Acta Poloniae Pharmaceutica – Drug Research, Vol. 68 No. 2 pp. 261–272, 2011 ISSN 0001-6837
Polish Pharmaceutical Society

PHARMACEUTICAL TECHNOLOGY

SIMULTANEOUS RELEASE OF DICLOFENAC SODIUM AND PAPAVERINE HYDROCHLORIDE FROM TABLETS AND PELLETS USING THE FLOW-THROUGH CELL APPARATUS DESCRIBED BY DIMENSIONLESS EQUATIONS

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Abstract: The release of diclofenac sodium and papaverine hydrochloride from tablets and pellets using the flow-through cell apparatus was studied. The influence of excipients and of a size of the solid dosage forms on the amount of the released substances at the intervals of time using the different rates of flow of the dissolution medium was investigated. Physical parameters corresponding to the dissolution process as the mass transfer coefficient, the thickness of the boundary diffusion layer and the concentration of the saturated solution at this layer were calculated. The results of release were described by dimensionless equations.

Keywords: diclofenac sodium, papaverine hydrochloride, release, dimensionless equation

The bioavailability of the active substances from pharmaceutical solid dosage forms depends on oral absorption of drug. One of the most important processes in oral absorption is the dissolution process. Dissolution has an important role in the release of drugs from pharmaceutical preparations. The release of medical substances from solid dosage forms is investigated in one of the pharmacopoeial apparatus e.g., the paddle or the flow-through cell apparatus (1). Recent publications describe researches comparing the release between the different types of pharmacopoeial apparatuses (2, 3), the influence of rotation rates of the paddle on the release from solid forms (4), predicting dissolution *via* hydrodynamics in cell apparatus (5). For interpretation of results of the release, pharmaocopoeial monograph (1) suggests expressing the quantity of the active substance dissolved in a specified time as a percentage of the content stated on the label. As the review of reports shows (6, 7), for the purpose of describing the data of the release the following mathematical models are used: Hixon and Crowell, Higuchi, Weibull, Langenbucher, Peppas and Monte Carlo simulations. Scientists try to describe the process of release from different pharmaceutical forms under given conditions using various operational equations describing the dependence between the amount of substance and time of the release (8–12).

However, during the dissolution process, the process of transfer of a solid mass occurs into a solvent on the solid-liquid boundary. Chemical engineering scientists (13) describe the dissolution process of a solid mass using a model of solid-liquid boundary. This theory assumes that in the moment of contact between a solid mass and a liquid, a thin diffusion layer forms of the saturated solution surrounding the solid surface from dissolving substance.

The dissolution process is caused by the concentration gradient on the boundary of solid-liquid. In basic equation describing the concentration gradient (dC) in an infinitesimal time (dt), physicochemical parameters are taken into consideration such as: the diffusion coefficient (D), the actual solid surface area (S), the volume of the dissolution medium (V), the thickness of the diffusion layer (h), concentration of the saturated solution (C_S), the substance concentration dissolved at defined volume of the solution (C_1), which can be calculated from Nernst-Brunner equation (6, 7) as follows:

$$dC/dt = [D \cdot S/V \cdot h] \cdot (C_s - C_1) \quad \text{Eq. 1}$$

In the chemical engineering, the mass transfer process on the boundary solid-liquid during the dis-

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solution of solid is described by dimensionless equations (13). In order to describe the release data in pharmaceutical sciences, scientists (14–17) attempted to use the dimensionless equation as:

$$Sh = \phi \cdot Sc \cdot Re \cdot B^{1/2} \quad \text{Eq. 2}$$

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 formed from disintegration of the tablet mass in the dissolution medium in the dissolution cell and ϕ is the proportional ratio. These parameters can be calculated from the following expressions:

$$Sh = K \cdot dz/D \cdot \rho \quad \text{Eq. 3}$$

$$Sc = \mu/D \cdot \rho \quad \text{Eq. 4}$$

$$Re = \rho \cdot dz \cdot \nu/\mu \quad \text{Eq. 5}$$

$$B = V_{sg}/V_c \quad \text{Eq. 6}$$

where K is the mass transfer coefficient, dz is the average diameter of solid grains, D is the diffusion coefficient of solid to liquid, ρ is the density and μ is the viscosity of the dissolution medium, ν 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.

The linear rate of flow liquid (ν) can be obtained from the equation (13, 14, 16):

$$\nu = (\Delta V/dt) : (\pi \cdot d^2/4) \quad \text{Eq. 7}$$

where ΔV is the volume of liquid flowing outside with the dissolution cell at time dt; d is the diameter of the dissolution cell.

The dimensionless numbers describe the dissolution rate of solid taking into account parameters such as changing of a solid surface area, the size of an active substance grains, the mass transfer coefficient, the thickness of the boundary diffusion layer, physicochemical properties of the dissolution medium such as density, viscosity, the diffusion coefficient of solid to liquid and the size of a dissolution cell.

However, the description of the release lasting under different hydrodynamic conditions of two active substances with different solubility and created interactions between themselves from oral solid forms of different sizes and excipients is interesting to be tested. Interpretation of the release process by the dimensionless numbers has its advantages as it presents the quality dependences between the changing values of dissolution rate constant and relevant of the parameters corresponding to the dissolution. Proposed expressions make possible the planning of the drug form with required profile release under given conditions.

The aim of this study is to describe the simultaneous release of two medical substances with different solubility from solid dosage forms containing different excipients in the tablet mass and different sizes of forms such as tablets and pellets using the flow-through cell apparatus with different rate of flow of the dissolution medium by the dimensionless equations.

MATERIALS AND METHODS

Materials

Diclofenac sodium (DIC) produced by Caesar and Loretz, GmbH, Hilden, Germany, papaverine hydrochloride (PAP) obtained from Galfarm PPH, Cefarm Lublin, Poland, polyvinylpyrrolidone (PVP) K 22, mannitol (M), potato starch (PS), hydroxypropylmethylcellulose (HPMC), microcrystaline cellulose (MC), magnesium stearate (MS), trisodium citrate dehydrate, citric acid monohydrate, methanol and water were the products of Merck, Germany. All other reagents used were of analytical grade (pure for analysis).

Methods

Composition of the solid dosage forms

Composition and preparation of the tablets were presented in the Polish Patent (18).

Tablets 1 (T1): One tablet (T1) consists of 50 mg DIC, 20 mg PAP and excipients as PVP, M and PS to 300 mg of weight.

Tablets 2 (T2): One tablet (T2) consists of 50 mg DIC, 20 mg PAP and excipients as PVP, M, HPMC, MC, MS to 300 mg of weight.

Pellets (PEL): Composition of 300 mg single dose is the same as showed (T1).

Preparation of the solid dosage forms

Tablets were prepared by separate dissolution of DIC and PAP in methanolic solution of PVP, followed by addition of the powdered excipients, evaporation of solvent, granulation of the wet mass (granulator Erweka, Germany with a 1.6 mm sieve), then by drying the granulas and tabletting the granulas in a tablet machine (Erweka, Germany). Prepared tablets (T1 and T2) have strengh 4 mm (± 5%), lengh 9 mm (± 5%) and average mass 300 mg (± 5%), a hardness ratio larger than 0.1 kg/mm^2, the desintegration time of the tablets in water at 37^{o}C no longer than 15 min.

Pellets were prepared using the extrusion and spheronization method (Caleva extruder, England and Caleva spheronizer, England). The obtained beads have strengh 1.9 mm and lengh 2.4 mm (± 7.5%) and average mass of $6.68 \cdot 10^{-3}$ g (± 10%).

Drug content

The content of active substances was assayed by HPLC method published in earlier reports (19,

20). In the studies, 50 mg DIC (± 5%) and 20 mg PAP (± 5%) in one tablet at 300 mg weight of T1 and T2 and one dose of 300 mg of pellets were determined.

Release studies

The release tests of active substances from tablets and pellets were carried out at the flow-through cell apparatus similar to pharmacopoeial apparatus 4, previously used at the releasing tests (14–16), equipped with the dissolution cell with internal diameter of 2 cm and internal heigh of 2.5 cm made from a transparent plastic, in which there were two glass filters at pore size 15–40 μm setting on upper and lower part of the cell. The tablet was set horizontally on the down glass filter in the dissolution cell. The dissolution medium – citric buffer at pH 6.5, was pumped with 0.024 mL/s, 0.048 mL/s, 0.071 mL/s, 0.145 mL/s or 0.193 mL/s flow rates by the peristaltic pump (Cole Parmer, Masterflex, L/S, USA). The apparatus was maintained at 37°C by water heated from the thermostat (MLW, Mechanik, Medingen, Germany).

The accurately weighed tablet or one dose of pellets was placed into the dissolution cell, the dissolution medium flown with suitable rate and 20 mL portions of effluents were collected from each of the flow rates. Five milliliters of each effluent 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 or six dose of pellets for each of the flow liquid rate.

Parameters of the dissolution liquid

Characteristic of the citric buffer at pH 6.5 solution at 37°C: density (ρ) = 1.0129 g/cm^3, viscosity (μ) = 7.958?10^{-3} g/cm·s. The volume of the dissolution cell (V_c) = 5.024 cm^3. The diameter of the dissolution cell (d) = 2 cm.

HPLC analysis

The quantity of DIC and PAP in each effluent was determined using an HPLC method. The HPLC system consisted of a series of 200 HPLC pump, a series of 200 autosampler equipped with a 100 μL loop, a UV/VIS detector series of 200 set at 278 nm, a vaccum degasser series 200 and a chromatography interface of 600 series LINK, all of each purchased from Perkin Elmer (USA). The column was a Zorbax SB-C 18, 150 mm × 4.6 mm, 5 μm (Agilent, USA). A mobile phase of methanol : water (60:40, v/v) was used at a flow rate of 1.0 mL/min. Samples of 10 μL were injected into the column by autosampler and chromatogram was developed for 15 min. The UV signals were monitored and peaks were integrated using the software version 6.2.0.0.0:B27. The quantity of DIC and PAP were calculated according to the published method (20).

RESULTS AND DISCUSSION

Diclofenac sodium, (sodium [2-(2,6-dichloroanilino)phenyl]acetate), belongs to the non-steroidal anti-inflammatory drugs, sparingly soluble in water and alkaline solutions, pH of the aqueous solutions is 7 to 8.5. 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, it has a direct relaxant effect on smooth muscle (21). The obtained tablets and pellets consisting of both active substances offer the advantage of simultaneous acitivity and cause a greater analgetic effect of diclofenac sodium (22).

However, studying preparation of tablets and pellets and finding the suitable dissolution medium for the release became a problem. There is an interaction between both active substances dissolved in the aqueous solution and as a consequence, the precipitation residues causes double change reaction in which the sodium cation from diclofenac sodium reacts with chloride anion from papaverine hydrochloride forming sodium chloride and another chemical substances of different solubility in water (23). This interaction can be prevented by separate dissolution of each active substance in the methanolic solution of PVP.

Bearing in mind different solubility of DIC and PAP, choosing a suitable dissolution medium for the release study was not easy. Previous tests showed that from tablet prepared according to the formula for T1 without PAP (single T1) DIC released into the phosphate buffer at pH 6.8 in 100%, whereas PAP from single T1 (without DIC) only in 26.7%. When this buffer was changed to the citric, at pH 6.8 DIC released in 93.1% and PAP in 25.4%. These tests were also carried out for composed formulas with DIC and PAP (T1) into the phosphate buffer at pH 6.8, where DIC released in 83% and PAP in 55 % and into the citric buffer at pH 6.5, a release was 100% for DIC and 70% for PAP after approximately 70 min. According to above analyses, the citric buffer at pH 6.5 was chosen for simultaneous release of both substances. Stability time of absorbance of the DIC and PAP solutions were longer than in phosphate buffer at pH 6.5 and 6.8 (24).

Table 1. Quantity of DIC and PAP released from T1 in 20 mL portions of eluates (dV_e) flowing outside from the dissolution cell with rates (V).

V(mL/s)	0.024		0.048		0.071		0.145		0.193	
dt (s)	833		417		282		138		104	
Eluate	dm (g) × 10^{-3}									
no.	DIC	PAP	DIC	PAP	DIC	PAP	DIC	PAP	DIC	PAP
1.	8.99	2.51	6.98	1.58	5.72	1.18	2.45	0.95	1.68	0.81
2.	14.55	4.17	11.80	2.51	7.50	2.07	2.85	1.09	3.34	1.17
3.	12.10	3.06	11.13	2.73	7.93	2.29	3.96	1.21	4.46	1.20
4.	7.12	1.64	8.71	2.46	8.93	1.74	6.01	1.24	4.08	1.26
5.	2.67	0.68	6.63	1.71	7.70	1.58	5.45	1.44	4.05	1.35
6.	1.04	0.49	3.56	1.08	4.25	1.43	4.45	1.38	3.60	1.29
7.	0.46	0.36	1.71	0.76	3.54	1.08	4.15	1.14	3.58	1.18
8.	0.23	0.31	0.76	0.52	2.45	0.83	3.53	1.10	3.53	1.06
9.	0.11	0.26	0.33	0.34	1.03	0.61	3.26	0.93	3.45	0.94
10.			0.15	0.29	0.77	0.49	3.20	0.80	3.13	0.80
11.					0.13	0.39	2.11	0.67	2.86	0.75
12.							1.97	0.61	2.21	0.65
13.							1.86	0.59	1.88	0.52
14.							1.64	0.48	1.78	0.42
15.							1.43	0.41	1.55	0.39
16.							0.66	0.33	1.31	0.37
17.							0.12	0.26	1.18	0.30
18.							0.09	0.24	0.96	0.28
M_t (g) ×10^{-3}	47.27	13.48	51.76	13.98	49.95	13.69	49.19	14.26	48.63	14.74
t (s)	7497		4170		3102		2484		1872	

The quantities of the released DIC and PAP (dm) in the 20 mL portions of effuents (dVe) collected in the period of time (dt) and the total quantity of the substances (M_t) released after the time (t) are presented in Tables 1–3.

In the initial fractions of effluents the quantity of the released substances were increased until to "maximum" then in the following fractions systematically decreased. In the initial fractions, the inversed dependence between the quantity of released substances (dm) and the rate of the liquid flow (V) can be observed. The changes (dm/dV_e) were expressed as (dC). The values (dC) collected for fractions after "maximum" were presented as a function: dC = f (ln t), where ln t = ln (i·dt) (Fig.1 as an example for T1 and V = 0.024 mL/s).

When the regression line with slope α for points created from the function dC = f (ln t) was drawn, the C_{ex} values can be obtained. C_{ex} is the extrapolated concentration at time t = 0 determined by extrapolation of slope α to dC axe and numerical values of Cex and a slope α can be calculated from the respective equations (16):

$$C_{ex} = dC + \alpha \cdot \ln t \qquad \text{Eq. 8}$$

and $\alpha = (dC_1 - dC_2)/(\ln t_2 - \ln t_1)$ Eq. 9

where dC_1 and dC_2 are the concentrations of active substances at the intervals of time dt_1 and dt_2. Values of C_{ex} and α are presented in Tables 4–6.

Values (C_{ex}) presented as function (V) enables to graphically determine the concentrations of saturated solutions on the boundary diffusion layer (C_0) in stationary conditions (V = 0) by extrapolation of the line of slope β as shown in Figure 2.

The C_0 value can be also obtained from expression (16):

$$C_0 = C_{ex} + \beta \cdot V \qquad \text{Eq.10}$$

and β coefficient from:

$$\beta = (C_{ex1} - C_{ex2})/(V_2 - V_1) \qquad \text{Eq. 11}$$

Table 2. Quantity of DIC and PAP released from T2 in 20 mL portions of eluates (dV_e) flowing outside from the dissolution cell with rates (V).

V(mL/s)	0.024		0.048		0.071		0.145		0.193	
dt (s)	833		417		282		138		104	
Eluate	dm (g) × 10^{-3}									
no.	DIC	PAP	DIC	PAP	DIC	PAP	DIC	PAP	DIC	PAP
1.	6.53	1.21	3.32	0.68	2.50	0.63	1.97	0.18	1.22	0.41
2.	9.18	1.65	6.43	1.37	3.25	0.79	2.71	0.22	1.31	0.40
3.	8.79	1.64	7.29	1.71	4.02	1.05	3.21	0.85	1.63	0.45
4.	7.64	1.43	6.22	1.56	4.00	1.08	3.28	0.97	1.64	0.44
5.	5.33	0.98	5.74	1.48	3.65	1.02	2.93	0.92	1.84	0.51
6.	3.73	0.69	5.41	1.39	3.63	1.04	2.90	0.89	1.75	0.48
7.	2.29	0.50	4.61	1.17	3.59	1.01	2.65	0.86	1.81	0.53
8.	1.07	0.34	3.94	1.08	3.58	1.02	2.61	0.83	1.75	0.51
9.	0.72	0.21	3.24	0.89	2.94	0.86	2.64	0.71	1.80	0.57
10.	0.30	0.20	2.07	0.68	2.65	0.79	2.65	0.65	1.91	0.58
11.					2.23	0.67	2.24	0.63	1.84	0.56
12.					2.19	0.66	2.20	0.62	1.77	0.55
13.					1.56	0.49	2.06	0.61	1.51	0.47
14.					1.33	0.42	2.03	0.62	1.49	0.48
15.					1.18	0.31	1.89	0.57	1.54	0.50
16.					1.01	0.30	1.88	0.54	1.48	0.46
17.					0.84	0.22	1.75	0.41	1.47	0.45
18.					0.68	0.20	1.72	0.39	1.43	0.42
19.					0.30	0.18	1.35	0.38	1.35	0.41
20.							1.05	0.36	1.34	0.40
M_t (g) ×10^{-3}	45.58	8.85	48.27	12.01	45.13	12.74	45.72	12.21	31.88	9.58
t (s)	8330		4170		5358		2760		2080	

Table 3. Quantity of DIC and PAP released from PEL in 20 mL portions of eluates (dV_e) flowing outside from the dissolution cell with rates (V).

V(mL/s)	0.024		0.048		0.071		0.145		0.193	
dt (s)	833		417		282		138		104	
Eluate	dm (g) × 10^{-3}									
no.	DIC	PAP	DIC	PAP	DIC	PAP	DIC	PAP	DIC	PAP
1.	20.58	4.56	14.86	4.32	12.27	4.02	8.85	3.05	7.46	2.14
2.	15.72	3.88	18.43	5.45	14.46	3.96	10.12	3.38	8.36	2.16
3.	3.24	0.68	9.51	2.63	10.29	2.28	9.71	3.37	8.27	2.37
4.	0.98	0.40	2.40	0.77	2.82	0.80	9.02	2.80	7.83	2.19
5.	0.46	0.30	0.69	0.32	0.78	0.36	3.13	0.80	6.00	1.75
6.	0.29	0.27	0.38	0.24	0.36	0.21	1.22	0.62	4.48	1.54
7.	0.15	0.19	0.25	0.16	0.20	0.13	1.02	0.15	1.54	0.16
8.							0.32	0.07	0.35	0.10
M_t (g) ×10^{-3}	41.42	10.28	46.52	13.89	41.18	11.76	43.39	14.24	44.29	12.41
t (s)	5831		2919		1974		1104		832	

Table 4. The parameters describing the release process DIC and PAP from T1 at different flow rates of the dissolution medium.

Parameter	V (mL/s)				
for DIC	0.024	0.048	0.071	0.145	0.193
C_{ex} (g/mL)	3.674×10^{-3}	3.178×10^{-3}	3.346×10^{-3}	1.792×10^{-3}	1.013×10^{-3}
α (g/mL×s)	4.196×10^{-4}	3.799×10^{-4}	4.172×10^{-4}	2.292×10^{-4}	1.265×10^{-4}
C_0 (g/mL)			4.021×10^{-3}		
D (cm^2/s)			5.462×10^{-6}		
K ($g/cm^2\cdot s$)	4.448×10^{-6}	8.959×10^{-6}	1.335×10^{-5}	2.814×10^{-5}	3.734×10^{-5}
a (s^{-1})	1.184×10^{-3}	2.376×10^{-3}	3.521×10^{-3}	7.234×10^{-3}	9.61×10^{-3}
h (cm)	4.61×10^{-3}	2.3×10^{-3}	1.55×10^{-3}	7.55×10^{-4}	5.68×10^{-4}
r (cm)			0.0121		
dz (cm)			0.0242		
V_{sg} (cm^3)			7.4169×10^{-6}		
ν (cm/s)	7.643×10^{-3}	0.01529	0.02261	0.04618	0.06146
Sh	0.01946	0.03919	0.0584	0.12309	0.16333
Sc			1438.42		
Re	0.02354	0.0471	0.06964	0.14224	0.18931
φ			0.4836		
For PAP					
C_{ex} (g/mL)	9.426×10^{-4}	8.262×10^{-4}	6.257×10^{-4}	3.802×10^{-4}	3.161×10^{-4}
α (g/mL×s)	1.050×10^{-4}	9.744×10^{-5}	7.573×10^{-5}	4.683×10^{-5}	3.978×10^{-5}
C_0 (g/mL)			1.047×10^{-3}		
D (cm^2/s)			4.643×10^{-6}		
K ($g/cm^2\cdot s$)	1.154×10^{-6}	2.318×10^{-6}	3.448×10^{-6}	7.278×10^{-6}	9.66×10^{-6}
a (s^{-1})	1.185×10^{-3}	2.372×10^{-3}	3.55×10^{-3}	7.235×10^{-3}	9.601×10^{-3}
h (cm)	3.92×10^{-3}	1.96×10^{-3}	1.31×10^{-3}	6.42×10^{-4}	4.84×10^{-4}
r (cm)			3.46×10^{-3}		
dz (cm)			6.92×10^{-3}		
V_{sg} (cm^3)			1.7342×10^{-7}		
ν (cm/s)	7.643×10^{-3}	0.01529	0.02261	0.04618	0.06146
Sh	1.698×10^{-3}	3.4108×10^{-3}	5.0735×10^{-3}	0.01071	0.01421
Sc			1692.15		
Re	6.8427×10^{-3}	0.01369	0.02024	0.04134	0.05502
φ			0.8049		

where C_{ex1} and C_{ex2} are extrapolated concentrations in the rate of the flow of liquid V_1 and V_2.

As presented in Tables 4–6, the calculated C_0 values were $4.021\cdot10^{-3}$ g/mL for DIC and $1.047\cdot10^{-3}$ for PAP g/ml determined from T1 and PEL and $3.5075\cdot10^{-3}$ g/mL for DIC and $4.8706\cdot10^{-4}$ g/mL for PAP from T2. Different values of C_0 in substances in the preparation were caused by different excipients which modified the dissolution of the active ingredients.

Knowing the C_0 values and based on the Eq.1, the surface areas of DIC and PAP grains (S) into desintegrated mass can be calculated from the expression:

$$(D/h)\cdot S = dm/[dt\cdot(C_0 - dC)] \quad \text{Eq.12}$$

where D is the diffusion coefficient of active substance, h is the thickness of the boundary diffusion layer.

Considering the expression [(D/h)·S] it can be noticed that (S) is changing its value during the whole dissolution process and it decreases proportionally to

Table 5. The parameters describing the release process DIC and PAP from T2 at different flow rates of the dissolution medium.

Parameter	V (mL/s)				
for DIC	0.024	0.048	0.071	0.145	0.193
C_{ex} (g/mL)	2.829×10^{-3}	2.168×10^{-3}	1.186×10^{-3}	8.604×10^{-4}	4.219×10^{-4}
α (g/mL×s)	3.099×10^{-4}	2.452×10^{-4}	1.346×10^{-4}	1.021×10^{-4}	4.694×10^{-5}
C_0 (g/mL)			3.5075×10^{-3}		
D (cm^2/s)			5.462×10^{-6}		
K ($g/cm^2\cdot s$)	3.895×10^{-6}	7.82×10^{-6}	1.2×10^{-5}	2.547×10^{-5}	3.295×10^{-5}
a (s^{-1})	1.188×10^{-3}	2.394×10^{-3}	3.54×10^{-3}	7.241×10^{-3}	9.616×10^{-3}
h (cm)	4.598×10^{-3}	2.282×10^{-3}	1.543×10^{-3}	7.543×10^{-4}	5.68×10^{-4}
r (cm)			0.0104		
dz (cm)			0.0208		
V_{sg} (cm^3)			4.7094×10^{-6}		
Sh	0.01464	0.0294	0.04512	0.09576	0.12388
Sc			1438.42		
Re	0.02023	0.04048	0.05986	0.12226	0.16271
φ			0.5383		
For PAP					
C_{ex} (g/mL)	4.634×10^{-4}	4.523×10^{-4}	4.016×10^{-4}	2.078×10^{-4}	1.634×10^{-4}
α (g/mL×s)	4.996×10^{-5}	4.958×10^{-5}	4.584×10^{-5}	2.399×10^{-5}	1.899×10^{-5}
C_0 (g/mL)			4.643×10^{-6}		
D (cm^2/s)			4.643×10^{-6}		
K ($g/cm^2\cdot s$)	5.253×10^{-7}	1.025×10^{-6}	1.604×10^{-6}	3.312×10^{-6}	4.453×10^{-6}
a (s^{-1})	1.186×10^{-3}	2.4×10^{-3}	3.537×10^{-3}	7.255×10^{-3}	9.615×10^{-3}
h (cm)	3.915×10^{-3}	1.935×10^{-3}	1.313×10^{-3}	6.4×10^{-4}	4.829×10^{-4}
r (cm)			1.543×10^{-3}		
dz (cm)			3.086×10^{-3}		
V_{sg} (cm^3)			1.538×10^{-8}		
Sh	3.447×10^{-4}	6.726×10^{-4}	1.0525×10^{-3}	2.1733×10^{-3}	2.922×10^{-3}
Sc			1692.15		
Re	3.0021×10^{-3}	6.0057?10^{-3}	8.8809×10^{-3}	0.01814	0.02414
φ			1.2522		

decreasing quantity of the dissolving substance until zero, so the quotient (D/h) is constant under given hydrodynamic conditions and it corresponds to the proportional ratio of the changing concentrations in time (a) in the numerical name. Values of average (ā) ratio were calculated from the equation (16):

$$a = [(C_0 - dC_1)/(C_0 - dC_2)]/dt \quad \text{Eq. 13}$$

and presented in Tables 4–6.

The values of the expression [(D/h)·S] were divided by the average (ā) ratio for each of the flow rate (V) yielding the values of the changing surface (S) (16) from the equation:

$$S = [(D/h)\cdot S]/\bar{a} \quad \text{Eq. 14}$$

The greatest surfaces of the active substances grains into the desintegrated mass solid were observed at 0.024 mL/s and after 28 min (S) was 4.479 cm^2 for DIC and 5.034 cm^2 for PAP from T1, 3.043 cm^2 for DIC and 4.128 cm^2 for PAP from T2 and after 14 min 7.211 cm^2 for DIC and 5.782 cm^2 for PAP from PEL, while (S) is the smallest at 0.193 mL/s. From the (S) values, the possibility of faster or slow absorption of the drug can be predicted. Different values of (S) can result from various excipients in mass tablet, the size of solid forms or the rate of flow of the dissolution medium through the cell of the apparatus.

Table 6. The parameters describing the release process DIC and PAP from PEL at different flow rates of the dissolution medium.

Parameter	V (mL/s)				
for DIC	0.024	0.048	0.071	0.145	0.193
C_{ex} (g/mL)	3.583×10^{-3}	4.473×10^{-3}	3.661×10^{-3}	2.726×10^{-3}	2.693×10^{-3}
α (g/mL×s)	4.186×10^{-4}	5.713×10^{-4}	4.879×10^{-4}	3.834×10^{-4}	3.901×10^{-4}
C_0 (g/mL)			4.021×10^{-3}		
D (cm^2/s)			5.462×10^{-6}		
K ($g/cm^2\cdot s$)	4.265×10^{-6}	8.577×10^{-6}	1.289×10^{-5}	2.676×10^{-5}	3.551×10^{-5}
a (s^{-1})	1.145×10^{-3}	2.324×10^{-3}	3.454×10^{-3}	7.133×10^{-3}	9.489×10^{-3}
h (cm)	4.77×10^{-3}	2.35×10^{-3}	1.581×10^{-3}	7.657×10^{-4}	5.756×10^{-4}
r (cm)			0.01169		
dz (cm)			0.02338		
V_{sg} (cm^3)			6.6882×10^{-6}		
Sh	0.01802	0.03625	0.05447	0.11309	0.15006
Sc			1438.42		
Re	0.02274	0.0455	0.06728	0.13742	0.18289
φ			0.4871		
For PAP					
C_{ex} (g/mL)	8.009×10^{-4}	1.291×10^{-3}	8.132×10^{-4}	9.126×10^{-4}	9.152×10^{-4}
α (g/mL×s)	9.248×10^{-5}	1.645×10^{-4}	1.060×10^{-4}	1.288×10^{-4}	1.339×10^{-4}
C_0 (g/mL)			1.047×10^{-3}		
D (cm^2/s)			4.643×10^{-6}		
K ($g/cm^2\cdot s$)	1.126×10^{-6}	2.197×10^{-6}	3.301×10^{-6}	6.792×10^{-6}	9.194×10^{-6}
a (s^{-1})	1.156×10^{-3}	2.317×10^{-3}	3.428×10^{-3}	7.094×10^{-3}	9.478×10^{-3}
h (cm)	4.016×10^{-3}	2.004×10^{-3}	1.354×10^{-3}	6.545×10^{-4}	4.899×10^{-4}
r (cm)			3.35×10^{-3}		
dz (cm)			6.7×10^{-3}		
V_{sg} (cm^3)			1.574×10^{-7}		
Sh	1.6042×10^{-3}	3.13×10^{-3}	4.7028×10^{-3}	9.6763×10^{-3}	0.0131
Sc			1692.15		
Re	6.518×10^{-3}	0.01304	0.01928	0.03938	0.05241
φ			0.8185		

Nomenclature

C_{ex} the extrapolated concentration at time t = 0, (g/mL)
α the proportional ratio of the function C_{ex} = f (ln t), (g/mL×s)
C_0 the concentration of saturated solution on the boundary diffusion layer in stationary conditions (V = 0), (g/mL)
D the diffusion coefficient of active substance, (cm^2/s)
K the mass transfer coefficient, ($g/cm^2\cdot s$) a the proportional ratio of the changing concentrations at time, (s^{-1})
h the thickness of the boundary layer, (cm)
r the radius of a grain of the active substance, (cm)
dz the diameter of the grain, (cm)
v the linear rate of flow liquid, (cm/s)
V_{sg} the volume of the single grain, (cm^3)
Sh the Sherwood number
Sc the Schmidt number
Re the Reynolds number
φ the proportional ratio of the dimensionless equation

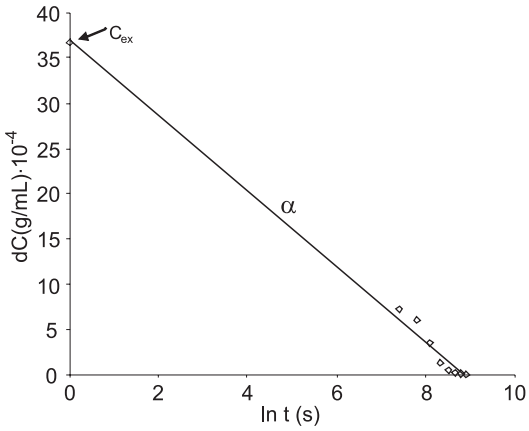


Figure 1. Concentration of DIC released from T1 as function of ln t at V = 0.024 mL/s

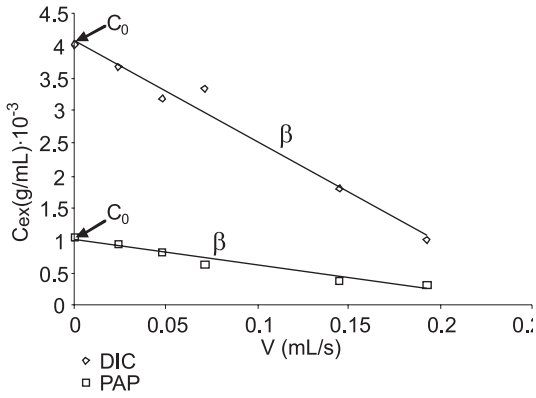
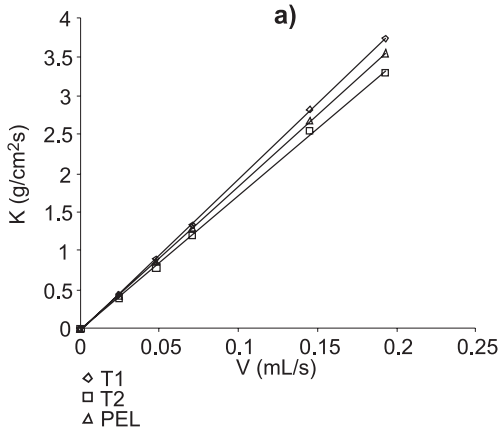


Figure 2. Dependence between the liquid flow rate and the extrapolated concentrations of DIC and PAP released from T1



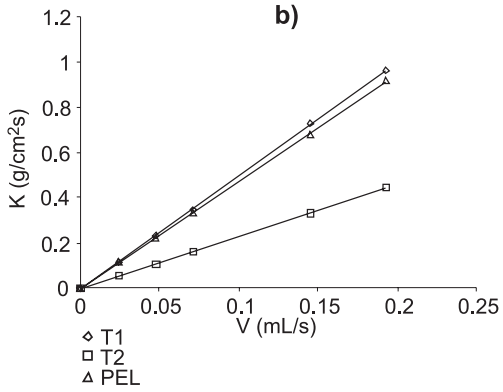


Figure 3. Dependence of K from V for a) DIC and b) PAP

Knowing (S) values, the mass transfer coefficient (K) can be calculated (16) from the equation:

$$K = dm/S \cdot dt \qquad \text{Eq.15}$$

and results are presented in Tables 4–6.

The plots of K = f(V) (Figs. 3 a, b) show that there are linear directly proportional relationships between (K) and the rate of flow of the dissolution medium (V).

The (K) values increase with the increase of the rate of the flow of the liquid and are almost the same for T1 and PEL, and different for T2, so the mass transfer process runs considerably slowly from T2, particularly for PAP.

The diffusion coefficients (D) of DIC and PAP in citric buffer at pH 6.5 were obtained from Othmer equation (25):

$$D_{AB} = 14 \cdot 10^{-5}/[(r^B/r^w) \cdot v_A^{0.6} \cdot \eta_B \ (cm^2/s) \qquad \text{Eq.16}$$

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 atomic volumes (mL/mol), and $[(r_B/r_w) \cdot 1]$ is the quotient of the molar heats of vaporization of the buffer and water.

The calculated values of diffusion coefficients (D) were 5.462×10^{-6} (cm^2/s) for DIC and 4.643×10^{-6} (cm^2/s) for PAP and insignificantly increased from 1.27% to 2.50% for DIC and PAP, respectively, compared to (D) values experimentally determined by improved Graham's method (26).

For evaluation of the mass transfer process on the boundary solid-liquid it is necessary to calculate (h) ratio from the expression (16):

$$h = D/a \qquad \text{Eq. 17}$$

The calculated (h) values are shown in Tables 4–6.

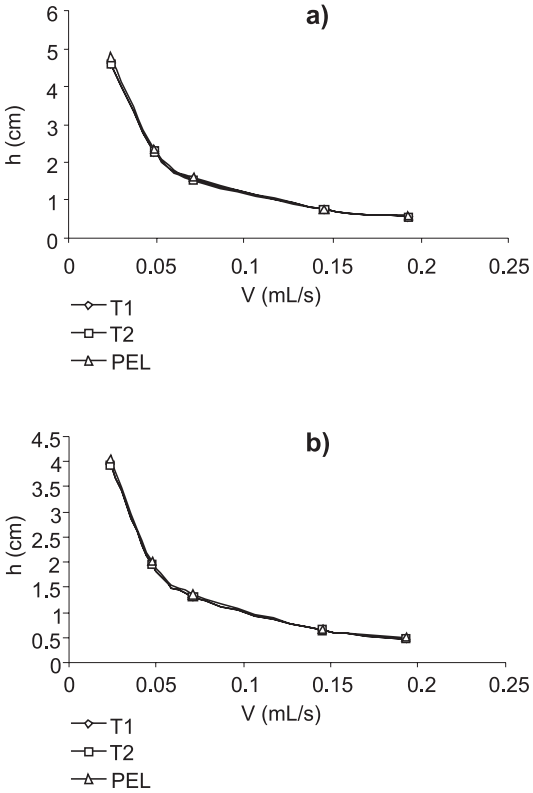


Figure 4. Dependence between h and V for a) DIC and b) PAP

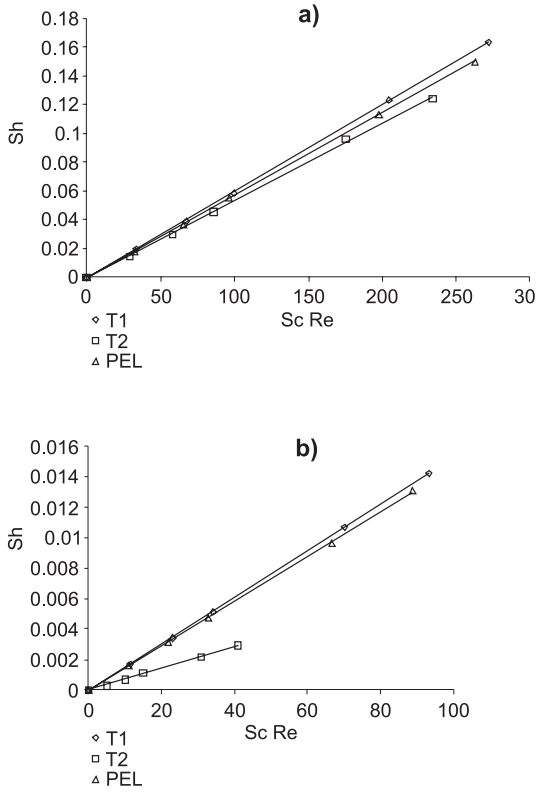


Figure 5. Dependence between Sh and Sc×Re for a) DIC and b) PAP

The relationship between (h) and the rate of flow of the dissolution medium (V) are presented in Figures 4 a, b. As shown there, an increase of (V) values is caused by a decrease of the thickness of boundary of the diffusion layer (h) values for all preparations independently on composition or a size of solid forms.

For calculation, the dimensionless numbers are necessary to obtain the average diameter of single grain (dz) of DIC and PAP in all preparations as shown below.

At the end of the dissolution process, the quantity of the active substances dissolved in the period of time (dt) occupied by the volume (V_{dm}) as expressed by(16):

$$V_{dm} = (V_{mol} \times dm)/m_{mol} \quad \text{Eq. 18}$$

where V_{mol} is the molar volume of substance, m_{mol} is the molar mass of the active substance. The average diameter of grains (dz) is not changed because during dissolution process the big grains became smaller and smaller grains are dissolved (27, 28). Assuming that the shape of the grains was oval, the diameter (dz), the volume (V_{sg}) and the surface area (S_{sg}) of single grain can be expressed as (16):

$$dz = 2 \cdot r \quad \text{Eq. 19}$$

$$V_{sg} = (4/3) \cdot \pi \cdot r^3 \quad \text{Eq. 20}$$

$$S_{sg} = 4 \cdot \pi \cdot r^2 \quad \text{Eq. 21}$$

where r is the radius of grain.

From the system of equations:

$$V_N = N \cdot (4/3) \cdot \pi \cdot r^3 \quad \text{Eq. 22}$$

$$\text{and } S_N = N \cdot 4 \cdot \pi \cdot r^2 \quad \text{Eq .23}$$

where N is the number of grains dissolved in the period of time (dt), it is possible to calculate the average (r) values of the DIC and PAP grains releasing from the preparations. The obtained values of (r), (dz) and (V_{sg}) are presented in Tables 4–6. The average diameters of a single grain od DIC and PAP (dz) are the same for T1 and PEL and a bit smaller for T2, that may be a result of addition of various excipients.

Analysis of S, h, K values cannot accurately explain the mass transfer process, so in this case it is described by the values of dimensionless numbers calculated from Eqs. 3–5 and presented in Tables 4–6. The Sh number describes the changing of the rate of transfer mass on the boundary solid-liquid. The Sh values may change depending on (K) and (dz) of grains of active substances in different prepa-

rations. The Sh values increase with the increase of the flow rate of the liquid, so for T1 they change within the range of 0.0195 to 0.1633 for DIC and 0.0017 to 0.0142 for PAP, and comparing to the Sh values for pellets remain lower by 7.6% in average for DIC and by 7.9% for PAP, and for T2 are lower by 23.8% and 79.5% for DIC and PAP, respectively. These Sh values show that the release runs slower from T2.

The Sc number describes the diffusion process of the active substances to the dissolution medium with suitable density and viscosity, so the values of this number are only different depending on the kind of active substance for DIC and PAP.

The Re number describes the hydrodynamics of the liquid surrounding the solid and its values change with the diameter of DIC and PAP of grains (dz) and the linear rate of liquid (v) calculated from Eq. 7 and given in Table 4. The Re numbers increase with the increase of the flow rate of the liquid for all preparations. For T1, Re changes within the range of 0.0235 to 0.1893 for DIC and 0.0068 to 0.055 for PAP, so for pellets Re decreases on average by 3.4% for DIC and 4.7% for PAP, whereas for T2 decreased by 14% for DIC and 56% for PAP. These dependences are probably caused by the smaller diameter of grains of the active substances at T2 than T1 or PEL and different excipients.

The proportional ratios (φ) showed in Tables 4–6 were calculated from dimensionless equation (Eq. 2). These (φ) ratios are almost the same for T1 and PEL corresponding to DIC and PAP, whereas for T2 increased by 10.9% for DIC and 54.3% for PAP.

As shown (Figs. 5 a, b), the Sh numbers are directly proportional to the products of Sc·Re and the linearity dependences of this change are presented by (φ) ratio.

Despite the active substances, PVP and M, the compositions of T1, PEL and T2 consist of different excipients, so T1 and PEL comprise PS and T2 HPMC, MC and MS. In this case it may be suggested that during the preparation of wet granulation mass the gel structure was formed by PS and derivatives of cellulose as HPMC and MS dissolved in methanolic solution, caused change of grains size of DIC and PAP in the preparations. As a result, a difference in the release of DIC and PAP from tablets and pellets can be observed. However, various profiles of the release can be also caused by different sizes of solid forms, which can be observed with changes of Sh numbers. The apparatus conditions such as the size of the dissolution cell or various flow rates of the dissolution medium can be analyzed based on the Re number. The capacity of diffusion of the active substances into the dissolution medium of suitable physical properties can be observed based on the Sc number. The Re number can be used in hypothetical calculations to determine the hydrodynamics of the liquid surrounding of the dissolution grains both *in vitro* and *in vivo*, assuming that each portion of the released drug is immediately adsorbed *via* dissolution into the circulatory system. This confirms the conditions of the dissolution process that depend directly on the release and absorption of the active substance.

CONCLUSIONS

Presented parameters of the dimensionless equations are the example of analysis of the release process in different rate flow of the dissolution medium with the use of the flow through the cell of the apparatus, from tablets and pellets with different sizes, excipients and comprising two active substances with different solubility. Knowing the parameters of release, the suitable conditions for lasting of the process can be planned as well as the flow rate of the liquid through the cell of the apparatus and predicted the effect of composition of solid dosage form on the release process and absorption of drug. This study shows the possibility of calculation of the parameters of the release of active substances from solid dosage forms comprising two active substances with different solubility using the dimensionless equation.

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Received: 16. 12. 2009