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Soluble filler as a dissolution profile modulator for slightly soluble drugs in matrix tablets

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Abstract

The purpose of this experimental work was the development of hydrophilic–lipophilic matrix tablets for controlled release of slightly soluble drug represented here by diclofenac sodium (DS). Drug dissolution profile optimization provided by soluble filler was studied. Matrix tablets were based on cetyl alcohol as the lipophilic carrier, povidone as the gel-forming agent, and common soluble filler, that is lactose or sucrose of different particle size. Physical properties of tablets prepared by melt granulation and drug release in a phosphate buffer of pH 6.8 were evaluated. In vitro studies showed that used filler type, filler to povidone ratio and sucrose particle size influenced the drug release rate. DS dissolution profile could be changed within a wide range from about 50% per 24 hours to almost 100% in 10 hours. The release constant values confirmed that DS was released from matrices by the diffusion and anomalous transport. The influence of sucrose particle size on the drug release rate was observed. As the particle size decreased, the drug release increased significantly and its dissolution profile became more uniform. Soluble fillers participated in the pore-forming process according to their solubility and particle size. Formulations containing 100 mg of the drug, 80 mg of cetyl alcohol, 40 mg of povidone, and 80 mg of either lactose or sucrose (particle size 250–125 μm) were considered optimal for 24-hour lasting dissolution of DS.

Key words: *Diclofenac sodium; drug release; fillers; matrix tablets; particle size; release mechanism*

Introduction

Diclofenac sodium (DS) is a nonsteroidal antiphlogistic drug involving anti-inflammatory, analgesic, and antipyretic effects[1]. Low bioavailability (60%), short biological half-life (1–2 hours), and low therapeutic index suggest the need for controlled release dosage forms[2]. DS as a sodium salt of a phenylacetic acid ($pK_a \sim 4$)[3] exhibits a pH-dependent solubility. Moreover, its solubility is significantly dependent also on the ionic strength and composition of dissolution medium used. DS is slightly soluble in water, very slightly in phosphate buffer solutions of pH 6.8 and 7.2, and practically insoluble in hydrochloric acid of pH 1.1[4].

Thus, incorporation of DS into the prolonged release matrices is difficult: DS cannot be included into insoluble matrices because of its incomplete release and low bioavailability; favorable hydrophilic matrix tablets based on hypromelose (HPMC) are useless as the combination of DS and phosphate ions from the buffer, and ubiquitous in human body, inhibit hydration and swelling of HPMC, that is, retarding gel layer formation[5], and matrices containing DS and lipid carrier only are also considerably limited because of their fast disintegration caused by total insolubility of this system. Some positive results concerning the prolonged DS release from HPMC matrices were obtained when a combination of DS and chondroitin sulfate was used[6]. Hypromelose concentration of 40% was capable to prolong the release of both drugs for 9 hours. DS was used as a model drug also for evaluation of natural gum copal and dammar as the novel sustained release matrix-forming materials in tablet formulation[7]. The matrix tablets containing 30% of gum copal and gum dammar showed prolonged drug release for more than 10 hours.

Several factors, such as the polymer type and concentration, the drug and polymer particle size, and the presence of some other additives in the final formulation can modify the drug release from matrices[8].

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The influence of drug particle size depends on aqueous solubility, being especially important with moderately soluble drugs[9]. The size of particles is a statistically significant variable for the drug release; the smallest particles dissolve more easily, form larger surface area when dissolution media penetrates through the matrices resulting in increased diffusion. On the other hand, the larger particles dissolve less readily and are therefore more prone to erosion at the matrix surface.

Besides the influence of drug particle size on drug release rate, the effect of carrying polymer particle size on drug dissolution was studied. In their experimental work, Heng, Chan, Easterbrook, and Xiaoman[10] used HPMC of different particle size fractions obtained by a sieving in matrix systems. They observed that particle size of HPMC played an important role in the release behavior of aspirin. As the mean particle size of HPMC decreased, the drug release rate generally decreased. More significant results were obtained when polymer particle size was 113 μm or higher and polymer content exceeded 10%.

Mitchell and Balwinski[11] investigated the influence of different sizes of HPMC particles of four viscosity grades on dissolution profiles of six selected drugs. For some investigated formulations, the impact of HPMC particle size change was characterized by apparent shift in release rate and drug release mechanism when less than 50% of the HPMC passed through a 230 mesh screen, that is, the particle size diameter was smaller than 63 μm.

Liew, Chan, Ching, and Heng[12] employed sodium alginate particle size to modify chlorpheniramine maleate release from matrix tablets. Obtained results confirmed the possibility of using this polymer for modification of water-soluble drug release. Reduction in alginate particle size resulted in slower release and diminished the initial burst effect.

With respect to the above-mentioned problems, a new type of hydrophilic–lipophilic matrix tablet for DS 24-hour release was proposed. In this formulation consisting of cetyl alcohol as a lipophilic carrier, povidone as a gel-forming hydrophilic polymer, sucrose, or lactose monohydrate, respectively, were used as fillers. This experimental work is focused on the characteristics of proposed matrices formed from granulates with respect to the utilization of commonly used filler and/or its particle size as a modulator for drug dissolution profile optimization.

Materials and methods

Materials

DS (Amoli Organics, Mumbai, India) was the model drug; cetyl alcohol (Cognis, Monheim, Germany) was used as a lipid carrier. Povidone 30 (PVP-30; BASF, Ludwigshafen, Germany), sucrose (Cukrovary, Dobrovice, Czech Republic), or α-lactose monohydrate (Cerapharm, Vienna, Austria) were hydrophilic excipients. Magnesium stearate (Peter Greven, Bad Műnstereifel, Germany) and colloid silica (Degussa, Vicenza, Italy) were used to improve granulate flow properties. All materials were of Ph. Eur. quality.

Particle size characterization

Particle size of the drug and excipients was determined by an optical analysis using the optical microscope (DN 45; Lambda, Prague, Czech Republic) connected to the CCD camera (Alphaphot, Nikon, Tokyo, Japan) and operated by Ia32 software. Measurements of 200 particles were carried out, in the case of nonsieved sucrose 600 particles were examined.

Granulates preparation and evaluation

Three hundreds grams of powder blends containing DS, cetyl alcohol, PVP-30, and sucrose (nonsieved or selected size fraction of sucrose) or lactose were homogenized in Turbula mixer (TC2, Basel, Switzerland) for 10 minutes. For composition of prepared tablet samples see Table 1. The mixtures were oven-heated (RS 401A/1; Chirana, Prague, Czech Republic) at 55°C for 5 minutes using cetyl alcohol (melting point of 49–52°C) to form granules[13]. Prepared granulates were evaluated according to Ph. Eur. 5 for flowability (Medipo, Brno, Czech Republic; diameter of outflow opening 15.0 ± 0.01 mm), Hausner ratio—HR,

Table 1. Matrix tablets composition.

Sample	Diclofenac sodium (mg)	Cetyl alcohol (mg)	PVP-30 (mg)	Sucrose (mg) particle distribution	Lactose monohydrate (mg)
L1	100	80	60	—	60
S2	100	80	60	60, nonsieved	—
L3	100	80	40	—	80
S4	100	80	40	80, nonsieved	—
S5	100	80	40	80, 500–250 μm	—
S6	100	80	40	80, 250–125 μm	—
S7	100	80	40	80, 125–80 μm	—
S8	100	80	40	80, <80 μm	—

Compressibility Index—CI (SVM 102, Erweka, Heusenstamm, Germany), and pycnometric density (Pycnomatic ATC, Porotec, Hofheim, Germany). When magnesium stearate (2.5%) and colloid silica (0.5%) were added mixing procedure continued for another 10 minutes.

Matrix tablets preparation and evaluation

Matrix tablets of approximate weight (309.3 mg) and similar hardness were compressed using 10 mm diameter flat-faced punches (Korsch, EK 0; Korsch Pressen, Berlin, Germany). Tablets of similar hardness were prepared under controlled compression force for more accurate dissolution profiles comparison. Pressure force used to produce matrix tablets was monitored to observe the compressibility of granulates.

Tablet characteristics: their weight uniformity, drug content, hardness (C50 Tablet Hardness & Compression Tester, Engineering Systems, Notthingham, Great Britain), and friability (TAR 10, Erweka, Heusenstamm, Germany) were evaluated according to Ph. Eur. 5. The average value of hardness was obtained from 10 measurements of each sample, and that one of tablet friability from three measurements.

The porosity of the tablets was calculated according to Vueba, Batista de Carvalho, Veiga, Sousa, and Pina[14]:

$$\varepsilon(\%)=\left(1-\frac{p_a}{p_t}\right)\cdot 100, \tag{1}$$

where ε is the porosity, p_a is the apparent density, and p_t is the true density. Tablet apparent density and the true density of powder mixtures of the identical compositions were measured by helium pycnometer (Pycnomatic ATC; Porotec, Hofheim, Germany). All density measurements were performed in triplicate.

Determination of dissolution profiles and their variability

Dissolution profiles of prepared samples were determined (SOTAX AT 7 On-Line System—Donau Lab, Zurich, Switzerland) using paddle method at 100 rpm in 1000 mL of a phosphate buffer (pH 6.8) at 37°C. Samples were analyzed for the released drug amount in a UV spectrophotometer (Lambda 25, Perkin Elmer, Wellesley, USA) at 276 nm for DS. The mean value of six samples and a standard deviation of each tablet batch were calculated. The evaluation of dissolution profiles was carried out twice.

Difference and similarity factor analysis

To compare dissolution profiles of tablet batches, the difference factor f_1 and the similarity factor f_2 were calculated as these analyses are currently used to evaluate the significance of changes in dissolution curves. Difference and similarity factors were determined for samples L1–S2, L3–S4, and L3–S8 due to the possible influence of used filler (lactose versus sucrose) and for samples L1–L3 and S2–S4 to examine the effect of filler to PVP-30 ratio. To study the effect of different sucrose particle fractions in matrix tablets on drug dissolution, these methods were applied to compare sample S5 (500–250 μm) chosen as a reference with remaining samples, that is, S6 (250–125 μm), S7 (125–80 μm), and S8 (<80 μm), respectively. The data were analyzed by the Equation 2 for difference factor and by Equation 3 for similarity factor[15]:

$$f_1=\frac{\sum_{i=1}^{n}|R_i-T_i|}{\sum_{i=1}^{n}R_i}\times 100 \tag{2}$$

$$f_2=50\times\log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{i=1}^{n}|R_i-T_i|^2\right]^{-0.5}\times 100\right\}, \tag{3}$$

where n is the number of time points, R_i and T_i are the dissolution data of a reference and tested samples at the time i.

The difference factor value between 0 and 15 ensures the equivalence of dissolution profiles[16]. The similarity factor takes values between 0 and 100. When it is 100, the two profiles are identical and when it approaches 0 their dissimilarity increases. Values of over 50 were accepted as similar[17].

Drug release studies

To propose the drug release mechanism from matrix tablets, the experimental data were treated according to the following equations[18]:
Zero-order equation

$$\frac{M_t}{M_\infty}=K_0 t. \tag{4}$$

First-order equation

$$\frac{M_t}{M_\infty}=1-e^{-K_1 t}. \tag{5}$$

Square root-time kinetics (Higuchi model)

$$\frac{M_t}{M_\infty} = K_{\mathrm{H}}\sqrt{t}. \tag{6}$$

Korsmeyer–Peppas equation

$$\frac{M_t}{M_\infty} = K_{\mathrm{KP}}t^n. \tag{7}$$

Hixson–Crowell model

$$(M_\infty)^{1/3} - (M_t)^{1/3} = K_{\mathrm{HC}}t. \tag{8}$$

Baker–Lonsdale model

$$\frac{3}{2}\left\{1-\left[1-\left(\frac{M_t}{M_\infty}\right)\right]^{2/3}\right\} - \frac{M_t}{M_\infty} = K_{\mathrm{BL}}t, \tag{9}$$

where M_t is the amount of drug released in time t; M_∞ is the absolute cumulative amount of drug released at infinitive time; K_0, K_1, K_{H}, K_{HC}, and K_{BL} are the zero-order, first-order, Higuchi, Hixson–Crowell, Baker–Lonsdale release constants, and K_{KP} is the release constant comprising the structural and geometrical characteristics of tablets. Release exponent n characterizes the mechanism of drug release, in particular, n = 0.5 corresponds to a Fickian diffusion release, $0.5 < n < 1.0$ to an anomalous transport, n = 1.0 to a zero-order release kinetics, and $n > 1.0$ to a super case II transport[1,18].

With regards to inconstant variance of some measured data, the weighted least squares method was applied to dissolution data. The release constant average value of each model with confidential regions (CR) (at significant level $P \leq 0.05$) and determination coefficient R^2 of regression analysis were calculated. Observing that R^2 is only an orientational measure for regression function suitability, the autocorrelation test of residua deviations (Durbin–Watson test) was determined. Regression diagnostics were calculated by means of QC.Expert$^{\mathrm{TM}}$ 2.5 software.

Results and discussion

Particle size characterization

Mean particle diameter of drug and excipients was calculated from the data obtained from microscopic measurements. DS had the mean particle diameter of 57.9 μm and PVP-30 of 47.3 μm.

As can be observed from the stereomicroscopic photographs (Figure 1), the particle size distribution of particular sucrose fractions obtained by sieving corresponded to the declared particle size data. Mean particle diameter of nonsieved sucrose was 119.52 μm (distribution of 600 particles: 291 particles, 10–80 μm; 146 particles, 80–125 μm; 137 particles, 125–250 μm; 54 particles, 250–500 μm; 2 particles, 500–800 μm). Mean particle diameters ($\bar{d}$) of selected sucrose fractions were as follows: $\bar{d}$ of 500–250 μm fraction was 368.79 μm, $\bar{d}$ of 250–125 μm fraction was 183.07 μm, $\bar{d}$ of 125–80 μm fraction was 99.31 μm, and $\bar{d}$ of the sucrose fraction less than 80 μm was 35.88 μm. The particle size range of α-lactose monohydrate mesh 200 was 5–85 μm (mean particle diameter 31.22 μm) and could be approximately comparable to sucrose fraction containing particles smaller than 80 μm.

Granulates evaluation

Table 2 shows some properties of prepared granulates. It is evident that obtained granulates exhibited good flowability. According to the literature data, the samples of HR value under 1.25 are suitable for producing tablets[19]. However, within the samples that differed in filler particle size, some differences can be found. For example, as the particle size of sucrose decreased (samples S5–S8), their flowability was slower, HR values and Carr's index values increased, thus indicating a deterioration of granulates flow properties. These although not very significant results could be related to smaller filler particle size on one hand and constant amount of the lipid binder on the other hand. It is well known that the higher proportion of a binder used for granulation process leads to the enlargement of granulate particle diameter[20]. In this experiment, the amount of melted binder was constant; however, the filler particle size (i.e., 36% of the solid powder during granulation) changed depending on the fraction used. Granulation of a starting material with smaller particles (and thus larger surface area) using the same amount of binder resulted in smaller granule size which could explain their worse flowability, HR, and CI[21].

Matrix tablets characteristics

Determination of matrix tablets quality parameters is presented in Table 3. Results showed that compression process yielded tablets uniform in weight (312.51–318.52 mg) and drug content (98.66–103.86% of the desired amount). Tablet hardness as mentioned before ranged in narrow interval from 79.2 to 88.9 N, with the exception of sample S2. For this formulation, it was not possible to achieve higher tablet hardness than 63.2 N with high SD despite using higher pressure force. Tablet friability was in between 0.27 and 0.53% for all samples with the excep-

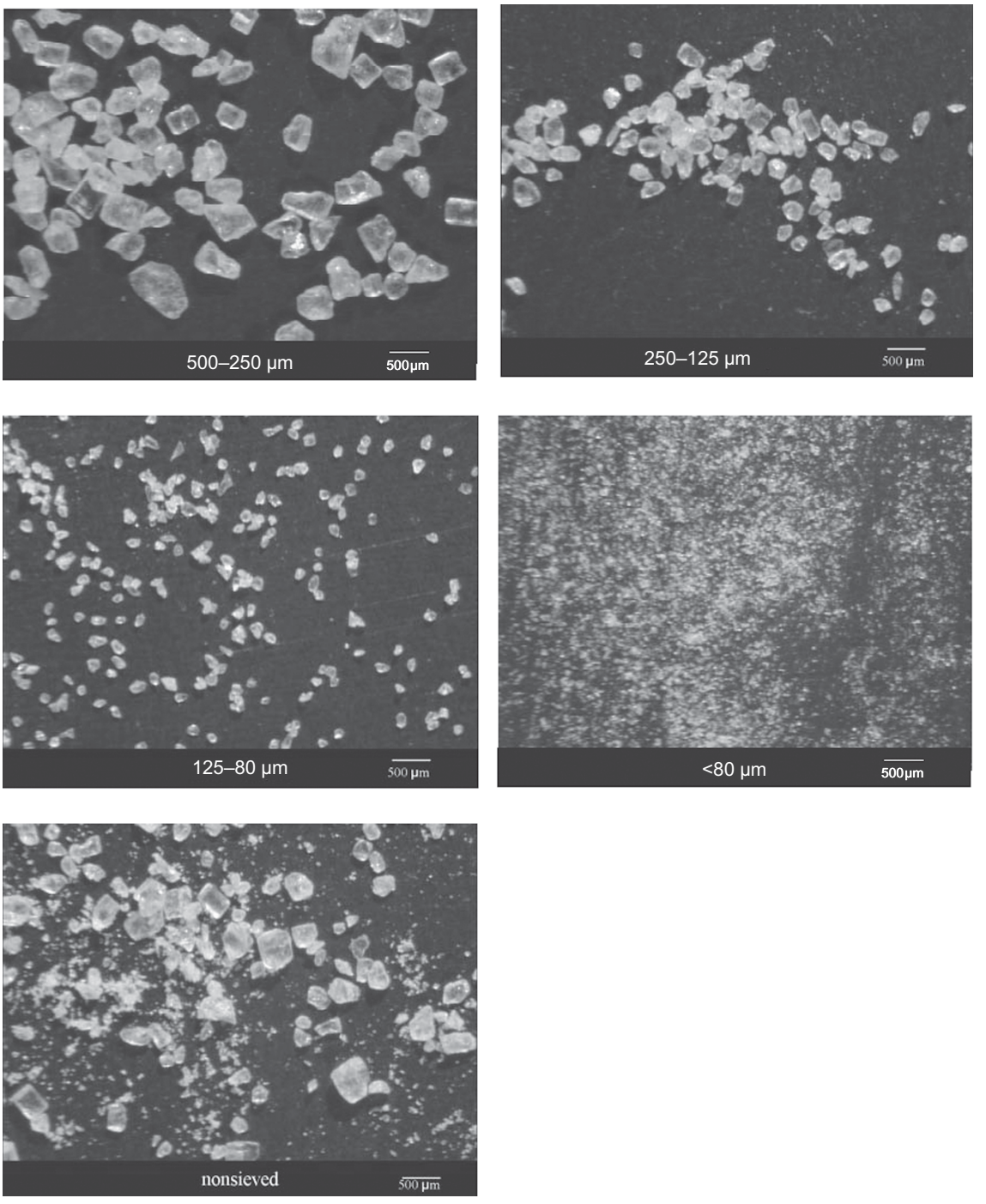

Figure 1. Stereomicroscopic photographs of sucrose fractions and nonsieved sucrose material.

tion of sample S2 again when the fracture of three tablets was observed within the test. From these results, it seems that nonsieved sucrose in lower concentration (20% in sample S2 versus 26.7% in sample S4) negatively influenced the mechanical properties of matrix tablets. Hardness values (79.20–88.90) and friability (under 1%) of the other samples, that is, L1, L3, S5–S8, did not differ significantly and can be ascribed to the narrower particle size distribution. Similar findings were reported also by Korhonen et al.[22] Furthermore, the results showed that granulates containing sucrose of smaller particle size fractions led to formation of matrices with better mechanical properties as indicated by their higher hardness and lower friability (samples S5–S8, Table 3).

Porosity values of tablets rose with the decreasing particle size of sucrose. This observation corresponded

Table 2. Granulates flowability, hausner ratio, carr's index, and pycnometric density.

Sample	Flowability (seconds)	Hausner ratio	Carr's index (%)	Flow evaluation	Pycnometric density	
					Powder blends before granulation (g/mL)	Granulates (g/mL)
L1	5.7 ± 0.2	1.17 ± 0.01	15.17 ± 0.33	Good	1.2512 ± 0.0006	1.2174 ± 0.0026
S2	4.95 ± 0.06	1.16 ± 0.02	13.64 ± 0.01	Good	1.2596 ± 0.0011	1.2329 ± 0.0004
L3	4.8 ± 0.2	1.15 ± 0.01	12.79 ± 0.88	Good	1.2738 ± 0.0011	1.2384 ± 0.0022
S4	4.43 ± 0.02	1.14 ± 0.02	12.67 ± 0.25	Good	1.2783 ± 0.0010	1.26 ± 0.14
S5	4.02 ± 0.01	1.09 ± 0.00	8.09 ± 0.02	Excellent	1.2785 ± 0.0009	1.26 ± 0.12
S6	4.20 ± 0.03	1.12 ± 0.01	10.76 ± 0.83	Good/Excellent	1.2766 ± 0.0018	1.26 ± 0.11
S7	4.52 ± 0.04	1.17 ± 0.02	14.3 ± 1.6	Good	1.2806 ± 0.0012	1.27 ± 0.20
S8	5.42 ± 0.08	1.20 ± 0.01	16.67 ± 0.78	Fair	1.2743 ± 0.0014	1.26 ± 0.15

Table 3. Matrix tablets characteristics.

Sample	Compression force (kN)	Average weight (mg) (n = 20)	Hardness (N) (n = 10)	Friability (%) (n = 20)	Porosity (%) (n = 10)	Drug content (%) (n = 10)
L1	14.04	318.52 ± 1.20	79.20 ± 3.5	0.37	0.43	100.58 ± 1.21
S2	35.10	313.43 ± 1.16	63.2 ± 12.8	Fracture of three tablets	0.12	103.21 ± 1.11
L3	12.29	315.04 ± 1.50	83.60 ± 2.6	0.38	0.86	101.28 ± 1.85
S4	14.04	316.60 ± 1.56	83.30 ± 5.2	0.53	0.11	103.86 ± 1.68
S5	21.06	312.66 ± 3.47	80.90 ± 3.1	0.46	0.12	102.36 ± 2.33
S6	21.06	312.51 ± 2.70	83.20 ± 1.9	0.41	0.45	98.66 ± 1.98
S7	21.06	316.14 ± 1.00	88.90 ± 1.5	0.39	0.52	103.11 ± 2.51
S8	12.28	313.30 ± 1.37	87.40 ± 3.1	0.27	0.62	100.75 ± 2.81

n is number of measurements.

to the data of Riepma et al.[23] although it was reported that sucrose tablet characteristics should not be affected by particle size because of the high degree of fragmentation of crystalline sucrose particles[24]. Relatively low porosity of samples containing nonsieved sucrose (i.e., S2–0.12% and S4–0.11%) was probably created by better particle impaction which is characteristic for material with wide particle distribution[25]. These data are supported also by the porosity value of sample S5–0.12% with the second largest sucrose particles (250–500 μm).

Dissolution profiles, difference and similarity factors analyses

Dissolution studies were performed in two media of different pH values (pH 1.2 and 6.8, respectively). Within 12-hour dissolution test in acidic medium, no amount of DS from all studied samples was released due to DS insolubility under these conditions, matrix tablets did not disintegrate within this test what is the good presumption for their successful passage through stomach (data not presented as the values were close to zero). Similar results were obtained by Su et al.[2] for Voltaren® SR tablets. Within 24-hour lasting dissolution test in phosphate buffer at pH 6.8, it was observed that the samples differing only in the filler type, that is, lactose or sucrose (L1 versus S2, L3 versus S4, L3 versus S8), released DS faster when sucrose was used in formulations (Figure 2). This fact could be explained by the different water solubility of used fillers (2.0 g of sucrose in 1 g of water versus 0.89 g of α-lactose monohydrate in 1 g of water at 25°C) and faster dissolution of sucrose[26,27]. Nevertheless, from f_1 and f_2 analyses results (Table 4) could be observed that dissolution profiles of L1 : S2 (f_1 = 14.21; f_2 = 57.78) and L3 : S4 (f_1 = 6.45; f_2 = 66.51)

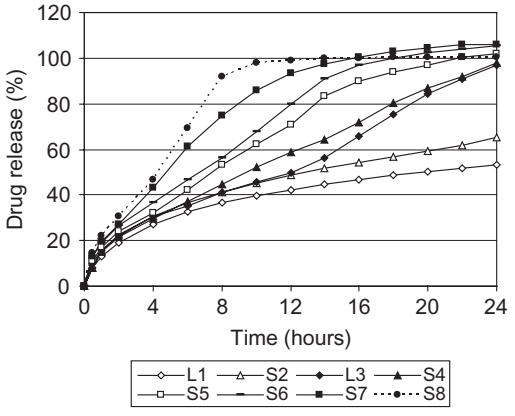

Figure 2. Drug dissolution profiles of matrix tablets samples in phosphate buffer of pH 6.8.

Table 4. Variability of dissolution profiles.

	Standard deviations (%) obtained from dissolution data in time intervals (minutes)														Diference and similarity factors
Sample	30′	60′	120′	240′	360′	480′	600′	720′	840′	960′	1080′	1200′	1320′	1440′	f_1, f_2/Reference
L1	0.08	0.07	0.23	0.45	0.55	0.69	0.73	0.75	0.69	0.55	0.73	0.40	0.47	0.71	14.21, **57.78**/S2
															28.65, **34.17**/L3
S2	0.35	0.35	0.43	0.52	0.35	0.35	0.88	1.33	1.38	1.34	1.50	1.52	1.57	2.08	22.14, **38.78**/S4
L3	0.30	0.36	0.42	0.86	1.26	1.75	2.21	2.53	2.62	2.22	1.80	1.98	2.33	1.72	6.45, **66.51**/S4
															42.18, **25.60**/S8
S4	0.02	0.44	0.37	0.70	3.72	5.96	9.01	14.37	15.19	15.66	15.74	14.05	12.69	7.96	Reference Sample
S5	0.35	0.69	1.33	3.85	9.58	10.03	11.41	12.52	13.20	11.92	9.02	8.22	6.96	5.38	Reference Sample
S6	0.57	0.86	0.68	1.68	4.15	5.59	4.56	4.99	2.67	2.45	2.67	2.57	3.39	3.49	7.10, **63.47**/S5
S7	0.65	1.18	1.10	4.16	3.56	7.96	7.49	3.75	2.12	0.47	1.00	2.57	3.39	3.49	16.35, **43.73**/S5
S8	0.53	1.00	1.26	3.24	1.86	1.25	0.28	0.31	0.39	0.30	0.44	0.54	0.54	0.54	25.00, **35.53**/S5

exhibited similarity probably because of slower dissolution rate of large sucrose particles present in nonsieved material. However, in the case of formulations L3 and S8 (f_1 = 42.18; f_2 = 25.60), the differences between both dissolution data were significant. The effect of different filler solubility thus could be fully demonstrated as similar filler particle size (d of lactose was 31 μm and d of sucrose was 36 μm) was used and other parameters of compared samples were kept constant.

Important aim of this experimental study was to investigate the effect of different particle size of sucrose on the dissolution profile of DS (Figure 2 and Table 4). Samples S4–S8 differed from each other only in the size and size distribution of sucrose particles. To compare their dissolution profiles, f_1 and f_2 factors of these samples were calculated choosing sample S5 as the reference. The calculation showed on one hand a similarity between samples S5 and S6 (f_1 = 7.10; f_2 = 63.47) and, on the other hand, dissimilarities between samples S5 and S7 (f_1 = 16.35; f_2 = 43.73) and S5 and S8 (f_1 = 25.00; f_2 = 35.53). Generally, obtained results indicated that formulations containing smaller particles of sucrose released DS faster; this feature was markedly significant in sample S8 (sucrose particles smaller than 80 μm). This fact could be explained by increased surface area of smaller filler particles and thus rising number of pores formation.

Interesting observation was made when the SD values of released drug amount in all samples were compared. The dissolution profiles of matrices L1 and L3 exhibited low SD_{max} value (0.75 and 2.62%, respectively, Table 4). Different situation was found in samples S4–S8 containing nonsieved sucrose particles and sucrose particles of different size fractions (Table 4). According to the SD_{max} value, the uniformity of dissolution profiles was monitored as the next parameter was potentially influenced by sucrose particle size. On one hand, the value of SD_{max} in sample S4 (15.74%) and S5 (13.20%) showed variable drug dissolution profiles; on the other hand, the value of SD_{max} for other samples reached lower values (sample S6 of SD_{max} 5.59, sample S7 of SD_{max} 7.96, and sample S8 of SD_{max} 3.24%). It is apparent that more uniform DS release from matrix tablets was ensured by batches with narrower particle size distribution of sucrose. Variable dissolution profiles (S4, S5) were caused probably due to different dissolution rate of larger sucrose particles and thus the formation of differing size pores within the matrix systems.

The increase in filler to PVP-30 ratio demonstrated significantly faster DS release from matrix tablets with difference factor f_1 = 28.65 (f_2 = 34.17) for samples L1 and L3, and f_1 = 22.14 (f_2 = 38.78) for samples S2 and S4 (Table 4). Lower amount of PVP-30 in tablets contributed on the one hand to decreased gel formation and on the other hand to faster tablet dissolution because of the higher sugar content. These factors together with slower PVP dissolution[28] might be responsible for the dissolution profiles dissimilarity.

Drug release studies

Both mechanisms—diffusion and erosion—could contribute to drug release process from hydrophilic matrix tablets. Thanks to considerable amount of the lipophilic carrier (cetyl alcohol, 25% [wt/wt]), the prepared samples L1–S8 cannot be considered as typical examples of hydrophilic swellable matrices and thus great attention was paid to the evaluation of drug release mechanisms. Based on the release exponent values (n = 0.49–0.64, Table 5) calculated from the empiric Korsmeyer–Peppas equation, the balance between the two major release mechanisms was investigated. It is generally well known that slightly soluble drugs are predominantly released due to surface erosion and water-soluble drugs mainly by diffusion across the gel layer[14]. DS is a substance very slightly soluble in phosphate buffer of pH 6.8 used as a dissolution medium. Therefore, erosion as the predominant release as well as the release exponent value near 1.0 was expected. This presumption was in agreement with findings observed by Avachat and Kotwal[6]. They found the release exponent n very close to 1.0 (0.94) when DS was released from hypromelose-based matrices in phosphate buffer at pH 6.8. Further, the release data of very slightly soluble drug theophylline[29] from pectin matrix tablets in the same dissolution medium were fitting to Korsmeyer–Peppas equation with release exponent n values in range 0.85–0.88[30].

The release data of all samples obtained during dissolution test were treated according Equations 4–9 and are summarized in Table 5. Durbin–Watson (DW) test was applied to all dissolution data to recognize a risk of apparent regression existence by means of the autocorrelation of residual deviations. The dissolution data showed good agreement with Korsmeyer–Peppas model ($R^2 > 0.98$). Despite the very slight solubility of DS at pH 6.8, the release exponent n average value between 0.49 and 0.50 confirmed that diffusion is the predominant release mechanism in samples L1, S2, and L3 ($n \sim 0.5$), whereas both could participate in drug release from samples S4–S8 as suggested by $n \sim 0.56$–0.64. Generally, this observation could be ascribed to the effect of rapidly and highly soluble sugar fillers (lactose, sucrose), which could participate and help to produce pores and channels throughout the whole volume of almost insoluble matrix tablet[31], and it can be further positively influenced by the osmotic effect of sugars[32,33].

As observed from Figure 3, the surface differences between samples S8 and S5 after 2 hours were not significant yet, but after 5 hours, they were obvious. On the one hand, the relatively smooth surface with created pores within the matrix tablet of sample S8 could be observed

Table 5. Fittings of DS release data to different kinetic equations.

Model	Zero order	First order	Higuchi	Korsmeyer-Peppas		Hixson-Crowell	Baker-Lonsdale
	K_0 (h^{-1})	K_1 (h^{-1})	K_H ($h^{-1/2}$)	K_{KP} (h^{-n})		K_{HC} ($h^{-1/3}$)	K_{BL}
	(CR)	(CR)	(CR)	(CR)	n	(CR)	(CR)
Sample	R^2	R^2	R^2	R^2	(CR)	R^2	R^2
L1	2.50	0.09	0.113	0.128	0.49	0.049	0.0031
	(1.96–3.04)	(0.06–0.12)	(0.104–0.123)	(0.119–0.137)	(0.45–0.52)	(0.040–0.059)	(0.0029–0.0033)
	0.9043	**0.7490**	**0.9891**	**0.9869**		**0.9348**	**0.9968**
S2	2.99	0.08	0.141	0.144	0.50	0.063	0.0044
	(2.20–3.78)	(0.04–0.12)	(0.129–0.155)	(0.128–0.162)	(0.44–0.56)	(0.050–0.076)	(0.0042–0.0046)
	0.8818	**0.7688**	**0.9843**	**0.9818**		**0.9283**	**0.9981**
L3	3.46	0.09	0.151	0.150	0.50	0.076	[a]0.0057
	(3.02–3.90)	(0.07–0.12)	(0.140–0.162)	(0.142–0.158)	(0.47–0.53)	(0.067–0.086)	(0.0044–0.0071)
	0.9738	**0.8637**	**0.9926**	**0.9944**		**0.9826**	**0.9811**
S4	4.90	0.17	0.178	0.167	0.64	[a]0.107	[a]0.0060
	(3.90–5.91)	(0.10–0.25)	(0.166–0.190)	(0.121–0.132)	(0.59–0.68)	(0.091–0.122)	(0.0043–0.0078)
	0.9777	**0.5931**	**0.9979**	**0.9867**		**0.9957**	**0.9986**
S5	5.31	0.12	0.231	0.171	0.59	[a]0.166	[a]0.010
	(4.69–5.93)	(0.09–0.16)	(0.213–0.249)	(0.164–0.177)	(0.56–0.61)	(0.137–0.195)	(0.006–0.015)
	0.9841	**0.8157**	**0.9929**	**0.9957**		**0.9938**	**0.9931**
S6	5.73	0.13	0.238	0.191	0.56	[a]0.148	[a]0.013
	(5.19–6.26)	(0.09–0.16)	(0.210–0.265)	(0.178–0.205)	(0.52–0.61)	(0.127–0.170)	(0.008–0.018)
	0.9909	**0.8923**	**0.9862**	**0.9904**		**0.9910**	**0.9850**
S7	6.59	0.14	0.271	0.200	0.61	0.215	0.022
	(5.76–7.42)	(0.09–0.18)	(0.258–0.284)	(0.189–0.211)	(0.58–0.64)	(0.194–0.235)	(0.015–0.029)
	0.9787	**0.8522**	**0.9936**	**0.9959**		**0.9967**	**0.9884**
S8	8.74	0.16	0.350	0.227	0.62	0.307	0.036
	(7.69–9.78)	(0.11–0.22)	(0.310–0.390)	(0.186–0.276)	(0.53–0.71)	(0.241–0.374)	(0.022–0.050)
	0.9836	**0.9338**	**0.9847**	**0.9879**		**0.9768**	**0.9653**

[a]autocorrelation of residual deviations were found (Durbin-Watson test).

(sucrose particle size less than 80 μm; Figure 3A), on the other hand Figure 3B shows both created pores and eroded tablet surface of sample S5 (sucrose particle size of 500–250 μm). It is obvious that the formed pore size corresponded to the sucrose fraction used and the release exponent n drop was expected when the particle size of the pore-forming agent decreased. The higher n value pointed out the increasing participation of erosion mechanism. Because of the relatively wide n confidential regions of S5–S8, this trend could not be confirmed using this model.

The good correspondence of the data with Higuchi model ($R^2 > 0.98$) supported the theory of predominant Fickian diffusion-type release mechanism. Zero-order kinetics describes the systems where drug release rate is independent of the drug concentration. Prepared samples except L1 and S2 follow zero-order model as confirmed by high values of determination coefficient ($R^2 > 0.97$). The samples L1 and S2 containing the higher amount of PVP-30 formed more viscous environment inside the matrix tablet. This effect probably led to deceleration of drug liberation from these samples within the time when compared to other samples containing only lower amount of PVP-30. It was found that the first-order equation was not a suitable mathematical model for description of our experimental dissolution data ($R^2 < 0.94$).

To evaluate the drug release with changes in tablet surface area and tablet diameter, the data were plotted using the semiempirical Hixson–Crowell model[34]. Despite high value of R^2, the Hixson–Crowell model adequacy was contradicted for samples S4–S6 because the autocorrelation of residual deviations (DW test) was found; it could be explained as a neglect of other explaining variable or unsuitable model. This model, however, could be useful for samples S7 and S8 ($R^2 > 0.97$) indicating the change in matrix tablet shape. This finding might support the participation of erosion mechanism of drug release in these samples which could not be confirmed using the Korsmeyer–Peppas model. Autocorrelation of residual deviations (DW test) was also diagnosed when the Baker–Lonsdale model was applied on the dissolution data in samples L3 and S4–S6. The drug release from samples L1 and S2 was found to be very close to Baker–Lonsdale kinetic model ($R^2 > 0.996$). Thus, it assumed the fact that the drug release from these samples took place by a diffusion

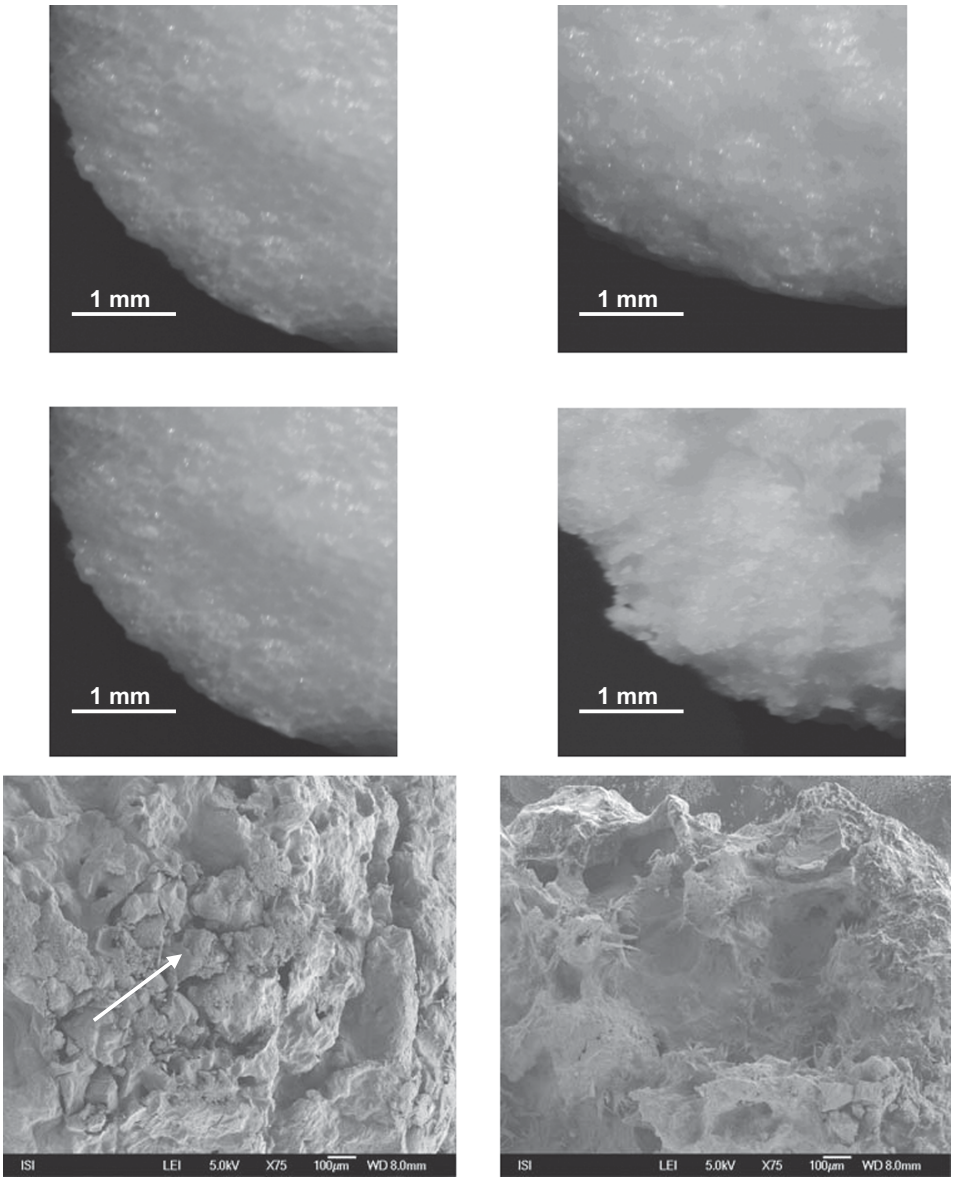

Figure 3. Stereomicroscopic and SEM photographs of tablet surface of samples S8 (A) and S5 (B) after 2 hours (top) and after 5 hours of dissolution test (middle and bottom).

through water-filled channels[35]. These findings corresponded with results arisen from Higuchi model (R^2 > 0.984 for L1, S2) and Korsmeyer–Peppas equation (R^2 > 0.98 for L1, S2 and n = 0.49–0.50).

According to release constant values calculated from fitting kinetics equations (zero-order, Higuchi, Korsmeyer–Peppas) showed in Table 5, it can be concluded that the release rate of DS increased as the particle size of sucrose decreased. As confirmed by the f_1 and f_2 analyses, this dependence is statistically significant. Similar significant dependence was obtained when the filler to PVP-30 ratio increased.

Conclusion

Because of the higher content of cetyl alcohol as the lipophilic carrier, the prepared matrix tablets exhibited the release behavior atypical for swellable matrices, with diffusion as the dominated release mechanism despite slight solubility of DS in phosphate buffer of pH 6.8. The dissolution profile of DS could be influenced not only by used fillers and combinations of other excipients but also very significantly by sucrose particle size. With decreasing sucrose particle size, DS released markedly faster with more uniform dissolution profile.

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