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Optimization of Drug Release from Compressed Multi Unit Particle System (MUPS) Using Generalized Regression Neural Network (GRNN)

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The purpose of this study was development of diclofenac sodium extended release compressed matrix pellets and optimization using Generalized Regression Neural Network (GRNN). According to Central Composite Design (CCD), ten formulations of diclofenac sodium matrix tablets were prepared. Extended release of diclofenac sodium was acomplished using Carbopol® 71G as matrix substance. The process of direct pelletisation and subsequently compression of the pellets into MUPS tablets was applied in order to investigate a different approach in formulation of matrix systems and to achieve more 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® 71 G and X_2- crushing strength of the MUPS tablet. In vitro dissolution time profiles at 5 different sampling times were chosen as responses. Results of drug release studies indicate that drug release rates vary between different formulations, with a range of 1 hour to 8 hours of dissolution. The most important impact on the drug release has factor X_1 -the percentage of polymer Carbopol® 71 G. The purpose of the applied GRNN was to model the effects of these two causal factors on the in vitro release profile of the diclofenac sodium from compressed matrix pellets. The aim of the study was to optimize drug release in manner wich enables following in vitro release of diclofenac sodium during 8 hours in phosphate buffer: 1 h: 15-40%, 2 h: 25-60%, 4 h: 35-75%, 8 h: >70%.

Key words: Matrix pellets, Multi unit particle system (MUPS), Direct pelletization, Diclofenac sodium, Carbopol® 71G, Extended release

Selected by Editors

INTRODUCTION

Hydrophilic gel-forming matrix tablets are widely used as oral extended-release dosage forms (Nellore et al., 1995; Kranz et al., 2005). The overall rate of drug release is regulated by the viscosity and thickness of the gel layer formed from the matrix tablets. 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 (Jamzad et al., 2004). *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.) (Bettini et al., 2001). Carbopol is a cross-linked polymer of acrylic acid with a high molecular weight that forms a hydrogel 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 (Tapia-Albarran and Villafuerte-

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Robles, 2004; Park et al., 2007) There is a study on production of granules containing carbomer by extrusion-spheronization method (Gomez-Carracedo et al., 2001). However, there is no literature data concerning formulation of multiparticulate compressed drug/ 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 (Jeon, 2007).

MUPS-multi unit particle system is tablets whose sub-units (pellets) are compacted after embedding in appropriate excipients/ cushioning agents. MUPS is 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 (Tunon, 2003). Another way to formulate oral modified release dosage form is to prepare matrix pellets, with drug dispersed into polymer matrix, and compressed into MUPS tablets. In such dosage form, changes of drug release affected by film coating damages are avoided. In this study, uncoated pellets were compessed into MUPS tablets.

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 (Haslam et al., 1998; Johansson et al., 1998). 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 consolidate. 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 readily deformed (Haslam et al., 1998; Johansson et al., 1998; Maganti and Celik, 1994).

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 blood 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 (Su et al., 2003).

The purpose of the study was to model the effects of formulation factors on the *in vitro* release profile of diclofenac sodium from compressed matrix pellets using different optimization techniques ,design of experiment (DOE) and artificial neural network (ANNs). ANNs can be considered as a nonlinear regression analysis tool, and could be applied to quantify a nonlinear relationship between causal factors and pharmaceutical responses by means of iterative training of data obtained from a designed experiment. (Ibric et al., 2002). ANNs are characterized by architecture, transfer function and learning paradigm.

The purpose of the present study was to apply the optimization method incorporating a generalized regression neural network (GRNN) to development of dic lofenac sodium matrix MUPS tablets which has optimized release behaviour during 8h in phosphate buffer: 1 h: 15-40%, 2 h: 25-60%, 4 h: 35-75%, 8 h: >70%. Carbopol 71®G (chosen as matrix substance) and crushing strength of tablet were screen out as the most important (causal) factors responsible for the in vitro release profile of the diclofenac sodium from compressed matrix pellets.

MATERIALS AND METHODS

Materials

Model drug used in this study, diclofenac sodium obtained from Novartis (Lot # 125471), had following characteristics: particle size distribution D (v,0.1) 16.96 μm, D (v,0.5) 55.60 μm, D (v,0.9) 126.99 μm; true density 1.5016 g/mL; melting point 291.309 °C; residual moisture 0.34% and HR 1.7716. Carbopol® 71 G obtained from Gattefosse (Lot #TW69GAJ075); had following characteristics: viscosity 5740cps, pH 3,5-4,0; residual moisture 1,09%. Excipients used in this study were of pharmaceutical grade, Avicel® PH 101 (Lot #6918), Magnesium stearate (Lot #84804) and Aerosil® (Lot #011054) purchased from FMC, Sandoz Pharma AG, and Evonik, respectively. All other reagents purchased from commercial sources were of analytical grade.

Design of experiment (DOE)

The formulations were made according to Central Composite Design (CCD) where two formulation variable factors were evaluated.

The independent variables were (levels):

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

X_2 - crushing strength of the tablets (40-80N)

The dependent variables were:

Y_1 - percentage of diclofenac sodium release after half hour

Y_2 - percentage of diclofenac sodium release after 1 h,

Y_3 - percentage of diclofenac sodium release after 2 h,

Y_4 - percentage of diclofenac sodium release after 4 h,

Y_5 - percentage of diclofenac sodium release after 8 h,

Applying CCD, two independent variables were varied on two levels; there were ten formulations with different combinations of these variables. Real and coded values of evaluated factors are shown in Table I. The experimental design with corresponding formulations is shown in Table II.

The formulation of diclofenac sodium compressed matrix pellets was optimized using neural network as optimization method. In this case study –generalized regression network (GRNN) was used. GRNN was applied using commercially available Statistica Neural Network Software (StatSoft Inc.).

GRNN is based upon statistical techniques for kernel-based estimation of probability density functions for classification and regression problems respectively. It is characterized by simple, fast training algorithms and large, slow-executing resulting networks. GRNNs, comparing to the other ANNs, model the function more-or-less directly from the training data. This has the advantage that there is no need for training or at least for "training" which is actually very simple, consisting of little more than changing the form in which training data are held.

Table I. Real and coded values of evaluated factors

Factors	Levels	
	-1	+1
X_1 [%]	10	30
X_2 [N]	40	80

Table II. Model formulations (F_1-F_{10})-real and coded values of independent variables for CCD

Pellets	X_1	Crushing strength of the tablet [N]	X_2	Carbopol® 71G %
F_1	-1	40	-1	10
F_2	+1	80	-1	10
F_3	-1	40	+1	30
F_4	+1	80	+1	30
F_5	$-2^{1/2}$	31.7	0	20
F_6	$+2^{1/2}$	88.3	0	20
F_7	0	60	$-2^{1/2}$	5.86
F_8	0	60	$+2^{1/2}$	34.14
F_9	0	60	0	20
F_{10}	0	60	0	20

Pelletization process

According to the Central Composite Design CCD, ten formulations of pellets F_1-F_{10} were prepared by direct pelletization in a rotary fluidized bed granulator GPCG1, fed with air of standardized humidity of 40 ± 5% at 21 ± 1°C. In these formulations two different factors were varied on two levels (-1) and (+1): percentage of polymer Carbopol® 71 G (10%, 30%) and the crushing strength of the tablet (40N, 80N), as shown in Table I. Excipients were Avicel® PH 101, Carbopol® 71 G. Starting materials (excipients and 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) using tangentially spraying nozzle. After spraying, the pellets were dried under smooth agitation for the 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 III. 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.

Table III. Process conditions during pelletization

Process parameters	Settings
Batch size (g)	500
Type of disc	smooth
Inlet air volume (m^3/h)	43-45
Inlet air temperature (°C)	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/sec)	5/3

Pellet characterization

The pellets F_1-F_{10} were analysed on residual moisture, particle size distribution, flowability, true density, Hausner ratio and Scanning Electron Microscopy (SEM).

Particle size: The average particle size was determined by Malvern, Mastersizer X. 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).

The following instrument settings had been done: the air pressure was set between 1-3 bars, the number of sweeps was set to 30000 in a time frame of 60s; 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 the particle size distribution of the samples including mean and medium particle size could be calculated from the raw data.

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) 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) 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). Sample in quantity of 100 g was placed into a graduated cylinder. The volumes at the beginning (bulk volume V_O) 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 $V_{O,}$ while the tapped density (ρ_t) was calculated as a ratio of mass and tapped volume $V_{1250.}$ The Hausner ratio (HF) was calculated according to following equation:

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

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: The residual moisture content was determined by an infrared drying unit. Mettler Toledo Type LP 16 M (Mettler Instruments). Samples of approximately 1g were prepared. They were heated up to 20 min to 110°C giving the loss of moisture in percent by weight.

Flowability: The values of fowability were determined with a hopper made of plexiglass (centre angle: 37.5°C, orifice diameter: 9 mm), which was connected to a balance (PC 8000 Mettler Toledo Gmbh). The increase in weight could be measured 375 times per minute. The data were transferred to a computer and automatically put in an excel sheet with the software Balance link (Mettler Toledo, Balance link V 3.01). 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. (2). The measurement was carried out 5 times for each sample.

$$\text{Flowability} = \text{mass} / \text{flowing time} \quad (2)$$

Scanning electron microscopy: The morphology of the pellets and the surface of MUPS tablets were determined by Scanning Electron Microscopy (SEM). SEM images were taken using an ESEM XL 30 FEG . (Philips). The samples were mounted with carbon adhesive on aluminum holder, sputtered with gold and photographed at a voltage of 10 Kv. In the case of MUPS tablets, Ag was used as additional conductor.

Compression of pellets into tablets

The pellets F_1-$F_{10,}$ with added lubricants Aerosil® and Magnesium stearate, were compressed into tablets on the Presster™ compaction simulator (Metropolitan Computing Corporation). 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. Bi-convex faced punches of 7 mm, D-tooling, in diameter (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 was 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 and superficial morphology by SEM using a Philips ESEM XL 30 FEG.

Drug release study

The drug release of diclofenac sodium from MUPS tablets was examined using Erweka dissolution tester type DT-80. The test was performed in following conditions: 900 mL of media, pH 6.8 phosphate buffer during 8h of examination at temperature 37 ± 5°C using the paddle apparatus with stirring speed of 50 rpm. The concentration of diclofenac sodium was determined by UV-VIS spectrophotometric method at wavelength 276 nm. Cumulative percentage of drug release was calculated and used in data analysis. The results are mean of three replicates.

RESULTS AND DISCUSSION

Pellet characterization

Result of the pellet characterization showed that there were no significant differences between formulations of pellets with different percentage of polymer. The formulation with 34.14% of polymer had the smallest particle size and due to viscous structure of polymer slow flowabilty rate although result for Hausner ratio was less than 1.25. Formulation with lowest amount of polymer had fastest flowabilty rate as expected with HR value below 1.25. Result for density properties were similar, therefore compressibility of pellet formulations were not significantly different. Formulation with 20% of polymer had greatest particle size, not uniform particle size distribution and slowest flowability properties. SEM characterization of F_1-F_{10} showed that not all products were pellets. Some formulations of the pellets were not regular pellet spherical shape due to a different percentage of polymer. They were practically granules and not pellets. The parameters: sphericity, roughness and aspect ratio show the main difference between granules and pellets as they are directly related to the surface properties. For a pharmaceutical use, the more spherical pellets of smoother surface are better, since they are more appropriate for a further process, such as coating. The content of polymer in formulation was crucial for the pellet shape; higher percentage of polymer resulted in tacking, the contact between particles was intensive and water could penetrate into the cracks leaving the rough surface, thus the carbomer particle in powder blend had more chance to form a gel. The same spheronization step could lead to even distribution of spraying water in the powder bed with low percentage of polymer because there was no tacking and the surface of pellets were smooth without cracks and fissures. A rolling action after the pelletization affected the surface morphology of the pellets. It improved the surface plasticity of wet mass, therefore the smoother surface was found. With a lot of viscous polymer in the powder rolling action was difficult and disabled. It was indicated that 10 min of spheronization step led to a remarkable improvement in sphericity. With higher level of polymer it was 5 min. Although the powder particles were not fully agglomerated, some partial aggregate could occur. Therefore, the less spherical and oversized pellets or granules were produced. Roughness can be also explained by the correlation with sphericity. The more spherical and smoother pellets show the smaller aspect ratio and roughness. Since aspect ratio is closely related with sphericity, it is decreased as the sphericity increased. Polymer percentage affected negatively the sphericity of pellets, aspect ratio was increased. There were no anti tack action in the system in order to investigate a behavior of the different percentage of polymer in the pelletization process. The pellets shape were formulations F 1,2 and 7 which had the lowest percentage of polymer: respectively 10, 10 and 5.86 %. Formulation F_8 had the largest amount of polymer and product without the shape and sphericity, with rough edges, which lead to conclusion that polymer Carbopol® 71G content in pellet formulation should not exceed 20% applying technique of direct pelletization.

Table IV. Results for the pellets characterization

Carbopol 71 G [%]	Residual moisture [%]	Particle size distribution average [μm]	True density [g/mL]	HR	Flowability [s/100g]
10.00	2.20	645.00	1.4955	1.2048	16.20
30.00	2.94	754.61	1.4717	1.2306	18.83
20.00	3.44	796.30	1.4960	1.1684	20.30
5.86	2.98	628.40	1.4435	1.2399	11.83
34.14	2.11	509.83	1.4864	1.1354	19.50

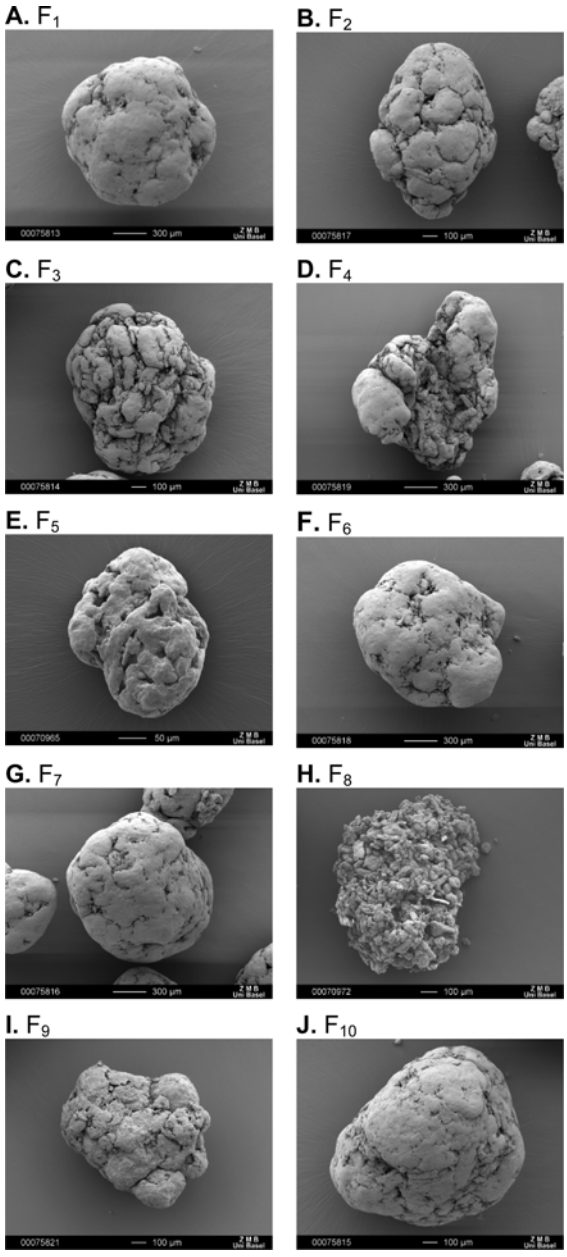

Fig. 1. SEM for F_1- F_{10} pellets

Tablet (MUPS) characterization

Results of the MUPS characterization showed that even with significantly different ratio of polymer experimentally designed crushing strength of tablets was reached, with corresponding tablet thickness, diameter and weight. All ten formulations were very highly compressible resulting in MUPS tablets of different value for crushing strength, with RSD less then 5% as shown in Table V. That led to conclusion that presence of hydrophilic polymer, with different concentrations, 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 percentage of polymer. However, influence of crushing strength of compressed matrix pellets was less significant. Friability of the MUPS tablets were in the limits, below 1% after 4 min of testing. Friability results were significantly higher with MUPS tablets F_5, which had lower tablet crushing strength and lowest ratio of polymer. Concerning that flowability of the pellets was good, pellets with added lubricants, magnesium stearas and Aerosil filled the dye fluently and the weight of the tablets were very uniform.

Results of the MUPS tablet SEM characterization showed that MUPS tablets as well as pellets had different morphology due to a different amount of polymer. Formulations of MUPS with lower ratio of polymer on the surface and on the cross section had visible spheres with regular shape. A formulation of tablets with larger amount of polymer had no visible shapes or spheres only the surface which is not clearly divided. SEM analyse showed that compressed pellets F_2, F_4 and F_6 had smoother surface because they had higher crushing strength than F_1, F_3, and F_5. Compaction force 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

Table V. Results for the MUPS tablet characterization

	Tests					
MUPS	Crushing strength [N]	RSD [%]	Thickness [mm]	Weight [mg]	Friability [%]	Diameter [mm]
F_1	47.10	1.41	2.75	90.05	0.55	7.01
F_2	84.20	3.12	2.38	89.64	0.48	7.03
F_3	45.15	2.15	2.84	90.54	0.81	7.12
F_4	83.12	3.13	2.49	89.50	0.47	7.64
F_5	35.70	2.58	2.86	91.12	0.97	7.16
F_6	91.30	3.55	2.31	88.70	0.35	6.99
F_7	67.50	4.11	2.67	89.92	0.63	7.34
F_8	65.50	3.10	2.56	88.05	0.75	7.13
F_9	62.00	2.12	2.60	90.21	0.61	7.21
F_{10}	60.21	1.12	2.45	91.35	0.45	7.35

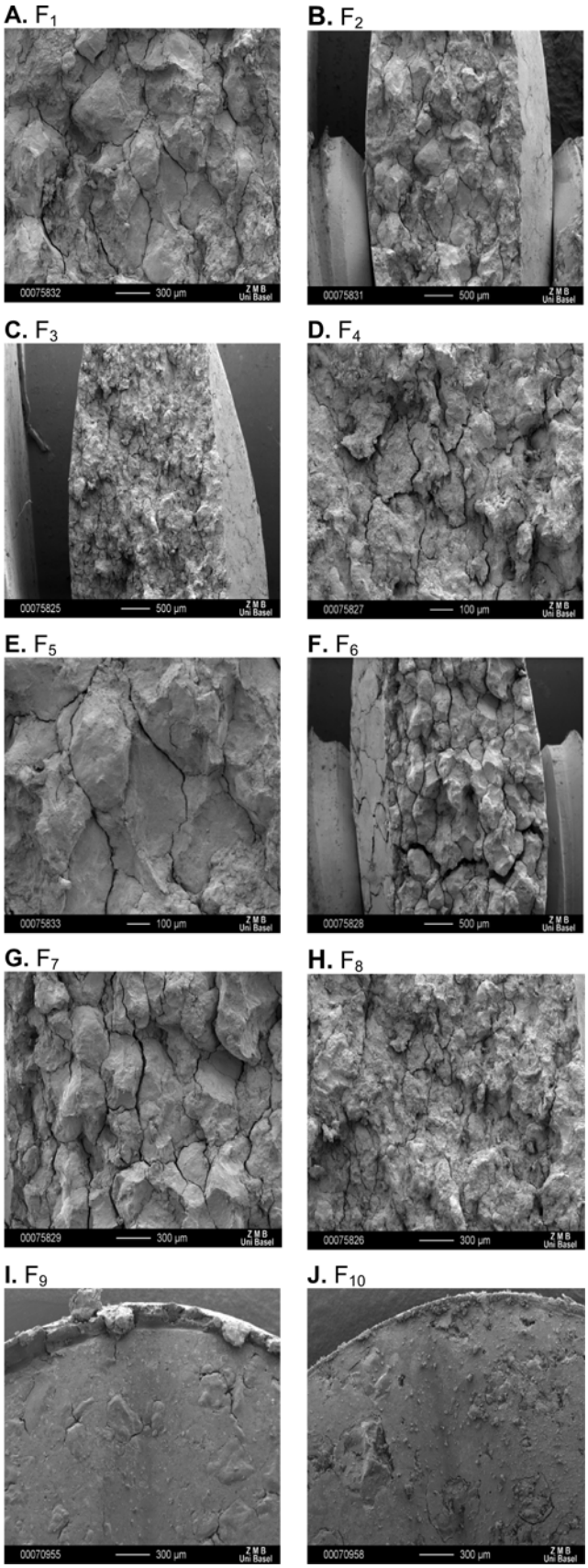

Fig. 2. SEM for F_1- F_{10} MUPS (tablets)

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.

Drug release study

Results of drug release studies indicated that drug release rates varied between different formulations F_1-F_{10}., with a range of 1 h to 8 h of complete drug release.

For diclofenac sodium release profile comparison similarity factor (f_2) was calculated. All these values were less than 50 and indicated that formulations did not have similar release profiles.

The conclusion is that only factor (X_1) concentration of the polymer had influence on the release properties of the diclofenac sodium. Increasing percentage of polymer resulted in decreasing release rates of the drug. Compressibility properties of the different formulations and resulting crushing strength of the tablet did not impact dissolution profiles. Therefore, the factor crushing strength of the tablet (X_2) did not have significant influence on diclofenac sodium release. This demonstrates that with hydrophilic polymer in formulation, crushing strength of the tablet does not have the influence on the drug release. 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 (Maganti and Celik, 1994). Compaction of less porous pellets resulted in a considerably increased drug release rate, while the release rate from pellets of high porosity was scarcely affected by compaction.

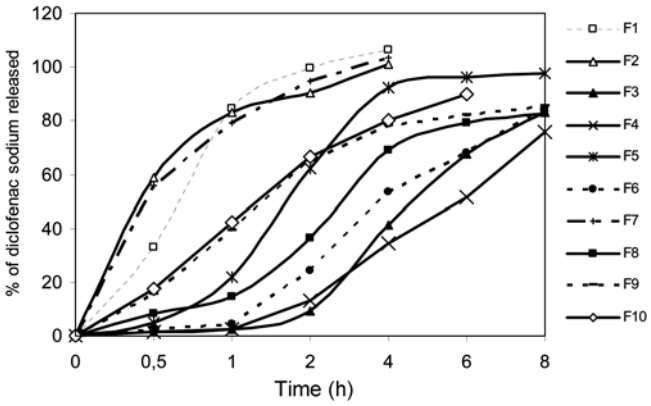

Fig. 3. Release profiles of diclofenac sodium from model formulations F_1-F_{10} according to CCD

Application of GRNN-structure, training and testing

Selected GRNN structure had four layers: first layer with two input units: X_1 - % Carbopol® 71G (5.86% - 34.14%) and X_2 – crushing strength of the tablet (31.7 – 88.3N). Second layer of the network had 10 hidden units. This units in hidden layer were assigned using *K means Centar Assignment* algorithm. A third layer had six units. Fourth layer had five output units-percent of released diclofenac sodium after 0.5, 1, 2, 4 and 8 h.

Inputs:

X_1 - % Carbopol® 71G (5.86% - 34.14%)

X_2 - crushing strength of the tablet (31.7N – 88.3N)

Outputs:

Y_1 - % diclofenac sodium released after 0.5 h

Y_2 - % diclofenac sodium released after 1 h

Y_3 - % diclofenac sodium released after 2 h

Y_4 - % diclofenac sodium released after 4 h

Y_5 - % diclofenac sodium released after 8 h

Selected GRNN was trained with data set results from formulations F_1-F_{10} according to CCD. The learning period was completed when minimum root mean square-RMS was reached. RMS reached after the training was 0.04% which is an acceptable value.

$$RMS = [(\Sigma yip - yim)^2/n]^{1/2}$$

RMS - error function

yp - response obtained in the experiment

ym - predicted response

n - number of experiments, training data for GRNN

When process of learning was over, GRNN was tested with set of test data. Test formulations, **Test 1** and **Test 2**, were prepared for validating the ability for prediction of GRNN: **Test 1:** 9% of Carbopol® and 70N crushing strength of tablet and **Test 2**: 32% of Carbopol® and 50N crushing strength of tablet. Selected values for percent of Carbopol 71 G and crushing strength of tablet were within the design spaceand they were random. RMS reached after the training was 0.124% which is an acceptable value. Drug release from these test formulations were analyzed.

In order to select the optimum GRNN model correlation plots were constructed of the experimentally obtained and responses predicted by GRNN for test the formulation **Test 1** and **Test 2.**

If square coefficient r^2 is satisfactory (> 0.98), GRNN is capable to process and predict responses for new cases and to generalize the problem. Square coefficient r^2 was for Test 1: r = 0.98060 and for Test 2: r = 0.98473, showing that the GRNN was properly trained and validated to generalize the problem. Correlation plots of predicted and obtained values of drug release for test formulations showed that the GRNN model had a regression plot with square coefficient r^2 that was close to the value of 1.0 which indicated that optimum GRNN model was reached. Obtained results showed

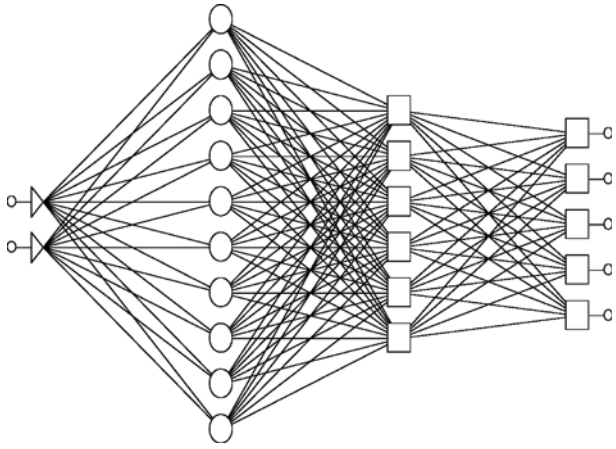

Fig. 4. Architecture of GRNN applied in optimization of diclofenac sodium extended release compressed matrix pellets

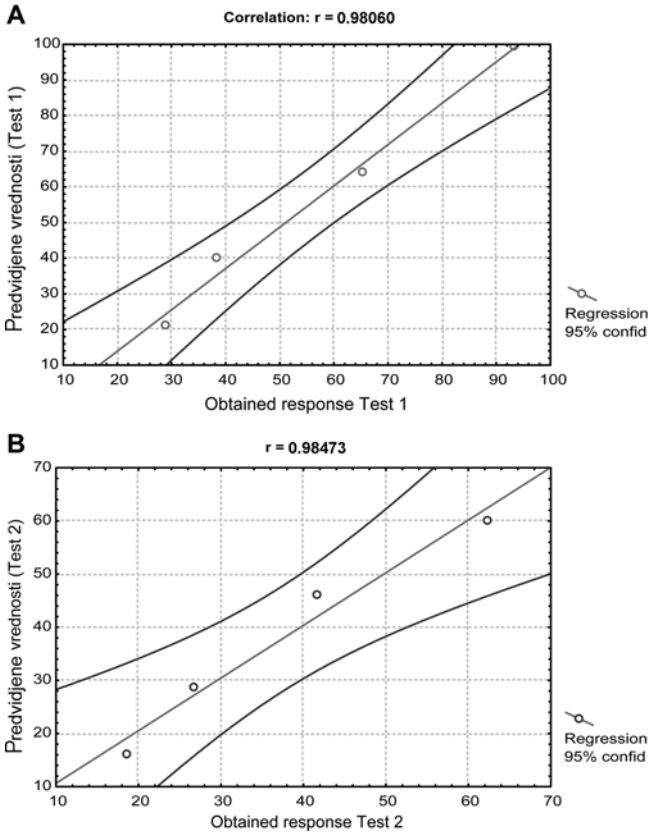

Fig. 5. Correlation plot for obtained and predicted responses for Test 1 (**A**) and Test 2 (**B**) formulations

that the GRNN was properly trained and capable to generalize problem.

Optimization

Optimization was the final step in the application of GRNN and it considered calculation of the optimal network input, percentage of polymer and crushing strength of tablet which enables optimal diclofenac sodium release specified as the aim of this study. Learned GRNN was used for modeling, simulation and optimization of the model extended release formulation by testing experimental results in experimental fields, searching for the optimal solutions. Contour plots in Fig. 6(A-E) present separated contours and areas, which satisfies demands regarding the diclofenac sodium release after 0.5, 1, 2, 4, and 8 h. Folding over,

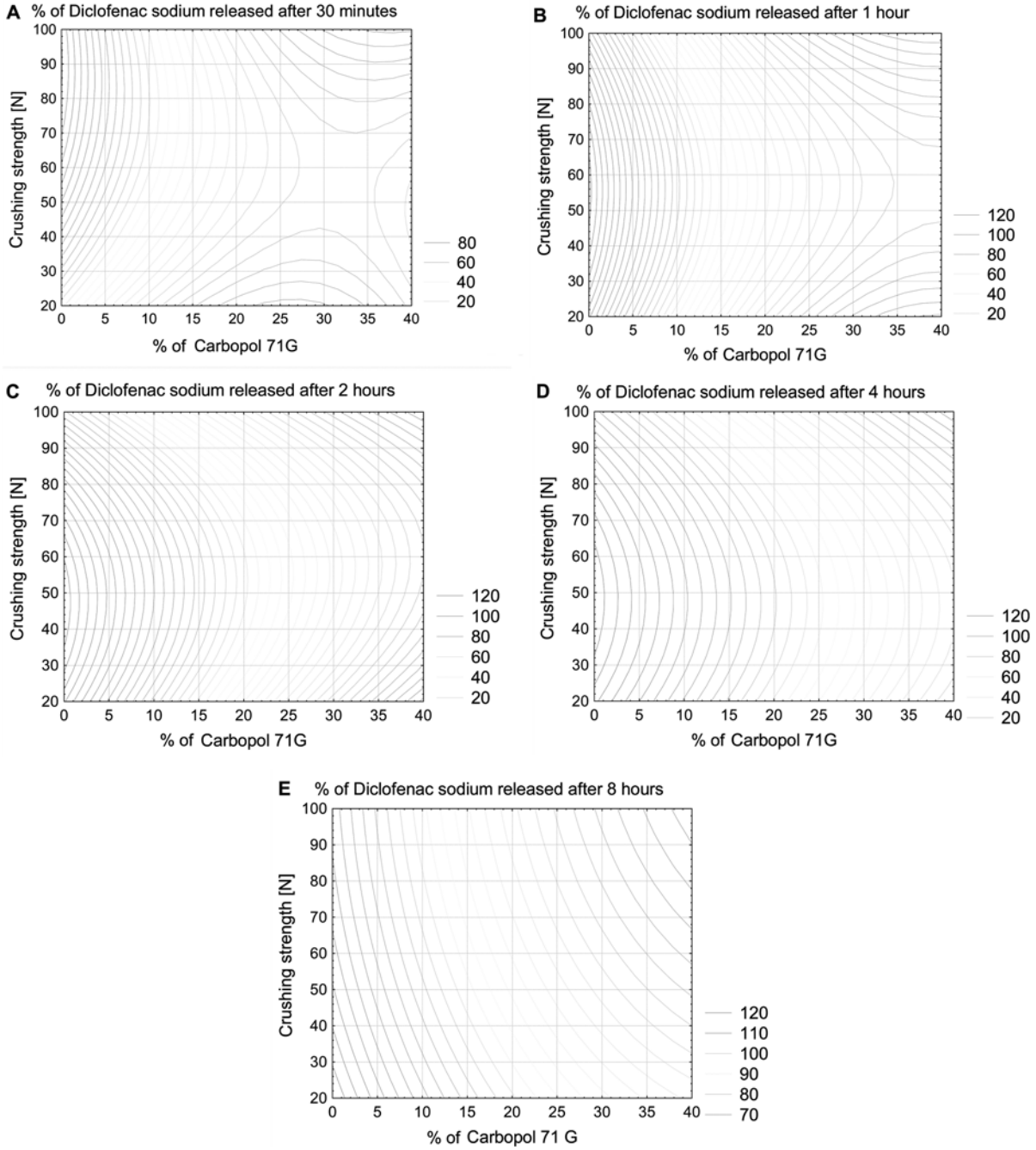

Fig. 6. Contour plots of the influence of Carbopol 71G and crushing strength of tablets on diclofenac sodium release from compressed matrix pellets predicted by GRNN (**A**) after 30 minutes of drug release test, (**B**) after 1 h, (**C**) after 2 h, (**D**) after 4 h, (**E**) after 8 h of drug release test

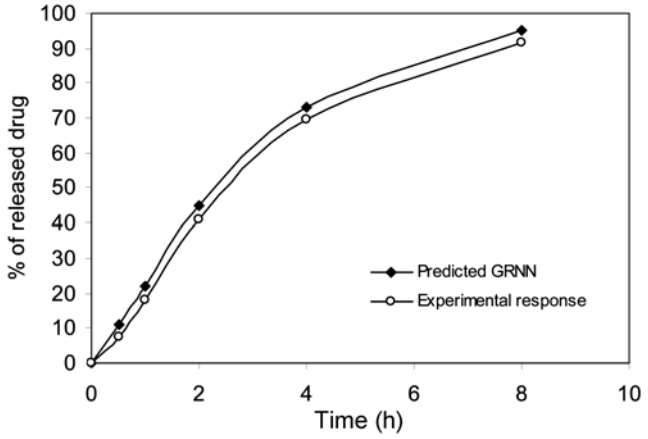

Fig. 7. Predicted and experimental responses of diclofenac sodium release from optimal formulation

these contours give area of combinations of independent variables, which satisfies all demands. This area is limited with three contours and every combination of polymer percentage and crushing strength of tablet in this area should satisfy all demands regarding the diclofenac sodium release in phosphate buffer.

Optimal solution estimated with GRNN, formulation with 19% Carbopol 71 G and 65N crushing strength of tablet was examined and obtained results for diclofenac sodium release were satisfactory and similar to the responses predicted by GRNN. Fig. 7 shows release profiles of diclofenac sodium obtained in experiments and predicted by GRNN.

It is indicated that polymer and crushing strength of tablet values for optimal formulation predicted by GRNN and obtained in the experiment gave similar response.

For diclofenac sodium release profile comparison of predicted and obtained formulation f_1 (*difference factor*) and f_2 (*similarity factor*) were calculated. Obtained values $f_1 = 6.93$ and $f_2 = 77.72$ showed that compared formulations were similar and that GRNN was a satisfactory method for optimization. Based on the results presented in this study conclusion is that application of GRNN, as optimisation method completely realized the purpose of this experiment: optimal formulation of diclofenac sodium extended release compressed matrix pellets with Carbopol® 71G as matrix substance.

CONCLUSION

Conclusions based on results from this study are following.

Concerning the great differences in applied concentrations of Carbopol® 71 G as matrix substance, obtained values of physical characterization of pellets and MUPS were very similar. 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. Increasing percentage of Carbopol® 71G resulted in decreasing release rates of the drug. 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 compressed matrix pellets.

Application of GRNN, as optimisation method completely realized the purpose of this study: Optimal formulation of diclofenac sodium compressed matrix pellets with Carbopol® 71G as a matrix substance was achieved even without the presence of anti-tack action of electrolytes and excipients which may induce different release profile of drug from matrix pellets compressed into MUPS tablets. Therefore it has been presented the efficiency of the GRNN in handling nonlinear data makes it suitable for the formulation problem, even when present completely different type of matrix substance, Carbopol71®G and different technology process of tablet manufacturing.

REFERENCES

Bettini, R., Catellani, P. L., Santi, P., Massimo, G., Peppas, N. A., and Colombo, P., Translocation of drug particles in HPMC matrix gel layer: effect of drug solubility and influence on release rate. *J. Control. Release.*, 70, 383-391 (2001).

Gomez-Carracedo, A., Alvarez-Lorenzo, C., Gomez-Amoza, J. L., and Concheiro, A., Extrusion-spheronization of blends of carbopol 934 and microcristaline cellulose. *Drug Dev. Ind. Pharm.*, 27, 381-391 (2001).

Haslam, J. L., Forbes, A. E., Rork, G. S., Pipkin, T. L., Slade, D. A., and Khossravi, D., Tabletting of controlled release multiparticulates, the effect of millisphere size and protective overcoating. *Int. J. Pharm.*, 173, 233-242 (1998).

Ibric, S., Jovanovic, M., Djuric, Z., Parojcic, J., and Solomun. Lj., The application of generalized regression neural network in the modeling and optimiyation of aspirin extended release tablets with Eudragit RS PO as matrix substance. *J. Control. Release*, 82, 213-222. (2002).

Jamzad, S., Tutunji, L., and Fassihi, R., Analysis of macromolecular changes and drug release from hydrophilic matrix systems. *Int. J. Pharm.*, 292, 75-85 (2004).

Jeon, Im-Jak., Development and Formulation of Carbomer 934P-containing mucoadhesive pellets by fluid-bed techniques. Doctoral dissertation, Halle. (2007).

Johansson, B., Niklasson, F., and Alderborn, G., Effect of pellet size on degree of deformation of densification during compression and on compactability of microcrystalline cellulose pellets. *Int. J. Pharm.*, 163, 35-48 (1998).

Kranz, H., Guthmann, C., Wagner, T., Lipp, R., and Reinhard, J., Development of a single unit extended release formulation for ZK 811 752, a weakly basic drug. *Eur. J. Pharm. Sci.*, 26, 47-53 (2005).

Maganti, L. and Celik, M., Compaction studies of pellets II Coated pellets. *Int. J. Pharm.*, 103, 55-67 (1994).

Nellore, R. V., Singh Rekhi, G., Hussain, A. S., Tillman, L. G., and Augsburger, L. L., Development of metoprolol tartrate extended-release matrix tablet formulations for regulatory policy consideration. *J. Control. Release.*, 50, 247-256 (1998).

Park, S. H., Chun, M. K., and Choi, H. K., Preparation of an extended-release matrix tablet using chitosan/Carbopol interpolymer complex. *Int. J. Pharm.* (2007).

Su, S. F., Chou, C. H., Kung, C. F., and Huang, J. D., *In vitro* and *in vivo* comparison of two diclofenac sodium sustained release oral formulations. *Int. J. Pharm.*, 260, 39-46 (2003).

Tapia-Albarran, M. and Villafuerte-Robles, L., Assay of amoxicillin sustained release from matrix tablets containing different proportions of Carbopol 971P NF. *Int. J. Pharm.*, 273, 121-127 (2004).

Tunon, A., Preparation of Tablets from Reservoir Pellets with an Emphasis on the Compression Behaviour and Drug Release. Comprehensive Summaries of Uppsala Dissertations from the Faculty of Pharmacy, 288 (2003).