Arch Pharm Res Vol 23, No 5, 507-512, 2000

Optimization Study on the Formulation of Roxithromycin Dispersible Tablet Using Experimental Design

Kwon-Yeon Weon, Kyung-Tae Lee[1], and Sung-Hoon Seo[1]

Galenical Research Team/R&D Center, Handok Pharmaceuticals Co., Ltd, 37, Taepung-ri, Taeso-myon, Chungbuk Province, Korea and [1]Department of Pharmaceutics, College of Pharmacy, Kyung-Hee University, 130-701, Korea

(Received March 20, 2000)

This study set out to improve the physical and pharmaceutical characteristics of the present formulation using an appropriate experimental design. The work described here concerns the formulation of the dispersible tablet applying direct compression method containing roxithromycin in the form of coated granules. In this study 2^3 factorial design was used as screening test model and Central Composite Design (CCC) associated with response surface methodology was used as optimization study model to develop and to optimize the proper formulation of roxithromycin dispersible tablet. The three independent variables investigated were functional excipients like binder (X1), disintegrant (X2) and lubricant (X3). The effects of these variables were investigated on the following responses: hardness (Y1), friability (Y2) and disintegration time (Y3) of tablet. Three replicates at the center levels of the each design were used to independently calculate the experimental error and to detect any curvature in the response surface. This enabled the best formulations to be selected objectively. The effect order of each term to all response variable was X3> X2> X1> X1*X2> X2*X2> X2*X3> X3*X3> X1*X3> X1*X1 and model equations on each response variables were generated. Optimized compositions of formula were accordingly computed using those model equations and confirmed by following demonstration study. As a result, this study has demonstrated the efficiency and effectiveness of using a systematic formulation optimization process to develop the tablet formulation of roxithromycin dispersible tablet with limited experiment.

Key words: Optimization, Factorial design, Dispersible tablet, Roxithromycin

INTRODUCTION

Roxithromycin is a semi-synthetic erythromycin derivative. The antibiotics is known to have almost odorless, bitter taste, crystalline powder (Susan *et al.*, 1996) and used for the treatment of infections in the upper and lower respiratory tracks. Although the drug is formulated in a form of film-coated tablet dosage form to mask the bitter taste, administration of the formulation to children has been a problem (Morant and Ruppanner, 1990). Currently, there is no pharmaceutical alternative to circumvent the circumvent the compliance problem for roxithromycin and, thus, other taste masking technique for roxithromycin is necessary to achieve an improved patient compliance to this drug especially in children.

Dispersible tablets are uncoated or film-coated tablets intended to be dispersed in water before administration giving a homogeneous dispersion (British Pharmacopoeia Commission, 1998). Since roxithromycin is known to have patient compliance problem due to a bitter taste of the drug, formulation of the antibiotic based on dispersed tablet design may have practical value.

In general, the development of a new pharmaceutical formulation usually has an optimization problem. The application of an optimization technique consisting of statistically experimental design to pharmaceutical formulation study would provide an efficient and economical method to acquire the necessary information to understand relationship between controllable (independent) variables and performance or quality (dependent) variables (Stetsko, 1986; Seham *et al.*, 1996). The technique of optimization is well reported in the literature for the development of tablet formulations (Seham *et al.*, 1996; Dawoodbhai *et al.*, 1991; Bos *et al.*, 1991), microcapsules (Oner and

Correspondence to: Sung-Hoon Seo, Department of Pharmaceutics, College of Pharmacy, Kyung-Hee University, Seoul 130-701, Korea
E-mail: seong@nms.kyunghee.ac.kr

Kass, 1998; Gupta *et al.*, 1989), fluid bed spray coating (Johansson *et al.*, 1987), a dry powder blend to be filled into hard gelatin capsules (Gurk and Lendrem, 1991), a hydrocolloid dressing (Nangia *et al.*, 1990), and suspension (Dimitrova *et al.*, 1989). However, the rational approach for the formulation development has not been applied for dispersed tablets. Therefore, the objective of this study was to develop an optimized formula for rdxithromycin dispersed tablet based on the optimization technique. General steps in statistical experimental research are recognition of and statement of the research problem, choice of factors, defining the levels and ranges, selection of the response variable, designing the experiment, performing the experiment, statistical analysis of the data, conclusions and recommendations (Park, 1997). In this study, the formulation was developed by a two-step approach. A preliminary study (screening study) was designed to select suitable functional excipients among various candidates, and then a formulation optimization study was followed to define the proper formulation range by optimizing the level of each factor at the experimental design.

MATERIALS AND METHODS

Materials

Roxithromycin coated granule (Roussel-Uclaf, France) is white to creamy-white particle coated granules with methacrylic acid copolymer in order to prevent bitter taste. Microcrystalline cellulose 302, NF (Avicel PH302) was purchased from FMC Corp. (USA). Crospovidone and vinylpyrrolidone/vinyl acetate copolymer, EP (Kollidone VA64) were obtained from BASF (Germany). Pregelatinized starch, USP was purchased from Colorcon Ltd. (UK) and sodium starch glycolate, USP from Edward Mendell Co. Inc.(UK). All other raw materials were pharmaceutical grade products.

Prepaparation of the dry mixture and dispersible tablets

All the powder ingredients in the prescription (Table I) except magnesium stearate were mixed using powder blender (Bohle mixer, Germany) for 10 min at a rotation speed of 6 rpm. The whole powder was then mixed with magnesium stearate for additional 5 min using the same mixer and conditions. After that, tablets were manufactured with each composition of final mixtures using a single punch tablet press (Manesty, England) fitted with round, flat, Φ7 mm punch and die at the 20kN of compression force.

Test methods on physical properties of dispersible tablet

Table I. The prescription of roxithromycin dispersible tablet

Name of ingredients	Qty per tablet	Remark
Roxithromycin coated granule	77.0 mg	Active principle
Flavor aid	15.0 mg	Fixed quantity
Sweetening agent	10.0 mg	Fixed quantity
Surfactant	1.0 mg	Fixed quantity
Anti-adherent	2.0 mg	Fixed quantity
Aromatic agent	5.0 mg	Fixed quantity
Avicel PH 302	q. s.	Filler
Kollidone VA64(X_1)	3.6~10.8 mg	X1 variable
Pregelatinized starch(X_1)	9.0~27.0 mg	X1 variable
Crospovidone(X_2)	3.6~14.4 mg	X1 variable
Sodium starch glycolate(X_2)	7.2~18.0 mg	X1 variable
Magnesium stearate(X_3)	0.54~2.16 mg	X1 variable
Total weight of tablet	180.0 mg	

Hardness was tested using Erweka TBH 30 automatic tester. The sample size was 10 tablets on each system. In case of tablet friability was carried out according to <1216>Tablet Friability in USP XXIII, Supplement 6 and disintegration time was determined by British Pharmacopoeia 1998

The Experimental design

A 2^3 factorial design was utilized in screening test and central composite design (CCC) for optimization study. The three independent variables investigated were functional excipients like binder (X1), disintegrant (X2) and lubricant (X3). The effects of previously mentioned variables were investigated on the following responses: tablet hardness (Y1), friability (Y2) and disintegration time (Y3) of tablet. The levels of three independent variables are shown in Table II and each independent variables were translated into physical units using below equation for easy application to statistical analysis.

Coded value = (Original value-M)/S
M: average of the max. and min.
S: the half of the differences between the max. and min.

Three replicates at the center levels of the each design were investigated to allow for an independent estimation of the experimental error and to check the linearity of the factor effect. The main purpose of screening test was to select better efficiency of excipients for this product and following optimization study optimized its composition using statistical design/analysis software (MODDE Ver. 4.0, Umetri AB, Sweden). This analysis program is a comprehensive Windows based software that helps formulator set up designs and analyze the data.

Table II. Translation of the levels of each independent variables into physical units

Coded Factor	Proposed Level	Variable 1(X_1)		Variable 2(X_2)		Variable 3(X_3)
		Kollidon VA64	Pregelatinized Starch	Crospovidone	Sod.starch Glycolate	Mg. Stearate
-1	Low	2%	5%	2%	4%	0.30%
0	Middle	4%	10%	5%	7%	0.75%
+1	High	6%	15%	8%	10%	1.20%

Statistical analysis

An analysis of variance, effects and interactions of each terms on the each responses were calculated by above-mentioned statistical computer software. Its analysis steps are as follows; View of data, fitting the model (by PLS or MLR algorithm), review the fit (as R2 and Q2), diagnostics (by residual plots and lists), interpret the model (by coefficient and effect plot) and refine the model (remove bad outliers and insignificant terms). R2 and Q2 are two different kinds of the quality of the fit. R2 is the fraction of the variation of the response explained by the model and Q2 is the fraction of the variation of the response that can be predicted by the model. R2 and Q2 close to 1 indicate excellent model. With a poor model Q2 can be negative.

RESULTS AND DISCUSSION

Preliminary study

As described in experimental section, we set functional excipients like binder, disintegrant, lubricant as independent variables. We select two candidates as binder and disintegrant (binder: kollidone VA64 and pregelatinized starch, disintegrant: crospovidone and sodium starch glycolate) among various functional excipients through literature investigations. All systems used magnesium stearate as lubricant. Finally, 4 systems have designed as preliminary study. System 1: kollidone VA64-crospovidone system, System 2: kollidone VA64-sodium starch glycolate system, System 3: pregelatinized starch-crospovidone system, System 4: pregelatinized starch-sodium starch glycolate system. Test results on the three dependent variables obtained from each system were analyzed and evaluated using statistical analysis software. This analysis computes goodness of fit statistics and displays a "Summary of the Fit" plot. This plot displays the quality of the fit of the model. Table III summarizes the R2 and Q2 of each system. Q2 values on Y1, Y3 responses were relatively higher than those of Y2 response, but all systems were regarded fit-to-the model as a whole. Table IV and V summarize the comparative efficiency of binders and disintegrants used in preliminary study. On the basis of these analysis results, we could conclude that kollidone VA64 (binder) and crospovidone (disintegrant) show better efficiency than other functional excipients in this formulation. So, we proceeded optimization study with the composition of system 1 by using CCC design.

Optimization study

Star point distance was set at +/- 1.444 considering minimum required level of lubricant for direct compression. Table VI summarizes the test results on physical properties of dispersible tablet prepared by CCC design. Friability was within our target (NMT 1.0%) at all tested compositions. Tablet friability represents the resistance to attribution. So, it means any compositions of this system will show high productivity. Optimization study results were also analyzed by statistical software in order to generate a model equation that provides a means of evaluating changes in response due to changes in the

Table IV. Summary of the X1 coefficients on Y1 response

X2 \ X1	Kollidone VA64	Pregelatinized starch
Crospovidone	2.091	-3.466
Sod. starch glycolate	1.029	-4.830

Table V. Summary of the X2 coefficients on Y3 response

X2 \ X1	Kollidone VA64	Pregelatinized starch
Crospovidone	-125.6	-36.8
Sod. starch glycolate	-75.8	38.6

Table III. R2 and Q2 data on each response variables in preliminary study

	System 1			System 2			System 3			System 4		
	Y1	Y2	Y3	Y1	Y2	Y3	Y1	Y2	Y3	Y1	Y2	Y3
R2	0.964	0.920	0.887	0.789	0.820	0.984	0.911	0.780	0.942	0.973	0.856	0.949
Q2	0.759	0.530	0.573	0.324	0.186	0.732	0.463	0.238	0.578	0.688	0.002	0.540

Table VI. Tablet properties in optimization study using CCC design

Run Order	Weight (mg)	SD	Hardness (N)	SD	Friability (%)	Disinteg.Time(sec.)	SD
1	179.90	3.58	38.70	4.47	0.11	94.60	27.62
2	180.40	1.87	44.80	7.15	0.06	669.80	67.12
3	182.10	2.38	33.90	1.97	0.08	22.33	3.50
4	181.70	3.55	37.40	2.67	0.07	60.00	6.66
5	179.00	3.45	26.00	2.79	0.14	65.40	7.67
6	180.90	1.64	28.70	1.57	0.22	495.40	53.14
7	182.00	1.76	24.30	3.86	0.53	15.83	5.31
8	179.40	1.43	29.90	4.77	0.14	96.00	35.08
9	180.50	2.25	32.50	3.44	0.14	28.00	3.74
10	180.80	1.56	35.50	4.53	0.08	335.00	50.35
11	180.30	2.14	33.90	3.78	0.11	717.40	216.50
12	179.90	1.78	31.80	5.09	0.14	35.67	7.58
13	181.10	1.34	42.20	6.44	0.11	63.80	26.96
14	180.50	2.08	32.20	4.32	0.17	143.40	67.96
15	181.00	1.83	33.60	3.24	0.08	95.50	19.74
16	180.70	3.30	34.60	3.37	0.11	128.17	26.75
17	181.30	2.47	33.60	4.01	0006	105.00	40.85

independent variable levels and find out optimum composition adapted to desired tablet properties (target properties on each response : Y1=>30N, Y2=max. 1min., Y3=max. 1.0%).

R2 on each response variables were 0.925, 0.730, 0.937 and Q2 were 0.520, 0.023, 0.596, respectively. ANOVA displays 9 DF (degrees of freedom) in the model, 7 DF for the residuals and SS (sum of square) by regression on each response variables were 399.938(Y1), 0.140(Y2), 767398.688(Y3). They were greater than those of SS by residuals (Y1:32.664, Y2:0.052, Y3:52000.238). By these results, we could see that the model is significant.

Fig. 1 show normalized coefficients overview for all 3 responses. This plot provides a general picture of the relative contributions of every term in the model on all responses. We confirmed again the effects of two functional excipients with this plot. As a statistical analysis results, following model equations were generated. These equations were set after examining the importance of the terms on the model, residuals and refining the model. Single terms effects were more important at all responses than those of interactions and double terms.

Y1=1.610X1-1.153X2-4.298X3+0.032X1*X2+1.087X2*X3-0.930X2*X2+0.758X3*X3

Y2=-0.033X1+0.024X2+0.057X3-0.042X1*X2+0.032X2*X3+0.018X2*X2+0.024X3*X3

Y3=111.179X1-150.092X2-5.655X3+0.032X1*X2+1.087X2*X3-0.930X2*X2+0.758X3*X3

Fig. 2 and 3 show the contour plot of hardness and disintegration time. Finally, we got the 8 optimized compositions that meet to our requirement. We could also predict each response variables of above 8 compositions using settled model equations. Those computing results are presented in Table VII.

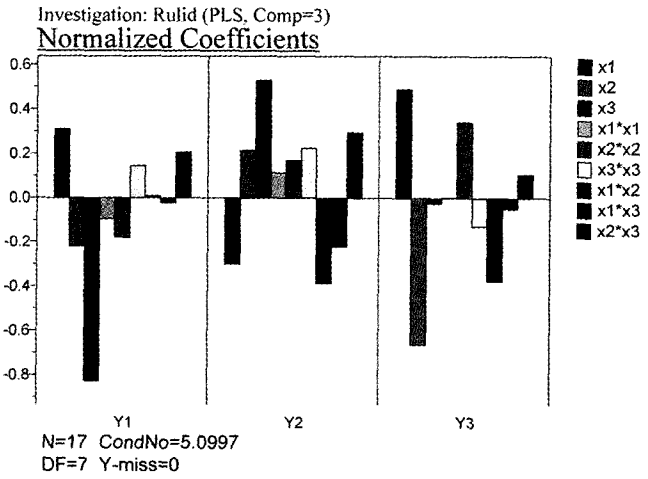

Fig. 1. Coefficient overview plot of optimiaztion study.

Demonstration study

The effectiveness of predicted values on optimized formula have to be confirmed by demonstration study. So, we conduct additional test for this purpose with No.1, No5 optimized formula. The test results are summarized in Table VIII. We find out that the observed values were very close to predicted values and tablet properties surely acceptable to our internal requirements. It means the model equations derived from this optimization study are statistically significant and predictable.

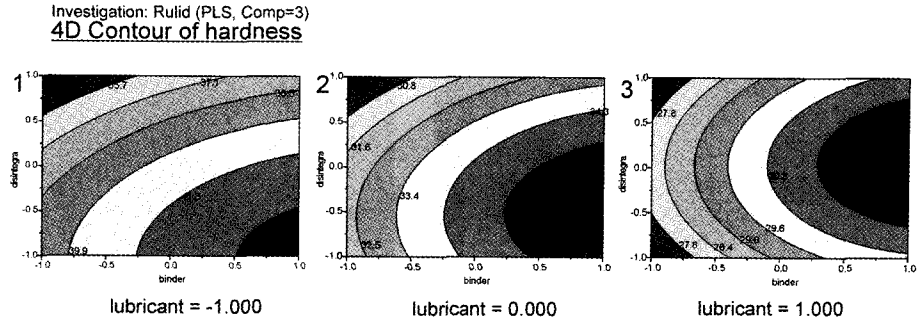

Fig. 2. 4D Contour plot of Hardness

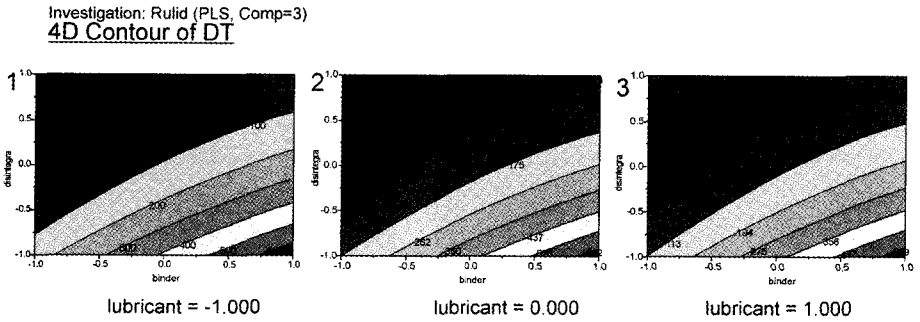

Fig. 3. 4D contour plot of disintegration time

Table VII. Predictions of optimum composition by statistical optimizer

Factor Setup								
		Factor	Role	Low Limit	High Limit			
	1	Binder	Free	-1.444	1.444			
	2	Disintegrant	Free	-1.444	1.444			
	3	Lubricant	Free	-1.444	1.444			
Response Setup								
		Response	Criteria	Weight	Min.	Target	Max.	
	1	Hardness	Target	1	30N	40N	50N	
	2	Disint. Time	Target	1	0″	30″	60″	
	3	Friability	Target	1	0%	0.25%	0.50%	
Simplex Runs								
	X1	X2	X3	Y1	Y2	Y3	Iteration	Log(D)
1	-0.5238	1.3707	-1.0402	32.96	0.146	29.98	147	-0.6516
2	-1.3889	1.4170	-1.3034	32.40	0.236	30.12	131	-0.7133
3	-0.9842	-0.3968	-1.2756	41.07	0.0960	19.32	212	-0.7631
4	1.4438	1.0215	1.4438	31.07	0.240	49.35	177	-0.3928
5	-0.8938	-0.3272	-1.1666	40.22	0.092	29.99	108	-0.8756
6	-0.6591	1.3994	-1.1061	32.86	0.160	30.01	187	-0.6710
7	-1.1100	1.3518	-1.1384	32.47	0.205	29.99	131	-0.6988
8	-0.0607	0.1437	-1.4414	42.45	0.068	36.38	113	-0.6748

As a results, we get the following conclusions : First, the use of experimental design and statistical analysis for formulation development of roxithromycin dispersible tablet enabled screening of a number of formulations with minimal tests. Second, Kollidone VA64 and Crospovidone showed better ability as functional excipients than Pregelatinized starch and Sodium starch glycolate. Third, the effect order of each terms at the optimization model was: X3>X2> X1>X1*X2>X2*X2>X2*X3>X3*X3>X1*X3>X1*X1.Fourth, predicted values for each response variables by the statis-

Table VIII. Comparison of the observed and predicted values on each response variable

Response Variables	Predicted Value	Observed Value	Confidence Interval
Y1(Hardness)	Test 1 : 32.96N	Test 1 : 30.96N	L:28.79, U:37.13
	Test 5 : 40.22N	Test 5 : 37.82N	L:37.47, U:42.97
Y2(Friability)	Test 1 : 0.146%	Test 1 : 0.25%	L:-0.027, U:0.319
	Test 5 : 0.092%	Test 5 : 0.11%	L:-0.022, U:0.206
Y3(Disint. Time)	Test 1 : 29.98 sec.	Test 1 : 41.28 sec.	L:-129.75, U:189.71
	Test 5 : 29.99 sec.	Test 5 : 48.66 sec.	L:-75.18, U:135.18

tical analysis of optimized model were within proper ranges (10%) compare with actual values. Based on our experimental results presented in this thesis, we could conclude that Kollidone VA64-Crospovidone-Mg.stearate System is the best formulation for achieving our targets on roxithromycin dispersible tablet.

REFERENCES

Bos, C.E., Bolhuis, G.K. and Lerk, C.F., Optimization of direct compression tablet formulation for use in tropical countries. *Drug Devel. Ind.Pharm.*, 17, 2373-2389 (1991).

British Pharmacopoeia Commission, *British Pharmacopoeia*, 1998, p.1452.

Dawoodbhai, S., Suryanarayan, E. R., Woodruff, C. W. and Rhodes C. T., Optimization of tablet formulations contain-ing talc. *Drug Devel. Ind. Pharm.*, 17, 1343-1371 (1991).

Dimitrova, I., Welikova, E. and Iontschev H., Optimization of the composition of granular materials for the preparation of a diazepam-containing suspension. *Die Pharmazie*, 44, 49-52 (1989).

Gupta, P. K., Hung, C. T. and Lam F. C., Factorial design based optimization of the formulation of albumin microspheres containing adriamycin. *J. Microencapsulation*, 6, 147-160 (1989).

Gurk, J. G. and Lendrem D. W., Use of statistical experimental design in laboratory scale formulation optimization and progression to pilot scale. *Drug Devel. Ind. Pharm.*, 17, 2341-2358 (1991).

Johansson, M. E., Ringbery, A. and Nicklasson M., Optimization of a fluid bed spray coating process using reduced factorial design. *J. Microencapsulation*, 4, 217-222 (1987).

Nangia, A., Lam F. and Hung C. T., Formulation optimization of a hydrocolloid dressing. *Drug Devel. Ind. Pharm.*, 16, 2109-2123 (1990).

Oner, L., Kas, H. S. and Hincal, A. A., Studies on zinc sulphate microcapsules (2): application of factorial design. *J. Microencapsulation*, 5, 225-229 (1988).

Morant, J. and Ruppanner, H., *Arzneimittel-Kompendium der Schweiz*, 1990, pp.1874-1875.

Park, S. H. : *Modern Design of Experiments*, Minyoung-Sa, Seoul, pp.11-24, 1997,.

Seham, A. E., Sabry, S. B. and Alia, A. B., Optimization of a reconstitutable suspension of rifampicin using factorial design. *Drug Devel. Ind. Pharm.*, 22, 623-630 (1996).

Stetsko, G., The application of an optimization technique to pharmaceutical formulation development. *Drug Devel. Ind. pharm.*, 12, 1109-1124 (1986).

Susan B., Maryadale J. O., Ann Smith, Patricia E. and Joanne F., *The Merck Index*, 12th Edition, pp.1424-1425, 1996.