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THE PROCESS OF MASS TRANSFER ON THE SOLID-LIQUID BOUNDARY LAYER DURING THE RELEASE OF DICLOFENAC SODIUM AND PAPAVERINE HYDROCHLORIDE FROM TABLETS IN A PADDLE APPARATUS

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Abstract: The release study of diclofenac sodium (DIC) and papaverine hydrochloride (PAP) from two formulations of the tablets in the paddle apparatus using different rotation speeds to characterize the process of mass transfer on the solid-liquid boundary layer was carried out. The dissolution process of active substances was described by values of mass transfer coefficients, the diffusion boundary layer thickness and dimensionless numbers (*Sh* and *Re*). The values of calculated parameters showed that the release of DIC and PAP from tablets comprising potato starch proceeded faster than from tablets containing HPMC and microcrystalline cellulose. They were obtained by direct dependencies between *Sh* and *Re* in the range from 75 rpm to 125 rpm for both substances from all tablets. The description of the dissolution process with the dimensionless numbers make it possible to plan the drug with the required release profile under given *in vitro* conditions.

Keywords: diclofenac sodium, papaverine hydrochloride, release, mass transfer, dimensionless numbers

One of the most important processes in an oral drug absorption is the dissolution process. The release study of active substances from solid dosage forms is carried out by one of the pharmacopoeial methods using the basket, the paddle and the flow through cell apparatus (1, 2). Dissolution testing is of primary importance for drug formulation and quality control. The ultimate role of dissolution testing is possibility of making the correlation of results obtained from *in vitro* with those from *in vivo* tests. The future of dissolution testing is discussed in terms of new initiatives in the industry such as quality by design, process analytical technology and design of experiments (3, 4).

Studies where the principles underlying the dissolution process are examined can be found in the literature. They concern the phenomenon of drug release in laminar flow in order to understand the effect of hydrodynamic conditions on drug dissolution better and to predict the drug dissolution from a solid dosage form (3, 5-10). A number of studies were conducted to compare the release of drugs between different types of pharmacopoeia apparatuses (6, 11, 12) and the effect of rotational speed of the paddle or basket stirrer on the dissolution profiles of active substances (7, 8, 11, 13, 14).

The data obtained from studies of the tablets using both the basket and the paddle apparatuses at various rotational speeds showed a faster dissolution of a substance using a paddle method and a relation between the amount of the drug released and the rotation speed of a stirrer: the amount of substances increased with the rotation speed. The rate of the dissolution also depended on the tablet surface, their shape, diameter and the area of the paddles used (6). This showed that hydrodynamic conditions, the type of dissolution testing used, and the design of the stirrer had an effect on the dissolution rate, mass transfer rate, and the film thickness underlying the dissolution process (6, 7). What is more, the effects of vibration on the paddle and the basket stirrer during the release study influenced the dissolution profiles (10).

In order to interpret the results obtained from the release study, pharmacopoeial requirements referring to the amount of a drug released in a period of time in percentage are set (1, 2). There are many reports describing the kinetics of the release process from modified and matrix tablets using

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mathematical models (15-18).The release kinetics of drugs is usually evaluated by plotting in various kinetic models, for example zero order or first order (16, 17). Based on the proposed kinetic models it is possible to determine the release rate constant, but it is not entirely possible to describe the phenomenon of mass transfer on the solid – liquid boundary layer during the release process. More precisely, the dissolution process of a solid substance in a dissolution medium is described by Nernst-Brunner equation, which takes into account the diffusion coefficient of a solid substance turning into liquid, the size of the solid surface and the thickness of the boundary layer (16). The effective hydrodynamic diffusion layer thickness of a drug particle dissolved into an agitated fluid is of great importance for oral absorption simulation (19). The process of mass transfer on the solid-liquid boundary layer during the dissolution of a solid was also described by dimensionless numbers (*Sh*, *Re*, *Sc*) (19-23). Sherwood number (*Sh*) is directly proportional to the mass transfer coefficient and it is characterized by the ability of a solid to diffuse into the liquid. Schmidt number (*Sc*) defines the diffusion of a dissolving solid into the liquid depending on the viscosity and density of the dissolution medium. Reynolds number (*Re*) describes hydrodynamics of the liquid surrounding of a dissolving solid (19-23). The *Re* is also used to determine the type of flow in apparatuses during the release process: laminar or turbulent (24-26). There were reports describing the use of *Re* numbers to calculate the theoretical size of the microparticles obtained by the emulsion technique (27), to determine rheological characteristics of fluids (28, 29) and to model the supercritical fluid extraction (30).

The *Re* and *Sh* numbers were used to describe the release process carried out in the paddle and flow apparatuses (7). Results showed that hydrodynamic conditions and the type of dissolution testing apparatus had an effect on dissolution and mass transfer rates as well as on thickness of the diffusion layer. The mass transfer coefficient is calculated to understand the role of an external hydrodynamic condition on mass transfer rate better (6). The expression of mass transfer coefficient is derived from the first principles for the turbulent non-Newtonian fluid flow in the membrane modules (28).

The aim of this study was to investigate the release process of diclofenac sodium and papaverine hydrochloride from composed tablets with different formulations of excipients in the paddle apparatus using different rotation speeds and to describe the mass transfer on the solid–liquid boundary during the dissolution process by the dimensionless numbers for a better understanding of the effect of hydrodynamic condition on drug dissolution, in order to predict drug dissolution from a tablet.

EXPERIMENTAL

Materials and Reagents

Diclofenac sodium (DIC) was produced by Caesar and Loretz, GmbH, Hilden Germany, papaverine hydrochloride (PAP) was purchased from Galfarm PPH, Cefarm Lublin, Poland, polyvinylpyrrolidone K 22 (PVP 22), mannitol (M), potato starch (PS), microcrystalline cellulose (MC) were the products of Merck, Germany, polyvinylpyrrolidone K 10 (PVP 10), β-lactose (lactose) were purchased from Sigma Aldrich, hydroxypropylmethylcellulose (HPMC) was purchased from Fluka. Pregelatinized starch (GPharmGel) produced by Cargill Benelux, microcrystalline cellulose (Avicel PH102, Avicel) and croscarmellose sodium (AcDiSol) produced by FMC BioPolymer Belgium were obtained as gift from IMCD, Warsaw, Poland. Colloidal silicon dioxide 200 (Aerosil) produced by Evonic Germany was obtained by gift from Chempol, Warsaw, Poland. Magnesium stearate (StMg) was purchased from POCh Gliwice, Poland. All the reagents and chemicals used were of analytical grade.

Characterization of tablets

The prepared and patented tablets contained following ingredients (31):

T1: DIC 50 mg, PAP 20 mg, PVP (K22), M, S to 300 mg of weight.

T2: DIC 50 mg, PAP 20 mg, PVP (K22), M, HPMC, CellM, StMg to 300 mg of weight.

Tablets were obtained by direct compression of granules which were previously prepared by a wet granulation method.

Powders of components were sieved through a 0.710 mm mesh screen. Then, the powders of each series of tablets were mixed manually, except for magnesium stearate. An alcoholic solution of PVP was added to the powder mixture. The obtained wet mass was granulated using a rotary granulator (Erweka, Germany) by passing it through a 1.0 mm mesh screen. Granules were dried in a hot air oven (Memmert INB-500) at a temperature of 40^{o}C for 1 h. The dried granules (moisture 3-5%) were passed through a 1.00 mm mesh screen. At the end, magnesium stearate was added and mixed manually. The tablets were obtained in a press tableting machine (Erweka, Germany) with 9 mm concave punches.

Physical properties

Physical properties of the prepared tablets were checked out in accordance with the pharmacopoeial requirements (1, 2). *Weight uniformity test* of the tablets was conducted using a weighing balance (Ohaus AV 513C, USA). *Tablets diameter and thickness* were measured using a Vernier Caliper (Digital Caliper 0-150 mm, Comparator). *Hardness* of the tablets was determined using an Erweka tablet hardness tester (Erweka, Germany). *Friability test* of the tablets was conducted using an Erweka friabilator (Erweka, Germany). *Disintegration time of the tablets* was measured using an USP Apparatus (Erweka, Germany).

Drug content analysis

Ten tablets from each series were crushed together and weighed exactly (300 mg). The powder sample was transferred into a 50 mL volumetric flask containing 30 mL of methanol. The flask was shaken for 5 min and the content was diluted with methanol to volume. The content of the flask was filtered using the Sartorius filter of 0.22 µm. The obtained solution was mixed with citrate buffer at pH 6.5 in ratio 1 : 1, v/v. The content of DIC and PAP was determined using HPLC according to the published method (32). The HPLC system consisted of a series 200 HPLC pump, a series 200 autosampler equipped with a 100 µL loop, a series 200 UV/VIS detector, a series 200 vacuum degasser and Chromatography Interface 600 series Link, all purchased from Perkin Elmer, USA. The column was a Zorbax SB-C, 150 mm × 4.6 mm, 5 µm (Agilent, USA).The detection wavelength was at 278 nm. 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. The UV signals were monitored and peaks were integrated using the software version 6.2.0.0.0:B27.

***In vitro* release study**

The release study of DIC and PAP from prepared tablets was carried out using a paddle apparatus (Erweka, Germany) (1, 2). As a dissolution medium 900 mL of citrate buffer at pH 6.5 at 37 ± 0.5°C was used. One tablet was set in each of six vessels of the apparatus and the paddle was rotated at different speeds: 25, 50, 75, 100, 125, 150 and 175 rpm. The release tests were conducted for 60 min or 120 min for T1 and T2, respectively. The samples (2 mL) were withdrawn with 5 or 10 min intervals for T1 and T2, respectively. For each sample, an equivalent volume of citrate buffer at pH 6.5 (2 mL) was added to the vessels. The samples were filtered by Sartorius filter of 0.22 µm. Each sample was mixed with methanol in ratio 1 : 1, v/v. The obtained solutions were analyzed by HPLC method described previously (32).

Statistical analysis was carried out using SAS 9.1.3 (SAS Institute, Cary, NC, USA). The data obtained were subjected to statistical analysis using one-way ANOVA and a "*p*" value of < 0.05 was considered as statistically significant.

Parameters of mass transfer process and values of dimensionless numbers

The dimensionless numbers (*Sh, Sc, Re*) were calculated from the following expressions (14-18):

$$Sh = K \cdot dz / D \cdot \rho \quad \text{Eq. 1}$$

$$Sc = \mu / D \cdot \rho \quad \text{Eq. 2}$$

$$Re = \rho \cdot dz \cdot v / \mu \quad \text{Eq. 3}$$

where *Sh* is Sherwood number, *Sc* is Schmidt number, *Re* is Reynolds number, *K* (g/cm²·s) is the mass transfer coefficient, *dz* (cm) is the diameter of the grain, *D* (cm²/s) is the diffusion coefficient of active substance, ρ (g/cm³) is the density of the dissolution medium, μ (g/cm·s) is the viscosity of the dissolution medium and v (cm/s) is the linear rate of flow liquid.

Characteristics of citrate buffer solution at pH 6.5 at 37°C: density (ρ) = 1.0129 (g/cm³) and viscosity $(\mu) = 7.958 \cdot 10^{-3}$ (g/cm·s).

The diffusion coefficients *(D)* of DIC and PAP in citric buffer at pH 6.5 were obtained from Othmer equation (20, 23):

$$D = 14 \cdot 10^{-5} / [\eta_w^{1.1} (r_B / r_w) \cdot v_4^{0.6} \cdot \eta_B] \ (\text{cm}^2/\text{s}) \quad \text{Eq. 4}$$

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 $[(r_B/r_w) \approx 1]$ is the quotient of the molar heats of vaporization of the buffer and water.

In order to calculate *Sh* and *Re* numbers, the values of average diameter of a single grain *(dz)* of DIC and PAP are necessary. Similarly, as published in the previous report (23), it is assumed that at the end of the dissolution process the quantity of the active substances *dm* dissolved in the period of time *dt* (s) occupied by the volume V_{dm} (cm³) as expressed:

$$V_{dm} = (V_{mol} \cdot dm) / m_{mol} \quad \text{Eq. 5}$$

where V_{mol} (cm³/mol) is the molar volume of the substance, m_{mol} (g/mol) is the molar mass of the active substance. The average diameter of grains *(dz)* is not changed because during the dissolution process the big grains become smaller and smaller grains are dissolved (33, 34). Having assumed that the shape of

the grains was oval, the diameter *(dz)*, the volume V_{sg} (cm^3) and the surface area S_{sg} (cm^2) of single grain can be expressed as:

$$dz = 2 \cdot r_g \quad \text{Eq. 6}$$

$$V_{sg} = (4/3) \cdot \Pi \cdot r_g^3 \quad \text{Eq. 7}$$

$$S_{sg} = 4 \cdot \Pi \cdot r_g^2 \quad \text{Eq. 8}$$

where r_g (cm) is the radius of the grain.

From the system of equations:

$$V_N = N \cdot (4/3) \cdot \Pi \cdot r_g^3 \quad \text{Eq. 9}$$

$$S_N = N \cdot 4 \cdot \Pi \cdot r_g^2 \quad \text{Eq. 10}$$

where N is the number of grains dissolved in the period of time (*dt*) it is possible to calculate the average (r_g) values of the DIC and PAP grains released from the tablets.

The linear rate of flow liquid (*í*) in the paddle apparatus was calculated from the equation:

$$\nu = rpm \cdot 2\Pi \cdot r \quad \text{Eq. 11}$$

where *rpm* is the rotation speed of the paddle stirrer, *r* (cm) is a radius of the paddle.

The mass transfer coefficient *(K)* was calculated from the expression:

$$K = dm/S \cdot dt \quad \text{Eq. 12}$$

where *dm* (g) is the amount of the released substance at intervals *dt* (s); *S* (cm^2) is the value representing the change in the surface area size of the of dissolving grains of DIC and PAP during the release process at different speeds of the rotation paddle. The (*S*) value was calculated from the Nernst-Brunner equation (16):

$$dC/dt = [D \cdot S/V \cdot h] \cdot (C_s - C_t) \quad \text{Eq. 13}$$

where *dC* (g/mL) is the concentration of the active substance in the dissolution medium after time dt (s), *V* (mL) is the volume of the dissolution medium, *h* (cm) is the thickness of the boundary layer, C_s (g/mL) is the concentration of saturated solution on the boundary diffusion layer.

The thickness of the boundary layer (*h*) was calculated from the equation (23):

$$h = D/\{(C_s - dC_{t1})/(C_s - dC_{t2})]/dt\} \quad \text{Eq. 14}$$

where dC_{t1} and dC_{t2} (g/mL) are the concentrations of the active substance in the dissolution medium in the period of time *dt* (s).

RRSULTS AND DISCUSSION

Physical properties

Physical properties of the obtained tablets (T1, T2) and the content of the active substances were in accordance with pharmacopoeial specifications (1, 2). An average weight (mg, SD) amounts to 300.54 ± 2.45 for T1 and 298.76 ± 2.35 for T2 (= 5%), a hardness ratio (kG/mm^2, SD) 0.105 ± 0.01 for T1 and 0.103 ± 0.02 for T2 (= 0.1), the disintegration time (min, SD) 7 ± 2.5 for T1 and 11 ± 3.7 for T2 (= 15 min), friability (%) 0.09 and 0.15 for T1 and T2 (= 1%), respectively, the content (%, SD) of DIC in T1 99.08 ± 1.17 and PAP 100.05 ± 1.76 and in T2 DIC 97.68 ± 2.51 and PAP 93.75 ± 2.43 (= 10%).

The release results

According to pharmacopoeia recommendations, interpretation of the release results is carried out based on the quantity of the active substance dissolved in a specified time which is expressed as a percentage of the declared content. Citrate buffer at pH 6.5 at 37 ± 0.5°C was used as a dissolution medium because previous tests showed that DIC and PAP were better dissolved in citrate buffer at pH 6.5 comparing with phosphate buffer at pH 6.8 (23).

Data in Figure 1 show that over 80% of DIC is released from tablets T1 depending on the rotation speed of a paddle at 50-175 rpm within 25 min to 15 min. At the lowest speed of 25 rpm, 76.89% DIC was released during a 60-min long test. The release of PAP was longer, so at 50 rpm 80% of PAP was released after 60 min, whereas at speeds of 75-175 rpm within 25-10 min, but at 25 rpm only 47.62% of PAP was released within the test time (60 min).

Analyzing the release results of the active substances from T2, it was noticed that the dissolution process from T2 for both substances was longer comparing to T1. At the rotation speed of 50-175 rpm over 80% DIC was released within 60-20 min. and PAP up to 70-20 min. At the lowest speed of 25 rpm within 120 min only 62.43% and 47.6% DIC and PAP were released, respectively. From the above results, it is clear that the release of both active substances increases with the agitation speed of the fluid in the paddle apparatus. A similar relation was observed by Saleh et al. (35), Wu et al. (6), Kincl et al. (11) and Mourão et al. (14) during the release study of active substances from the tablets.

Release process parameters expressed in dimensionless numbers

The values of the grain surface areas of the active substances involved in the release process (*S*), the mass transfer coefficients (*K*), the thickness of the diffusion boundary layer (*h*) and the dimensionless numbers were calculated in order to understand the process of mass transfer on the solid-liquid border during the release test of drug substances in a paddle apparatus at different agitation speeds.

Having analyzed the changes to the surface of DIC and PAP grains during the release process presented in Figure 2, it was observed that these surface areas were dynamically changed in the first minutes after turning on a paddle stirrer. After 5 min, the

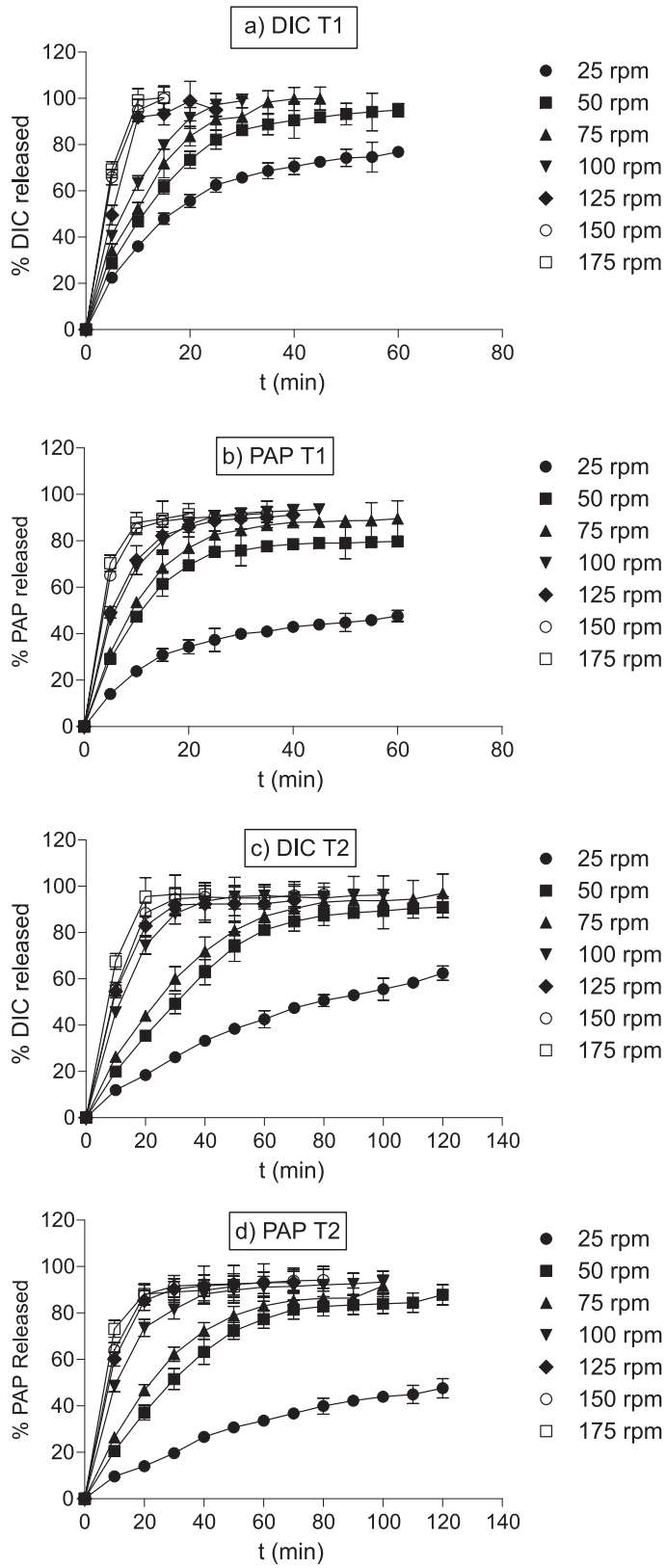

Figure 1. Mean dissolution profiles of the active substances (mean values, n = 6) in a paddle apparatus at different rotation speeds a) DIC from T1, b) PAP from T1, c) DIC from T2, d) PAP from T2

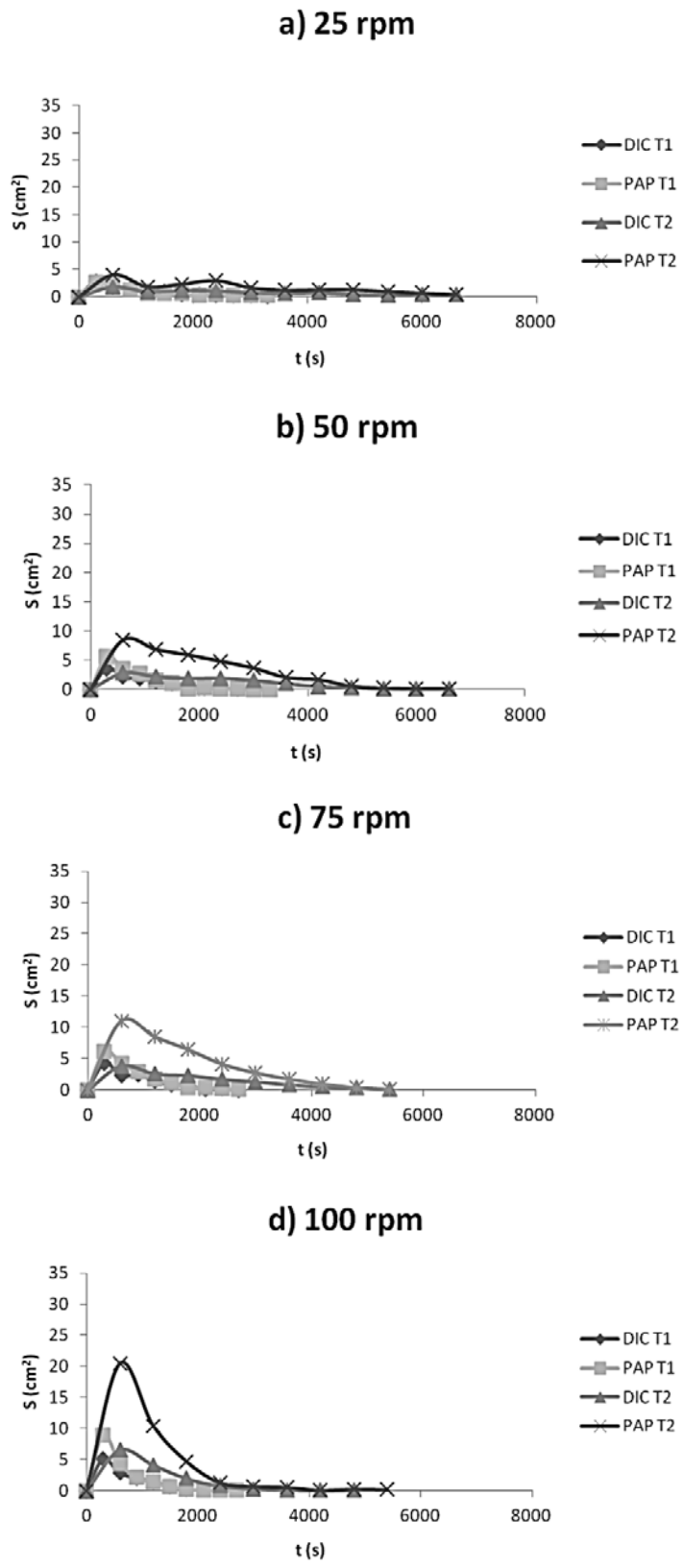

Figure 2. The change in the surface area size of the of dissolving grains of DIC and PAP during the release process at different speeds of the rotation paddle: a) 25 rpm, b) 50 rpm, c) 75 rpm, d) 100 rpm, e) 125 rpm, f) 150 rpm, g) 175 rpm

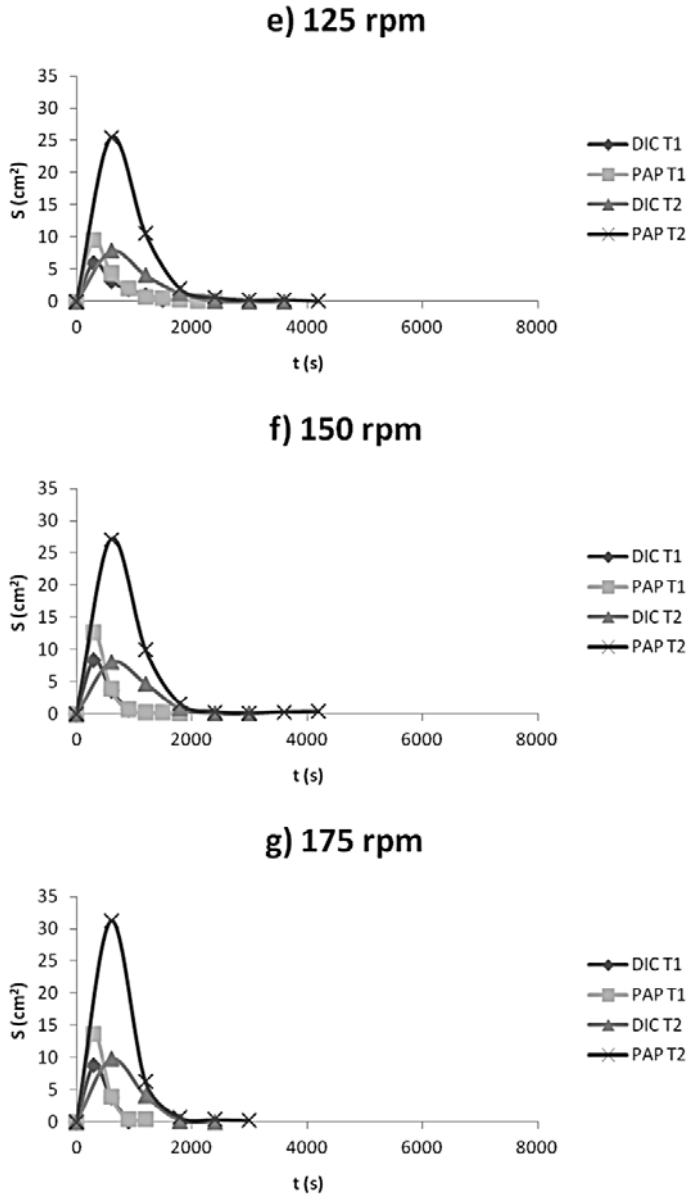

Figure 2. Continued

sizes of the surface areas of dissolving DIC grains released from T1 were 2.8 cm^2 and 8.7 cm^2, for PAP 2.7 cm^2 and 13.7 cm^2 at rotation speed of 25 and 175 rpm, respectively. However, it was observed that the initial surface areas of DIC grains after 5 min at 50 rpm had lower value than those of PAP grains and they amounted to 3.6 cm^2 (DIC) and 5.6 cm^2 (PAP), 75 rpm 4.3 cm^2 (DIC) and 6.1 cm^2 (PAP), 100 rpm 5.1 cm^2 (DIC) and 8.9 cm^2 (PAP), 125 rpm 6.2 cm^2 (DIC) and 9.1 cm^2 (PAP), 150 rpm 8.3 cm^2 (DIC) and 12.6 cm^2 (PAP). Greater the PAP surface areas than the DIC surface areas (with an exception at 25 rpm) are probably due to a lower than DIC solubility of PAP in citrate buffer at pH 6.5. It can be assumed that the grains of DIC dissolved rapidly after released from tablet T1, creating a smaller surface dissolution, and PAP remains in the diffusion layer for a longer period of time.

During the release test from T2, the surface areas of dissolving PAP grains were approximately 3 times larger than the ones of the DIC grains. Thus, after 10 min at 50 rpm the surface areas were equal to 2.9 cm^2 (DIC) and 8.5 cm^2 (PAP), at 175 rpm to 9.8 cm^2 (DIC) and 31.2 cm^2 (PAP), which is related

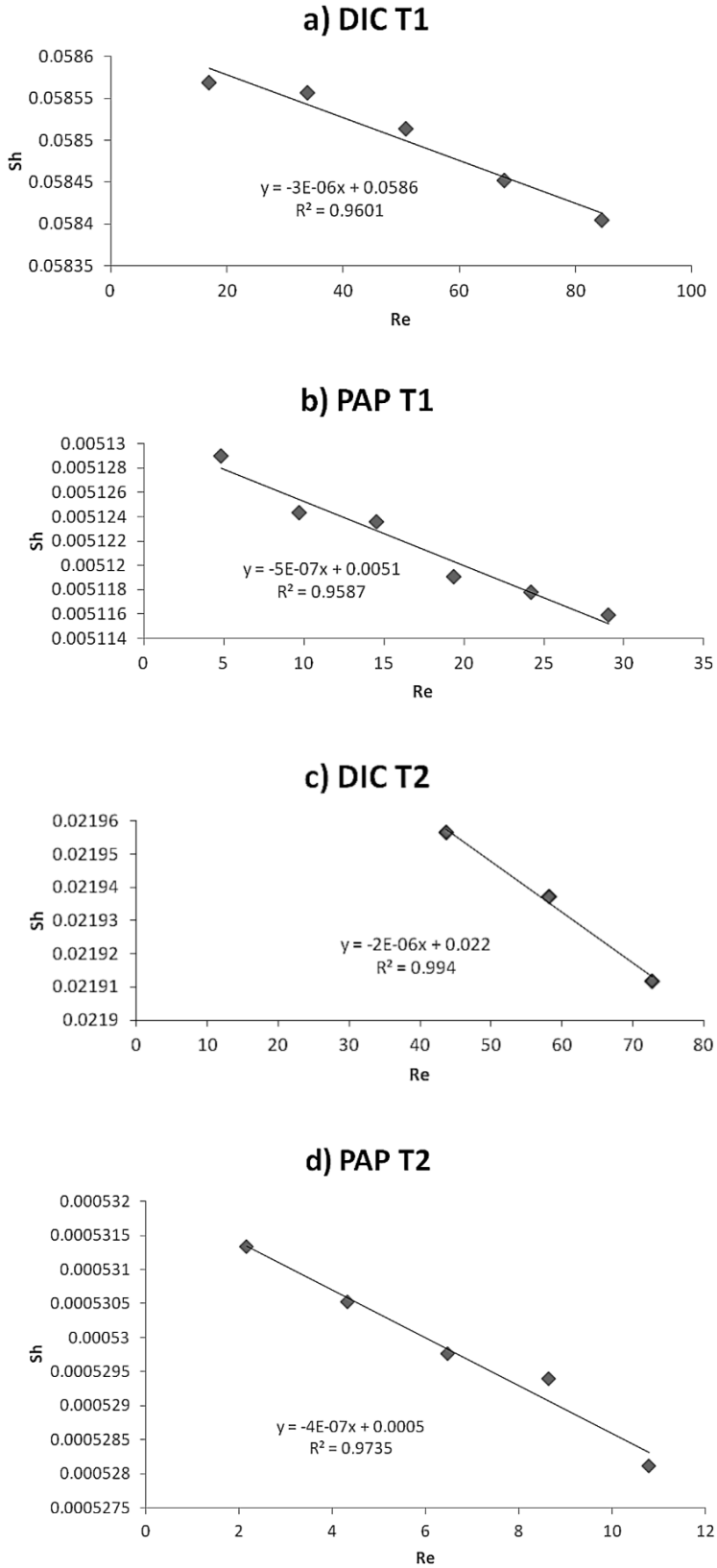

Figure 3. The dependence between *Sh* and *Re* for a) DIC from T1, b) PAP from T1, c) DIC from T2 and d) PAP from T2

Table 1. The parameters describing the release process of DIC and PAP from tablets in a paddle apparatus

Parameters		T1		T2	
		DIC	PAP	DIC	PAP
D (cm²/s)		$5.462 \cdot 10^{-6}$	$4.643 \cdot 10^{-6}$	$5.462 \cdot 10^{-6}$	$4.643 \cdot 10^{-6}$
dz (cm)		0.0242	$6.92 \cdot 10^{-3}$	0.0208	$3.086 \cdot 10^{-3}$
K (g/cm²·s) (± SD, %)		$1.3351 \cdot 10^{-5}$ (± 0.27)	$3.4747 \cdot 10^{-6}$ (± 0.5)	$5.8309 \cdot 10^{-6}$ (± 0.16)	$8.0681 \cdot 10^{-7}$ (± 0.26)
h (cm) (± SD, %)		$1.6409 \cdot 10^{-3}$ (± 0.26) [3]	$1.3938 \cdot 10^{-}$ (± 0.15)	$3.2797 \cdot 10^{-3}$ (± 0.15)	$2.7896 \cdot 10^{-3}$ (± 0.09)
Sh at rpm	25	0.058569	$5.1290 \cdot 10^{-3}$	0.021940	$5.3134 \cdot 10^{-4}$
	50	0.058556	$5.1243 \cdot 10^{-3}$	0.021945	$5.3053 \cdot 10^{-4}$
	75	0.058514	$5.1236 \cdot 10^{-3}$	0.021957	$5.2976 \cdot 10^{-4}$
	100	0.058452	$5.1191 \cdot 10^{-3}$	0.021937	$5.2940 \cdot 10^{-4}$
	125	0.058404	$5.1178 \cdot 10^{-3}$	0.021912	$5.2812 \cdot 10^{-4}$
	150	0.058170	$5.1159 \cdot 10^{-3}$	0.021917	$5.2881 \cdot 10^{-4}$
	175	0.058122	$4.4917 \cdot 10^{-3}$	0.021848	$5.2691 \cdot 10^{-4}$
Re at rpm	25	16.925	4.84	14.548	2.158
	50	33.851	9.68	29.095	4.317
	75	50.777	14.52	43.643	6.475
	100	67.702	19.359	58.19	8.633
	125	84.616	24.196	72.727	10.79
	150	101.553	29.039	87.286	12.95
	175	118.451	33.871	101.809	15.105
Sc		1438.42	1692.15	1438.42	1692.15

to the influence of T2 excipients on the dissolution of DIC and PAP. Differences in the surface area size of the dissolving grains of the active substances may have been caused by the change in the rate of tablet disintegration and by the modification of solubility of the substances caused by the presence of various excipients of the tablets. Changes of the surface area size values of the dissolving grains indicated that the excipients forming T2 caused a slow release of both DIC and PAP.

As shown in Table 1, the values of mass transfer coefficients (K) for DIC and PAP vary depending on the composition of tablets, but they do not depend on different rates of dissolution medium mixing (± 0.5%).Values of (K) for DIC were four and seven times higher than for PAP in T1 and T2, respectively, which suggests greater solubility of DIC from both T1 and T2 tablets. Values of (K) for the active substances included in T1 were higher both for DIC (2 times) and PAP (4 times) than in T2, indicating that T2 excipients caused a decrease in dissolution of both substances.

The values of diffusion boundary layer thickness (h) are slightly different for DIC and PAP in bothT1 and T2. However, the values of (h) are twice higher in T2 than in T1 for both active substances, which confirmed that the excipients forming T2 caused a decrease in the release of DIC and PAP. With an increasing rotation speed of the paddle, (h) values slightly decreased.

The release tests provided by Wu et al. (6) using theophylline tablets showed an increased mass transfer rate and decreased boundary diffusion thickness with an increasing basket rotation speed. The values tested at the same speed in a paddle apparatus presented higher mass transfer coefficient and lower boundary diffusion thickness than in the basket apparatus.

In our study, where the numbers of *Sh* for tablets T1 and T2 were compared, it can be observed that for DIC they were 2.7 times higher and for PAP 9.7 times higher in T1 than in T2. Having compared the average values *Sh* in the same formulation (T1), it was observed that the number *Sh* was 11.4 times higher for DIC compared with PAP and 41.5 times higher for DIC in T2 tablets. Higher values *Sh* indicated that the rate of mass transfer at the solid-liquid border was greater, which indicates a faster release of both substances from T1 and a faster dissolution of DIC than of PAP from both tablets.

As presented in the previously published study (23) carried out in the flow-through apparatus, the

Sh values for DIC were 24% and for PAP 80% lower in T2 comparing with T1. The *Sh* values, which represent the changing mass transfer rate of the solid-liquid boundary obtained from both apparatuses release results, were higher for DIC than PAP from T1 and T2.

The values of *Sc* number depended on the diffusion coefficient of the therapeutic substance in the soluble liquid, as well as its density and viscosity (14-18). That is why the values were different for each active substance (DIC and PAP) and independent of the apparatus used for the release examination.

The numbers *Re* were higher by 14% for DIC and by 55% for PAP in T1 compared with T2. However, the numbers *Re* were 3.5 and 7 times larger for DIC than PAP in T1 and T2, respectively. The values of numbers *Re* confirmed that the release of the active substances was faster from T1 than T2 and the release of DIC compared to PAP was faster from both formulations T1 and T2.

The values of *Re* number, representing fluid hydrodynamics for solid, increased together with an increase of both the mixing rate in the paddle apparatus and fluid flow rate in the flow-through apparatus (23) for T1 and T2. The values of *Re* numbers were higher for the flow-through as well as for the paddle apparatus in T1 tablets at approximately 14% for DIC and 57% for PAP in comparison to T2. This confirmed that the release of DIC occurs faster than that of PAP. The numbers *Re* were 3.5 times higher for DIC in T1, and 7 times higher in T2 than for PAP in both apparatuses. This fact may mean that various auxiliary substances in the formulations may influence the process of active substances release.

The *Re* numbers were also calculated from Eq. 3 without taking into account a grain diameter of active substances (*dz*), to represent the fluid hydrodynamics of the liquid at different agitation speeds in a paddle apparatus: 699.4 (25 rpm), 1398.81 (50 rpm), 2098.21 (75 rpm), 2797.61 (100 rpm), 3496.51 (125 rpm), 4196.42 (150 rpm) and 4894.68 (175 rpm). These *Re* numbers, calculated without taking into account the *(dz)* of DIC and PAP, describe the type of fluid flow in the release apparatus. Laminar flow of the liquid occurs at values of *Re* of less than or equal to 2300, but above 2300 a partially turbulent flow occurs (19). From this follows that the laminar flow, which is desirable for the release studies, occurred in a paddle apparatus at mixing rates 25, 50 and 75 rpm, whereas at higher speeds of 100, 125, 150 and 175 rpm a partially turbulent flow occurred. McCarthy et al. (36) showed that there are significant differences in the hydrodynamics of liquid flow in a paddle apparatus at different stirring speeds from 25 to 150 rpm. These researchers observed that the approximate time required to achieve a complete mixing varied between 2 to 5 s at 150 rpm and 40 to 60 s at 25 rpm.

Wu et al. (7), based on the results of the release study of two active substances from tablets, established an equation to predict drug dissolution from conventional tablets using the relationship of the values ofdimensionless numbers *Sh* and *Re*) In their study, it was demonstrated that hydrodynamic conditions and the type of the dissolution apparatus used have an effect on the dissolution rate, mass transfer rate and film thickness underlying dissolution process, and that the drug dissolution at a given time increases with the flow rate of the dissolution medium. The hydrodynamic conditions did not affect the drug dissolution from HPMC controlled release tablets indicating that the drug dissolution is controlled by the matrix.

In our study, as shown in Figure 3, we obtained direct dependences between *Sh* and *Re* numbers for DIC and PAP in both tablets at rotation speeds in the range from 25 rpm to 125 rpm (and even to 150 rpm for PAP in T1), except for DIC from T2 (direct dependences 75-125 rpm). Tablets T2 contained 10% HPMC as an excipient and may be the addition caused interruption in the dissolution process of DIC. Generally, we obtained direct dependences between *Sh* and *Re* in the range from 75 rpm and 125 rpm for both substances from all tablets.

The description of the dissolution process by the dimensionless numbers has advantages because it presents the mass transfer coefficient and relevant parameters of the dissolution medium such as density and viscosity, diffusion coefficient and the rotation speed of the paddle in the apparatus. Thus, it is possible to plan the drug with a required release profile under given *in vitro* conditions.

CONCLUSION

The release of diclofenac sodium and papaverine hydrochloride from tablets varied depending on the excipients in tablets. Generally, two active substances were released faster from tablets comprising potato starch than from tablets containing HPMC and microcrystalline cellulose. The mass transfer process on the solid-liquid boundary was characterized by values of mass transfer coefficients, the diffusion boundary layer thickness and dimensionless numbers (*Sh* and *Re*). Having known the parameters of release, the suitable conditions for lasting of the process can be planned, as well as the paddle rota-

tion speed in the apparatus and the effect of composition of solid dosage form on the released process in given dissolution medium can be predicted. The mass transfer coefficient and the dimensionless numbers can be used to anticipate the quantity of the dissolution active substance over time under the set or scheduled hydrodynamic conditions.

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