DOI: 10.7251/JEPMEN1406049S
UDK: 615.011:615.453.6:615.22
Scientific paper

DEVELOPMENT AND OPTIMIZATION OF CARVEDILOL FORMULATION USING EXPERIMENTAL DESIGN

Predrag Sibinovic[1], Valentina Marinkovic[1], Radosav Palic[2], Ivan Savic[3], Ivana Savic-Gajic[3], Dragan Milenovic[1], Rada Jankovic[1]
vana.savic@yahoo.com

[1] *Pharmaceutical and Chemical Industry Zdravlje-Actavis, 16000 Leskovac, Serbia*
[2]*University of Nis, Faculty of Science and Mathematics, Department of Chemistry, 18000 Nis, Serbia*
[3] *University of Nis, Faculty of Technology, 16000 Leskovac, Serbia*

Abstract

The aim of this paper was to develop and optimize the carvedilol tablets formulation using the full factorial design. The content of binder (PVP K30), content of disintegrant (crospovidone) and main compression force were used as the independent variables. Tablets were prepared by wet granulation. The percentage of released carvedilol from prepared formulation after 10 minutes was defined as the response. It has been found that formulation with the low content of binding agents (4.8%), high content of disintegrant (4.5%) and compression force of 50 N has the best profile of drug. The optimal formulation was defined based on implementation of pharmaceutical-technological tests (testing strength, friability, disintegrating, contents of drug substance, drug release profiles). The stability of the optimal formulation with carvedilol was estimated using the aging tests.

Keywords: *carvedilol, formulation, experimental design, dissolution profile.*

INTRODUCTION

Carvedilol is a non selective adrenergic blocking agent (Fig.1), i.e. a lipid soluble compound, which is practically insoluble in water and poorly absorbed from the gastrointestinal tract [1]. The slow absorption of carvedilol can be attributed to its poor water solubility [2, 3].

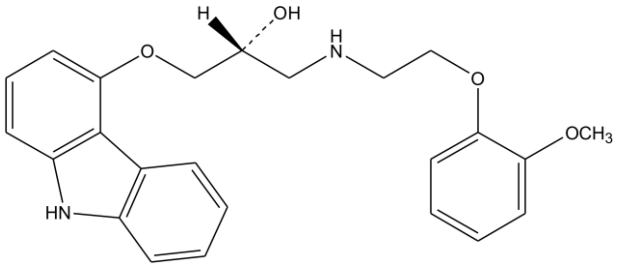

Figure 1. Chemical structure of carvedilol

Norepinephrine has the abilities to stimulate the nerves that control the heart muscles by binding to the β_1- and β_2-adrenergic receptors, i.e. to bind to the α_1-adrenergic receptors on blood vessels, causing them to constrict and raise blood pressure. In these case, carvedilol has an important role to block binding to the β_1- and β_2-adrenergic receptors [4], which both slows the heart rhythm and reduces the force of the heart's pumping. This pharmaceutical active substance blocks the α_1-adrenergic receptors [5], which lower blood pressure. Relative to other beta blockers, carvedilol has minimal inverse agonist activity [6]. This suggests that carvedilol has a reduced negative chronotropic and inotropic effect in compared with other beta blockers. However, to date this theoretical benefit has not been established in clinical trials, and the current version of the ACC/AHA guidelines on congestive heart failure management does not give preference to carvedilol over other beta-blockers. It is a racemic mixture in which non-cardioselective β-adrenergic receptor blocking activity is present in the *S*(-) enantiomer and selective α_1-adrenergic receptor blocking activity is present in both *R*(+) and *S*(-) enantiomers at equal potency. At higher concentrations it blocks the entry of Ca^{2+} into the vascular smooth muscle.

Experimental design is a well-known approach that commonly used in the development and optimization of the drug formulations [7-9]. This method enables that the desired formulation be achieved as fast as possible. Using this approach it is possible to analyze the influence of formulation factors on the selected response. Given that the types and quantities of excipients impact the release of the pharmaceutically active substance from the formulation, the aim of this study was the development and optimization of the composition of carvedilol formulation in the solid dosage form. The full factorial design with three variables at two levels was used to formulate the tablets with suitable physical and chemical properties.

MATERIALS AND METHODS

Materials. Karvileks tablets (Zdravlje-Actavis, Leskovac, Serbia) were used for the examinations. One tablet contains 12.5 mg of carvedilol and other ingredients. The average mass of the tablet is 120 mg. Dilatrend tablets were obtained as a gift sample from F. Hoffmann-La Roche, Switzerland. Polyvinylpyrrolidone K30 (PVP K30) was purchased from BASF, Germany and crospovidone was purchased from ISP Chemical, USA. All other chemicals were of analytical grade.

Experimental design. The pharmaceutical formulations were commonly developed using the traditional optimization technique so-called one-variable-at-a-time. This approach requires the higher consumption of time, employers, chemicals and energy in compared with methodology of experimental design. Also, it may be difficult to find the optimal formulation since the effect between the process variables are not estimated. Because of these reasons, it is important to use the established statistical tools, such as factorial design for optimization of the content of pharmaceutical formulations [10-12].

The number of experiments required for these studies is dependent on the number of independent variables. The response/s is/are measured for each trial and then either simple linear ($Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3$) or interactive ($Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3$...) or quadratic ($Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3$... + $b_{11}X_1^2$), where Y is the response, b_0 the intercept, b_1 the main coefficients, b_{xy} the interaction coefficients. Model is fitted by carrying out multiple regression analysis and F-statistics to identify statistically significant terms.

The reduced equation, an equation containing only statistically significant terms, then used for drawing response surface plots to visualize the impact of changing variables at a glance. The optimum point may be identified from the plot and replicate trials may be run to verify the prediction of optimum response. For simplicity, it was decided to perform a three variable study at two experimental levels to achieve the set objectives efficiently. Design-Expert software (version 7.1.6, Stat-Ease Inc., USA) was used for experimental design and statistical evaluation of the data.

Development of tablets. The composition of the different formulations of Karvileks uncovered tablets (Zdravlje-Actavis, Leskovac, Serbia) is shown in Table 1.

Table 1. Composition of uncovered tablets of Karvileks

Ingredients (mg per tablet)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Karvedilol	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
PVP K-30	6.00	6.25	6.00	6.25	6.00	6.25	6.00	6.25
Crospovidone	3.75	3.75	5.63	5.63	3.75	3.75	5.63	5.63
Lactose	94.75	94.50	92.88	92.63	94.75	94.50	92.88	92.63
Magnesium stearate	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Silicium dioxide	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6

The matrix tablets were prepared by wet granulation method using PVP K30:water (2:1) as a binder solvent, lactose as a diluent, and mixture of silicium-dioxide and magnesium stearate as the glidant and lubricant, respectively. Crospovidone was used as a disintegrant. The quantity of lactose which is used as an excipience was changed in order to achieve standard specified mass of tablets.

The ingredients were weighed accurately and passed through a 0.8 mm sieve to get uniform size particles and then they were mixed geometrically for 5 to 10 min. Granulation was done with a solution of PVP K30 in sufficient water. The granules (40 mesh) were dried in conventional hot air oven at 40 °C. Drying of the granules was stopped when the sample taken from the oven reached a loss on drying (LOD) value of 1-3%, as measured by a moisture balance at 105 °C. The dried granules were passed through a 1.0 mm, homogenized with crospovidone, silicium-dioxide and magnesium stearate and then compressed on a single punch tablet machine (Erweka EK 0, Germany). The tablets were round and flat with an average diameter of 7.0 ± 0.1 mm and a thickness of 2.6 ± 0.2 mm.

Characterization of tablets. The prepared tablets were evaluated for mass uniformity (20 tablets) [13]. Hardness (10 tablets) and thickness (10 tablets) was measured by an Erweka Multicheck tester (Germany), and friability was determined (10 tablets) using an Erweka Friability tester TDR 100 (Germany). Disintegration test was performed using Disintegration test apparatus by placing each tablet in each basket with the disc Erweka ZT301 (Germany). The process was carried out using water maintained at 37 °C.

The drug content in each formulation was determined by HPLC-UV (Agilent 1100 Series, USA), using a Lichrosorb Si60 column (250×4,6 mm, 7μm) at 20 °C, an injection volume of 20 μL and was detected at 280 nm.

The flow rate was adjusted at 2 ml/min, and the mobile phase was a mixture of 0.005 mol/l CH_3COON_a in methanol, 1,4 dioxan and acetic acid (88:10:2, v/v). The pH was adjusted to 4.0 with acetic acid. 20 tablets were powdered and average mass of one tablet was dissolved in mobile phase. The solutions were filtered through a 0.45 μm membrane filter, before analysis.

***In vitro* drug release studies**. The *in vitro* drug release studies were conducted using the USP 28 type II (10) (paddle) dissolution apparatus (Erweka). 1000 ml of citrate buffer (pH 4.5) was used as medium. The study was conducted at 37 ± 0.5 °C and at paddle rotation of 75 rpm. Samples of 5 ml were collected at predetermined time intervals and replaced with fresh citrate buffer. The samples were filtered and diluted and the drug content in the samples was estimated at 285 nm using an Agilent 8453 UV–VIS spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve. Mathematical models, zero-order, first-order and Korsmayer-Peppas were applied to analyze the release mechanism and pattern [14].

Similarity factor (f_2) analysis. *In vitro* release profile of carvedilol from selected Karvileks tablet formulations and the marketed sustained release tablets were performed under similar conditions. The similarity factor between the two formulations was determined using the data obtained from the drug release study. The data was analyzed by the equation 1:

$$f_2 = 50 \cdot \log\left[\frac{1}{\sqrt{1+\frac{1}{N}\sum(R_i - T_i)^2}} \cdot 100\right] \qquad (1)$$

where are N - number of time points, *Ri* and *Ti* - dissolution of reference and test products at time "i". If f_2 is greater than 50 it is considered that two formulations share similar drug release behaviors.

Stability studies. Optimized formulation tablets were packed in suitable primary packaging and then kept at 45 °C and 75% relative humidity (RH) for 6 months in order to perform the accelerated stability test. At the end of 3 months, the tablet properties including hardness, friability and disintegration time as well as drug content and dissolution were evaluated.

RESULTS AND DISCUSSION

Interpretation of the effects

The estimated effects are usually graphically or/and statistically interpreted, to determine their significance. In our opinion, combining a graphical with a statistical evaluation can be recommended. Graphical methods consist in drawing normal probability or half-normal probability plots. They can be constructed manually by the analyst or obtained by use of statistical software.

Both graphs plot the (absolute) factor effects as a function of values derived from a normal distribution. The non-significant effects are found on a straight line through zero line where as the significant effects deviate from this line. Half normal probability plot is shown in Figure 2.

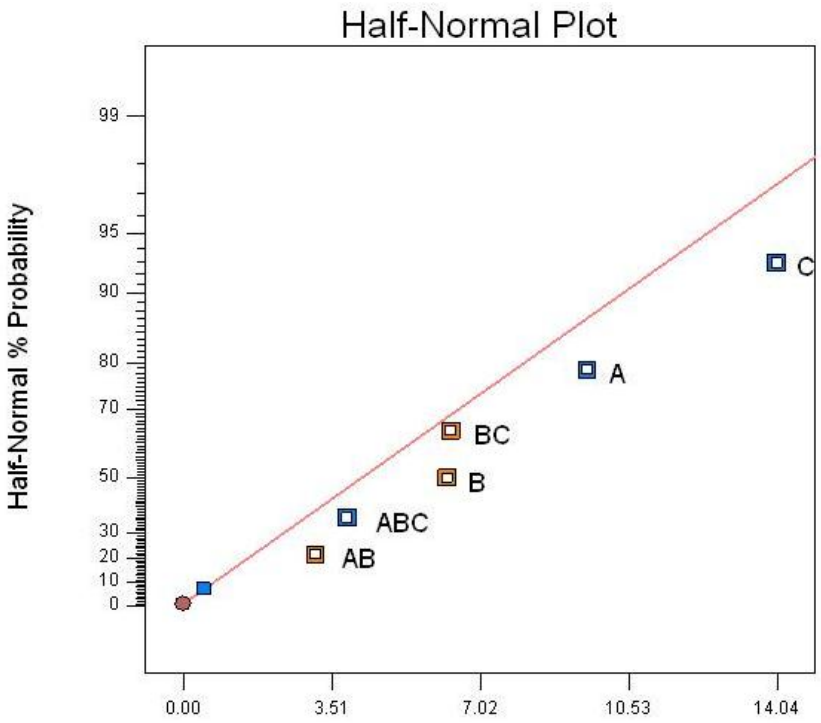

Figure 2. Half-normal probability plots for the seven effects on the response carvedilol dissolved

Building the model

After executing the experiments and determining the responses, the polynomial or factorial models describing the relationships between the responses and the considered factors can be built. Models usually includes an intercept, the main effect terms, the interaction terms, and quadratic terms. Occasionally, not all terms are included in the model and/or the non-significant terms are excluded, for instance, using the backward elimination regression procedure. Interactive statistical first-order complete model was generated to evaluate carvedilol disolved after 10 min. Final equation was given in terms of coded factors:

$$Carvedilol \quad dissolved_{Q_{10}} = 77.20 - 4.78X_1 + 3.12X_2 - 7.02X_3 + 1.57X_1X_2 + 3.16X_2X_3 - 1.94X_1X_2X_3$$

The main effects (X_1, X_2 and X_3) represent the average result of changing one factor at a time from its low to high value. The interactions (X_1X_2, X_2X_3 and $X_1X_2X_3$) show how the carvedilol disolved value changes when two or more factors are simultaneosly changed.

The carvedilol disolved values for the eight formulations show a wide variation, i.e. the response ranges from a minimum of 59.24 to a maximum of 93.20% in 10 min. The data clearly indicates that the carvedilol disolved is strongly dependant of the factors.

It may be concluded that the low levels of X_1 (binder concentration) and X_3 (main compression force) and high level of X_2 (desintegrant concetration) appear to favour the preparation of carvedilol tablets with desired dissolution after 10 min.

Evaluation of the model

After building the model, it can be interpreted graphically and/or statistically. Graphically, the model can be visualized by drawing 2D contour plots or 3D response-surface plots. A 2D contour plot shows the isoresponse lines as a function of the levels of two factors, while a 3D response-surface plot represents the response, on a third dimension, as a function of the levels of two factors. Graphical representation of the model built for the response carvedilol dissolved at hardness of 50 and 70 N as: (a) 2D contour plot, and (b) 3D response-surface plot are shown in Figures 3 and 4.

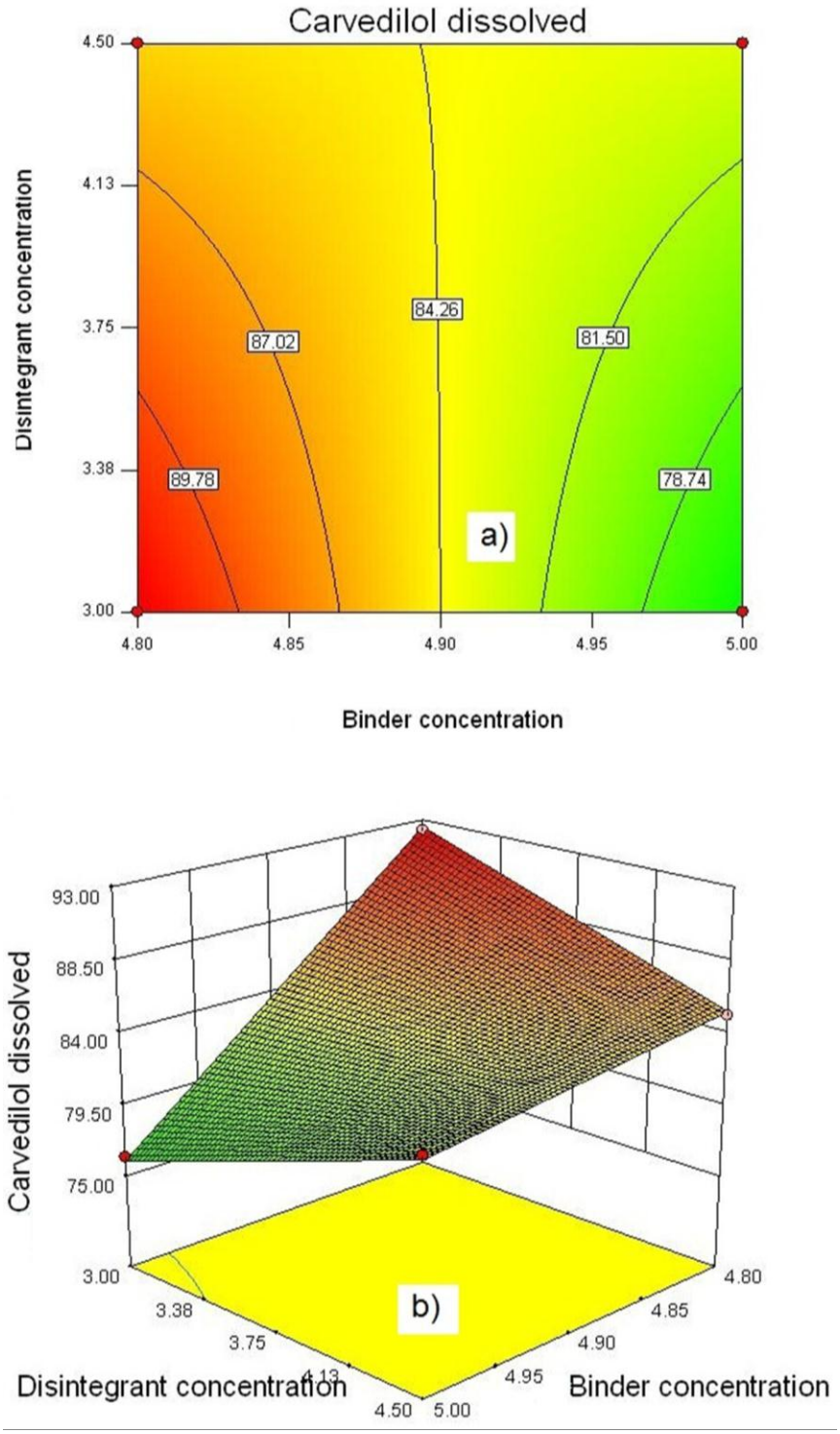

Figure 3. Graphical representation of the model built for the response carvedilol dissolved after 10 min at hardness 50 N as: (a) 2D contour plot, and (b) 3D response-surface plot

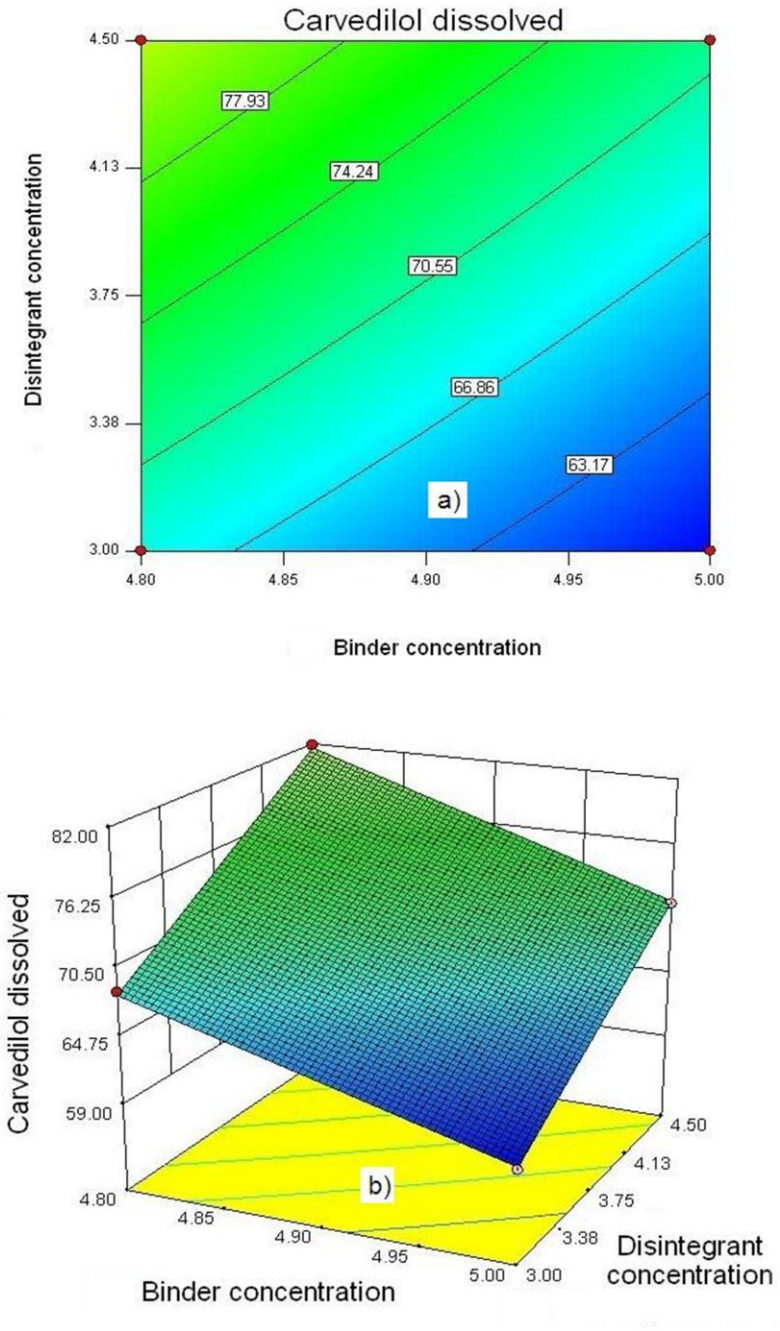

Figure 4. Graphical representation of the model built for the response carvedilol dissolved after 10 min at hardness 70 N as: (a) 2D contour plot, and (b) 3D response-surface plot

The ANOVA results of regression analysis for the simple model are depicted in Table 2. The obtained results showed that the main compression force (X_3) was the most significant carvedilol release factor: the lower hardness of tablets give better dissolution profile. Factor binding concentration PVP K30 (X_1) has less influence on dissolution profile of carvedilol, while factor disintegrant concentration crospovidone (X_2) had no significant influence in this study.

Table 2. ANOVA test of the experimental design results

factor	df	sum of squares	mean square
Model	6	784.74	130.79
X_1	1	182.60	182.60
X_2	1	78.00	78.00
X_3	1	394.24	394.24
$X_1 X_2$	1	19.66	19.66
$X_2 X_3$	1	80.14	80.14
$X_1 X_2 X_3$	1	30.11	30.11
Residual	1	0.48	0.48

Determination of the optimal formulation

In an optimization context, the model is most frequently used to predict the optimum. Often the optimum is selected from the graphical representation of the model. The overlay plot provided by the Design expert software showed an acceptable region that met the requirement of the response (Fig. 5).

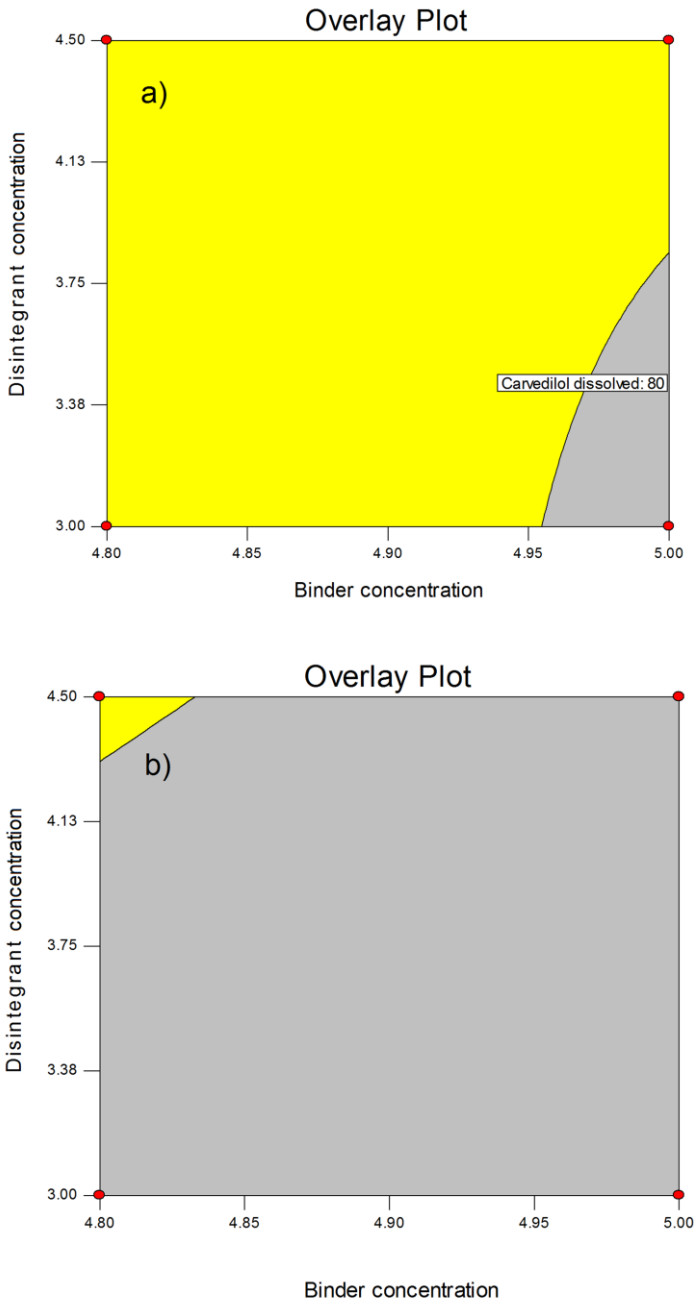

Figure 5. The overlay plot for carvedilol dissolved after 10 min at hardness of 50 N (a), and at hardness of 70N (b)

Evaluation of tablets

The uncovered tablets of Karvileks were prepared by wet granulation technique using lactose and PVP K30. The silica-dioxide, magnesium stearate and crospovidone were used in the phase of homogenization. The results of the physico-chemical characterization are shown in Table 3.

Table 3. Physico-chemical characterization of Karvileks tablets

Formulation	Uniformity of weight (mg)	Hardness (*N*)	Friability (%)	Disintegration time (min)	Drug content (mg)
F1	122.0	50	0.1	3.8	12.71
F2	120.3	50	0.13	4.5	12.48
F3	121.9	50	0.07	3.5	12.53
F4	121.4	50	0.1	3.8	12.58
F5	120.9	70	0.05	7.5	12.68
F6	120.8	70	0.08	9.5	12.39
F7	120.7	70	0.07	7.0	12.42
F8	120.9	70	0.03	8.1	12.55

The weight of the tablet varied between 120.3 mg to 122.0 mg for different formulations with low standard deviation values, indicating uniformity of weight. The variation in weight was within the range of ±7.5% complying with pharmacopoeial specifications. The hardness for different formulations was found to be between 50 to 70 N indicating satisfactory mechanical strength. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet.

The drug content varied between 12.39 to 12.71 mg in different formulations with low coefficient of variation (C.V.< 1.0%), indicating content uniformity in the prepared batches. The disintegration time was found to be in the range of 3.7 to 12.5 min for all the formulations.

In vitro dissolution studies

The pharmacokinetic parameters of carvedilol were used to calculate a theoretical drug release profile for an eight dosage form [15]. The percent of carvedilol dissolved was determined by UV-VIS spectrophotometric method at 285 nm, after 10, 20, 30 i 60 min. The *in-vitro* drug release profiles of carvedilol for all the formulations and the marketed product are shown in Figure 6.

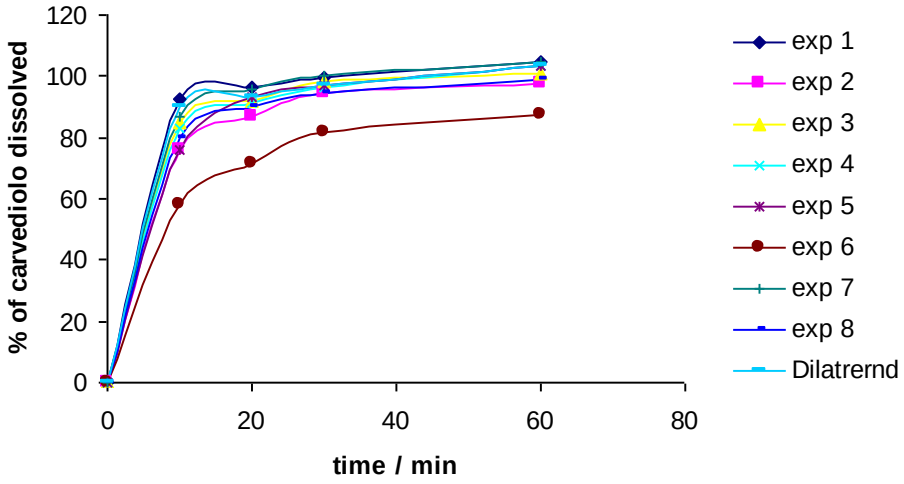

Figure 6. Dissolution properties of carvedilol

The experimental design 2^3 was applied with following independent variables: binder concentration PVP K30 (X_1), disintegrant concentration crospovidone (X_2), resistance to crushing (X_3), while percent of carvedilol dissolved (Y_1) after 10 min was used as dependent variable (Table 4).

Table 4. Experimental design table

Exp.	**X_0**	**X_1**	**X_2**	**X_3**	**X_1 Binder concentration (%)**	**X_2 Disintegrant concentration (%)**	**X_3 Hardness (N)**	**Y_1 % of carvedilol dissolved**
1	+	-	-	-	4.8	3.0	50	92.30
2	+	+	-	-	5.0	3.0	50	76.22
3	+	-	+	-	4.8	4.5	50	85.20
4	+	+	+	-	5.0	4.5	50	83.15
5	+	-	-	+	4.8	3.0	70	68.54
6	+	+	-	+	5.0	3.0	70	59.24
7	+	-	+	+	4.8	4.5	70	81.86
8	+	+	+	+	5.0	4.5	70	71.07

Drug release profiles of formulations F1-F4, (resistance to crushing of 50 N), showed a release of 92.30, 76.22, 85.20 and 83.15% in 10 min, respectively (Table 5).

Table 5. Drug release profiles of formulations F1-F8 and Dilatrend tablets

t, min	exp. 1	exp. 2	exp. 3	exp. 4	exp. 5	exp. 6	exp. 7	exp. 8	Dilatrend tablets
0	0	0	0	0	0	0	0	0	0
10	92.30	76.22	85.20	83.15	68.54	59.24	81.86	71.07	89.78
20	96.61	86.65	91.92	91.57	93.49	71.27	95.64	89.93	93.04
30	99.29	94.66	98.54	96.17	97.28	81.54	100.30	94.77	96.90
60	104.73	97.76	100.94	103.65	103.24	87.21	104.88	99.04	103.20

It is expected that the developed formulation should have the following theoretical drug release profile over 80% after 10 min [16]. Formulations F1, F3 and F4 met the needed theoretical drug release profile and from these reason, it was considered the suitable formulations among all the four formulations of this series.

Drug release profiles of formulations F5-F8 (resistance to crushing of 70 N) are shown in Table 5. The percentage of drug released from formulations F5-F8 was 76.12, 58.42, 86.64 and 79.70%, respectively, in 10 min. However, formulations F5, F6 and F8 failed to meet the required theoretical drug release profile. Formulation F7 met the desired theoretical drug release profile. Therefore, it was considered the best formulation among all the four formulations of this series.

However, formulation F3 met the theoretical drug release profile. Also, taking into consideration results for friability, desintegration and drug content, this formulation complied with all specified physical and chemical properties. Therefore, formulation F3 was considered the most suitable formulation among all the eight formulations.

Drug release kinetics

The data obtained from *in vitro* dissolution studies were fitted in different models zero order, first order and Korsemeyer's equation (Table 6). In order to confirm the exact mechanism of drug release from these tablets, the data were fitted in accordance with Korsemeyer's equation [17]. Regression analysis was performed and regression values r^2 were 0.888 to 0.998 for different formulations.

Table 6. Kinetics of in vitro carvedilol release from Karvileks tablets

Formulation	Zero order		First order		Korsemeyer model	
	k_0 (mg/min)	r^2	k_1 1/min	r^2	n	r^2
F1	0.235	0.957	0.119	0.968	0.079	0.998
F2	0.387	0.756	0.046	0.935	0.145	0.917
F3	0.289	0.779	0.115	0.928	0.098	0.950
F4	0.379	0.910	0.074	0.998	0.122	0.998
F5	0.457	0.717	0.108	0.986	0.168	0.888
F6	0.525	0.804	0.023	0.903	0.228	0.941
F7	0.326	0.819	0.112	1.000	0.103	0.968
F8	0.341	0.784	0.060	0.997	0.121	0.954

Similarity factor analysis between the formulation F3 of Karvileks and marketed product for the drug release showed the f_2 factor of 76.75, which is greater than 50. This value indicate that the release of the drug from the prepared tablets is similar to the marketed tablet.

Stability studies

Physical properties of the optimized formulation (F3) after keeping it in accelerated stability conditions (45 °C and 75% RH) are illustrated in Table 7. Hardness of tablets was in the range of 48.93 – 51.32 N, which was considered as acceptable for tablet formulations. After exposure to the stability testing conditions for three months, despite the fact that the disintegration time and friability of tablets were in the ranges of 3.50 – 4.10 min and 0.07 – 0.14%, respectively, the tablets were still within the limits defined for these variables. Drug content of tablets was ranged from 100.10 to 99.20% at the end of stability studies.

Table 7. Physicochemical characteristics of the optimized formulation (F3) after accelerated stability studies (45 °C and 75% RH)

Dependant variable	**Time (months)**		
	0	**3**	**6**
Hardness (N)	48.93 ± 3.17	51.04 ± 4.39	51.32 ± 3.41
Disintegration time (min)	3.50 ± 0.20	4.00 ± 0.10	4.10 ± 0.20
Friability (%)	0.07	0.12	0.14
Drug content (%)	100.10 ± 1.76	99.80 ± 1.23	99.20 ± 1.65
Q_{10}	85.20 ± 2.84	84.90 ± 1.98	83.02 ± 2.76
Q_{60}	100.94 ± 0.57	97.62 ± 2.43	99.89 ± 1.54

The results of dissolution studies for tablets after stability experiments are represented in Table 7. It was shown that the data were very close to the freshly prepared tablets and more than 80% of carvedilol got dissolved from all tablets in the first 10 min of the test (Q_{10}). As mentioned above, the disintegration time of tablets exposed to the stability testing conditions was increased compared to fresh tablets. The slight decrease of the drug dissolved from the tablets in the first 10 min could be attributed to the finding. In conclusion, the optimized formulation F3 could be considered stable even after 6 months of being kept under accelerated stability conditions.

CONCLUSION

This study demonstrates the use of factorial design for the development and optimization of carvedilol tablet formulation. This statistical technique allows scientists to examine more than one independent variable at a time. The desirable goals can be obtained by systematic formulation approach in shortest possible time. Obtained results showed that the most significant factor for dissolution profile of carvedilol from Karvileks tablets (Zdravlje-Actavis, Serbia) was the main compression forse. Considering the individual response evaluation, the most suitable carvedilol tablet formulation should present in its component PVP K30 - low level, disintegrant - high level, and main compression force-low level.

Acknowledgments. The financial support was provided from the Ministry of Education, Science and Technological Development of the Republic of Serbia under the project TRp-34012.

REFERENCES

[1] A. A. Othman, D. M. Tenero, D. A. Boyle, N. D. Eddington, M. J. Fossler, *AAPS J.*, 9(2007) pp.E208–E218.

[2] Y. Zhang, Z. Zhi, X. Li, J. Gao, Y. Song, *Int. J. Pharm.*, 454(2013) pp.403-411.

[3] K. Yuvaraja, J. Khanam, *J. Pharmaceut. Biomed.*, 96(2014) pp.10-20.

[4] P. C. Stafylas, P. A. Sarafidis, *Vasc. Health Risk Manag*., 4(2008) pp.23–30.

[5] A. A. Othman, D. M. Tenero, D. A. Boyle, *AAPS J*., 9(2007) pp.E208–E218.

[6] B. T. Vanderhoff, H. M. Ruppel, P. B. Amsterdam, *Am. Fam. Physician.* 58(1998) pp.1627-1634.

[7] I. M. Savic, K. Nikolic, G. Nikolic, I. Savic, D. Agbaba, M. Cakic, *Drug Dev. Ind. Pharm.*, 39(2013) pp.1084-1090.

[8] M. Cakic, Z. Mitic, G. Nikolic, I. Savic, I. M. Savic, *Expert Opin. Drug Dis.*, 8(2013) pp.1253-1263.

[9] I. M. Savic, G. S. Nikolic, I. M. Savic, K. Nikolic, D. Agbaba, *Acta Pol. Pharm.*, 69(2012) pp.739-749.

[10] I. S. Ahmed, R. N. Shamma, R. A. Shoukri, *Pharm. Dev. Technol.*, 18(2013) pp.935-943.

[11] A. K. Katharya, R. Chaudhary, R. Sharma, Y. Singh, U. V. S. Teotia, *Development*, 5(2013) pp.700-710.

[12] S. S. Mane, M. S. Kamble, O. R. Mane, V. G. Borwandkar, P. P. Aute, P. D. Chaudhari, A. V. Bhosale, *Indo Am.J. Pharm. Res.*, 3(2013) pp.4585-4593.

[13] European Pharmacopoeia 6th ed., Strasbourg, France, 2008.

[14] R. Korsmeyer, R. Gurny, E. Doelker, P. Buri, N. Peppas, *Int. J. Pharm*., 15(1983) pp.25-35.

[15] G. S. Banker, N. R. Anderson, *In the Theory and Practice of Industrial Pharmacy*, L. Lachmann, H. A. Liberman, J. L. Kaing, Eds. Varghese Publishing House, Bombay, 1987, pp.297-299.

[16] Z. Djuric, J. Parojcic, *Practical exercises of biopharmaci*, Nijansa, Zemun, Serbia, 2004.

[17] C. S. L. Chiao, J. R. Robinson, *Sustained-release drug delivery systems, in remington: The Science and Practice of Pharmacy*, 19th ed., Lippincott, Williams and Wilkins, Philadelphia, 2000, Vol. 2, pp.1660–1675.

DOI: 10.7251/JEPMEN1406049S
UDK: 615.011:615.453.6:615.22
Naučni rad

RAZVOJ I OPTIMIZACIJA FORMULACIJE KARVEDILOLA PRIMENOM EKSPERIMENTALNOG DIZAJNA

Predrag Sibinovic[1], Valentina Marinkovic[1], Radosav Palic[2], Ivan Savic[3], Ivana Savic-Gajic[3], Dragan Milenovic[1], Rada Jankovic[1]
vana.savic@yahoo.com

[1]*Farmaceutska i hemijska industrija Zdravlje-Actavis, 16000 Leskovac, Srbija*
[2] *Univerzitet u Nišu, Prirodno matematički fakultet, Departman za hemiju, 18000 Niš, Srbija*
[3]*Univerzitet u Nišu, Tehnološki fakultet, 16000 Leskovac, Srbija*

Izvod

Primenom metodologije punog faktorijalnog dizajna u radu je izvršen razvoj i optimizacija formulacije tableta na bazi karvedilola. Sadržaj vezivnog sredstva i sredstva za raspadanje, odnosno sila komprimovanja tokom izvođenja eksperimenta definisane su kao nezavisno promenljive veličine. Procenat oslodođenog karvedilola iz pripremljenih formulacija nakon 10 min izabran je kao zavisno promenljiva veličina. Na osnovu dobijenih rezultata utvrđeno je da formulacija sa niskim sadržajem sredstva za vezivanje (4,8%), visokim sadržajem sredstva za raspadanje (4,5%) i silom komprimovanja od 50 N ima najbolji profil oslobađanja lekovite supstance. Međutim, optimalna formulacija sa najboljim fizičkim svojstvima odabrana je nakon sprovođenja farmaceutsko-tehnoloških testova (ispitivanje čvrstine, friabilnosti, raspadljivosti, sadržaja lekovite supstance, profila oslobađanja lekovite supstance). Primenom testova starenja određena je stabilnost optimalne formulacije karvedilola.

Ključne reči: *karvedilol, formulacija, eksperimentalni dizajn, profil rastvaranja.*