient, ρ is the density of the dissolution medium, μ is the viscosity of the dissolution medium, v is the linear rate of flow liquid, V_{sg} is the volume of the single grain, V_c is the volume of the dissolution cell.

Description of the dissolution process by the dimensionless equation has advantages because it presents the quantity dependences between change in the values of dissolution rate constant and relevant parameters corresponding to the dissolution process. The proposed expressions make it possible to plan the drug with required release profile under given *in vitro* and *in vivo* conditions. The aim of this study was to establish a new method for interpretation of the release data of the active substance by the dimensionless equation.

MATERIAL AND METHODS

T a b l e t s. Tablets consisting of papaverine hydrochloride and other compounds were prepared according to the patent [14] by tabletted after granulation process. Papaverine hydrochloride (PAP) was obtained from Galfarm PPH, Cefarm Lublin, Poland.

R e l e a s e s t u d i e s. The release of the active substances from the tablet was studied using the flow-through cell apparatus equipped with an upper glass filter at pore size 15–40 μm [4, 5] at 37°C using as the dissolution medium citric buffer at pH 6.5 with 0.024 ml/s, 0.048 ml/s, 0.071 ml/s, 0.145 ml/s or 0.193 ml/s flow rates. The accurately weighed tablet was placed in the dissolution cell and when the citric buffer was flowing through the cell 20 ml portions of eluates collected at each of the flow rate. The 5 ml of each eluate was instantly diluted to 10 ml with methanol. The samples were filtered using 0.20 μm pore size HPLC filters (Spartan 13/0.2 RC, Aldrich). Experiments were performed for six tablets for each of the flow liquid rates.

P a r a m e t e r s o f t h e r e l e a s e • Characteristics of the citric buffer at pH 6.5 solution at 37°C: density (ρ) = 1.0129 g/cm^3, viscosity (μ) = $7.958 \cdot 10^{-3}$ g/cm·s • The volume of the dissolution cell (V_c) = 5.024 cm^3.

H P L C a n a l y s i s. The concentration of PAP was determined using an HPLC method. The HPLC system consisted of a series 200 HPLC pump, a series 200 autosampler equipped with a 100 μl loop, a UV/VIS detector series 200 set at 278 nm, a vaccum degasser series 200 and an chromatography interface 600 series LINK, all of each were purchased by Perkin Elmer (USA). The column was a Zorbax SB – C 18, 150 mm x 4.6 mm, 5μm (Agilent, USA). A mobile phase of methanol: water (60:40, v/v) was used at a flow rate of 1.0 ml/min. 10 μl samples were injected into the column by autosampler and chromatogram was developed for a period of 15 min. UV signals were monitored and peaks were integrated using the software version 6.2.0.0.0:B27. The quantity of PAP was calculated according to the earlier published method [13].

RESULTS AND DISCUSSION

Papaverine hydrochloride (6,7-dimethoxy-1-(3,4-dimethoxybenzyl) isoquinoline hydrochloride) is soluble in water, an aqueous solution has pH in the range from 3 to 4.5 [21]. The release study was carried out in the flow-through apparatus with the range of flow from 0.024 ml/s to 0.193 ml/s. The citric buffer at pH 6.5 as dissolution medium was chosen because previous tests showed that at the phosphoric and citric buffers at pH 6.8 only approximately 20% PAP was released from tablets. The release studies found that stability of the eluents at least a few hours in the citric buffer at pH 6.5 was better then in the phosphoric buffer at pH 6.5 [15]. Average results of determining the quantity of the released substance (dm) from six tablets in 20 ml fractions of the eluates (dV_e) collected in the period of time (dt) and the total quantity of the substance (M_t) released after the time (t) are presented in Table 1.

The results in Table 1 showed that in the initial fractions of eluates the quantity of the released substance increased until the "maximum" (*) and in the following fractions it systematically decreased in given rates of the flow liquid. In the initial fractions occurred an inverse dependence between the quantity of the released substances (dm) and the rate of the flow liquid was also evident (V). The changes (dm/dV_e) can be expressed as (dC). As shown in Fig. 1 the calculated values dC for fractions (i) collected after the maximum and presented as f(ln t) = dC arranged along the line on slope α, which extrapolation to dC axe enables the determination C_{ex} value at time t = 0 and the dependence is described by the equation $C_{ex} = dC_t + \alpha \cdot \ln t$ (Eq.7) and $\alpha = (dC_1 - dC_2)/(\ln t_2 - \ln t_1)$, (Eq.8),

where dC_1 and dC_2 are concentrations of the substances at the intervals of time dt_1 and dt_2, dC_t is the concentration at time t.

Table 1. Quantity of PAP released from tablet in 20 ml portions of eluates (dV_e) flowing outside from the dissolution cell with rates (V) in citric buffer at pH 6.5

V(ml/s)	0.024	0.048	0.071	0.145	0.193
dt (s)	833	417	282	138	104
Eluate number (i)	dm (g) $\cdot 10^{-3}$				
1	2.51	1.58	1.18	0.95	0.81
2	4.17*	2.51	2.07	1.09	1.17
3	3.06	2.73*	2.29*	1.21	1.20
4	1.64	2.46	1.74	1.24	1.26
5	0.68	1.71	1.58	1.44*	1.35*
6	0.49	1.08	1.43	1.38	1.29
7	0.36	0.76	1.08	1.14	1.18
8	0.31	0.52	0.83	1.10	1.06
9	0.26	0.34	0.61	0.93	0.94
10		0.29	0.49	0.80	0.80
11			0.39	0.67	0.75
12				0.61	0.65
13				0.59	0.52
14				0.48	0.42
15				0.41	0.39
16				0.33	0.37
17				0.26	0.30
18				0.24	0.28
M (g) $\cdot 10^{-3}$	13.48	13.98	13.69	14.26	14.74
t (s)	7497	4170	3102	2484	1872

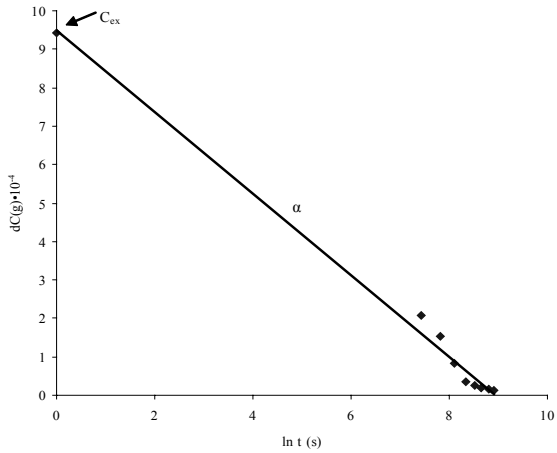

Fig. 1. Concentration of PAP in function ln t at V = 0.024 ml/s

The plot expressed as function $C_{ex} = f(V)$ enables to show the concentrations of the saturated solutions at the boundary diffusion layer (C_0) in stationary conditions (V = 0) by extrapolation the line of slope β as shown in Fig. 2.

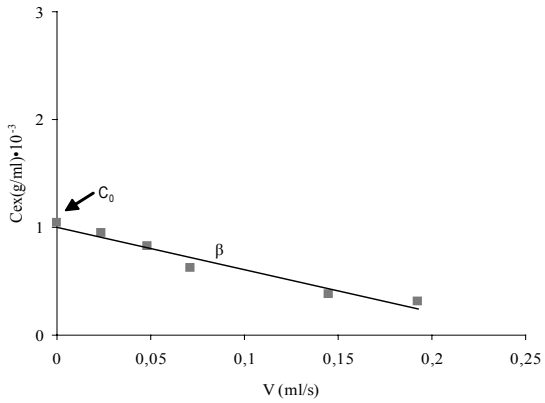

Fig. 2. Dependence between the flow liquid rate and the extrapolated concentration of PAP

The C_0 values were calculated from expression: $C_0 = C_{ex} + \beta \cdot V$ (Eq.9) and the results are presented in Table 2, and β coefficient from: $\beta = (C_{ex1}-C_{ex2})/(V_2-V_1)$ (Eq.10). Additionally, the C_0 values were confirmed experimentally by testing the dissolution of PAP in the mass tablet and as a substance in citric buffer at pH 6.5 at temp. 37°C so C_0 equaling $0.956 \cdot 10^{-3}$ g/ml.

Table 2. Extrapolated concentrations (C_{ex}) for PAP under given rates of flow the dissolution medium

V(ml/s)	α	C_{ex} SD
0.024	$1.050 \cdot 10^{-4}$	$9.426 \cdot 10^{-4}$ (0.9633-1.0477)
0.048	$9.744 \cdot 10^{-5}$	$8.262 \cdot 10^{-4}$ (0.9872-1.0240)
0.071	$7.573 \cdot 10^{-5}$	$6.257 \cdot 10^{-4}$ (0.9899-1.0043)
0.145	$4.683 \cdot 10^{-5}$	$3.802 \cdot 10^{-4}$ (0.9911-1.0726)
0.193	$3.978 \cdot 10^{-5}$	$3.161 \cdot 10^{-4}$ (0.9826-1.0190)
C_0 (g/ml)	$1.047 \cdot 10^{-3}$	

The diffusion coefficients of PAP in the citric buffer at pH 6.5 were calculated from Othmer's equation [11]: $D_{AB} = 14 \cdot 10^{-5}/[\eta_w^{1.1} (r^B/r^w) \cdot v^{0.6} \cdot \eta_B$ (cm^2/s) (Eq.11), where η_w is the viscosity of water under process temperature (0.7745 cP/37°C), η_B is the viscosity of the citric buffer at pH 6.5 (1.0528 cP/22°C), v_A is the molar volume of the diffused substance calculated by summarized the atomic volumes (ml/mol), $[(r_B/r_w) \approx 1]$ is the quotient the molar heats of vaporisation of the buffer and water. The calculated value of diffusion coefficients is equal to $4.643 \cdot 10^{-6}$ (cm^2/s) for PAP and this value is insignificantly higher (1.27% and 2.50%, respectively) than the values experimentally determined by improved Graham's method [5].

Knowing the data collected in Table 1 and the C_0 values and based on the Eq.1 it can be obtained from the equation: $(D/h) \cdot S = dm/[dt \cdot (C_0-dC)]$ (Eq.12) in which the expression $[(D/h) \cdot S]$ can be calculated, where (S) is a changing value during the whole dissolution process and decreasing proportionally with the decreased quantity of the dissolving substance until zero and the quotient (D/h) is constant under given hydrodynamic conditions corresponding to the proportional ratio (a) in the numerical name: $a = [(C_0-C_1)/(C_0-C_2)]/dt$ (Eq.13).

Table 3. Values of [(D/h)·S] calculated for PAP released from the tablet at different flow rates of the dissolution medium

V(ml/s)	0.024	0.048	0.071	0.145	0.193
i	[(D/h)·S] (cm^3/s) [$\cdot 10^{-3}$]				
1	3.270	3.914	4.235	6.888	7.738
2	5.970	6.532	7.780	7.958	11.4
3	4.109	7.190	8.708	8.888	11.7
4	2.040	6.385	6.427	9.122	12.3
5	0.806	4.265	5.788	10.7	13.3
6	0.575	2.608	5.198	10.2	12.6
7	0.420	1.806	3.857	8.344	11.5
8	0.361	1.221	2.927	8.035	10.3
9	0.302	0.792	2.128	6.736	9.038
10		0.674	1.699	5.757	7.639
11			1.346	4.790	7.143
12				4.349	6.161
13				4.202	4.897
14				3.400	3.936
15				2.894	3.650
16				2.321	3.459
17				1.822	2.795
18				1.680	2.606

The values of expression [(D/h)·S] presented in Table 3 were divided by the average ($\bar{a}$) ratio for each of flow rates (V) and the values of the changing surface (S) obtained from the equation: $S = [(D/h)\cdot S]/\bar{a}$ (Eq.14). The (S) values are presented in Table 4.

Table 4. Change of the surface area grains of PAP during release at different rates of liquid flow

V(ml/s)	0.024	0.048	0.071	0.145	0.193
i	S (cm^2)				
1	2.759	1.650	1.193	0.952	0.806
2	5.034	2.754	2.192	1.100	1.187
3	3.468	3.031	2.453	1.228	1.218
4	1.721	2.692	1.810	1.261	1.282
5	0.680	1.798	1.630	1.479	1.380
6	0.485	1.099	1.464	1.410	1.314
7	0.354	0.761	1.086	1.153	1.196
8	0.304	0.515	0.825	1.111	1.068
9	0.252	0.334	0.599	0.931	0.941
10		0.284	0.479	0.796	0.796
11			0.379	0.662	0.744
12				0.601	0.642
13				0.581	0.510
14				0.470	0.410
15				0.400	0.380
16				0.320	0.360
17				0.252	0.291
18				0.232	0.271

Knowing the change of the solid surface (S) of grains, the mass transfer coefficient (K) can be calculated from equation: $K = dm/S\cdot dt$ ($g/cm^2\cdot s$) (Eq.15).

Based on the hypothetic value (a) which is directly proportional to the quotient (D/h) and on the known diffusion coefficient (D) value of active substance the supposed thickness of the boundary diffusion layer (h) can be calculated from equation: h = D/a (cm) (Eq.16). The results are presented in Table 5.

Table 5. Parameters describing the release process PAP at different flow rates of the dissolution medium

Parameter	V (ml/s)				
	0.024	0.048	0.071	0.145	0.193
K (g/cm^2·s)	$1.154\cdot10^{-6}$	$2.318\cdot10^{-6}$	$3.448\cdot10^{-6}$	$7.278\cdot10^{-6}$	$9.660\cdot10^{-6}$
a	$1.185\cdot10^{-3}$	$2.372\cdot10^{-3}$	$3.550\cdot10^{-3}$	$7.235\cdot10^{-3}$	$9.601\cdot10^{-3}$
h (cm)	$3.92\cdot10^{-3}$	$1.96\cdot10^{-3}$	$1.31\cdot10^{-3}$	$6.42\cdot10^{-4}$	$4.84\cdot10^{-4}$
r (cm)	$3.494\cdot10^{-3}$	$3.446\cdot10^{-3}$	$3.326\cdot10^{-3}$	$3.515\cdot10^{-3}$	$3.517\cdot10^{-3}$
dz (cm)	$6.92\cdot10^{-3}$				
V_{sg} (cm^3)	$1.73419\cdot10^{-7}$				

Data in Table 5 show that the mass transfer coefficient is increased and the thickness of the boundary diffusion layer is decreased with an increasing the rate of the liquid flow. The mechanism of these changes is depicted in Figs. 3 and 4.

Table 6. Parameters of the dimensionless equations for PAP

V (ml/s)	Sh	Sc	Re at ν (cm/s)	
0.024	$1.69803\cdot10^{-3}$	1692.15	$6.8427\cdot10^{-3}$	$7.643\cdot10^{-3}$
0.048	$3.41077\cdot10^{-3}$		0.01369	0.01529
0.071	$5.07349\cdot10^{-3}$		0.02024	0.02261
0.145	0.010709		0.04134	0.04618
0.193	0.014214		0.05502	0.06146

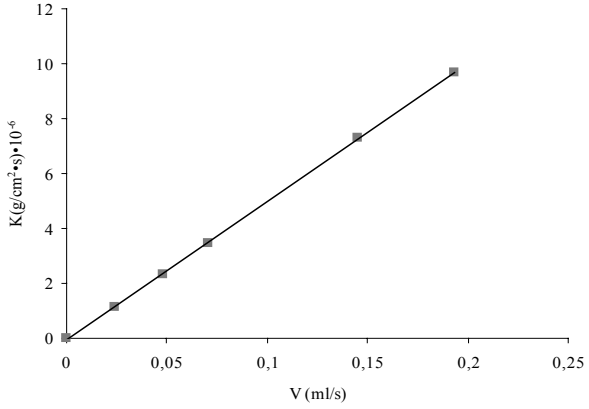

Fig. 3. K values for PAP in function of V

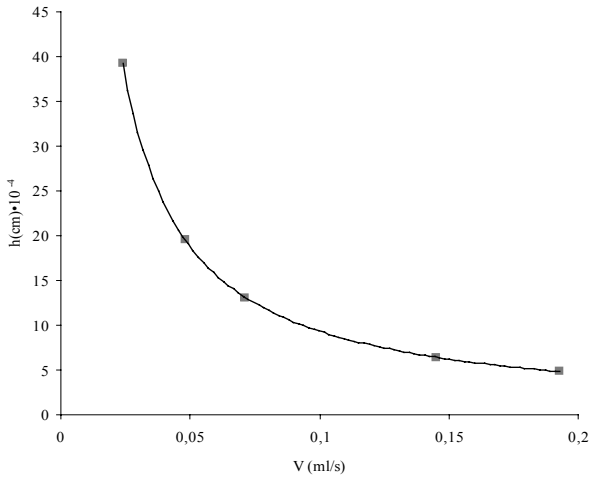

Fig. 4. Change of h values depending on the flow liquid rate

Fig. 3 shows a linear dependence between K and V which can be expressed by the equation: $K = (f_K) \cdot V$ (Eq.17), where $f_K = 4.9036 \cdot 10^{-5}$ ($\pm$ $1.0052 \cdot 10^{-6}$) is the proportional ratio.

Fig. 4 showed that the thickness of the diffusion layer is decreased exponentially with the increasing rate of the liquid flow what can be described by the equation: $h = (f_h) \cdot V^n$ (Eq.18), where $f_h = 9.354 \cdot 10^{-5}$ ($\pm$ $3.5947 \cdot 10^{-7}$) is the proportional ratio.

At the end of the dissolution process the quantity of the active substances dissolved in the period of time dt had volume (V_{dm}) which can expressed as: $V_{dm} = (V_{mol} \cdot dm)/m_{mol}$ (Eq.19), where V_{mol} is the molar volume of substance, m_{mol} is the molar mass of the active substance. Assuming that the shape of grains is spherical, the volume (V_{sg}) and surface area (S_{sg}) of the single grain can be expressed as: $V_{sg} = (4/3) \cdot \Pi \cdot r^3$ (Eq.20) and $S_{sg} = 4 \cdot \Pi \cdot r^2$ (Eq.21), so from the system of equations: $V_N = N \cdot (4/3) \cdot \Pi \cdot r^3$ (Eq.22) and $S_N = N \cdot 4 \cdot \Pi \cdot r^2$ (Eq.23) values (r) and (N) can be calculated where r is the radius of grain and N is the number of grains dissolved in the period of time (dt). The average diameters of grains ($dz = 2 \cdot r$) for PAP and volume of single grains (V_{sg}) are presented in Table 5.

The linear rate of liquid flow (ν) was calculated from the equation [3,22]: $\nu = (\Delta V/dt):(\Pi \cdot d^2/4)$ (cm/s) (Eq.24), where ΔV is the volume of liquid flowing outside with the dissolution cell at time dt, d is the diameter of the dissolution cell (2 cm). Having the above parameters and basing on Eqs. 3–7 the dimensionless numbers can be calculated and the results are presented in Table 6.

As shown in Fig. 5, changes of the Sh values are directly proportional to the product ($Sc \cdot Re_z$) and the slope of these lines describe the values obtained from expression: $[\varphi \cdot (V_{sg}/V_c)]^{1/2}$ so it equals $1.49546 \cdot 10^{-4}$ for PAP and coefficient (φ) equals 0.8049 for PAP. The dimensionless equation for the active substance is presented below: $Sh = 0.8049 \cdot Sc \cdot Re \cdot (V_{sg}/V_c)^{1/2}$ (Eq.25).

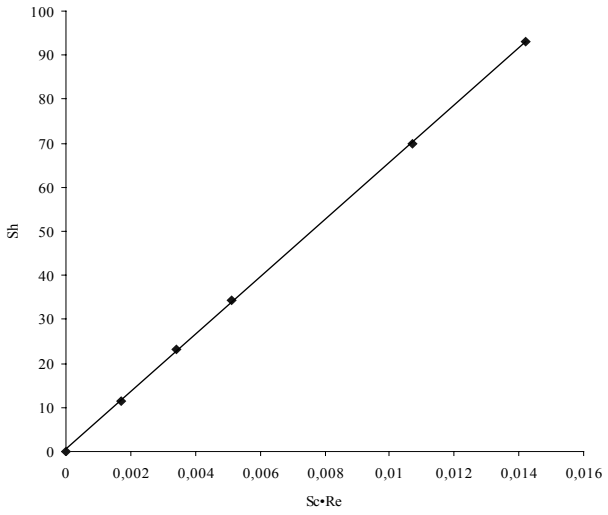

Fig. 5. Dependence between Sh and the product (Sc·Re)

CONCLUSIONS

A description of the release process of the medical substances from solid dosage forms such as tablets using the dimensionless equation was proposed first in 1981 by Czarnecki [3] and confirmed in 2000 [4] and in the present article. The dimensionless equation including Sherwood, Schmidt and Reynolds numbers allows to describe the release process of active substances from tablets in the dissolution media using the physicochemical parameters as the diffusion coefficient of the active substance and viscosity, density and hydrodynamic of the dissolution liquid. Moreover, basing on the experimental data of the dissolution process the hypothetic concentration of the saturated solution can be calculated in the boundary diffusion layer, the thickness of diffusion layer which depend on hydrodynamic liquid around dissolving grains of the active substances with a calculated hypothetic size. Knowing these parameters, it is also possible to determine the dissolution rate constant which depends on the quantity of the dissolved substance at a given period of the time from the actual surface area of grains.

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SUMMARY

The release of papaverine hydrochloride from tablets using the flow-through cell apparatus in a citric buffer at pH 6.5 was described by the dimensionless equations containing Scherwood, Schmidt and Reynolds numbers. The physicochemical parameters of the dissolution process such as the diffusion coefficient, the mass transfer coefficient, the thickness of the boundary diffusion layer and the concentration of the saturated solution at the boundary diffusion layer in stationary conditions were calculated. The dimensionless equation proposed for interpretation of the release data describes approximately 100 % experimental results.

STRESZCZENIE

Proces uwalniania chlorowodorku papaweryny z tabletek w aparacie przepływowym badanych w buforze fosforanowym o pH 6,5 został opisany równaniem bezwymiarowym zawierającym liczby Scherwooda, Schmidta i Reynoldsa. Obliczone zostały fizykochemiczne parametry procesu rozpuszczania, takie jak współczynnik dyfuzji, współczynnik wnikania masy, grubość granicznej warstwy dyfuzyjnej i stężenie nasyconego roztworu w granicznej warstwie dyfuzyjnej w warunkach stacjonarnych. Równanie bezwymiarowe zaproponowane do interpretacji wyników uwalniania opisuje około 100% doświadczalnych wyników.