—Regular Articles—

Evaluation of Diclofenac Sodium Release from Matrix Pellets Compressed into MUPS Tablets

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(Received February 27, 2009; Accepted August 18, 2009)

The purpose of the study was to screen the effects of formulation factors on the *in vitro* release profile of diclofenac sodium from matrix pellets compressed into multiple unit pellet system (MUPS) tablets using design of experiment (DOE). Extended release of diclofenac sodium was accomplished using Carbopol® 71G as matrix substance. According to Fractional Factorial Design FFD 2^{3-1} four formulations of diclofenac sodium MUPS matrix tablets were prepared. The process of direct pelletization and subsequently compression of the pellets into tablets was applied in order to investigate a different approach in formulation of matrix systems and to achieve a better control of the process factors over the principal response - the release of the drug. The investigated factors were X_1-the percentage of polymer Carbopol® 71G, X_2-crushing strength of the tablet and X_3-different batches of the diclofenac sodium. *In vitro* dissolution time profiles at 6 different sampling times were chosen as responses. Results of drug release studies indicated that drug release rates vary between different formulations, with a range of 1 to 8 h to complete dissolution. The most important impact on the drug release had factor X_1-the percentage of polymer Carbopol® 71G. The polymer percentage is suggested as release regulator for diclofenac sodium release from MUPS matrix tablets. All other investigated factors had no significant influence on the release profile of diclofenac sodium.

Key words——matrix pellet; direct pelletization; diclofenac sodium; Carbopol® 71G; multiple unit pellet system (MUPS); design of experiments

INTRODUCTION

Hydrophilic gel-forming matrix tablets are widely used as oral extended-release dosage forms.[1,2] The overall rate of drug release is regulated by the viscosity and thickness of the gel layer formed by the matrix tablet. Water penetrates the polymer matrix leading to polymer's swelling by decreasing the glass transition temperature of polymer to the experimental temperature thus leading to transformation of glassy polymer into a rubbery phase.[3] *In vitro* release of water-soluble drugs from hydrophilic matrix systems is mainly controlled by diffusion out of the gel layer, whereas release for poorly soluble drugs is usually controlled by polymer relaxation-dissolution. Concentration of a matrix forming polymer in the matrix tablet's formulation is crucial for adequate drug release mechanism and also for other tablet's characteristics (mechanical properties, drug dissolution rate, disintegration time, water uptake, *etc.*).[4] Carbopol is a cross-linked polymer of acrylic acid with a high molecular weight that forms a hydro gel in aqueous solutions depending on the degree of hydration of the carboxyl group in the molecule. Carbopol has many advantages as a candidate for an extended-release tablet matrix, *e.g.*, a good gel-forming ability and mucoadhesive property.[5,6] Although there are few studies for the production of granules containing carbomer by extrusion-spheronization method,[7] there is no literature data concerning formulation of multiple unit pellet system -MUPS/Carbopol units, intended for drug's extended release. All types of carbomer induces serious problems regarding formulation processes owing to their swelling and gelling properties in water, the reduction of tack is necessary for a successful formulation development. Formulation changes, with the presence of anti-tack action of electrolytes and excipients may induce different release profile of drug from matrix pellets compressed into MUPS tablets.[8]

MUPS are tablets whose sub-units (pellets) are compacted after embedding in appropriate excipients

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/cushioning agents. MUPS are reservoair type of devices with or without coating. The active pharmaceutical ingredient may also be blended or granulated with polymers to provide additional level of control. One way to design oral modified release systems is to coat spherical pellets with a polymer that regulates their drug release rate. Such pellets can be compacted into multiple unit tablets which are normally intended to disintegrate into discrete pellets in the gastrointestinal tract and the drug should subsequently be released in a controlled manner from the individual pellets. One challenge in the production of such tablets is maintaining the desired drug release after compaction, as the application of compaction pressure can lead to structural changes in the film coating and, consequently, altered drug release.[9] The compression induced changes in the structure of a film coating may depend on formulation factors, such as the type of coating, the properties and the structure of the pellets and the incorporated excipients. In this study, different approach of design oral modified release systems is applied, where uncoated pellets were compessed into MUPS tablets and influence of different formulation factors on drug release mechanism was investigated.

Compression behaviour of uncoated pellets can provide basis for the formulation of multiple unit tablets from barier coated pellets without damaging their coating. Pellets have been found to react differently to compaction and consolidation than powders of the same material. The powders examined were found to compact by plastic deformation and produced strong compacts, while the pellets exhibited elastic deformation and brittle fragmentation resulting in compacts of lower tensile strength. This can be explained by the fact that pellets which are large and spherical in shape as compared to the small irregular powder particles they are composed of, have a low surface to volume ratio which might result in decreasing area of contact between the particles as they consilidate. The size of the pellets can also have the bearing on their compression behaviour. Small pellets have been found to be less affected than larger ones by the compaction process. Some were able to correlate this directly to the individual bead strength *i.e.*, the smaller beads wet significantly stronger, relative to their size, than the larger ones. Some, found the deformation of the individual pellets to be correlated to their size, *i.e.*, larger pellets were redily deformed.[10,11] The purpose of the study was to screen the effects of formulation factors on the *in vitro* release profile of diclofenac sodium from matrix pellets compressed into MUPS tablets using design of experiment (DOE). Finally release regulation using Carbopol is discussed and optimal formulations are suggested.

Diclofenac sodium was selected as a model drug. It is generally known that diclofenac sodium migrates into the blood within 30 min and reaches the maximum concentration in blood within 2 h after oral administration and the blood concentration half life is as short as 1.3 h. Since diclofenac sodium is quickly absorbed in and excreted from blood, it is difficult to maintain in the therapeutic level for a long time. For this reason currently comercially available diclofenac sodium tablets must be taken three times a day. Oral administration of diclofenac sodium often induces various side effects including gastroenteritis. The utility of diclofenac sodium which is a non-steroidal anti-inflamatory drug is highly appreciated because of its strong anti-inflamatory and analgesic actions. Therefore there is a strong need for the development of a long acting diclofenac sodium preparation which is capable of exhibiting the effect in a most safe and efficiency manner over an extended period of time.[12]

MATERIALS AND METHODS

Materials Diclofenac sodium batch A (manufacturer A, Switzerland), Diclofenac sodium batch B (manufacturer B, Switzerland), Carbopol® 71G (Lubrizol, USA), Avicel® PH 101 (FMC, USA), Magnesium stearate (Sandoz Pharma AG, Switzerland) and Aerosil® (Evonik, Germany).

Powder Characterization

Particle size distribution Two different batches of diclofenac sodium were characterized.The average particle size was determined by Malvern, Mastersizer X, (Worcestershire, UK). The measurements were carried out at least 3 times for each sample. The average and the median particle size of all samples were measured using MS 64-Dry powder feeder (Model MSX 64, Malvern Instruments, Worcestershire, UK).

For examination of pellets particle size distribution the following instrument settings had been done: The federate was set to level 5 and the air pressure was set between 1–3 bars, the number of sweeps was set to 30 000 in a time frame of 60 s; the active beam length

was set to 10 mm with a range lens of 1000 mm; a minimum obscuration value of 1–10% was obtained in all measurements. With the software (Malvern) the particle size distribution of the samples including mean and medium particle size could be calculated from the raw data. The function ''polydispers'' was activated. The average particle sizes of all samples mentioned above were $>50\,\mu$m, therefore, the ''Frauenhofer'' model was chosen (according to the recommendation of Malvern). For the API diclofenac sodium which was in powdery form, different settings had to be done because it was not possible to determine the particle size distribution with the dry powder feeder without generating artefacts: Huge powder clusters appeared ($>1000\,\mu$m), that could not been separated by increasing the air pressure or by changing the feedrate. Therefore, the particle size distribution had to be determined in a liquid with a MS-1-Small Volume presentation sample unit (Model: MS 519, Malvern Instruments, Worcestershire, UK). For the different samples, different liquids need to be chosen, in order not to dissolve or swell the sample. The particle size of diclofenac sodium was determined in Aceton. The following settings has been done: The number of sweeps was set to 2000 and the sample time to 60 s. The active beam length was set to 2.4 mm using a lens of 300 mm. It was paid attention to get an obscuration value between 10–30% in all measurements. The polydispers function was activated. The mathematical model 2OFD was used (according to the recommendation of Malvern Instruments).

True and tapped density Different measurements were performed: true density, poured and tapped density and finally Hausner Ratio was calculated. The true density was measured with a helium pycnometer AccuPyc™ 1330 (Micromeritics Instrument Corporation, Nocross, USA) with a nominal cell volume of 10 ml. As the true density is expressed as a quotient of mass and volume, the samples were weighed on balance AX204 (Mettler Toledo, Switzerland) and placed in the cell. The volume was determined by purging each sample 10 times with helium. The first five runs were considered as an equilibrating procedure and the average of the last five measurements was taken as the value for true density.

The bulk and tap density were determined using an apparatus Type STAV 2003 (Engelsmann AG, Germany). 100 g sample was placed into a graduated cylinder. The volumes at the beginninig (bulk volume V_0) and after tapping 1250 times (tap volume V_{1250}) were noted. The bulk density (ρ_b) was calculated as a ratio of mass and initial volume V_0, while the tapped density (ρ_t) was calculated as a ratio of mass and tapped volume V_{1250}. The Hausner ratio (HR) was calculated according to following equation:

$$HR=\rho_t/\rho_b \quad (1)$$

HR values less than 1.25 indicate good flow, whereas values greater than 1.25 indicate poor flow. For values between 1.25 and 1.5 added glidant normally would improve flowability.

Residual moisture content The residual moisture content was determined by an infrared drying unit. Mettler Toledo Type LP 16 M (Mettler Instruments, Nanikon-Üster, Switzerland). Samples of approximately 1 g were prepared. They were heated up to 20 min to 110°C giving the loss of moisture in percent by weight. The approximate theoretical moisture content of the granulates was determined by the sum of the moisture contents of the different starting materials in equilibrium with 45% relative humidity at room temperature. The experimental values of the residual moisture content of the granulates coming from a wet state after granulation in contrast to the residual moisture content of the starting materials coming from a dry state-were transformed according to Eq. 2 to values that refer to a dry state of the sample.

$$M_d=100\times M_w/100-M_w \quad (2)$$

M_d is the content of water referred to the dry sample, while M_w is the content of water referred to the wet sample.

Flowability The flowability of all materials were determined with approximately 100 g of sample. By division of the mass through the flowing time, the fowability of different samples was calculated, Eq. 3. The measurement was carried out 5 times for each sample.

$$\text{Flowability}=\text{mass/flowing time} \quad (3)$$

The values of flowability were determined with a hopper made of plexiglass (centre angle: 37.5°, orifice diameter: 9 mm), which was connected to a balance (PC 8000 Mettler Toledo Gmbh, Greifensee, Switzerland). The increase in weight could be measured 375 times per minute. The data were transferred to a computer and automatically put in an excell sheet with the software Balance link (Mettler Toledo, Balance link V 3.01, Greifensee, Switzerland).

DSC analysis Melting point of different batches

of diclofenac sodium was determined by Differential Scanning Calorimetry (DSC) measurements. DSC measurements were performed using Differential Scanning Calorimeter, Pyris 1 (Perkin Elmer, USA). Diclofenac sodium samples of 5–6 mg were weighed into 30 m aluminium pans and scanned from 50 to 320°C at the heating rate of 20°C/min and at a flow rate of nitrogen gas of 20 ml/min. The Pyris 1 instrument was calibrated with indium and zinc prior to analysis. Baseline runs were performed by scanning empty aluminium pans in the temperature between 40 and 350°C in order to test termal behaviour of the measuring system itself. DSC measurements were performed in triplicate.

Morphology The samples were further analyzed on qualitative characteristics. The morphology of the bulk materials and the surface of MUPS tablets were determined by Scanning Electron Microscopy (SEM). SEM images were taken using a ESEM XL 30 FEG. (Philips, The Netherland). The samples were mounted with carbon adhesive on aluminium holder, sputtered with gold and photographed at a voltage of 10 Kv. In the case of MUPS tablets, Ag was used as additional conductor.

Design of Experiment (DOE) The purpose of this study was to investigate effect of formulation variables on drug release from matrix tablets which contained Carbopol® 71G as matrix substance. The formulations were made according to 2^{3-1} fractional factorial design (FFD) where three formulation variable factors were evaluated. Formulation contained API diclofenac sodium, polymer Carbopol® 71G, excipient Avicel PH 101 and lubricants magnesium stearat and Aerosil®.

The independent variables were (levels):

X_1–polymer concentration in formulation-Carbopol® 71G (10–30%)

X_2–crushing strength of the tablets (40–80N);

X_3–diclofenac sodium batch (batch B-batch A)

The dependent variables were:

Y_1–percentage of diclofenac sodium release after 30 min

Y_2–percentage of diclofenac sodium release after 4 h

Applying FFD 2^{3-1}, three independent variables were varied on two levels; there were four formulations with different combinations of these variables. Real and coded values of evaluated factors are shown in Table 1. The experimental design with corresponding formulations is shown in Table 2.

Table 1. Real and Coded Values of Evaluated Factors

Factors	levels	
	−1	+1
X_1 (%)	10	30
X_2 (N)	40	80
X_3 (batch)	B	A

Table 2. Model Formulations (E_1–E_4) and Responses for 2^{3-1} FFD

Formulation	Independent variables (coded values)			Responses	
	X_1	X_2	X_3	Y_1 0.5 h	Y_2 4 h
E_1	−1	−1	+1	29.03	93.96
E_2	+1	−1	−1	5.85	36.91
E_3	−1	+1	−1	20.39	99.18
E_4	+1	+1	+1	2.09	33.12

Design of experiment demonstrated different effects of formulation factors on response variables. The results from FFD were evaluated using the following linear model.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 \quad (4)$$

Where values b_1-b_3 represent regression coefficients, Y is the response variable, and X_1, X_2, X_3, represent the main effects of the formulation variables. Responses were: percent of diclofenac sodium released from tablets after 30 min of drug release examination (Y_1) and percent of diclofenac sodium released after four hours of testing (Y_2). In case of low or high level of polymer it was only investigated and discussed the effect of Carbopol® 71G and its specific behaviour and not the presence of Avicel which in this study is in the role of excipient.

Pelletization Process According to the fractional factorial design FFD 2^{3-1}, four formulations of pellets E_1-E_4 were prepared by direct pelletization in a rotary fluidized bed granulator GPCG1 (Glatt, Binzen, Germany), fed with air of standardized humidity of 40±5%. In these formulations three different factors were varied on two levels (−1) and (+1): batch of the diclofenac sodium (B, A), percentage of polymer Carbopol® 71G in formulation (10%, 30%) and the crushing strength of the tablet (40N, 80N), as shown in Table 1. Excipients were Avicel® PH 101, Carbopol® 71G. Starting materials (excipients and

Table 3. Process Conditions during Pelletization

Process parameters	setting
Batch size (g)	500
Type of disc	smooth
Inlet air volume (m^3/h)	43–45
Inlet air temperature (℃)	28–30
Sprayer pressure (bar)	1.5
Rotor rotation speed (%)	100
Process time (min)	45
Spheronization time (min)	10
Spray rate (g/min)	3–5
Shaking interval (time/s)	5/3

API) in quantity of 500 g were premixed (fluidized) and heated in the granulator. The granulation liquid-water was sprayed onto the fluidized bed continuously (approximately 3–5 g/min). After spraying, the pellets were dried under smooth agitation for 4 h on the tray in the oven Hereaus RVT 360, Hanau, Germany. The process of pelletization was controlled by a computer program, process parameters are shown in Table 3. All of the ingredients used in this study came from the same lot and the same procedure and equipment were used in the production and testing tablets.

Pellet Characterization The pellets E_1-E_4 were analysed on residual moisture, particle size distribution by laser diffraction, flowability, true density, Hausner ratio and SEM using the same conditions and equipment as for the powder characterization. Porosity of the pellets was determined by analyzing the specific surface area using the method of gas adsorption on Quantachrome Nova 2000E (Quantachrome Instruments, Florida, USA) using nitrogen gas as the adsorbate and applying the BET equation. Before performing a surface area analysis or pore size measurement, pellets were freed from possible contaminants. Surface cleaning (degassing) was carried out by placing a sample of pellets in a glass cell and heating it under a inert gas. Once degassed, the samples were brought to a constant temperature by means of an external bath, typically a dewar flask containing a cryogen like liquid nitrogen. Then, small amounts of a gas (the absorbate) are admitted in steps into the evacuated sample chamber. Absorbate molecules quickly fulfilled to the surface of every pore in the pellet sample. The process duration was 24 h. Measurements were performed in triplicate.

Compression of Pellets into Tablets The pellets E_1-E_4, with added lubricants Aerosil® and Magnesium stearate, were compressed into MUPS tablets on the Presster™ compaction simulator (Metropolitan Computing Corporation, East Hanover, US). The crushing strength of the tablet (−1) 40N and (+1) 80N was controlled by adjusting the gap between the upper and lower punch in the range of 2.5–3 mm. Biconvex faced punches of 7 mm in diameter-D-tooling (with a tablet weight of 90±4,5 mg) were used and a rotary tablet press (Killian type Pharma I) was simulated at the speed of 4000 tablets per hour corresponding to a dwell time of 28.3 ms. Constant distant between punches was 7.4 mm and constant linear velocity of the compaction 0.471 m/s. Matrix tablets were examined on weight, thickness, crushing strength and diameter using Erweka TBH 30 and friability using Erweka TA 20.

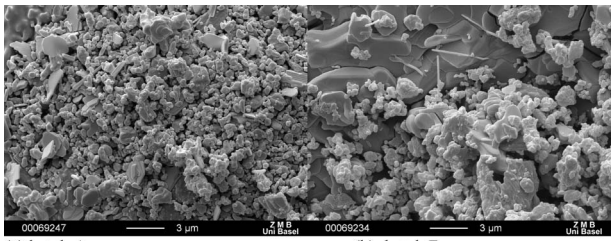
Drug Release Study The drug release of diclofenac sodium from MUPS tablets was examined using Erweka dissolution tester type DT-80. 900 ml of media were used at pH 6.8 phosphate buffer for 8 h of examination at 37±5℃, using the USP paddle apparatus with stirring speed of 50 rpm. The concentration of diclofenac sodium was determined by UV-VIS spectrophotometric method at wavelength of 276 nm. Cumulative percentage of drug release was calculated and used in data analysis. The results are mean of three replicates.

RESULTS AND DISCUSSION

Powder Characterization The results of the characterization of API diclofenac sodium are presented in Table 4. Characterization demonstrated that batch A showed better physical properties, especially in particle size distribution. Mean diameters for particle size distribution with batch A were D (v, 0.1) = 16.96 μm, D (v, 0.5) = 55.6 μm, D (v, 0.9) = 126.99 μm. Values for average particle size distribution of batch B were D (v, 0.1) = 3.39 μm, D (v, 0.5) = 74.04 μm, D (v, 0.9) = 291.46 μm. Results confirm that quality of the batch A was better and more uniform in respect of particle size distribution. Batch B is found to have coarse particles or more agglomerated comparing to batch A. DSC analysis indicated that there was no significant difference in the melting points between the two batches. The values for melting point were very similar around 291–292℃ during testing. SEM pictures showed different morphology

Table 4. Results for the Powder (API) Characterization

Tests	Diclofenac sodium batch A	batch B
Residual moisture [%]	0.34	0.25
Particle size distribution [μm]		
D (v, 0.1)	16.96	3.39
D (v, 0.5)	55.60	74.04
D (v, 0.9)	126.99	291.46
True density [g/ml]	1.5016	1.5466
DSC melting point [°C]	291.309	292.098
HR	1.7716	1.1110
Flowability [s/100 g]	n.a	n.a



(a) batch A (b) batch B

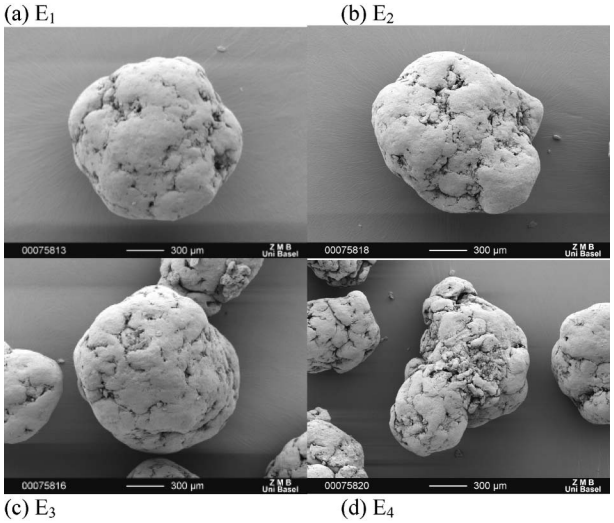
Fig. 1. SEM for Diclofenac Sodium Batch A and Batch B (magnification ×5000).

of the particles of the two batches: batch A had almost round and more homogenous shape than batch B where particles were more agglomerated and with rough surfaces as shown in Fig. 1(a) and (b). Results for both batches for the true density were similar. The calculated Hausner Ratio showed that ratio between tapped and poured density was higher at batch A. The Hausner ratio for batch A is 1.7716 which indicates very poor or even no flowability which is confirmed by flowability experiment. For batch B HR value (1.1110) is less but close to 1.25 and for batch B of diclofenac also is confirmed poor flowability in the flowability testing experiment. Respecting this values of the physical characterization for the formulation development batch A has small advantage because of more uniform particle size distribution. The problem of poor flowability is resolved with added lubricant in the formulation.

Pellet Characterization Tests demonstrated that flowability of the pellets E_2 and E_3, were lower using batch B. On the other side, pellets E_1 and E_4, containing bach A, showed higher flowability, especially pellet formulation E_1 which contains lower percentage of very viscous polymer (Table 5). Results

Table 5. Results for the Pellets Characterization

Tests	Pellet formulations E_1	E_2	E_3	E_4
Residual moisture [%]	2.13	2.09	2.01	1.81
Particle size distribution [μm]	403.75	473.55	483.4	755.6
True density [g/ml]	1.4929	1.4709	1.4892	1.4712
HR	1.0483	1.0363	1.0487	1.1378
Flowability [s/100 g]	11.830	24.370	23.100	15.400
Specific surface area [m^2/g]	0.791	0.455	0.620	0.085



(a) E_1 (b) E_2 (c) E_3 (d) E_4

Fig. 2. SEM for E_1, E_2, E_3, E_4 pellet (magnification ×50).

for the specific surface area showed that value is decreasing from E_1 to E_4. Pellet formulation E_4 had high level of polymer and contained batch A with smaller particles which resulted with low porosity. Pellet formulation E_1 had low level of polymer and batch A also but the pellets were with high porosity. Formulation E_4 had uniform average particle size distribution and the greatest particle size due to a high level of polymer and his adhesive properties and at the same time the lowest result for the specific surface area. True density measurements demonstrated similar results for all pellet formulations. SEM pictures showed that pellets E_1 and E_3 proper pellet, spherical shape and they consisted of smaller particles with similar size, compared to pellets E_2 and E_4 (Fig. 2).

Tablet Characterization All four formulations were very highly compressible resulting in MUPS tablets of 40N and 80N of crushing strength, with RSD around 1% as shown in Table 6. It was satisfactory behaviour of the MUPS tablets concerning

Table 6. Results for the Tablet Characterization

Tablet formulation	Tests					
	Crushing strength [N]	RSD [%]	Thickness [mm]	Diameter [mm]	Friability [%] 4 (20 min)	Weight [mg]
E_1	41.5	1.12	2.88	7.12	0.55 (1.11)	90.12
E_2	45.0	1.19	2.86	7.01	0.54 (1.39)	90.01
E_3	82.0	0.83	2.59	7.07	0.04 (0.23)	89.12
E_4	84.0	1.68	2.41	6.99	0.14 (0.61)	88.01

different percentage of the polymer in formulation. Friability of the MUPS tablets were in the limits, below 1% after 4 min of testing. But friability results were significantly lower with MUPS tablets E_3 and E_4. Both formulations had higher tablet crushing strength. Concerning that flowability of the pellets was good, pellets with added lubricants, magnesium stearat and aerosil filled the die fluently and the weight of the tablets were very uniform.

Results of the MUPS tablet characterization showed that beside of significantly different concentration of polymer in formulation experimentally designed crushing strength of tablets were reached, with corresponding tablet thickness, diameter and weight. That leads to conclusion that presence of hydrophillic polymer Carbopol® 71G, no matter the concentration did not influence the tablet hardness. That was especially interesting after observation of the results of the dissolution study, the controlling factor for the drug release was the concentration of polymer, on the other hand influence of crushing strength of MUPS tablets was less significant.

SEM shows that MUPS tablets as well as pellets had different morphology due to a different levels of polymer. Formulations of MUPS with lower concentration of polymer on the surface and on the cross section had visible spheres with regular shape MUPS E_1 and E_3. With larger amount of polymer there is no visible shapes or spheres, only the surface which is not clearly divided MUPS E_2 and E_4 (Fig. 3).

Compaction, however, decreased the pellet porosity and affected the shape of the individual pellets, resulting in more irregular pellets. Increasing the compaction pressure resulted in an increased pellet surface area and a reduced pellet thickness, which indicated that the shape was more irregular as the compaction pressure increased. As for densification of the pellets, the results imply a low reduction in porosity at the lowest compaction pressure. Thus, both the densification and the deformation of the pellets studied increased with increasing compaction pressure.

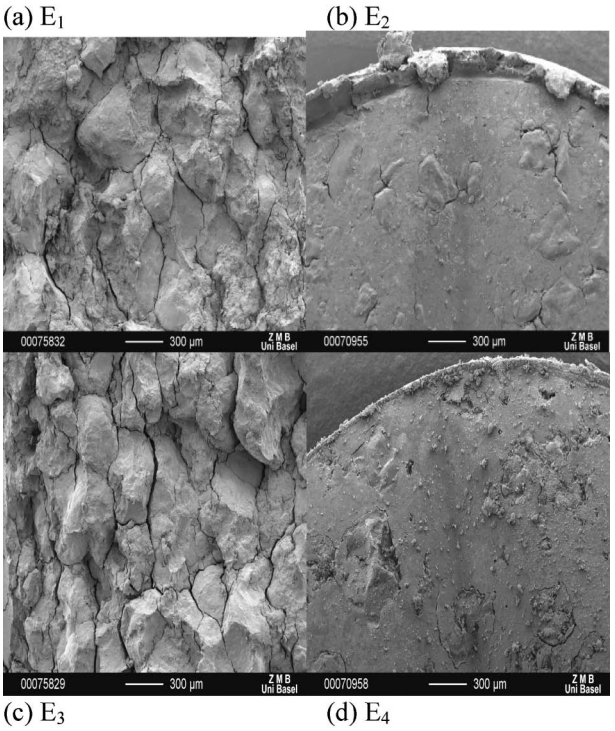


Fig. 3. SEM for E_1, E_2, E_3, E_4 MUPS Tablet (magnification ×50).

Drug Release Study Figure 4 demonstrates dissolution profiles from MUPS tablets E_1-E_4. For release profiles, similarity factor-f_2 was calculated. Value f_2 for E_1-E_3 was 59.29, showed that these two formulations were similar. These formulations had the same lower concentration of polymer Carbopol 71, but different batch of diclofenac sodium and different crushing strength of the tablet. Value f_2 for E_2-E_4 was 70.37, demonstrates even more similar release profiles than E_1-E_3; Formulations E_2-E_4 had higher concentration of polymer but different batch of diclofenac sodium and different crushing strength of the tablet. Values f_2 for formulations were follow-

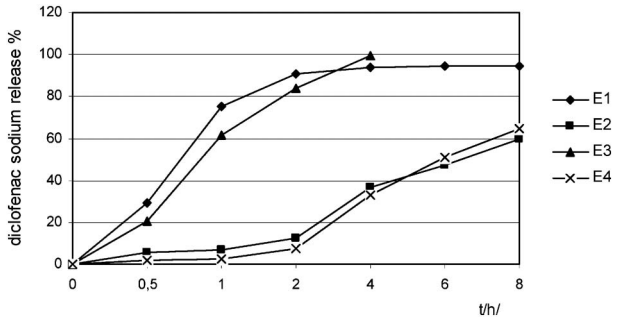


Fig. 4. Dissolution Profiles from E_1-E_4 MUPS Tablets

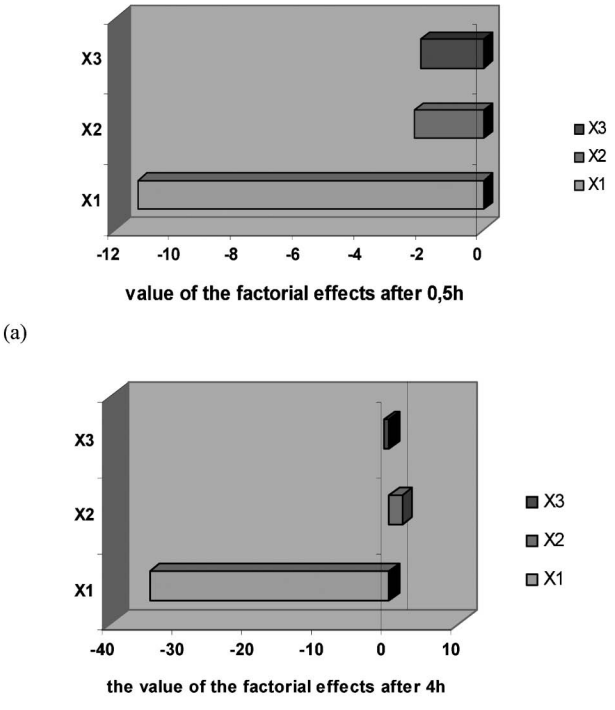


Fig. 5. Influence of Varied Factors on Profiles E_1-E_4 MUPS Tablets after 0.5 h and 4 h of Dissolution Testing

ing: for formulations E_1-E_2 was 16.16 (the same crushing strength of the tablet 40N, different batch of diclofenac sodium and different percentage of polymer), for E_1-E_4, f_2 was 17.03 (the same batch of diclofenac sodium, batch A, different tablet strength and polymer percentage); E_2-E_3, f_2 was 14.61 (the same batch of diclofenac sodium, batch B, different tablet strength and different polymer percentage); E_3-E_4, f_2 was 18.87 (the same crushing strength of the tablet 80N, different diclofenac sodium batch and different polymer percentage). All these values were higher than 50, indicating that formulations do not have similar release profiles.

The conclusion is that only factor X_1, *i.e.*, concentration of the polymer had influence on the release properties of diclofenac sodium. Different batches of diclofenac sodium, consequently different structure and physical characteristics of the starting material and pellets, did not influence drug release. Also different compressibility properties of the different formulations and resulting crushing strength of the tablet did not impact dissolution profiles.

Results of drug release studies from formulations obtained according to FFD 2^{3-1} were fitted into the linear model, and following models were calculated for responses: Y_1-drug release after 0.5 h and Y_2-drug release after 4 h of examination (Fig. 5):

$$Y_1 = 13.50 - 11.21X_1 - 2.26X_2 - 2.06X_3 \quad (5)$$

$$Y_2 = 62.30 - 34.27X_1 + 1.86X_2 - 0.74X_3 \quad (6)$$

At the start of the examination all the factors had negative impact on the drug release; concentration of the polymer had the greatest significance. The crushing strength of the tablet and batch of diclofenac sodium had approximated but not significant influence on drug release. After 4 h of examination factor crushing strength (X_2) had positive impact on the drug release but not significant one. Figure 5 demonstrates that the percentage of polymer Carbopol® 71G (X_1), had the most significant influence on diclofenac sodium dissolution profile from matrix tablets E_1 to E_4 during critical 0,5, 4 and 8 h examination, respectively. Increasing percentage of polymer resulted in decreasing release rates of the drug. The influence of the different batches of diclofenac sodium (X_3) on dissolution E_1-E_4 was not a significant factor. The dissolution profile was identical for both batches. The factor crushing strength of the tablet (X_2) did not have significant influence on diclofenac sodium release either. That demonstrated that with hydrophilic polymer in formulation, crushing strength of the tablet did not show influence on the drug release.

Decreased dissolution rates have been reported when coated pellets have been compressed without any excipient to ensure disintegration of the tablets[13,14] and matrix tablets have also been reported to form at high compaction pressures even with the excipients included in the tablet formation.[15] The limited effect of the compaction pressure on the release mechanism has been attributed to deformation or fragmentation of the pellets even at low pressures.[16] Compaction of less porous coated pellets resulted in a considerably increased drug release rate,

while the release rate from pellets of high porosity was scarcely affected by compaction.

CONCLUSION

The aim of this study was to produce pellets containing Carbopol 71G by rotary fluid bed granulator and then to compress them into the MUPS tablets. The influence of formulation related variables were investigated affecting the properties of pellets subsequently compressed into MUPS and the *in vitro* release profiles of diclofenac sodium from MUPS tablets.

The experiments presented in this study are result of different approach in a tablet technology and they are somewhere between a tablet as a single dosage form and MUPS as multi unit particle system. This method was applied in order to investigate a possible differences in technologies of matrix systems and maybe to achieve more control of the factors over the principal response - the release of the drug. The purpose of process of pelletization and subsequently compression of the pellets into the tablets was to point all factors and parameters that have to be considered respecting the release of the drug. The main objective here was not comparation of the drug release between different dosage forms but discussion of the formulation factor impact on drug release in such a specific matrix system using design of experiments. Experimental design was critically important tool in this study to improve principal response - the release of the drug. The application of experimental design techniques in formulation development reduced variability and closer conformance to target requirements, reduced development time, selection of formulation factors so that the product works well under a wide variety of conditions, so that the product is robust, determination of key formulation factor that impact formulation performance. This study could also be considered as factor screening with a relatively large region of interest because as we learn more about which factors are important and which levels produce the best results, the region of interest becomes narrower. The choice of design here involved consideration of sample size, selection of a suitable run order for the experimental trials, and determination of whether or not blocking or other randomization restrictions are involved.

Concerning the great differences in applied concentrations of Carbopol® 71G as matrix substance, obtained values of physical characterization of pellets and MUPS were very similar. On the other hand, qualitative characterization demonstrated differences in morphology of pellets and MUPS due to a different amount of polymer in formulations.

Results of drug release studies indicated that drug release rates varied between different formulations, with a range of 1 h to 8 h of dissolution. Increase of polymer resulted in decrease of percent of diclofenac sodium released after 8 h. Influence of crushing strength of the tablet was less significant.

The conclusion of the study is that the polymer's percentage was found to be a controlling factor in the release of diclofenac sodium from the MUPS matrix tablets. Increasing percentage of Carbopol® 71G resulted in decreasing release rates of the drug. All further investigated factors had no significant influence on the release profile of diclofenac sodium from MUPS matrix tablets. These results may assist in developing robust MUPS formulation.

Acknowledgments This work was done under the project no. TR23015 supported by the Ministry of Science and Technological Development, Republic of Serbia.

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