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Research Article

Quality by Design Approach: Application of Artificial Intelligence Techniques of Tablets Manufactured by Direct Compression

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Abstract. The publication of the International Conference of Harmonization (ICH) Q8, Q9, and Q10 guidelines paved the way for the standardization of quality after the Food and Drug Administration issued current Good Manufacturing Practices guidelines in 2003. "Quality by Design", mentioned in the ICH Q8 guideline, offers a better scientific understanding of critical process and product qualities using knowledge obtained during the life cycle of a product. In this scope, the "knowledge space" is a summary of all process knowledge obtained during product development, and the "design space" is the area in which a product can be manufactured within acceptable limits. To create the spaces, artificial neural networks (ANNs) can be used to emphasize the multidimensional interactions of input variables and to closely bind these variables to a design space. This helps guide the experimental design process to include interactions among the input variables, along with modeling and optimization of pharmaceutical formulations. The objective of this study was to develop an integrated multivariate approach to obtain a quality product based on an understanding of the cause–effect relationships between formulation ingredients and product properties with ANNs and genetic programming on the ramipril tablets prepared by the direct compression method. In this study, the data are generated through the systematic application of the design of experiments (DoE) principles and optimization studies using artificial neural networks and neurofuzzy logic programs.

KEY WORDS: artificial neural networks (ANNs); gene expression programming (GEP); optimization; quality by design (QbD).

INTRODUCTION

The studies and tests required to deliver a new drug to patients take no less than 15 years and cost estimate $800 million USD (1). Even after a drug is invented, its development may fail because of an inability to manufacture the drug safely on a large scale and in compliance with the manufacturer's specifications.

The length of the approval process has been a concern in the drug industry for many decades. Today, it is known that this process, which involves a considerable amount of paperwork for evaluation and approval of new product submissions, is slow, cumbersome, and causes excessive delays. For this reason, in recent years, the drug industry experienced major developments in production information, quality management systems, and risk management, and the industry developed modern production tools that can assist in ensuring product quality.

In 2002, the FDA introduced the amendments in the current Good Manufacturing Practices (cGMP) to the drug industry to improve and modernize the rules that regulate drug manufacturing and drug quality. Second, the guideline Q8, "Pharmaceutical Development", of the ICH, which harmonizes the technical requirements for pharmaceutical products in Europe, the USA, and Japan, was published in 2005. It introduced the concept of quality by design (QbD) into the drug industry (2). QbD is a systematic approach to pharmaceutical development that refers to designing and developing formulations and manufacturing processes that can generate a prescribed product quality. In other words, QbD adopts the understanding that "quality cannot be tested into products; it should be built-in during the designing phase" (3). Based on this understanding, the ICH guidelines Q9, "Quality Risk Management," and Q10, "Pharmaceutical Quality System," were published. The guideline Q9 offers principles for quality risk management that can be applied to different aspects of drug quality (4). As for Q10, it is a comprehensive approach that establishes an effective pharmaceutical quality system based on the ISO concepts, and it includes the regulations of cGMP and the components of ICH Q8 and ICH Q9 (5). In addition to these three guidelines, ICH Q11, "Development and Manufacture of the Drug Substances" which was prepared for the Active Pharmaceutical Ingredients committee, is in the pipeline at present (6).

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Pharmaceutical drug manufacturing, from formulation development to finished product, is very complex. This process includes multivariate interactions between raw materials and process conditions. These interactions are very important for the processability and quality of the finished product. Hence, these interactions should be taken into account early on, such that later loss of time and money is not incurred (7).

The use of artificial intelligence in pharmaceutical technology has increased over the years, and the use of technology can save time and money while providing a better understanding of the relationships between different formulation and process parameters. Neural networks, genetic algorithms, and fuzzy logic are rapidly growing technologies that could be applied to the formulation and processing of pharmaceutical products.

Using previous experiments to train the model is an important advantage of artificial intelligence technology that speaks to its efficiency. ANN programs are useful for understanding cause-and-effect relationships between inputs (as formulation parameters) and outputs (as product properties).

The genetic algorithm is an effective and useful tool to predict the results that arise from changes in the input parameters, such as the formulation. Using this approach with neural networks can be productive because it provides "what if" predictions and optimization (8, 9).

For controlling and decision-making, fuzzy logic is a very powerful problem-solving technique. It provides very useful rules from input data, in the form of "if… so… then" (10, 11). Fuzzy logic can be combined with neural networks as neurofuzzy logic. This combination provides more flexibility and capability to the technique and provides powerful results (12).

Ramipril tablet is used as a model drug. Ramipril is a white or off white, crystalline powder that freely soluble in methanol and sparingly soluble in water. With reference to the European Pharmacopeia Ramipril monograf, there are four qualified impurities called impurity A (ramipril methyl ester), impurity B (ramipril isopropyl ester), impurity C (hexahydroramipril), and impurity D (ramipril diketopiperazine). Impurity A and impurity B are process impurities. Impurity C is formed if the ramipril manufacturing starting material ethoxycarbonyl phenyl propyl amine contains cyclohexyl impurity. Impurity D can be a process or stability impurity according to heat or cyclisation between –COOH and –NH groups, impurity D may be formed (13). Ramipril is used for the treatment of congestive heart failure (CHF) and hypertension (high blood pressure) and prevents heart attacks, strokes, and deaths due to heart disease in patients who have risk factors for such events (14).

The modeling of ramipril tablet formulation and production using the new science- and risk-based techniques has many advantages over traditional modeling techniques, especially in the assessment of nonlinear relationships, which are frequently observed in pharmaceutical operations. The purpose of the study is to establish the tablet formulation containing the ramipril drug substance based on the ObD approach. By applying different formulation parameters related to the lubricants, we will use ANN programs to improve our understanding of how the critical quality attributes contribute to the overall quality of the drug product. Three commercial artificial intelligence software tools representing the three technologies were used in this study: INForm V.4 ANN for neural networks, FormRules V.3.32 for neurofuzzy logic and INForm V.4 GEP (15).

MATERIAL AND METHOD

Material

A tablet compression machine with 27 stations (Manesty BB3B, BB3B), a sieving machine (Erweka, AR 402), a high-performance liquid chromatography (HPLC) (Thermo Separation Products, AS 3000), an ultrasonic bath (BanbelinSonorex, RK 1,028H), a dissolution apparatus (Distek, EVOLUTION 6100), a V-type powder mixer (Aymes, AISI304), a Karl-Fischer titrator (Schott, D-551222), a hardness apparatus (Sotax, HT4), a friability apparatus (Sotax, F1), a disintegration apparatus (Distek, DISINTEGRATION 3100), an SEM (scanning electron microscope) (FEI, Quanda 250 FEG), the FormRules computer program (INtelligent Formulation, V.3.32), and INForm computer program (INtelligent Formulation, V.4) were used for this study. The raw materials used for the formulations were ramipril (Neuland Labs Ltd., India), hydroxypropyl methyl cellulose (HPMC) (viscosity: between 15 mPa.s) (BASF, Germany), lactose mono-hydrate (DMV, Holland), sodium hydrogen carbonate (Merck, Germany), croscarmellose sodium (CP Kelco, Holland), pregelatinized starch (Colorcon, England), yellow iron oxide (BASF, Germany) and red iron oxide (Merck, Germany), and MgSt (FACI S.p.A, Italy) and SSF (JRS PHARMA, Germany).

Data Set

In this study, a two-level hierarchical experimental design consisting of 16 experiments was used to evaluate the effect of two formulation variables on the quality of ramipril tablets manufactured by direct compression. The lubricant types that were selected were magnesium stearate (MgSt) and sodium stearyl fumarate (SSF). Lubricant concentrations ranged from 0.75 to 1.0% for MgSt and 0.6–1.2% for SSF (Tables I and II). Of the data produced, 15% of the experimental records were separated for use as test data and for validation. The remaining data were used for training the software.

Table I. Knowledge Area Data (Any Information on the Experimental Design)

No.	Formula no.	HPMC ratio (%)	Lubricant type	Amount of lubricant (%)
1	K1A1	0.25:1.0	MgSt	0.75
2	K1B1	0.25:1.0	MgSt	0.75
3	K1A2	0.25:1.0	MgSt	1.0
4	K1B2	0.25:1.0	MgSt	1.0
5	K1A3	0.25:1.0	SSF	0.6
6	K1B3	0.25:1.0	SSF	0.6
7	K1A4	0.25:1.0	SSF	1.2
8	K1B4	0.25:1.0	SSF	1.2
9	K2A1	0.75:1.0	MgSt	0.75
10	K2B1	0.75:1.0	MgSt	0.75
11	K2A2	0.75:1.0	MgSt	1.0
12	K2B2	0.75:1.0	MgSt	1.0
13	K2A3	0.75:1.0	SSF	0.6
14	K2B3	0.75:1.0	SSF	0.6
15	K2A4	0.75:1.0	SSF	1.2
16	K2B4	0.75:1.0	SSF	1.2

MgSt magnesium stearate, *SSF* sodium stearyl fumarate

Table II. Formulation Analysis Results

Spec.	Appearance	Tablet weight (mg)	Crushing strength (N)	Friability (%)	Disint. time (minutes)	Assay (ramipril) (mg\tb)	Dissolution in 30 min	Imp A (%)	Imp B (%)	Imp C (%)	Imp D (%)	Imp Total (%)
Form no.	Pink, oblong tablets with scored on both sides	130 mg±3% (126–134 mg)	Min.30 N	Max.1.0%	Max.15 min/ in water	5.0 mg/tablet (4.5–5.5 mg/tablet)	Min. 80%/ 30 min	Max. 0.5%	Max. 0.5%	Max. 0.5%	Max. 3.0%	Max. 5.0%
K1A1	Complies	129.80	65	0.10	2	4.760	92.00	0.00	0.00	0.01	0.160	0.24
K1A2	Complies	129.80	62	0.20	3	4.780	94.00	0.00	0.00	0.01	0.170	0.23
K1A3	Complies	130.00	66	0.40	1	4.600	88.00	0.00	0.00	0.01	0.160	0.24
K1A4	Complies	131.20	68	0.20	1	4.620	92.00	0.00	0.00	0.01	0.170	0.25
K2A1	Complies	129.80	58	0.20	1	4.700	92.00	0.00	0.00	0.02	0.170	0.21
K2A2	Complies	129.60	53	0.30	1	4.600	96.00	0.00	0.00	0.02	0.180	0.22
K2A3	Complies	131.00	62	0.30	1	4.830	100.00	0.00	0.00	0.02	0.180	0.21
K2A4	Complies	130.50	68	0.20	1	4.920	92.00	0.00	0.00	0.01	0.180	0.22
K1B1	Complies	129.80	62	0.20	2	4.550	96.00	0.00	0.00	0.02	0.250	0.31
K1B2	Complies	129.90	68	0.30	2	4.690	93.00	0.00	0.00	0.01	0.250	0.31
K1B3	Complies	129.70	64	0.20	1	4.510	96.00	0.00	0.00	0.01	0.270	0.33
K1B4	Complies	130.30	70	0.30	1	4.460	92.00	0.00	0.00	0.01	0.330	0.34
K2B1	Complies	129.80	63	0.30	2	4.750	98.00	0.00	0.00	0.02	0.270	0.29
K2B2	Complies	130.10	58	0.20	2	4.630	92.00	0.00	0.00	0.01	0.270	0.28
K2B3	Complies	130.70	61	0.20	2	4.650	92.00	0.00	0.00	0.01	0.300	0.31
K2B4	Complies	130.10	67	0.30	1	4.560	96.00	0.00	0.00	0.01	0.280	0.30

*Spec.*specification, *Imp* impurity

Table III. The Chromatographic Conditions for the Dissolution Method

Gradient program			
Time (min)	Solution A (%)	Solution B (%)	Flow rate (ml/min)
0	67	33	0.5
10	12	88	0.5
12	0	100	0.5
15	0	100	0.5
16	67	33	0.5
20	67	33	0.5

Tablet Formulation and Manufacturing

The drug substances and excipients in the amounts detailed in Table I were weighed in preparation of tablets. Ramipril and HPMC were mixed for 15 min in a V-type mixer and then sieved. Lactose mono-hydrate, sodium hydrogen carbonate, croscarmellose sodium, pregelatinized starch, yellow iron oxide, and red iron oxide were filtered through a sieve with a 0.85-mm aperture size and mixed for 15 min with a V-type mixer, added to the previous powder mass and then mixed again for 15 min. The final mixture was divided into four portions. The first two portions were mixed for 2 min with MgSt, and the other two portions were mixed with SSF with the V-type mixer for 2 min. The tablets were then compressed using an eccentric tablet compression machine using 4.06× 8.06-mm punch at a target weight of 130 mg.

Critical Quality Attributes

The crushing strength, the ability to dissolve within 30 min, the active ingredient content and the levels of impurity C (%) and impurity D (%) were selected as critical quality attributes at the end of the process and risk assessment studies. Measurements of the selected quality attributes were performed on the manufactured tablets.

The crushing strength of the tablets was determined using a Sotax HT4 hardness tester. The ability to dissolve within 30 min was measured using dissolution testing equipment at the conditions that are specified in the USP 24 method II (paddle) of the USP (16). HPLC was used to analyze the ramipril drug substance with "Ramipril EP Reference Standards A, B, C and D," and the chromatographic conditions for this method are given in "HPLC Analysis" section. For this assay, 10–20 tablets were ground and dissolved at a specific concentration and in an appropriate solvent. The chromatographic conditions for the method are indicated in the "HPLC Analysis" section.

HPLC Analysis

An isocratic chromatographic method was used for the analysis of the ramipril assay from the dissolution media. The HPLC system consisted of a Thermo Separation Products (AS 3000, USA) equipped with a Series 105 pump, a Series 105 autosampler, and a Series 095 UV/VIS detector. The analytical column was a Luna C18 (50×2.0 mm, 3 μm, Phenemonex Company, USA). The signal was monitored at 240 nm. The mobile phase consisted of methanol/phosphate buffer at a ratio of (45:55; *v*/*v*). The flow rate was set at 0.4 ml/min, and the injection volume was 100 μl. The chromatogram time was 8 min, and the retention time was approximately 4.7 min. The developed HPLC method was validated as per the ICH guideline (17). The gradient program is given in Table III. Also, validation parameters for the HPLC analytical method were specificity, linearity/range/repeatability, precision, accuracy, detection limit, quantitation limit, robustness, and system suitability.

The gradient chromatographic method was used for the assay of the ramipril. The same HPLC system used for the ramipril drug substance analysis was used. The analytical column was a Luna C18 (100×2.0 mm, 3 μm, Phenemonex Company, USA). The signal was monitored at 240 nm. The mobile phase consisted of solution A: methanol (8%)/phosphate buffer (92%) and solution B: methanol (80%)/phosphate buffer (20%). The flow rate was set at 0.5 ml/min, and the injection volume was

Table IV. INForm Study Conditions for Direct Compression Tablets

DC INForm ANN study conditions				
Model type: neural network		Training parameters		Inputs/outputs
Number of hidden layers (HL)	1	Back-propagation parameters		Inputs HPMC
		Momentum	0.8	Lubricant
Current hidden layer (CHL)	1	Learning rate	0.7	Lubricant Conc.
Number of nodes (NN)	2	Targets		Outputs Tb. weight
		Target epochs	1,000	C.S. Friability
Transfer function	Asymmetric sigmoid	Target MS error	0.0001	Disint. Time Diss. (%)
Output transfer function	Linear	Random seed	1,000	Assay Imp. A Imp. B Imp. C Imp. D

Conc. concentration, *Tb.* tablet, *C.S.* crushing strength, *Disint.* disintegration, *Diss.* dissolution, *Imp.* Impurity

Table V. Usage of Minimum and Maximum Study Results for Knowledge Area Study

	Minimum values						Maximum values					
	Property weight	Minimum	Mid.1	Mid.2	Maximum	Desirability function	Property weight	Minimum	Mid.1	Mid.2	Maximum	Desirability function
Crushing strength (N)	10	53	53.01	53.01	70	↓	10	53	69.99	69.99	70	↑
Diss. in 30 min (%)	10	88	88.01	88.01	100	↓	10	88	99.99	99.99	100	↑
Assay (mg/tablet)	10	4.46	4.47	4.47	4.92	↓	10	4.46	4.91	4.91	4.92	↑
Imp C (%)	10	0.01	0.02	0.02	0.02	↑	10	0.01	0.02	0.02	0.02	↓
Imp D (%)	10	0.16	0.17	0.17	0.33	↑	10	0.16	0.32	0.32	0.33	↓

Diss. dissolution, *Imp* impurity

100 µl. The chromatogram time was 20 min. The developed HPLC method was validated as per the ICH guideline (17). The aforementioned ramipril equipment and reagents were used for the impurity analyses. Standard and sample solutions were prepared as described in "The Preparation of Solutions" section.

The Preparation of Solutions

Solvent Solution. Acetonitrile:methanol (1:1; *v*/*v*).

Diluting Solution. Acetonitrile:methanol/phosphate buffer pH: 2.6 (12.5%:12.5%:75%; *v*/*v*/*v*).

Stock Standard Solution. In a 100-ml volumetric flask, 12.5 mg of ramipril standard was accurately weighed and dissolved into 25 ml of solvent solution. The flask was filled to its indicated capacity with phosphate buffer and mixed. The solution was passed through a 0.45-µm membrane filter, and the first filtered portion was discarded.

Working Standard Solution. Approximately 0.5 ml of ramipril stock standard solution was placed into a 100-ml volumetric flask, and the flask was filled to its indicated capacity with diluting solution and mixed. The solution was passed through a 0.45-µm membrane filter, and the first filtered portion was discarded (ramipril, 0.625 µg/ml).

Sample Solution (Two Prepared Solutions). Twenty tablets were weighed and ground into powder with a mortar and pestle. Into a 50-ml volumetric flask, 162.5 mg of sample (equivalent to 6.25 mg ramipril) was accurately weighed. Then, 12.5 ml of solvent solution was added, and the mixture was held for 10 min in an ultrasonic bath. Next, 20 ml of phosphate buffer was added, and the mixture was shaken in a magnetic mixer for 20 min. The remaining volume in the volumetric flask containing the solution was filled with phosphate buffer, and the solution was mixed. The solution was then passed through a 0.45-µm membrane filter. The first filtered portion was discarded, and the rest was injected (Ramipril, 125 µg/ml).

Operation. The standard solution was injected into the system three times. The average peak area and the RSD were calculated. The RSD should not exceed 2.0%. Sample solutions were prepared twice, and samples from each preparation were injected thrice. The standard solution was injected to the system three times, and the average peak area and RSD were calculated (RSD=maximum 2.0%).

Calculation of Impurities

$$\frac{A_I}{A_{\text{Std}}} \times \frac{W_{\text{Std}}/100 \times 0.5/100}{W_N/50 \times L_a} \times P_s \times 100 \times W_T = \text{impurity \%(\% of Ramipril)}$$

A_I Each of the peak areas of impurity A, impurity B, impurity C, and impurity D in the sample chromatogram
A_{Std} Ramipril peak area in the standard chromatogram
W_{Std} Ramipril standard mass, milligrams
P_{s} Ramipril standard, percent
W_N Sample mass, milligrams
W_T Average tablet mass (milligrams per tablet)
L_a Ramipril amount in the tablet (5 mg)

Table VI. Usage of Minimum and Maximum Pharmacopeia/in-house Limit Values for Design Space Study

	Minimum values						Maximum values					
	Property weight	Minimum	Mid.1	Mid.2	Maximum	Desirability function	Property weight	Minimum	Mid.1	Mid.2	Maximum	Desirability function
Crushing strength (N)	10	30	30.01	30.01	60	↓	10	30	59.99	59.99	60	↑
Diss. in 30 min (%)	10	80	80.01	80.01	110	↓	10	80	109.99	109.99	110	↑
Assay (mg/tablet)	10	4.5	4.51	4.51	5.5	↓	10	4.5	5.49	5.49	5.5	↑
Imp C (%)	10	0.00	0.01	0.01	0.5	↑	10	0.00	0.49	0.49	0.5	↓
Imp D (%)	10	0.00	0.01	0.01	3.0	↑	10	0.00	2.99	2.99	3.0	↓

Diss. dissolution, *Imp* impurity

The ramipril tablet specifications and control methods are specified and analyzed according to the European Pharmacopeia (13). The results are given in Table II.

EXPERIMENTS

Software Tools

Three commercially available artificial intelligence software tools were used to examine the production date generated in these studies. All software packages were provided by Intelligensys Ltd., (INForm V.4 ANN, INForm V.4 GEP, and FormRules V.3.32, Intelligensys Ltd., England). FormRules V.3.32 is a data-mining software package developed by Intelligensys Ltd., which makes use of neuro-fuzzy logic as the basic technology. The FormRules system was described previously by Shao *et al.*, 2007 (18). INForm software develops predictive models and optimizes these models (19). The program utilizes ANNs, genetic algorithms (GEP), and fuzzy logic (15).

Training Parameters

Because the training parameters influence the structure of the neural networks during the training process, the parameters in INForm V.4 and FormRules V.3.32 were manipulated to optimize the predictability of the trained networks (18, 20). After trying various parameters, it was determined that the suggested parameters in the manual of INFormV.4 and FormRules V.3.32 were suitable parameters to use. The FormRules settings used for training are given below. Additionally, the ANN program study conditions are given in Table IV. To validate the predictability of trained models, the nonlinear coefficient of determination R^2 was computed against the validation data set (21).

Model: structural risk minimization
Second order fuzzy set densities: 2/3
Fuzzy sets maximum submodel inputs: 4
Maximum node per input: 15

RESULTS AND DISCUSSION

Optimization of the data obtained for the direct compression of tablets was performed in this study using the INForm V.4 ANN. When the INForm ANN model was trained, the model was optimized with target values based on pharmacopeial and in-house specifications. The minimum and maximum values to be applied for optimization in the program were determined, with consideration of values for critical quality properties obtained from the studies (Table V).

Each property weight value was specified as 10 to evaluate the importance of each critical parameter on a scale of 0 to 10, with 10 being the most important. The other five columns —min, mid1, mid2, max, and desirability function are used to describe the values that wanted to be used from the properties. For the desirability function, up means that the values that lie above Mid1 are desirable (desirability function 100%) and down means that the values that lie below mid2 are desirable (desirability function 100%) (15). Optimization was performed separately for formulations containing MgSt and SSF. The same evaluations were conducted by taking into account the in-house limits and the values available in the pharmacopeia for design space studies (Table VI).

Formulation interactions were individually evaluated for two lubricants (MgSt/SSF) and tested with the INForm ANN program. After the training was completed, ANN recommended a set of conditions (formulation) at which the optimum levels for the quality attributes could be achieved (Tables VII and VIII). The tablets were prepared according to optimal formulation parameters, and various tests were performed on the prepared tablets.

The optimized data of the differences between the pharmacopeia min. and max. values was used to define the design area and minimum and maximum values of studied data to define the knowledge area. The knowledge and design area values of tablet parameters prepared by direct compression and using MgSt are given in Table IX. In addition, the knowledge and design area limits were

Table VII. Optimization Results of Minimum and Maximum Values on Direct Compressed Tablets According to Study Data (Knowledge Area Borders)

	Lubricant (MgSt)		Lubricant (SSF)	
	Minimum	Maximum	Minimum	Maximum
Inputs				
HPMC (%)	0.308	0.250	0.542	0.667
Lubricant concentration (%)	0.600	0.900	0.600	1.054
Outputs				
Crushing strength (N)	61.424	69.455	61.518	69.393
Diss. in 30 min (%)	94.014	94.805	94.427	94.697
Assay (mg/tablet)	4.663	4.670	4.685	4.680
Impurity C (%)	0.01	0.015	0.014	0.015
Impurity D (%)	0.208	0.219	0.228	0.256

MgSt magnesium stearate, *SSF* sodium stearyl fumarate, *HPMC* hydroxypropylmethylcellulose, *Diss.* dissolution

Table VIII. Optimization Results of Minimum and Maximum Values for Tablets According to Pharmacopeia/in-house Data (Design Area Borders)

	Lubricant (MgSt)		Lubricant (SSF)	
	Minimum	Maximum	Minimum	Maximum
Inputs				
HPMC (%)	0.250	0.750	0.250	0.750
Lubricant concentration (%)	0.900	1.200	1.200	1.200
Outputs				
Crushing strength (N)	59.46	61.291	61.500	69.999
Diss. in 30 min (%)	93.30	94.895	92.120	95.618
Assay (mg/tablet)	4.66	4.731	4.529	4.742
Impurity C (%)	0.011	0.020	0.010	0.015
Impurity D (%)	0.223	0.239	0.217	0.234

MgSt magnesium stearate, *SSF* sodium stearyl fumarate, *HPMC* hydroxypropylmethylcellulose, *Diss.* dissolution

Table IX. Knowledge and Design Area Values of Tablet Parameters Prepared by Direct Compression and MgSt

	Knowledge area	Design area
Inputs		
HPMC (%)	−0.188	2.00
Lubricant concentration (%)	0.500	0.333
Outputs		
Crushing strength (N)	0.131	0.031
Dissolution in 30 min (%)	0.008	0.017
Assay (mg/tablet)	0.002	0.015
Impurity C (%)	0.500	0.818
Impurity D (%)	0.0529	0.072

The positive values show the direction of increasing; the negative values show the direction of decreasing as percentage difference
HPMC hydroxypropylmethylcellulose

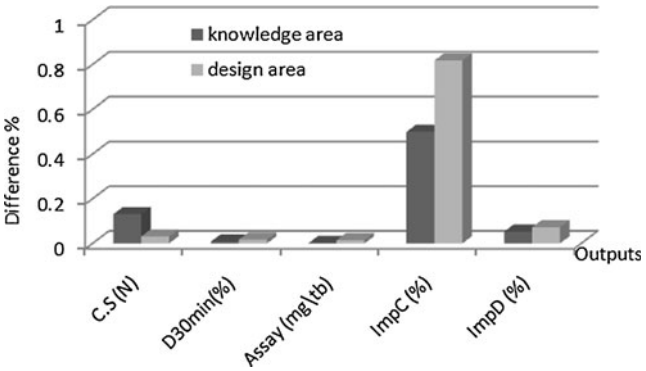

Fig. 2. Graphical image of knowledge and design area for outputs of tablets prepared by using HPMC/MgSt. *C.S.* crushing strength, *D30min* dissolution in 30 min, *Imp* impurity

handled as area calculations, and all values are shown in the figures (Figs. 1 and 2).

When the histograms given in Figs. 1 and 2 were examined, it was determined that the design area provided by the formulations that we provided was within the knowledge area for the hardness parameter. In addition, based on the data we acquired from FormRules, hardness was dependent on and inversely proportional to the HPMC concentration. To obtain the ideal formulation, we increased the HPMC concentrations being used to enter the design area, such that the lower concentration value increased from 0.25% to 0.30%. Because impurity C was remarkably affected based on the histogram data (Figs. 1 and 2), the formulation examinations performed with FormRules were assessed. Based on FormRules, it was ascertained that the amount of impurity C was also inversely proportional to the lubricant concentration. Although there was a limit to how high impurity C could be based on the formulation, optimization values were taken into account, and the concentration interval that was suitable for achieving an ideal concentration was determined. This was performed in consideration of the need to keep impurity C at a minimum (as would be achieved in an ideal formulation).

As a result, it was concluded that the amount of HPMC should be between 0.25% and 0.30% and that MgSt should be between 0.60% and 0.90% for an optimum formulation, according to histogram data and optimization data (Table X).

Additionally, the knowledge area and design area values were made in the same manner for the HPMC/SSF tablets, and the values are given in Table XI. All values are shown in Figs. 3 and 4.

When we examined the histogram of the data for formulas using SSF, the hardness, impurity C, and impurity D were critical parameters (Fig. 4). In consideration of the histogram of the data, it can be inferred that the design area is outside of the knowledge area with respect to the hardness parameter. It can be observed that the design area we were provided based on our formulations was within the information area in terms of the parameter for impurity D. With respect to impurity C, a significant difference can be observed between the design area and the information area (Fig. 4). Therefore, the relation between the crucial parameters and the formulation parameters was assessed, and the histograms of the data and the FormRules data were assessed in terms of the formulation variables. Based on the FormRules, it can be concluded that the hardness was associated with and directly proportional to the lubricant concentration. Impurity C was not affected by the HPMC concentration, and impurity D was not affected by the lubricant concentration. When we examine the histogram

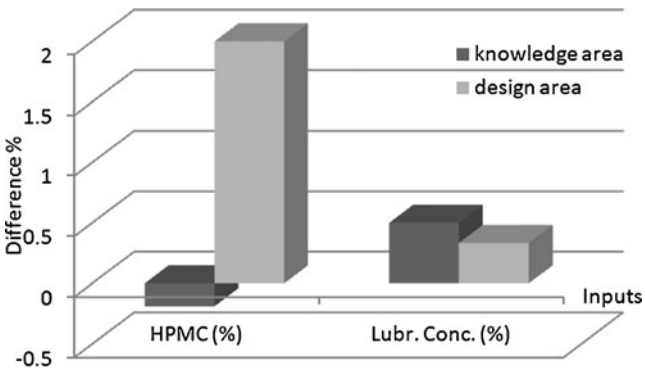

Fig. 1. Graphical image of knowledge and design area for inputs of tablets prepared by using HPMC/MgSt. *HPMC* hydroxypropylmethylcellulose, *Lubr. Conc.* lubricant concentration

Table X. Finished Product Analysis Results of Direct Compressed Tablets Prepared by Using MgSt According to Area

	Knowledge area limits	Design area limits	Analysis data
Inputs			
HPMC (%)	0.250–0.308	0.250–0.750	0.275
Magnesium stearate (%)	0.600–0.900	0.900–1.200	0.750
Outputs			
Crushing strength (N)	61.424–69.455	59.46–61.291	61
Dissolution in 30 min (%)	94.014–94.805	93.30–94.895	94
Assay (mg/tablet)	4.663–4.670	4.66–4.731	4.5
Impurity C (%)	0.01–0.015	0.011–0.020	0.01
Impurity D (%)	0.208–0.219	0.223–0.239	0.2

HPMC hydroxypropylmethylcellulose

Table XI. Knowledge and Design area Values of Tablet Parameters Prepared by Direct Compression and HPMC/SSF

	Knowledge area	Design area
Inputs		
HPMC (%)	0.231	2.000
Lubricant concentration (%)	0.757	0
Outputs		
Crushing strength (N)	0.128	0.138
Dissolution in 30 min (%)	0.003	0.038
Assay (mg/tablet)	−0.001	0.047
Impurity C (%)	0.071	0.500
Impurity D (%)	0.123	0.078

Note: The positive values show the direction of increasing; the negative values show the direction of decreasing as percentage difference. *HPMC* hydroxypropylmethylcellulose

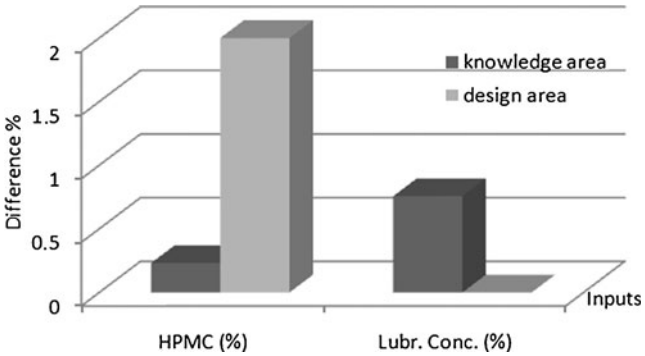

Fig. 3. Graphical image of knowledge and design area for inputs of tablets prepared by using HPMC/SSF. *HPMC* hydroxypropylmethylcellulose, *Lubr. Conc.* lubricant concentration

data with respect to the formulation variables, it can be observed that the amount of lubricant was far greater than the amount indicated in our design area, and a decrease in the amount of lubricant should cause a decrease in the amount of impurity D, thus returning this parameter back within the boundaries of the design area. Based on all these data, the concentration interval suitable for the ideal formulation was determined.

Based on the histogram of the data and on the optimization data (Table XI), it was concluded that the percentage of HPMC should be between 0.542% and 0.667% and that SSF should be between 0.60% and 1.054% for the optimum formulation. For concentrations falling between the previously mentioned values, trial studies were conducted on a laboratory batch, and complete product analysis was performed. The results generated were consistent with the optimization data (Table XII).

CONCLUSION

Though neural networks are not a solution on their own, they support decision-making processes, and they are useful tools for obtaining the details of the processes with formulations. In this study, it is clear that ANNs provide a huge time benefit, also these programs are not used for pharmaceutical industry as much as other industries.

The commercial software program FormRules was trained to describe the relationships between raw materials and output properties. Using the key inputs, another commercial software package, INForm, was used. The object of the study was to optimize ramipril tablet formulation and to create knowledge and design spaces which was the new approach for the pharmaceutical product development with the aid of an ANN program and genetic programming. After the optimization, it was confirmed that the explored formulation was within the design space. Additionally, given that the knowledge and the design areas were too close to each other, we realized that it was possible to acquire more information regarding the knowledge area through trials using HPMC and lubricants in proportions other than those used in the present study.

In addition to the effect of the formulation on the tablet properties, the determination of the values that may create a model is of importance for design area studies. Using different computer programs for this study provided a significant benefit in terms of evaluating the accuracy of the findings. This was especially true for the programs that generated an equation at the end, such as GEP. Especially the programs working with the principle of giving an equation at the end, such as GEP are factors in getting rid of the suspicious approaches suspecting the artificial neural

Table XII. Finished Product Analysis Results of Direct Compressed Tablets Prepared According to Optimization Data by Using SSF

	Knowledge area limits	Design area limits	Analysis data
Inputs			
HPMC (%)	0.542–0.667	0.250–0.750	0.600
Sodium stearyl fumarate (%)	0.600–1.054	1.200–1.200	0.825
Outputs			
Crushing strength (N)	61.518–69.393	61.5–69.999	69
Dissolution in 30 min (%)	94.427–94.697	92.120–95.618	94
Assay (mg/tablet)	4.680–4.685	4.529–4.742	4.5
Impurity C (%)	0.014–0.015	0.010–0.015	0.01
Impurity D (%)	0.228–0.256	0.217–0.234	0.2

HPMC hydroxypropylmethylcellulose

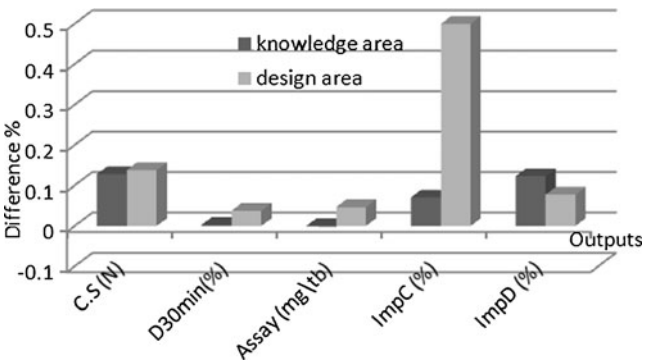

Fig. 4. Graphical image of knowledge and design area for outputs of direct compressed tablets prepared by using HPMC/SSF. *C.S.* crushing strength, *D30min* dissolution in 30 min, *Imp* impurity

networks and genetic programming to be "black boxes" emphasized Colbourn *et al.*, 2011 (22).

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