International Journal of Drug Delivery 4 (2012) 59-69

http://www.arjournals.org/index.php/ijdd/index

Original Research Article

ISSN: 0975-0215

Quality by design approach for tablet formulations containing spray coated ramipril by using artificial intelligence techniques.

Buket AKSU[1*], Marcel de MATAS[2], Erdal CEVHER[3], Yıldız OZSOY[3], Tamer GUNERI[4], Peter YORK[2]

***Corresponding author:**

Dr. Buket AKSU

[1*]Santa Farma Pharmaceuticals, Istanbul, Turkey

[2] Institute of Pharmaceutical Innovation, University of Bradford, UK

[3] Department of Pharmaceutical Technology, Faculty of Pharmacy, Istanbul University, Istanbul, Turkey

[4] Department of Pharmaceutical Technology, Faculty of Pharmacy, Ege University, Izmir, Turkey

Abstract

Different software programs based on mathematical models have been developed to aid the product development process. Recent developments in mathematics and computer science have resulted in new programs based on artificial neural networks (ANN) techniques. These programs have been used to develop and formulate pharmaceutical products. In this study, intelligent software was used to predict the relationship between the materials that were used in tablet formulation and the tablet specifications and to determine highly detailed information about the interactions between the formulation parameters and the specifications. The input data were generated from historical data and the results obtained from analyzing tablets produced by different formulations. The relative significance of inputs on various outputs such as assay, dissolution in 30 min and crushing strengths, was investigated using the artificial neural networks (ANNs), neurofuzzy logic and genetic programming (FormRules, INForm ANN and GEP).

This study indicated that ANN and GEP can be used effectively for optimizing formulations and that GEP can be evaluated statistically because of the openness of its equations. Additionally, FormRules was very helpful for teasing out the relationships between the inputs (formulation variables) and the outputs.

Keywords: Quality by Design, Artificial Neural Networks, FormRules, ramipril, spray drying, tablet

Introduction

Pharmaceutical product development knowledge is intensive, and the product development process is quite complex and takes a long time. Recently, the drug industry has experienced major developments in production information, quality management systems and risk management and has developed modern production tools that can assist in ensuring the production quality. A variety of tools helps manufacturers to identify, analyze, correct and prevent problems and constantly enhance the production processes.

The drug substance ramipril is a prodrug that is transformed into ramiprilat, its active form, in the liver. Ramipril is demonstrated to decrease the mortality risk related to congestive heart failure, myocardial infarction, paralysis and cardiovascular events and is specifically used to treat hypertension (1). Different factors such as manufacturing process, storage conditions, moisture and alkaline pHs affect the stability of ramipril (2-4). Especially wet granulation technique, which is used to fabricate the ramipril tablet formulations, significantly reduces the stability of ramipril due to its moisture sensitivity. There are several methods for moisture protection of drugs including reduction of drug solubility, modification of chemical structure, moisture-resistant packaging and encapsulation of active agents (5). Encapsulation process also gives more stability to active agents from compression and other stress conditions during formulation and storage conditions. Spesific polymers such as HPMC and PVP have been frequently used to provide moisture-protection to hygroscopic and moisture-sensitive drug substances (5,6). Spray drying is a method of producing a dry powder from a liquid or dispersion by rapidly drying with a hot air. The air supplies the heat for evaporation and conveys the dried product to the collector, and then the air is exhausted with the moisture. The feed droplets, while losing its moisture to hot air, remain at temperatures much below the hot air temperature for a very short time. Hence, spray drying is an

efficient encapsulation technique to produce stable powders of moisture and heat sensitive drugs (7,8).

The latest advances in mathematics and computer science have developed methods that may aid data analysis, and thus, different software products based on mathematical models have been developed to help streamline the product development process. Some of the techniques include neural networks, genetic algorithms and fuzzy logic for optimizing pharmaceutical formulations (9,10). Artificial neural networks are calculation models inspired by biology that consist of hundreds of units and artificial neurons connected by factors (weights) that establish the neural network (9-11). Nonetheless, the most important factor in deciding to use genetic algorithms to solve a problem concerns whether the data represent the solution of the problem. Fuzzy logic allows the use of more instinctual statements and definers, which represent shades of gray, in addition to the black and white of conventional logic (11).

In present study, ramipril was coated with HPMC and PVP using spray drying technique to improve its stability against moisture, compression and stress conditions. Ramipril tablets were fabricated by direct compression technique and two-level hierarchical experimental design consisting of 32 experiments was used to evaluate the effect of formulation variables on the quality of the attributes of ramipril tablets. Magnesium stearate (MgSt) and sodium stearyl fumarate (SSF) as lubricants was chosen at concentrations of 0.75-1.0% and 0.6-1.2%, respectively. The crushing strength, the percentage dissolution in 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 formulation knowledge and risk assessment studies.

The models and predictions for formulation development were created to demonstrate the design space using the data obtained via these new methods and programs.

Materials and Methods

Materials

Ramipril was purchased from Neuland Labs Ltd., India. Hydroxypropyl methylcellulose (HPMC), crospovidone (PVP) and yellow iron oxide from BASF, Germany; spray-dried lactose monohydrate from DMV, Holland; sodium hydrogen carbonate and red iron oxide from Merck, Germany; croscarmellose sodium from CP Kelco, Netherland; pregelatinized starch from Colorcon, England were purchased. All other chemicals were of analytical grade.

Data Set

In this study, two-level hierarchical experimental designs consisting of 32 experiments were used to evaluate the effect of two formulation variables on the quality of the attributes of ramipril tablets manufactured. The lubricant types were magnesium stearate (MgSt) and sodium stearyl fumarate (SSF). The lubricant concentrations studied were 0.75-1.0% for MgSt and 0.6-1.2% for SSF (Table 1). *Tablet Formulations and Manufacturing*

The drug substances and excipients were weighed out as described in Table 1 to manufacture the formulations. Hydroxypropyl methylcellulose (HPMC) or crospovidone (PVP) with ramipril were dissolved in a required amount of deionized water. The aqueous solution was then sprayed in a Buchi B-290 mini spray dryer with a 0.7 mm nozzle and the spray-dried powder was obtained in the following operating conditions: inlet temperature: 105°C; outlet temperature: 50-55°C; spray flow rate: 600 L/h; pump setting: 2.5 mL/min; aspirator setting: 100%.

Lactose monohydrate, sodium hydrogen carbonate, croscarmellose sodium, pregelatinized starch, yellow iron oxide and red iron oxide were then passed through a 0.85 mm sieve and mixed for 15 min in the V-type mixer (Aymes, AISI304, Turkey). This powder mixture was added to the spray-dried powder mass and mixed in same mixer for 10 min. The final mixture was divided into four equal parts. The first two parts were mixed for 2 min with MgSt, and the other two parts with SSF. The oblong tablets were then compressed using a tableting machine (Manesty, BB3B,UK) using 4.06 mm x 8.06 mm punch at 130 mg total tablet weight.

Critical Quality Attributes

The crushing strength, the percentage dissolution in 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 formulation knowledge and risk assessment studies.

The selected quality attributes were measured for the tablet samples, which included the crushing strength of the tablets that was determined using a hardness tester (Sotax HT4, Switzerland). A Distek dissolution system (Evolution 6100, USA) was used to analyze the percentage dissolution of tablets in 30 min. The dissolution tests were conducted at the conditions specified in the USP 24 method II. For the assay, 10-20 tablets were ground to a fine powder and dissolved at a specified concentration in the appropriate solvent. HPLC was used to analyze the ramipril content in solution using the “Ramipril EP Reference Standards A, B, C, D”.

High Pressure Liquid Chromatogtraphy (HPLC) Analysis

A gradient chromatographic method was used to analyze the ramipril content in formulations. 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 mm x 2.0 mm, 3 μm, Phenemonex Company, USA). The signal was monitored at 240 nm. The mobile phase consisted of Methanol:Phosphate Buffer (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 run time was approximately 4 min. The developed HPLC method was validated

according to the ICH guidelines (12). Same method was used for impurity analyses.
The final product specifications and control methods for ramipril tablets were specified and analyzed according to the European Pharmacopeia (13).

Software Tools

Three commercial artificial intelligence software tools were used to obtain the production date generated in these studies. All software packages (INForm V.4 ANN, INForm V.4 GEP and FormRules V.3.32) were provided by Intelligensys Ltd., United Kingdom. FormRules V 3.32 is a data mining software package developed by Intelligensys Ltd. that makes use of the neurofuzzy logic as its basic technology. FormRules and Inform ANN software were used in these studies as previously described by Shao et al., 2007 (14). While a central model is established by the neural network element, the genetic algorithms embedded in the software are used for optimization (15). The Genetic Algorithm Program (GEP/Gene Expression Program) was used as an alternative to ANN for generating models to describe the linkages between the input and output parameters. The genetic programming tool operates on the principle survival of a detailed description of the software package has been reported in a previous publication (16). A mathematical expression relating the input parameters to an output can be generated, unlike the black-box approach of ANNs, for which the underpinning mathematical relationships in the data are too complex to be interpreted.

Training Parameters

The parameters in INForm V.4 and FormRules V.3.32 were manipulated to optimize the predictability of the trained networks because training parameters influence the structure of the neural networks during the training process (14). The suggested parameters in the manual of INFormV.4 and FormRules V.3.32 were suitable parameters to use after having tried a variety of different parameters. The FormRules settings used for training are given below:

Model = Structural Risk Minimization (SRM)
SRM parameter: 1
CV parameter: 10
Fuzzy sets Max. submodel inputs: 4
Max. nodes per input: 15

The ANN program study conditions for this study are given in Table 2.

Measurement of the predictability of the trained models

The non-linear coefficient of determination (R^2) was computed against the validation data set to validate the predictability of trained models (17).

Results and Discussion

The data obtained for direct compression tablets were optimized using INForm V.4 ANN. Once the INForm ANN model was trained, the model was optimized with target values according to the pharmacopeial and in-house specifications. The minimum and maximum values for optimization in the program were determined by considering the values for critical quality properties obtained from the studies.
All critical parameters were of maximal importance, which set the weight value for each of them to 10. Optimization was conducted separately for formulations containing MgSt and SSF.
The same evaluations were conducted by taking into account the in-house limits and the values for those available in pharmacopeia for design space studies (Table 3).
Formulation interactions were individually evaluated for different ratios of HPMC:ramipril and crospovidone:ramipril (0.25:1 – 0.75:1) and different lubricant types and concentrations (MgSt: 0.75% - 1.0% and SSF: 0.6% - 1.2%) by using the INForm ANN program.
ANN gave the optimal formulation parameters after the training was completed.
The “knowledge area” was provided by the optimization results obtained from the study data while the “design area” was provided by the optimization results obtained from in-house/pharmacopeia data (Table 4 and Table 5). Additionally, the knowledge and design area limit values were handled as area calculations; all values are shown in the Figures 1 and 2.

The histograms in Figure 1 and 2 show that the percentage dissolution in 30 min and the amount of impurity D were among the sensitive crucial quality characteristics. The FormRules data show that the amount of dissolution in 30 min was inversely proportional to the HPMC concentration and directly proportional to impurity D. However, the information area in impurity C was broad, but because the FormRules program did not test with impurity C values as they were equal, no conclusions can be drawn about its relative impact. We concluded that we could decrease the high value of both our crucial quality characteristics because we had the opportunity to decrease the HPMC concentration according to the “design area”. It should also be noted that impurity D was sensitive to HPMC. Moreover, the “design area” information for lubricant concentration showed that the lubricant concentration was fixed. When we compared the information area with the design area, we found that a high ratio of MgSt was used in formulations. The value used needed to be smaller because the design area parameters are fixed (Figure 2).
Additionally, the knowledge area and design area for the HPMC/SSF tablets were evaluated in the same way as used for evaluating the HPMC/MgSt tablets. The resulting values are given in Table 5, and all values are shown in Figure 2 and Figure 3.
When we examined the histogram data of the formulas, we found that the lubricants had a significant impact on tablets prepared by using HPMC/SSF (Figure 3). The HPMC concentration did not affect either the information or design areas, indicating that we

had the results required in terms of impurity D. Furthermore, the percentage dissolution in 30 min increased even more with a decrease in the HPMC concentration. Unlike the MgSt formulations, the SSF ratio could also be decreased in the HPMC/SSF formulations. The SSF ratio used in the HPMC/SSF formulation was irrelevant to the design area, and the impurity C ratio showed large deviations in the histogram. No support was received for evaluating impurity C in the FormRules program, leading to the conclusion that this formulation cannot be used.

The knowledge area and design area evaluations were performed in the same way as for HPMC tablets for the PVP/MgSt and PVP/SSF tablets. The resulting values are given in Table 6 and 7, and all values are shown in Figures 5-8.

When we evaluated the optimization results of the formulations prepared using PVP, the histogram data and FormRules data were parallel. There was a direct relationship between impurity C and PVP, and there was an inverse relationship between impurity D and PVP (Figures 5-8). However, the PVP concentration and lubricant ratios could also be decreased because the impurities are within the design area when the PVP concentration was decreased in the histogram of PVP/SSF. The PVP/MgSt and PVP/SSF amounts need to be decreased to decrease impurities C and D in PVP formulations. However, in this case, the limits of the design area become much smaller and approach a single point value, which is counter to the principle of providing quality with design.

Conclusions

Many tablet experiments with spray coated ramipril were carried out over a wide range of formulation conditions. Experimental relationships between ingredient ratios and outputs were obtained.

The commercial software package FormRules was trained to generate "fuzzy rules", expressed linguistically, that describe the relationships between ingredient characteristics, process conditions and output properties. Using the key inputs from FormRules, a second commercial software package, INForm, was trained and optimized. The trained model was used to provide quantitative relationships between the same sets of inputs and outputs and to estimate the process parameters that are necessary to obtain a desired product from a given starting material.

Through our study, which is focused on the formulation of design, we acquired substantial amounts of data, which are unobtainable through research and development studies, by evaluating many experiments to understand formulation via neural networks. Although neural networks were not solutions on their own, they supported the decision processes and were useful tools for obtaining the process details using the formulations. Moreover, artificial neural networks clearly enabled a significant time savings.

Employing different computer software programs also increased the accuracy of the findings. The software packages that worked on the principle of yielding an equation like GEP were especially helpful in avoiding suspicious approaches, such as the artificial neural networks, which are "black boxes".

These model studies helped develop models based on the known data results to estimate the unknown results for the data sets.

References

[1]. Martindale, W. Martindale, The Extra Pharmacopeia, 33. ed. The Pharm. Press, London. 1996.

[2]. Hanysova L, Vaclavkova M, Dohnal J, Klimes J. Stability of ramipril in the solvents of different pH. J. Pharm. Biomed. Anal. 2005;24:335–342.

[3]. Hogan BL, Williams M, Idiculla A, Veysoglu T, Parente E. Development and validation of a liquid chromatographic method for the determination of the related substances of ramipril in Altace capsules. J. Pharm. Biomed. Anal. 2000;23:637–651.

[4]. Shafiq S, Shakeel F, Talegaonkar S, Khar RK, Ali M. Nanoemulsion as Carrier for Stability Enhancement of Ramipril. J. Dispers. Sci. Technol. 2010;31:975–979.

[5]. Abbaspour MR, Sharif Makhmalzadeh B, Jalali S. Study of free-films and coated tablets based on hpmc and microcrystalline cellulose, aimed for improve stability of moisture-sensitive drugs. Jundishapur J. Nat. Pharm. Prod. 2010;5:6- 17.

[6]. Lee S, Dekay HG, Banker GS. Effect of water vapor pressure on moisture sorption and the stability of aspirin and ascorbic acid in tablet matrices. J. Pharm. Sci. 2006;54:1153–1158.

[7]. Maurya M, Murphyb K, Kumarb S, Shib L, Leea G. Effects of process variables on the powder yield of spray-dried trehalose on a laboratory spray-dryer. Eur. J. Pharm. Biopharm. 2005;59:565–573.

[8]. Heinrich S, Henneberg M, Peglow M, Drechsler J, Mörl L. Fluidized bed spray granulation: analysis of heat and mass transfers and dynamic particle populations. Braz. J. Chem. Eng. 2005; .: 22-2.

[9]. Rowe RC, Roberts JR. Intelligent software for product formulation, Chapter 1. Product formulation and artificial intelligence. Taylor & Francis, London. 1998;1-8.

[10]. Rowe RC, Roberts JR. Intelligent software for product formulation, artificial intelligence in pharmaceutical product formulation: Neural computing and emerging technologies. Pharm. Sci. Technol. Today 1998;1:200-205.

[11]. Colbourn E, Rowe CR. Neural computing and formulation optimization.

Encyclopedia of Pharmaceutical Technology (Ed: Swarbrick J), Informa Healthcare, New York. 2007;2399-2412.

[12]. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Validation of analytical procedures: Text and methodology Q2 (R1), 1996.

[13]. The European Pharmacopoeia (online), 2010.

[14]. Shao Q, Rowe RC, York P. Investigation of an artificial intelligence technology-Model trees novel applications for an immediate release tablet formulation database. Eur. J. Pharm. Sci. 2007;31:137-144.

[15]. Ritchie MD, White BC, Parker JS, Hahn LW, Moore JH. Optimization of neural network architecture using genetic programming improves detection and modeling of gene-gene interactions in studies of human diseases. BMC Bioinformatics 2003;4:1-14.

[16]. Shao Q, Rowe RC, York P. Comparison of neurofuzzy logic and neural networks in modeling experimental data of an immediate release tablet formulation. Eur. J. Pharm. Sci. 2006;28:394-404.

[17]. Bourquin J, Schmidli H, Hoogevest PV, Leuenberger H. Comparison of artificial neural networks (ANN) with classical modeling techniques using different experimental designs and data from a galenical study on a solid dosage form. Eur. J. Pharm. Sci. 1998;6:287–300.

Table 1. Examples of Knowledge area data (Any information on the experimental design)

No	Formulation No	HPMC: Ramipril ratio (%)	PVP: Ramipril ratio (%)	Lubricant type	Amount of lubricant (%)
1	S1A1	0,25 : 1,0	---	MgSt	0,75
2	S1B1	0,25 : 1,0	---	MgSt	0,75
3	S1A2	0,25 : 1,0	---	MgSt	1,0
4	S1B2	0,25 : 1,0	---	MgSt	1,0
5	S1A3	0,25 : 1,0	---	SSF	0,6
6	S1B3	0,25 : 1,0	---	SSF	0,6
7	S1A4	0,25 : 1,0	---	SSF	1,2
8	S1B4	0,25 : 1,0	---	SSF	1,2
9	S2A1	0,75 : 1,0	---	MgSt	0,75
10	S2B1	0,75 : 1,0	---	MgSt	0,75
11	S2A2	0,75 : 1,0	---	MgSt	1,0
12	S2B2	0,75 : 1,0	---	MgSt	1,0
13	S2A3	0,75 : 1,0	---	SSF	0,6
14	S2B3	0,75 : 1,0	---	SSF	0,6
15	S2A4	0,75 : 1,0	---	SSF	1,2
16	S2B4	0,75 : 1,0	---	SSF	1,2
17	S3A1	---	0,25 : 1,0	MgSt	0,75
18	S3B1	---	0,25 : 1,0	MgSt	0,75
19	S3A2	---	0,25 : 1,0	MgSt	1,0
20	S3B2	---	0,25 : 1,0	MgSt	1,0
21	S3A3	---	0,25 : 1,0	SSF	0,6
22	S3B3	---	0,25 : 1,0	SSF	0,6
23	S3A4	---	0,25 : 1,0	SSF	1,2
24	S3B4	---	0,25 : 1,0	SSF	1,2
25	S4A1	---	0,75 : 1,0	MgSt	0,75
26	S4B1	---	0,75 : 1,0	MgSt	0,75
27	S4A2	---	0,75 : 1,0	MgSt	1,0
28	S4B2	---	0,75 : 1,0	MgSt	1,0
29	S4A3	---	0,75 : 1,0	SSF	0,6
30	S4B3	---	0,75 : 1,0	SSF	0,6
31	S4A4	---	0,75 : 1,0	SSF	1,2
32	S4B4	---	0,75 : 1,0	SSF	1,2

Of the data obtained, 15% of the experimental records were separated to use as test data and for validation. The remaining data were used for software training.

Table 2: INForm study conditions for direct compression tablets

SG INForm ANN Study Conditions
Network Structure

Model Type: Neural Network		Training Parameters:		Inputs/Outputs	
Number of hidden layers (HL)	1	Back-propagation Parameters		Inputs	HPMC or PVP Lubricant Lubricant Conc.
		Momentum	0,8		
Current hidden layer (CHL)	1	Learning rate	0,7		
Number of nodes (NN)	2	Targets		Outputs	Tb. Weight Crush. Str. Friability Disint. Time Diss. in 30 min (%) Assay Imp. A Imp. B Imp. C Imp. D Imp. Total Ramiprilat
		Target epochs	1000		
Transfer function	Asymmetric Sigmoid	Target MS error	0,0001		
Output transfer function	Linear	Random seed	1000		
Parameters Apply To: All Property Models					

Table 3: Usage of minimum and maximum pharmacopeia / in-house limit values for design space study

	Minimum Values						Maximum Values					
	Tablet weight	min	mid1	mid2	max	desirability function	Tablet weight	min	mid1	mid2	max	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/tb)	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	↓

Table 4: Knowledge and design area values of tablet parameters prepared by HPMC/MgSt

	Knowledge Area	Design Area
HPMC (%)	-1.00	-0.704
Lubricant concentration (%)	-2.070	0
Crushing strength (N)	0.026	0.016
Dissolution at 30 min (%)	0.422	0.346
Assay (mg/tablet)	0.179	0.170
Impurity C (%)	0.879	0.089
Impurity D (%)	-0.836	-0.733

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

Table5: Knowledge and design area values of tablet parameters prepared by spray granulation method and HPMC/SSF

	Knowledge Area	Design Area
HPMC (%)	0.000	0.000
Lubricant concentration (%)	1.200	-0.504
Crushing strength (N)	0.042	0.042
Dissolution at 30 min (%)	0.138	0.139
Assay (mg/tablet)	0.155	0.154
Impurity C (%)	-1.820	-1.814
Impurity D (%)	0.067	0.067

Note: The positive values show the direction of increasing; the negative values show the direction of decreasing as percentagedifference.

Table 6: Knowledge and design area values of tablet parameters prepared by PVP/MgSt

	Knowledge Area	Design Area
Crospovidone (%)	-1.00	-1.00
Lubricant concentration (%)	-0.465	-0.473
Crushing strength (N)	0.003	-0.010
Dissolutionin 30 min (%)	0.105	0.142
Assay (mg/tablet)	0.208	0.202
Impurity C (%)	-0.989	-0.968
Impurity D (%)	2.231	0.957

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

Table 7: Knowledge and design area values of tablet parameters prepared by PVP/SSF

	Knowledge Area	Design Area
Crospovidone (%)	-1.00	-1.00
Lubricant concentration (%)	-0.417	-0.420
Crushing strength (N)	0.066	0.065
Dissolution in 30 min (%)	0.138	0.139
Assay (mg/tablet)	0.194	0.193
Impurity C (%)	-1.067	-0.932
Impurity D (%)	0.305	0.303

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

Figure 1: Graphical image of knowledge and design area for inputs of tablets prepared by using HPMC/MgSt

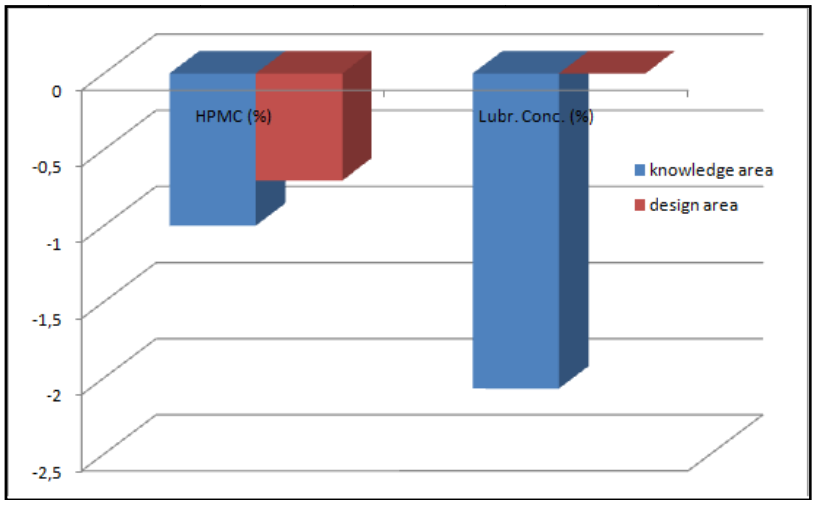

Figure 2: Graphical image of knowledge and design area for outputs of tablets prepared by using HPMC/MgSt

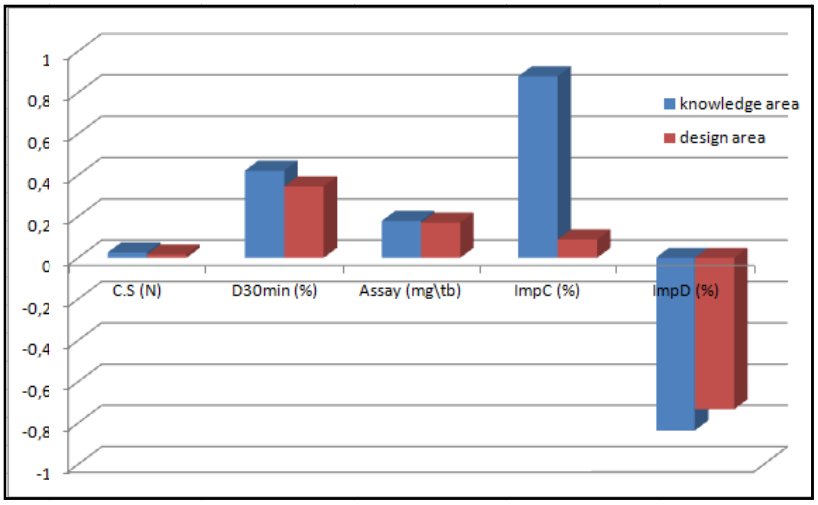

Figure 3: Graphical image of knowledge and design area for inputs of tablets prepared by using HPMC/SSF

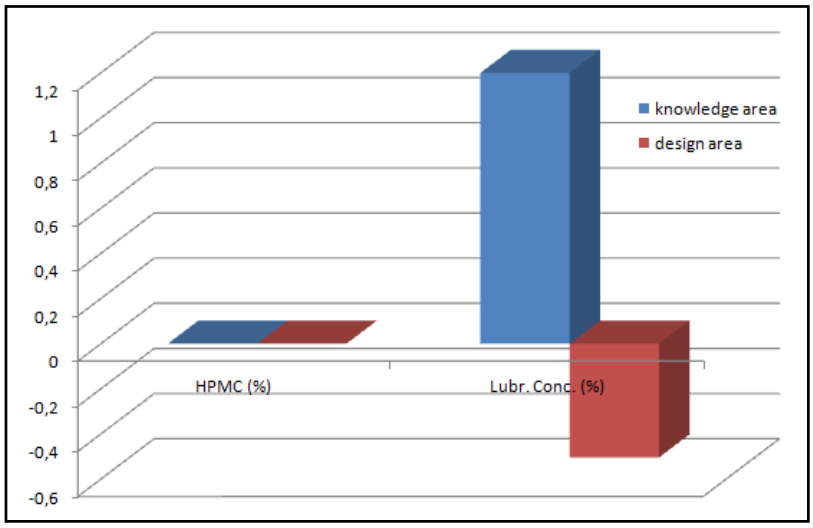

Figure 4: Graphical image of knowledge and design area for outputs of tablets prepared by using HPMC/SSF

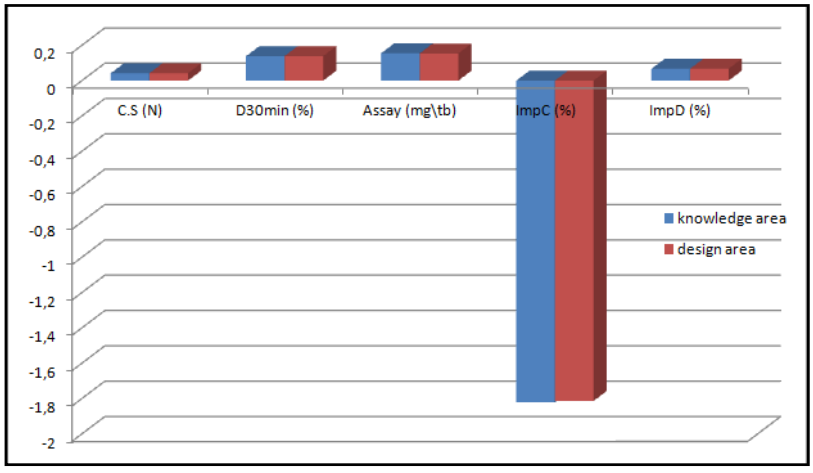

Figure 5: Graphical image of knowledge and design area for inputs of tablets prepared by using PVP/MgSt

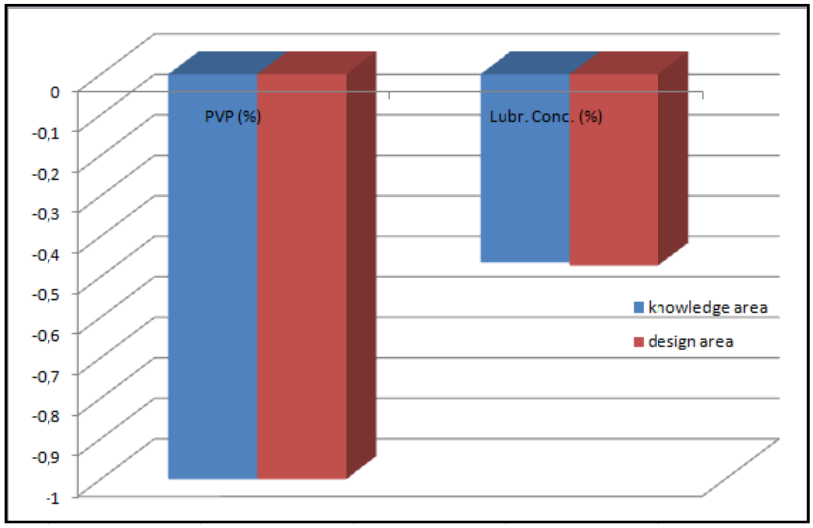

Figure 6: Graphical image of knowledge and design area for outputs of tablets prepared by using PVP/MgSt

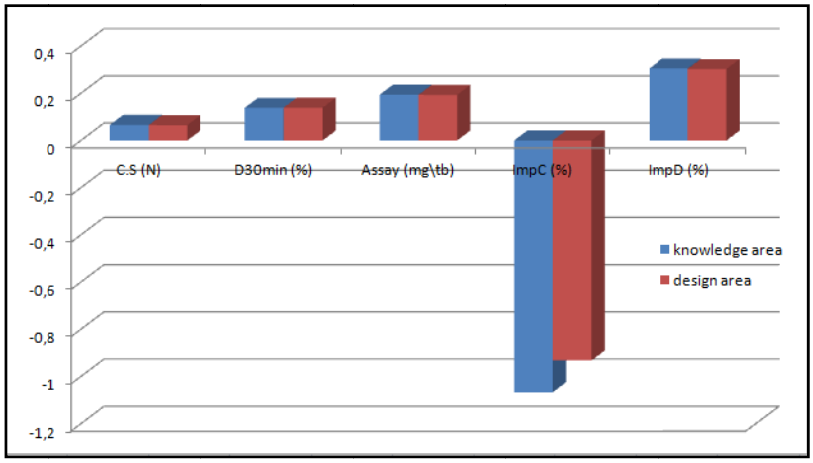

Figure 7: Graphical image of knowledge and design area for inputs of tablets prepared by using PVP/SSF

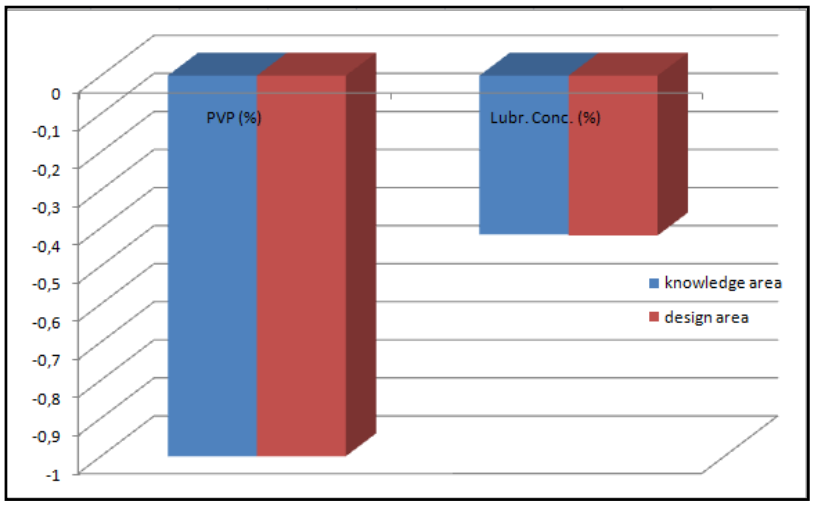

Figure 8: Graphical image of knowledge and design area for outputs of tablets prepared by using PVP/SSF