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THE EFFECT OF EXCIPIENTS ON THE RELEASE KINETICS OF DICLOFENAC SODIUM AND PAPAVERINE HYDROCHLORIDE FROM COMPOSED TABLETS

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Abstract: For increased analgesic effect, new composed tablets containing diclofenac sodium (DIC) with an addition of papaverine hydrochloride (PAP) were prepared to investigate the mechanism of release of the active substances from tablets with different excipients in eight different formulations. To detect the possible interactions between active substances and excipients differential scanning calorimetry (DSC) was used. A shift of the melting point and enthalpy values of the physical mixtures of tablets components suggested a kind of interaction between components in certain formulations, however, the tabletting process was not disturbed in any of them. Kinetics of drug release from formulations was estimated by zero order, first order and Higuchi and Korsmeyer–Peppas models using results of dissolution of DIC and PAP from tablets. The study revealed that the mechanism of release of active substances was dependent on the excipients contained in tablets and the best fitted kinetics models were obtained for formulations with potentially prolonged release of DIC and PAP.

Keywords: diclofenac sodium, papaverine hydrochloride, tablets excipients, dissolution kinetics, differential scanning calorimetry

Diclofenac sodium {sodium 2-[(2,6-dichlorophenyl)amino]phenylacetate, DIC} is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. It is taken to reduce inflammation and as an analgesic reducing pain in the long-term treatment of degenerative diseases such as rheumatoid arthritis and osteoarthritis (1, 2). In order to increase the therapeutic effect or decrease the adverse effects of diclofenac sodium, the composed pharmaceutical dosage forms were obtained (3–5). Papaverine hydrochloride (PAP) was assessed as a spasmolytic agent, for the treatment of renal colic as a single and in combination with sodium diclofenac (6). For increased analgesic effect, composed tablets containing diclofenac sodium with addition of papaverine hydrochloride were prepared and patented (7).

The successful formulation of a stable and effective solid dosage form depends on the selection of the excipients. Because the drug has intimate contact with the excipients, assessment of possible interactions between the active substance and different excipients is an important part of the development of dosage forms (8). Physical analysis, such as differential scanning calorimetry (DSC) was used to detect possible drug : carrier interactions (9). Incompatibilities of components can be deduced from appearance, shift or disappearance of peaks and/or variations in the corresponding enthalpy values obtained from DSC traces (10). It is of importance to detect any possible interactions, since it has been shown that certain interactions can change the bioavailability or stability of the product (11).

Thermodynamic behavior, including the solubility of a solid in a liquid, plays an important role in drug design as well as in the design and optimization of production processes (12). However, solubilities of diclofenac sodium and papaverine hydrochloride are different and depend on pH of the dissolution medium. Diclofenac sodium is almost insoluble in acidic pH of the stomach and soluble in phosphate buffer at pH 6.8 (13, 14). Solubility of papaverine

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hydrochloride increases proportionally to the decrease of pH of the medium (15, 16).

In vitro dissolution is one of the most important elements of the drug development process. The quantity of the active substance dissolved in a specified time is expressed as a percentage of the content stated on the label. Several models may be used to describe dissolution profiles where f (t) is a function of t time (t) that is related to the amount of drug dissolved from a dosage form. The quantitative interpretation of the values generated in dissolution studies is facilitated by the use of generic equations. The equations translate dissolution curves mathematically as a function of certain parameters related to the dosage forms under investigation. In some cases, the equations can be deduced by a theoretical analysis of the processes to which the dosage form is subjected. A water-soluble drug incorporated into a hydrophilic matrix is released mainly by a diffusion-controlled process, whereas for a poorly water-soluble compound, the principal mechanism of release is a function of erosion of the matrix that carries the drug (17).

The use of mathematical modeling turns out to be very useful as this approach enables to predict the release kinetics before the release systems are realized. More often, it allows the measurement of some important physical parameters, such as the drug diffusion coefficient and resorting to model fitting on experimental release data. Thus, mathematical modeling, whose development requires the comprehension of all the phenomena affecting drug release kinetics, has a very important value in the process optimization of such formulation (18, 19).

The aim of the study was to investigate the mechanism of release of diclofenac sodium and papaverine hydrochloride from tablets with different excipients using different formulations. To detect the possible interactions drug : drug or drugs : excipients the differential scanning calorimetry (DSC) was used.

EXPRIMENTAL

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) and 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 gifts from IMCD, Warszawa, Poland. Colloidal silicon dioxide 200 (Aerosil) produced by Evonic, Germany was obtained as a gift from Chempol, Warszawa, Poland. Magnesium stearate (StMg) was purchased from POCh, Gliwice,

Table 1. Different tablet compositions.

Name of component	Quantity (%) per tablet of 300 mg weight							
	T1	T2	T3	T4	T5	T6	T7	T8
Diclofenac sodium	16.67	16.67	16.67	16.67	16.67	16.67	16.67	16.67
Papaverine hydrochloride	6.67	6.67	6.67	6.67	6.67	6.67	6.67	6.67
PVP 10	5	5	5	5	5	5	-	-
PVP 22	-	-	-	-	-	-	23.3	23.3
Avicel PH102	20	-	33.3	-	60.2	33.3	-	-
MC	-	-	-	-	-	-	-	5
HPMC	-	-	-	-	-	-	-	10
Lactose	40.7	45.7	36.8	50.2	-	21.8	-	-
Mannitol	-	-	-	-	-	-	23.3	37.3
Potato starch	-	-	-	-	-	-	30	-
CPharmGel	-	20	-	20	-	10	-	-
Aerosil	-	-	0.5	0.5	0.5	0.5	-	-
AcDiSol	10	5	-	-	10	5	-	-
Magnesium stearate	1	1	1	1	1	1	-	1

Table 2. Physical properties of tablets prepared.

Test	Results							
	T1	T2	T3	T4	T5	T6	T7	T8
Weight (mg) SD	299.33 ± 1.21	292.83 ± 1.43	304.74 ± 3.02	302.43 ± 1.69	300.97 ± 2.64	299.71 ± 2.97	300.54 ± 2.45	298.76 ± 2.35
Thickness (mm) SD	4.28 ± 0.01	3.89 ± 0.02	3.97 ± 0.02	3.78 ± 0.01	6.11 ± 0.03	4.22 ± 0.01	4.02 ± 0.02	4.15 ± 0.03
Disintegration time (min) SD	8 ± 1.7	28 ± 2.2	31 ± 4.2	33 ± 2.7	0.6 ± 0.1	18 ± 3.5	7 ± 2.5	11 ± 3.7
Hardness (kG/mm^2), SD	0.09 ± 0.03	0.085 ± 0.02	0.105 ± 0.02	0.102 ± 0.04	0.004 ± 0.001	0.095 ± 0.02	0.105 ± 0.01	0.103 ± 0.02
Friability (%)	0.044	0.21	0.11	0.13	0.14	0.06	0.09	0.15
Drug content (%) DIC, SD	98.02 ± 2.34	99.56 ± 3.65	100.14 ± 4.12	97.24 ± 3.42	98.24 ± 2.75	97.50 ± 2.63	99.08 ± 1.17	97.68 ± 2.51
(%) PAP, SD	98.35 ± 1.64	100.15 ± 4.73	97.05 ± 2.14	92.70 ± 2.39	94.85 ± 3.05	99.95 ± 3.32	100.05 ± 1.76	93.75 ± 2.43

SD = mean standard deviation

Poland. All the reagents and chemicals used were of analytical grade.

Preparation of tablets

The composition of various formulations of tablets (T1–T8) are given in Table 1.

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

Powders of the components were sieved through a 0.710 mm mesh screen. All of the components, except the lubrificant (magnesium stearate), were mixed manually with addition of aqueous solution of PVP (10 or 22), to obtain the desired consistency of the mass.

The wet mass was then 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 40°C for 1 h. The dried granules (moisture 3–5%) were passed through a 1.00 mm mesh screen. At the end, 1.0% (w/w) of the lubrificant magnesium was added, and mixed manually. From the granules, the 300 mg tablets were obtained in a press tabletting machine (Erweka, Germany) with 9 mm concave punches.

Evaluation of physical properties of formulation tablets

The tablets were tested according to standard procedures for weight variation (n = 20), thickness (n = 20), hardness (n = 6), friability (n = 20), disintegration time (n = 6) and drug content (n = 10) (Table 2).

Weight uniformity test

For each formulation twenty tablets were selected randomly and weighed together and their mean weight was calculated. Next, they were individually weighed using a weighing balance (Ohaus AV 513C, USA).

Tablet dimensions

Tablet diameter and thickness were measured using a Vernier Caliper (Digital Caliper 0–150 mm, Comparator).

Hardness test

Hardness of tablet was determined by using an Erweka tablet hardness tester (Erweka, Germany).

Friability test

An Erweka (Germany) friabilator was used for the test.

Twenty tablets were weighed and subjected to attrition at 25 rpm for 4 min and the tablets were reweighed. The percentage loss in weight equivalent to friability was calculated from the equation:

Friability (%) = (loss in weight/initial weight) × 100

Disintegration time

Disintegration time was measured by using the pharmacopoeia method (USP) by using a USP Apparatus (Erweka, Germany).

Each of six tablets was put into a basket-rack in a vessel and it was covered with a disk. After the apparatus was turned on, the disintegration time of the tablets was observed.

Drug content analysis

Drug content of DIC and PAP were analyzed by measuring the absorbance of standard and samples at 238 nm for PAP and 278 nm for DIC, using UV/visible spectrophotometer (model Helios Omega UV-VIS, Spectro-Lab, Thermo Scientific, England) with 10 mm matched quartz cell.

Ten tablets from each series were selected at random, weighed together and the mean weight was determined. The tablets were crushed together and exactly 300 mg in powder form (n = 6) was weighed, dissolved in methanol in a 50 mL volumetric flask, filtered by using the Whatman filter and appropriately diluted with methanol. The obtained solution was mixed with phosphate buffer at pH 6.8 in 1 : 1 proportion. The absorbance of the diluted solutions were read in a UV/visible spectrophotometer. The drugs content for each series of tablets was calculated based on simultaneous equation method reported earlier (20). This method obeys Beer's Law in the employed concentration ranges of 2.5–25 µg/mL for two active substances. The limit of quantification (LOQ) was determined to be 1.5 µg/mL for DIC and 1.8 µg/mL for PAP. The limit of detection (LOD) was calculated as 0.5 µg/mL and 0.6 µg/mL for DIC and PAP, respectively. The calibration curves of DIC, at 238 nm $y = 0.0231x + 0.0074$, $R^2 = 0.9993$, at 278 nm $y = 0.0309x + 0.0147$, $R^2 = 0.9997$; for PAP, at 238 nm $y = 0.134x – 0.047$, $R^2 = 0.9998$, at 278 nm $0.0105x + 0.0449$, $R^2 = 0.9992$, were determined.

Differential scanning calorimetry

Samples (about 5 mg) of DIC, PAP and physical mixtures of DIC with PAP, and DIC, PAP and excipients in eight different formulations were hermetically sealed in aluminum pans. DSC analyses

Table 3. Dissolution kinetics of DIC.

Formulation	Zero order		First order		Higuchi		Korsmeyer–Peppas	
	k	r^2	k	r^2	k	r^2	n	r^2
T1	0.3958	0.3139	0.00115	0.2511	4.6855	0.482	0.1807	0.7055
T2	1.6266	0.9634	0.05136	0.9438	15.192	0.9938	0.8231	0.9927
T3	0.6597	0.9806	0.00942	0.9858	6.3131	0.984	0.5573	0.9946
T4	1.5208	0.8983	0.04606	0.9762	15.073	0.9668	0.7925	0.9757
T5	0.0392	0.2305	0.00115	0.2224	0.2944	0.1422	0.0035	0.0438
T6	0.9772	0.7533	0.04145	0.9063	10.135	0.8878	0.3556	0.9546
T7	1.0152	0.6727	0.02602	0.7608	10.776	0.8303	0.5579	0.8972
T8	0.9947	0.7969	0.01958	0.8456	10.178	0.9141	0.6075	0.9582

Table 4. Dissolution kinetics of PAP.

Formulation	Zero order		First order		Higuchi		Korsmeyer–Peppas	
	k	r^2	k	r^2	k	r^2	n	r^2
T1	0.4361	0.4615	0.01405	0.5168	4.8724	0.6312	0.1745	0.8024
T2	1.5865	0.9866	0.0456	0.8769	14.834	0.9861	0.8974	0.9956
T3	0.1824	0.8524	0.0009	0.8384	1.6234	0.7399	0.4501	0.7389
T4	1.2032	0.914	0.02188	0.9643	11.87	0.9746	0.9433	0.9719
T5	0.1566	0.6711	0.00253	0.7	1.6257	0.7929	0.0883	0.8822
T6	0.6795	0.7069	0.01267	0.7471	7.1349	0.8541	0.3895	0.9386
T7	1.0061	0.6808	0.02695	0.7805	10.664	0.8381	0.5271	0.9033
T8	0.9911	0.8055	0.01958	0.8582	10.13	0.9219	0.6018	0.9584

were carried out using DSC Q200 Thermal Analyzer (TA Instruments, USA). Indium standard was used to calibrate the temperature and enthalpy scale. The samples were heated at a constant rate of 10°C/min, over a temperature range from 40°C to 310°C in nitrogen atmosphere at the flow rate of 50 mL/min. As a reference an empty pan was used.

***In vitro* dissolution study of the tablets**

The dissolution of DIC and PAP from prepared tablets was carried out by Erweka (Germany) dissolution tester using USP apparatus 2 (paddle method). One tablet was set in each of six vessels and rotated at 100 rpm for 60 min. As a dissolution medium, 900 mL of phosphate buffer at pH 6.8 at 37 ± 0.5°C was used. The samples (2 mL) were drawn after 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 and 60 min. For each sample drawn, an equivalent volume of phosphate buffer at pH 6.8 (2 mL) was added to the dissolution medium. After dilution of each of the drawn samples, the solutions were analyzed spectrophotometrically at 238 nm and 278 nm. The amount of the released substances was calculated by reference to a Beer's plot by using the method reported earlier (20).

Drug release kinetics

To study the release kinetics of the drug, data obtained from *in vitro* drug release studies were plotted in various kinetic models: zero order (Eq. 1) as a cumulative percentage of drug release *vs*. time, first order (Eq. 2), as a log of the amount of drug remaining to be released *vs*. time and Higuchi's model (Eq. 3), as a cumulative percentage of drug release *vs*. square root of time.

The zero order kinetics describes the systems where the drug release is independent of its concentration.

$$Q = K_0 t \qquad \text{(Eq. 1)}$$

where Q is the amount of drug released in time t, K_0 is the zero order rate constant expressed in units of concentration (21).

The first order kinetics describes the release where release rate is concentration depended.

$$Log\ Q = Log\ Q_0 - Kt/\ 2.303 \qquad \text{(Eq. 2)}$$

where Q is the amount of drug released in time t, Q_0 is the initial concentration of drug and K is the first order rate constant (22).

Higuchi's model describes the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion.

$$Q = K\ t^{1/2} \qquad \text{(Eq. 3)}$$

where Q is the amount of drug released in time t, K is the constant reflecting the design variables of the system (23).

Mechanism of drug release

To evaluate the mechanism of drug release from tablets, data of drug release were plotted according to Korsmeyer et al. (24) equation (Eq. 4), as a log of cumulative percentage of drug released *vs*. log time, and the exponent n value was calculated through the slope of the straight line.

$$M_t /M8 = Kt^{n} \qquad \text{(Eq. 4)}$$

For a cylindrical matrix tablets, if the exponent n = 0.45, then the drug release mechanism is Fickian diffusion, and if 0.45 < n < 0.89 then it is non-Fickian diffusion. An exponent value of 0.89 is indicative of case II transport or typical zero order release, n > 0.89 is super case-II transport (25).

Statistical and kinetic analyses were made using a Statistica 8.0 software.

RESULTS AND DISCUSSION

Physical properties

The physical properties of prepared tablets and the drugs content are shown in Table 2. Average weight, thickness, hardness, friability and the drugs content of all prepared tablets were within pharmacopoeial specification (26).

The DSC analyses

DSC thermograms of the active substances (DIC and PAP), physical mixture of active substances (DIC + PAP) and mixtures of components of tablets T1–T8 are shown in Figure 1.

The DSC trace for DIC showed that DIC melted at temperatures in the range from 285 to 292°C with enthalpy of about 110 J/g. The melting endotherm was followed by decomposition of the substance. Bucci et al. (27) reported that the thermal decomposition of DIC is a two-step process: one of this is endothermic melting peak 285°C, and second partially overlapped the exothermic peak at 294°C. The studies conducted by Palomo et al. (28) showed that DIC melted in the range from 280.45 to 349.96°C, but Szűts at al. (29) reported that it was in the range from 280 to 294°C.

Thermal activity of PAP was found in the range from 226 to 230°C with enthalpy 220 J/g. This is in agreement with studies conducted by Ventura et al. (30) and Marciniec et al. (31). Their studies showed that PAP had a single melting endotherm with a peak at 230°C.

The DSC thermogram for the mixture (DIC + PAP) was different from those of the individual substances. Thermal activity of the mixture started at 135°C with a process resembling a glass transition. A wide and complex melting endotherm with a peak

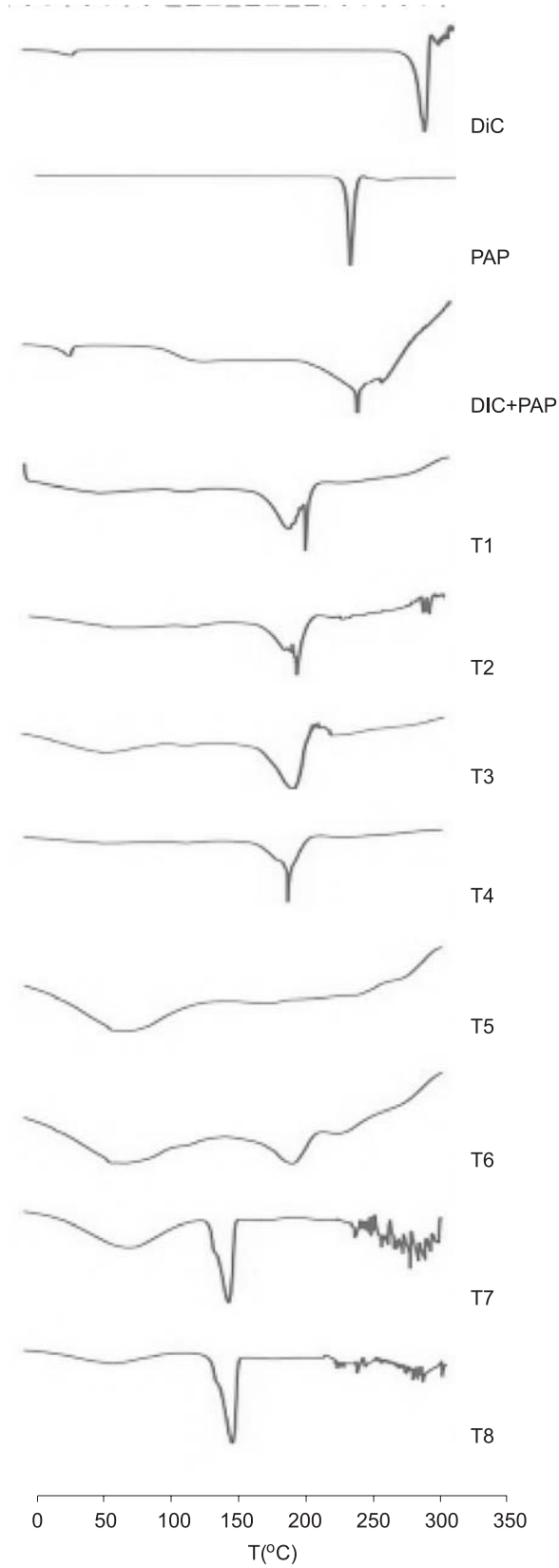

Figure 1. DSC in nitrogen of DIC, PAP, mixture of powders DIC and PAP (DIC + PAP) and tablets T1–T8

at 245°C and enthalpy change 80 – 85 J/g was followed by an exothermal process. The DSC trace for (DIC + PAP) suggested a possible interaction of DIC with PAP. If the solid-solid interaction is weak or non-existent, the reduction of the melting point is usually inconsequential (10).

The DSC traces for T1, T2 and T4 were similar to each other. A glass transition at 124–132°C was followed by a wide endotherm between 180 and 220°C overlapped with a narrow and deep peak at 200–210°C. The enthalpy of the endotherm (DH) for T1, T2 and T4 was equal to 70 J/g, 70 J/g and 100 J/g, respectively. The shape of DSC traces for T1, T2 and T4 was similar to the trace for (DIC + PAP). One can conclude that an addition of Avicel, AcDiSol in T1 or CPharmGel, AcDiSol in T2 and CPharmGel, Aerosil in T4 together with lactose did not change thermal properties of (DIC + PAP) and that excipients, which are contented in these tablets, should not cause interactions between components. In the DSC thermograms of T3 and T6 one can observed a wide endothermic peak in the range from 80 to 90°C and a larger one with the melting point at 204°C and enthalpy about 50 J/g for T3 and 25 J/g

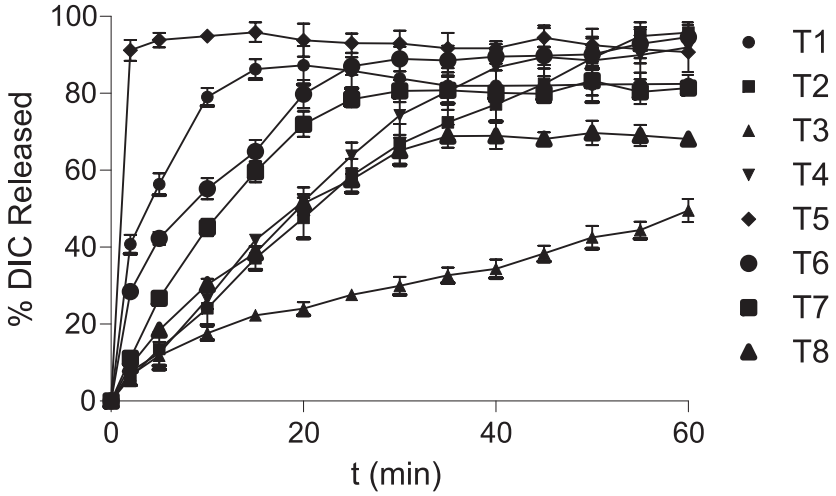

Figure 2. Mean dissolution profiles of DIC from composed tablets (mean values, n = 6)

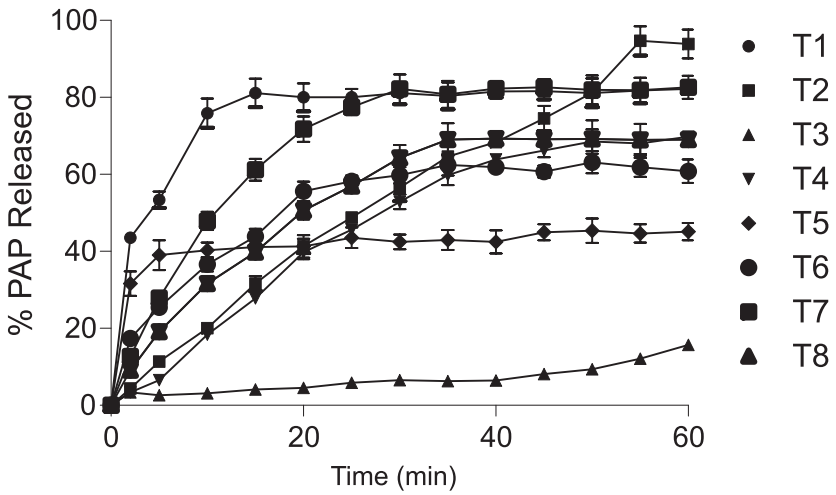

Figure 3. Mean dissolution profiles of PAP from composed tablets (mean values, n = 6)

for T6. The mixtures of T3 i T6 contained the same quantity of Avicel (33.3%) and Aerosil (0.5%), but they were different by the amount of lactose T3 (36.8%), T6 (21.8%) and an addition of CPharmGel (10%) and AcDiSol (5%) in T6. In the DSC thermogram of T5 there was only a wide endothermic process in the range from 85 to 102°C with the maximum at 94°C and enthalpy 65 J/g and no thermal activity at higher temperatures. T5 was different from other formulations by a large contents of Avicel (60.2%) and a lack of sugars.

The putative interactions between components in formulations T3, T5 and T6 indicated a risk of a strong solid-solid interaction that might occurr while compressing powders or granules in a press tabletting machine (32). However, the tabletting process in our study was not disturbed for any formulation.

The DSC traces for T7 and T8 showed lowering of melting temperature as compared to the endotherm of the mixture of active substances (DIC + PAP) but the enthalpy values were not changed that indicated that the interaction or incompatibility should not occurr.

The DSC trace for T7 showed a melting point at 162°C with ΔH = 110 J/g, following glass transition at 96°C and for T8, melting point at 153°C with ΔH = 111 J/g and glass transition at 87°C.

The release study

The dissolution profiles of DIC and PAP for each formulation (T1–T8) are presented in Figures 2 and 3.

From T1, 86.5% DIC and 81.15% PAP were released within 15 min and from T2, above 80% of active substances were released within 50 min (80.04% DIC and 81.2% PAP). The difference in release time for about 80% of both active substances from T1 and T2 was about 35 min and difference in disintegrating time of tablets was 20 min (8 min T1 and 28 min T2). These formulations are similar in quantities of lactose (40.7% T1 and 45.7% T2) and different in additions of Avicel (20%) and AcDiSol (10%) in T1 or CPharmGel (20%) and AcDiSol (5%) in T2. This indicated that an addition of CPharmGel instead the Avicel may result in prolonged release time, but on that time may affect also 5% more of AcDiSol in T1.

In T6, there are both Avicel (33.3%) and CPharmGel (10%) and lactose (21.8%), AcDiSol (5%), Aerosil (0.5%). The release study showed that above 80% DIC (87.08%) was released within 25 min (94.66% after 60 min), but PAP 60.8% within 60 min. The disintegrating time of this tablets is 18 min. Comparing T6 to T1 and T2 it can be observed that DIC was released slower about 10 min from T6 than from T1 and 25 min faster from T6 than from T2. PAP was not released in 80% from T6. The quantity of released PAP from T6 in comparison with T1 and T2 shows that inhibition of the release process of PAP can be caused higher of quantity of Avicel in T6 about 13% (in comparison with T1) and less of the quantity of CPharmGel on 10% in T6 (in comparison with T2) at simultaneously decreased the quantity of AcDiSol on 5% in T6 (comparing to T1).

Tablets T3 and T4 comprised lactose at different quantities (36.8% T3 and 50.2% T4) and Aerosil at the same quantities (0.5%), but they are different in an addition of Avicel (33.3%) in T3 and CPharmGel (20%) in T4. Within 60 min, only 49.52% DIC and 15.7% PAP from T3 were released, but within 35 min 80.58% DIC (91.98% within 60 min) and within 60 min 69.75% PAP from T4 were released, although the disintegration times of both of tablets are similar (31 min T3 and 33 min T4). Both formulations do not contain AcDiSol as a disintegrator. From this it follows that the release process is highly affected by other excipients such as Avicel, CPharmGel and lactose.

When comparing T3 and T4 it can be noticed that addition of CPharmGel in a quantity of 20% in T4 increased the quantity of released DIC and PAP, but Avicel, in an addition of 33.3% in T3, without AcDiSol, caused inhibition of the release process of the active substances.

Avicel in a quantity of 60.2%, with the addition of 10% AcDiSol and 0.5% Aerosil in T5, caused a fast disintegrated process of a tablet (0.6 min), but there occurs the difference of the release process. Within 2 min, 91.18% DIC and within 60 min 45.1% PAP from T5 were released. In comparison with T1, it can be observed that the absence of lactose in T5 caused the fast release process of DIC, but inhibition of the release of PAP.

Within 30 min, 80.59% of DIC and 82.19% of PAP from T7 and within 60 min 68.14% of DIC and 69.04% of PAP from T8 were released. Tablets T7 and T8 were similar in content of mannitol at different quantities (23.3% T7 and 37.3% T8), but varied in addition of potato starch to T7 and microcrystalline cellulose and HPMC to T8. The data of the release study showed that cellulose and their derivatives, especially HPMC, in T8 caused prolonged the release of both active substances. The differences in the release process of DIC from tablets can be caused by different production process, different excipients or differences at size of particle of active substance. The effect of different excipients on the

dissolution profiles of diclofenac sodium from tablets or pellets were reported by Bertocchi et al. (2), Savaser et al. (33), Kibria et al. (34) and Mourão et al. (35).

According to pharmacopoeial requirements for uncounted tablets (26), 80% of active substances were released from T1 and T7 within 45 min. The disintegration times of these tablets were 8 and 7 min for T1 and T7, respectively. The disintegration times for tablets T2, T3, T4 and T6 exceeded 15 min as recommended by Polish Pharmacopoeia (26) and were in the range from 18 to 33 min. The release process of active substances from tablets T2, T4 and T6 run similarly; as above, 80% of DIC were released within 45 min. However, amounts of released PAP were lower and equal in the range from 60.70 to 74.52%. The disintegration time of T3 was 18 min, but only 38.36% DIC and 8.1% PAP were released within 45 min. The differences observed within the release process and disintegration times were probably caused by type of binder added to the formulation. In tablets T2 and T4, 20% of CPharmGel was added, in T6 10% CPharmGel and 33.3 % of Avicel, and in T3 only 33.3% of Avicel was added. Moreover, the release process can also be influenced by addition of a disintegrator and a lubricant. In formulas T3 and T4, only Aerosil (0.5%) was added resulting in disintegration time 31–33 min. An addition of 5% of AcDiSol to T2 caused a bit shorter time (28 min). When 5% of AcDiSol and 0.5% of Aerosil in T6 were used, the disintegration time was 18 min. Bearing in mind the above data, it can be noticed that mixing of different excipients considerably changed the release process of active substances from uncoated tablets. The positive effect of a binder on pore structure and tablet strength resulted in an increased disintegration time. Although addition of a disintegrator generally improved the disintegration time, the effect was decreased when the formulation included more deformable binders (36).

Kinetic analysis of dissolution data

The obtained drug release data were analyzed by zero order, first order, Higuchi and Korsmeyer–Peppas models, to know the mechanism of drug release from the formulations. The release rate constants were calculated from the slope of the appropriate plot and determination coefficient (r^2) were determined (Tables 3 and 4).

In this study, the *in vitro* release profiles of DIC from formulations T2 and T4 containing CPharmGel and T3 containing Avicel as base excipients were explained by Higuchi model, where the determination coefficient (r^2) is in the range from 0.9968 to 0.9938; for the first order r^2 equals from 0.9438 to 0.9858) and for the zero order r^2 equals from 0.8983 to 0.9806). The release of DIC from formulation T2 was best explained by Higuchi's equation as the plot showed the highest linearity (r^2 = 0.9938) followed by zero order (r^2 = 0.9634). This indicates that the release of drug from the matrix is a square root of time dependent process and is close to zero order release kinetics. The best linearity for formulations T3 and T4 were found in first order rate equation plot describing the drug release rate relationship with concentration of DIC, so r^2 equals 0.9858 for T3 and 0.9762 for T4, respectively.

The *in vitro* release profiles of PAP from formulation T2 showed the highest linearity with the zero order kinetics (r^2 = 0.9866), followed by Higuchi's (r^2 = 0.9861) and from T4 was best explained by Higuchi's model (r^2 = 0.9746), followed by the first order equation (r^2 = 0.9643).

The obtained data were plotted according to the Korsmeyer-Peppas equation to know the confirmed diffusion mechanism.

For DIC release, the formulations T2 and T3 showed good linearity (r^2 equals 0.9927 and 0.9946, respectively) with exponent (n) values 0.8231 (T2) and 0.5573 (T3), indicating a coupling of the diffusion and erosion mechanism so called anomalous transport (non-Fickian). For PAP release, the formulation T2 showed good linearity (r^2 = 0.9956) with release exponent 0.8947, indicating zero order release where concentration was nearly independent of drug release profile. The formulations T4 and T8 showed release exponent (n) 0.7925 (T4) and 0.6075 (T8) with r^2 0.9757 (T4) and 0.9582 (T8) for DIC release, indicating anomalous transport.

For PAP release, formulation T4 showed release exponent (n) 0.9433 with r^2 = 0.9719 characteristic for super case II transport and for T8 (n) 0.6018 with r^2 = 0.9584, indicating anomalous transport. Case II generally refers to erosion of polymeric chain and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled drug release (17).

Formulation T6 slope (n) values equal 0.3556 (DIC) and 0.3895 (PAP), indicating Fickian type of diffusional release occuring by usual molecular diffusion of the drug due to chemical potential gradient.

The tablet T5 containing high amount of Avicel pH 102 with dissolution time 0.6 min represents fast dissolving tablets (FDT). The tablets formulations T1, T2 and T8 are typical uncoated tablets with disintegration time up to 15 min. The tablet for-

mulation T3 containing Avicel and T2 or T4 containing CPharmGel can be considered as matrix tablets with potentially prolonged release. Drugs release from tablet formulation T2 was found to be very close to zero order release kinetics. Formulation T6 represents uncoated tablets with diffusion type of release. The type of excipient used as a matrix of tablet induce effect on release rate and mechanism.

CONCLUSION

The shift of the melting point and the enthalpy values for the mixtures of tablets components suggested a possible interaction of the components in some mixtures but the tabletting process was not influenced in none of the formulations. The tablet formulation containing high amount of Avicel PH 102 (60.2%) and PVP 10 (5%), AcDiSol (10%), Aerosil (0.5%) with dissolution time 0.6 min. represents fast dissolving tablets. The formulations containing PVP 10 (5%) and CPharmGel (20%), lactose (45.7%), AcDiSol (5%) or PVP 10 (5%), Avicel (33.3%), lactose (36.8%), Aerosil (0.5%) or PVP 10 (5%), CPharmGel (20%), lactose (50.2%), Aerosil (0.5%) can be considered as tablets with prolonged release, because the *in vitro* release profiles of DIC and PAP from these formulations were fitted to the kinetic models describing the dissolution of drug from modified release dosage forms.

REFERENCES

1. Martindale: The Complete Drug Reference, 37th edn. p. 44, The Pharmaceutical Press, London 2011.
2. Bertocchi P., Antoniella E., Valvo L., Alimonti S., Memoli A.: J. Pharm. Biomed. Anal. 37, 679 (2005).
3. Lala L.G., D'Mello P.M., Naik S.R.: J. Ethnopharmacol. 91, 277 (2004).
4. León-Reyes M.R., Castañeda-Hernández G., Ortiz M.I.: J. Pharm. Pharm. Sci. 12, 280 (2009).
5. Mukherjee J., Das A., Chakrabarty U.S., Sahoo B., Sengupta P., Chatterjee B., Roy B., Pal T.K.: Arzneimittelforschung 60, 8, 506 (2010).
6. Snir N., Moskovitz B., Nativ O., Margel D., Sandovski U., Sulkes J., Livne P.M., Lifshitz D.A.: J. Urol. 179, 1411 (2008).
7. Kasperek R.: Polish Patent No. P 380847 (2010).
8. Fathy M., Hassan M.A., Mohamed F.A.: Pharmazie 57, 825 (2002).
9. Fini A., Fazio G., Fernández-Hervás M.J., Holgado M.A., Rabasco A.M.: Int. J. Pharm. 121, 19 (1995).
10. Kerč J., Srčič S., Urleb U., Kanalec A., Kofler B., Šmid-Korbar J.: J. Pharm. Pharmacol. 44, 515 (1992).
11. Li Wan Po A., Morso P.V.: Int. J. Pharm. 18, 287 (1984).
12. Žilnik L.F., Jazbinšek A., Hvala A., Vrečer F., Klamt A.: Fluid Phase Equilibr. 261, 140 (2007).
13. Bravo S.A., Lamas M.C., Salamón C.J.: J. Pharm. Pharm. Sci. 5, 213 (2002).
14. Kincl M., Meleh M., Veber M., Vrečer F.: Acta Chim. Slov. 51, 409 (2004).
15. Miyajima M., Koshika A., Okada J., Kusai A., Ikeda M.: J. Control. Release 56, 85 (1998).
16. Serajuddin A.T.M., Rosoff M.: J. Pharm. Sci. 73, 1203 (1984).
17. Costa P., Sousa Lobo J.M.: Eur. J. Pharm. Sci. 13, 123 (2001).
18. Grassi M., Grassi G.: Curr. Drug Deliv. 2, 97 (2005).
19. Dash S., Narashima M.P., Lilakanta N., Prasanta C.: Acta Pol. Pharm. Drug Res. 67, 217 (2010).
20. Kasperek R., Zimmer Ł., Świąder K., Belniak P., Poleszak E.: Curr. Issues Pharm. Med. Sci. 25, 182 (2012).
21. Hadjiioannou T.P., Christian G.D., Koupparis M.A.: Quantitative Calculations in Pharmaceutical Practice and Research, p. 345, VCH Publishers Inc., New York 1993.
22. Bourne D.W., Banker G.S., Rhodes C.T.: Modern Pharmaceutics, 4th edn., p. 67, Marcel Dekker Inc., New York 2002.
23. Higuchi T.: J. Pharm. Sci. 52, 1145 (1963).
24. Korsmeyer R.W., Gurny R., Doelker E., Buri P., Peppas NA.: Int. J. Pharm. 15, 25 (1983).
25. Siepmann J., Peppas N.A.: Adv. Drug Deliv. Rev. 48, 139 (2001).
26. The Polish Pharmacopoeia IX, pp. 355, 359, 837, Polish Pharmaceutical Society, Warszawa 2011.
27. Bucci R., Magrì A.D., Magrì A.L.: Fresenius J. Anal. Chem. 362, 577 (1998).
28. Palomo M.E., Ballesteros M.P., Frutos P.: J. Pharm. Biomed. Anal. 21, 83 (1999).
29. Szűts A., Sorrenti M., Catenacci L., Bettinetti G., Szabó-Révész P.: J. Therm. Anal. Calorim. 95, 885 (2009).

30. Ventura C.A., Puglisi G., Zappalà M., Mazzone G.: Int. J. Pharm. 160, 163 (1998).
31. Marciniec B., Kozak M., Naskrent M., Hofman M., Dettlaff K., Stawny M.: J. Therm. Anal. Calorim. 102, 261 (2010).
32. Hosaka S., Sadoshima T., Sato M., Hamada C., Takahashi Y., Kitamori N.: Chem. Pharm. Bull. 55, 793 (2007).
33. Savaşer A., Özkan Y., Işimer A.: Farmaco 60, 171 (2005).
34. Kibria G., Roni M.A., Absar M.S., Jalil R.: AAPS PharmSciTech. 9, 1240 (2008).
35. Mourão S.C., da Silva C., Bresolin T.M.B., Serra C.H.R., Porta V.: Int. J. Pharm. 386, 201 (2010).
36. Mattsson S., Nyström C.: Eur. J. Pharm. Sci. 10, 53 (2000).

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