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Optimisation of Orodispersible Tablet of Amlodepine, Ramipril in Fixed Dose Combination by Using Quality by Design (QbD) Approach

Kapil Joshi [1, 2], Abhay Asthana *[2], Gyati Shilakari Asthana [2], Subhash Pande [4],
[1] *Dr. Reddy's Laboratories Ltd,*
Village Mauja Thana, Baddi-Solan, 173205, Himachal Pradesh, India.
[2] *Pharmaceutics Research Lab, M.M. College of Pharmacy,*
M.M. University, Mullana-Ambala, 133207, Haryana, India.
[3] *Zydus Cadila Healthcare Ltd,*
Moraiya, Sanand, 382110, Gujarat, India.

Abstract

The aim of this work was to prepare and optimise the orodispersible tablet containing amlodipine and ramipril using based on quality by design (QbD) approach. The two factor, three level (3^2) factorial designs was used to study the effect of independent variables, disintegrant (X1) and coating level (X2) on the critical quality attributes (CQA), disintegration time and hardness. Orodispersible tablets were prepared by direct compression. Multiple linear regression analysis was used for generation of polynomial equation and optimization of formulation. The optimized formulation consisted of sodium starch glycolate (4.15 mg) and magnesium stearate (1.57 mg) and provided a release profile which is closed to the estimated values.

Keywords: Quality by design, Orodispersible, 3^2 factorial design, optimization, critical quality attributes.

INTRODUCTION

Due to several advantages such as cost effectiveness in manufacturing, excellent stability, most convenient in transportation and high patient compliance, tablets are the most popular and preferred drug delivery system from several decades [1]. But some patients, particularly paediatric and geriatric patients have difficulty in swallowing or chewing solid dosage forms. Orodispersible tablets offer a favourable solution for this problem and improve patient compliance [2]. Orodispersible tablets disintegrate rapidly in the saliva without the need of water and release the drug. Rapid disintegration is accomplished generally by using various disintegrants including croscarmellose sodium, crospovidone and sodium starch glycolate in the formulation[3]. Sodium starch glycolate, a modified starch is reported to aid disintegration via rapid uptake of water and swelling[4].

Lubricant is a key excipient to maintain the quality and manufacturing efficiency of tableting process. Lubricants acts by reducing friction by interposing a film of low shear strength between the powder bed and the die wall during compression and ejection. Hence, it eases compression of the formulation and ejection of the tablets. It also improved flow properties of powder. Lubricant also has significant effects on hardness, disintegration time and drug dissolution [5, 6].

Hypertension is currently a contributing risk factor to global mortality 1. Extensive clinical trials have supported the use of combinations of antihypertensive medications to adequate blood pressure (BP) control. Recently use of single-pill combinations of 2 antihypertensive agents, commonly called fixed-dose combinations (FDCs) have started gaining popularity and acceptance to achieve better BP control by improving compliance. A meta-analysis reported that use of FDCs of antihypertensive drugs is associated with a significant improvement in compliance and persistence with therapy and with possible beneficial trends on BP levels and also reported less adverse effects compared with supplying 2 separate antihypertensive agents given separately[7].

Ramipril, 2-[N-[(S)-1-(ethoxycarbonyl)-3-phenylpropyl)] -L-alanyl]-(1S, 3S, 5S)-2-azabicyclo [3-3-0] octane carboxylic acid, is an angiotensin-converting enzyme (ACE) inhibitor. Amlodipine (AMLO), chemically, 2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-1, 4-dihydro- 6-methyl-3, 5-pyridinedicarboxylic acid 3-ethyl, 5-methyl ester, is an anti-hypertensive and an antianginal agent in the form of the besylate salt. Fixed dose combination of ramipril- amlodepine is available in the form conventional solid dosage form.

Quality by design (QbD) is an intelligent approach established by the ICH and other regulatory bodies, to built quality in product and increase operational flexibility.In the current study, amlodepine –ramipril orodispesable tablets were formulated with an objective of achieving rapid disintegration with optimum hardness. Therefore, in a view to pursue the aim, orodispersable tablets were prepared by using direct compression method. Initially a number of trials were conducted to establish the process variables and studying their influence on the quality attributes, that is, disintegration time and hardness. These investigations were accomplished by application of design of experiment to establish the relationship between independent variables and response variables. Preliminary experiments revealed that amount of disintegrants and amount of lubricants are the factors significantly affecting the critical quality attributes (CQAs). Hence, 3^2 factorial designs were employed in order to optimize the Orodispersible tablet of amlodepine-ramipril combination with less disintegration time and optimum hardness.

MATERIAL AND METHODS

Materials

Amlodepine and ramipril were obtained as a gift sample from Dr. Reddy's Laboratories Ltd. Baddi, India. Sodium starch glycolate was obtained as a gift sample from S.D.Fine Chem Ltd, Mumbai, India. Microcrystalline cellulose and magnesium stearate were procured from Colorcon Asia Pvt.Ltd., Goa, India. Talc, Aerosil 200 and Aspartame were purchased from Loba Chemie Pvt. Ltd., Mumbai, India.

Experimental Design

A 3^2(two factor at three levels) full factorial design was used for optimization of orodispersible tablet containing amlodepine and ramipril. Design Expert 9.0.6 (Minneapolis, MN, USA) used for generation and evaluation of the empirical second order polynomial model. These models were used to analyse effect of independent variables on the responses. One-way ANOVA was used to determine the significance of the model ($P < 0.05$) and individual response. The amount of sodium starch glycolate and amount of magnesium stearate are the prime selected independent variables (factors), which were changed at three levels (-1. 0 and +1). Levels for two factors are presented in Table 1. The matrix of 3^2factorial design was shown in table 2. Nine trial batches of orodispersible tablets were prepared as suggested by 3^2 factorial designs. The disintegration time (*DT*, sec) and hardness (kg/cm2) were investigated as the critical quality attributes (responses).

Table 1: Independent variables and critical quality attributes (response) of the 3^2 factorial designs

Independent variables	Level		
	-1	0	+1
X1 = Amount of SSG (mg)	2	4	6
X2 = Amount of MgSt (mg)	1.5	2.0	2.5
Critical quality attributes (response)			
Y1 = Disintegration time (Sec)			
Y2 = Hardness (kg/cm^2)			

SSG= Sodium starch glycolate. MgSt= Magnesium stearate

Table 2: 3^2 Factorial design matrix.

Run	Independent variables (Factor)		Dependent variables (Response)	
	X1	X 2	Y1	Y2
1	-1.000	1.000	38	2.8
2	0.000	-1.000	22	3.1
3	-1.000	0.000	33	2.9
4	1.000	0.000	23	2.8
5	0.000	1.000	30	2.6
6	-1.000	-1.000	29	3.2
7	1.000	1.000	25	2.5
8	1.000	-1.000	19	2.9
9	0.000	0.000	26	2.6

Y1 = Disintegration time (Sec), Y2 = Hardness (kg/cm^2), X1 = Amount of SSG (mg) and X2 = Amount of MgSt (mg)

Preparation of orodispersible tablets

Table 3 presents composition of orodispersible tablet of amlodepine and ramipril. Total nine formulations were developed as per factorial design; changing the levels of the independent variales, i.e. amount of sodium starch glycolate (2, 4 and 6 mg) and amount of magnesium stearate (1.5, 2 and 2.5 mg), as shown in table 2. Orodispersible tablets were prepared by direct compression. The drugs and all the excipients were passed through a # 40 mesh screen. The blend was prepared by mixing drug and excipients except lubricant, manually in a polyethylene bag for 15 min. The lubricant was added to this blend and mixed properly again for 2 min and then compressed on single punch tablet machine (Cadmach Machinery Co. Pvt. Ltd., India) using 6mm round and flat punches.

Table 3: Detailed composition of ramipril-amlodepine orodispersible tablet

S.no	Ingredients	Amount (mg)
1	Ramipril	2.5
2	Amlodipine besilate	5.0
3	Mannitol (SD 200)	40
4	Sodium Starch Glycolate	2/4/6
5	Aerosil 200	4
6	Aspartame	10
7	Talc	2
8	Magnesium Stearate	1.5/2/2.5
9	MCC (Avicel 112) qs	200

Disintegration test

Orodispersible tablet is disintegrated in the mouth due to the action of saliva, however amount of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate *in vivo* conditions [8]. A modified disintegrating apparatus method was used to determine disintegration time of the tablets. A cylindrical vessel was used in which 10-mesh screen was placed in such way that only 2 ml of disintegrating or dissolution medium could be placed below the sieve. To determine disintegration time, 6 ml of Sorenson's buffer (pH 6.8), was placed inside the vessel in such way that 4 ml of the media was below the sieve and 2 ml above the sieve. Tablet was placed on the sieve and the whole assembly was then placed on a shaker. The time at which all the particles pass through the sieve was taken as a disintegration time of the tablet. Six tablets were chosen randomly from the composite samples and the average value was determined [6, 9].

Hardness

Pfizer Hardness Tester was used to determine hardness of prepared orodispersible tablets. Hardness of the ten tablets of each trial batch was measured and mean value was determined.

Selection of optimized formulation

Optimized formulation was selected on the basis of rapid disintegration with optimum hardness.

Validation of experimental design

Polynomial equations for both responses were generated using Design expert software version 9.0.2 (Stat-Ease, Inc, USA). The model was validated by preparing optimized

formulation along with three random formulations covering the entire range of independent variables. The observed and predicated values of the responses were quantitatively compared. The linear regression analysis between observed and predicted values of the response was also performed using Graph pad prism 5.00.

RESULT AND DISCUSSION

Owing to the manufacturing ease and cost effectiveness, direct compression method was selected in this present work [10]. In our previous work, we studied different super disintegrants to formulate fast-disintegrating tablets of amlodipine and ramipril, by the direct compression method [11]. In our previous work, sodium starch glycolate was found to be effective within the range of 2 to 6 mg. Hence, in this present study we selected the amount of SSG as independent variable, to optimise orodispersible tablet of amlodipine and ramipril. It is well known that magnesium stearate decreases the wettability due to hydrophobic nature. Magnesium stearate (2 mg) was used in our previous work to prepare tablets, however the effect of magnesium stearate on disintegration time and physicochemical property of the formulation was not evaluated. Therefore concentration of magnesium stearate was selected as other independent variables for the experimental design.

Experimental design, model fitting and analysis of data

Trial formulations were evaluated for their post-compression properties like organoleptic, physical and quality control parameters. All tablets were found to be in circular shape with no cracks. Average weight of all the experimental batches was found to be in a range of 205.2 ± 1.00 – 219.2 ±1.701 mg (Fig. 1) and complied with the pharmacopoeial limits. Thicknesses of all formulations were almost similar and ranged from 1.97 ± 0.20 to 2.26 ± 0.25 mm (Fig.2). This similarity in tablet weight and thickness parameters between all trial batches indicated rare chances of any variability due to compression machine and method of preparation. The observed values for responses: disintegration time of fast disintegrating tablets (*Y*1) and hardness (*Y*2) were summarised in table 1. Disintegration time and hardness value for all experimental batches ranged from 19 to 38 sec and 2.5 to 3.2 kg/cm^2, respectively. All values were fitted in to design expert 9 (Stat-Ease) to analyse and generate mathematical models for both responses. The responses were analyzed using ANOVA and polynomial models. Interaction and quadratic terms were generated for each response variables using multiple linear regression analysis (MLRAs).

The result of the analysis of variance (ANOVA) for responses *Y*1 and *Y*2 ($P > 0.05$) were shown in table 4. The F value in the ANOVA table was the ratio of model mean square (MS) to the appropriate error (i.e. residual) mean square. The larger the F value and the more likely that the variance contributed by the model was significantly larger than random error. The larger F-value and high R square values indicated that assumed regression models were significant and valid for each of the responses ($p < 0.05$).

The polynomial equation generated by multiple regression analysis was as follows:

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where y_i is the dependent variable, b_0 is the arithmetic mean response of the 9 runs; and b_1 and b_2 are the estimated coefficients for the independent factors, X_1 and X_2, respectively. The main effects (X_1 and X_2) represent the effect of these independent factors on the response. Coefficients with more than one factor, represent interaction term (X_1X_2). It indicates how the response changes when independent variables are changed simultaneously. The higher order polynomial terms (X_1^2 and X_2^2) are denoting investigating nonlinearity. The positive sign indicates a synergistic effect while a negative sign signifies for an antagonistic effect.

The polynomial equation for each response variable was as follows:

$$Y_1 = +26.11 - 5.50\,X_1 + 3.83X_2 - 0.75\,X_1X_2 + 1.83\,X_1^2$$
$$Y_2 = +2.82 - 0.12\,X_1 - 0.22\,X_2$$

The above equations were derived by the best-fit method to describe quantitative effect of process variables (X_1 and X_2) and their interactions on the responses Y_1 and Y_2.

The results of multiple linear regression analysis (table 5) reveal that coefficient b_1 bear a negative sign and coefficient b_2 carry a positive sign for disintegration times (Y1); which indicate antagonistic effect of amount of sodium starch glycolate (X1) and positive effect of amount of magnesium stearate (X2). For hardness (Y2), both the coefficient b_1 and b_2 bear a negative sign. Therefore, increasing the amount of sodium starch glycolate and magnesium stearate was expected to reduce the hardness.

The three dimensional response surface graph was the graphical presentation of regression equations. It shows the effects of independent variables *X*1 and *X*2 on the responses *Y*1 and *Y*2. Figure 3 shows, a curvilinear relationship of response disintegration time (Y_1) with both the factors. This can be due to interaction between two variables, interpreting that each factor is inclining to change the effect of another factor towards the disintegration time. Disintegrating agent, sodium starch glycolate (*X*1) had negative effect on the disintegration time of the optimized fast disintegrating tablet formulation. However, disintegration time increased with the increased amount of the magnesium stearate (*X*2). This delayed disintegration is due to the general agreed observation that magnesium stearate forms a hydrophobic membrane on the surface of the powder particles. Hence, disintegration time would increase with the increased concentration of magnesium stearate[12, 13].

Amount of sodium starch glycolate (X1) and amount of magnesium stearate (*X2*) had negative effect on the hardness of an optimized fast disintegrating tablet formulation (Fig. 4). Moreover, the effect of X2 (the amount magnesium stearate) was more significant than the effect of X1 (the amount of sodium starch glycolate). Magnesium stearate spreads over the surface of the powder particles due to its high extensibility and prohibited inter-particulate forces[14].

Table 4: Analysis of variance (ANOVA) for the response Y1 and Y2

Source of Variation	Df	SS	MS	F	R^2	*p*-value
ResponseY1, Disintegration time (sec)						
Model	4	278.64	69.66	303.97	0.9967	< 0.0001
Residual	4	0.92	0.23			
Total	8	279.56				
ResponseY2, Hardness (kg/cm^2)						
Model	2	0.36	0.18	15.09	0.9989	0.0046
Residual	6	0.72	0.012			
Total	8	0.44				

DF indicates: degrees of freedom; SS, sum of squares; MS, mean of squares; F, fischer's ratio; R^2 , regression coefficient..

Table 5: Coefficient and *p*-value of each factor, for response Y1 and Y2

Factor	Y1 Disintegration time (sec)		Y2 Hardness (kg/cm^2)	
	Coefficient	*p*-value	Coefficient	*p*-value
X1	-5.50	< 0.0001	- 0.12	0.0046
X2	+ 3.83	< 0.0001	- 0.22	0.0029
X1X2	- 0.75	0.0351	-	-
X_1^2	+ 1.83	0.0056	-	-
X_2^2	- 0.17	**0.689**	-	-

Significant factor (p < 0.05).All bold values have p- value > 0.05, hence considered insignificant.

Table 6: Constraints, level of independent variables and predicated responses for optimization of orodispersible tablets.

Constraints			
Name	**Goal**	**Lower limit**	**Upper Limit**
Amount of sodium starch glycolate (mg)	In range	2	6
Amount of magnesium stearate (mg)	In range	1.5	2.5
Disintegration time (sec)	Target < 30	19	38
Hardness (kg/cm^2)	Target ≥ 3.0	2.5	3.2

SOLUTION

Amount of sodium starch glycolate (mg)	Amount of magnesium stearate (mg)	Disintegration time (sec)	Hardness (kg/cm^2)	Desirability
4.15	1.57	22.35	3.0	1.00

Table 7. Comparison between observed and predicated value for response Y1 (Percentage Drug release at 5 hr) and Y 2 (Percentage Drug release at 5 hr) for different check points.

S.no	Experimental trial Factors (Coded)		Response	Observed value	Predicated value	Percent predication error
	X1	X2				
1	0.8	-0.6	Y 1 Y 2	20.45 2.88	20.94 2.85	- 2.39 1.041
2	-0.80	0.6	Y 1 Y 2	35.08 2.80	34.34 2.78	2.10 0.714
3	0.2	-0.2	Y 1 Y 2	24.12 2.87	24.34 2.84	- 0.91 + 1.05

Percent predication error was calculated by using formula $\frac{(observed\ value - predicated\ value)}{Observed\ value} x\ 100$

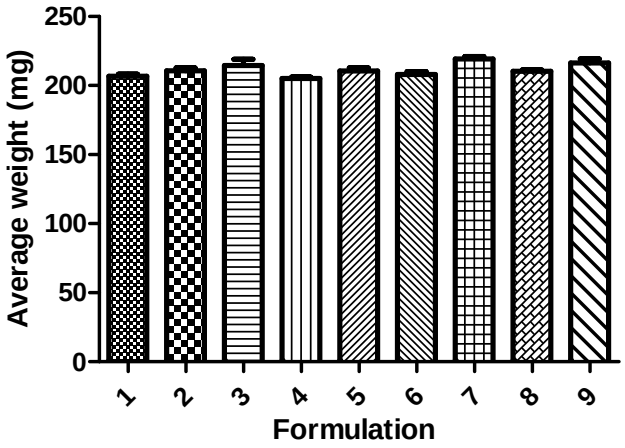

Figure 1: Average tablet weight of orodispersible formulations

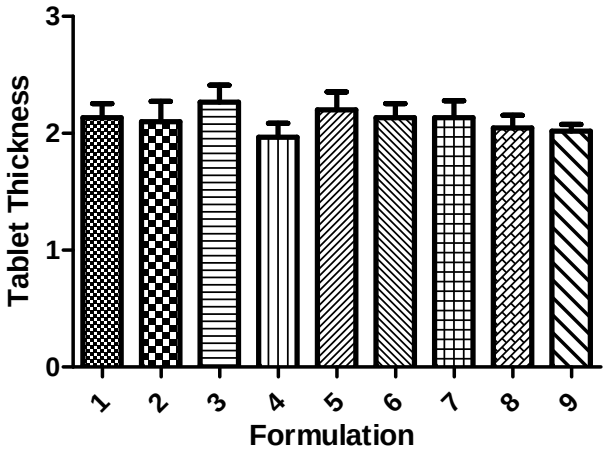

Figure 2: Thickness of orodispersible formulations

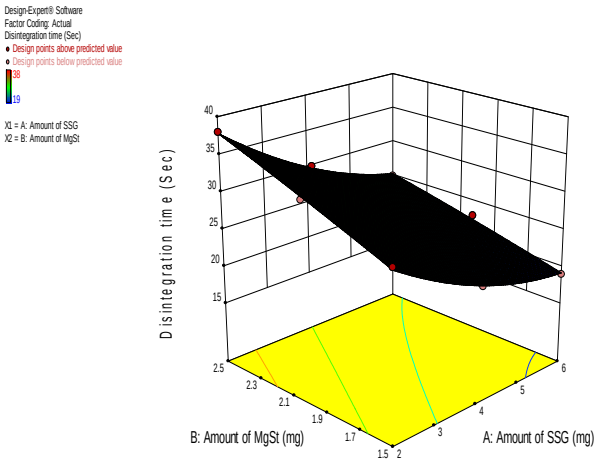

Figure 3: Response surface plot, the influence of X1(amount of SSG) and X2 (Amount of MgSt) on response Y1 (disintegration time).

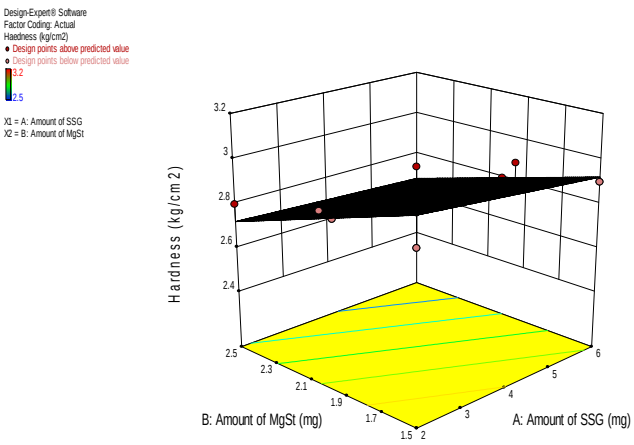

Figure 4: Response surface plot showing the influence of X1(amount of SSG) and X2 (Amount of MgSt) on response Y2 (hardness).

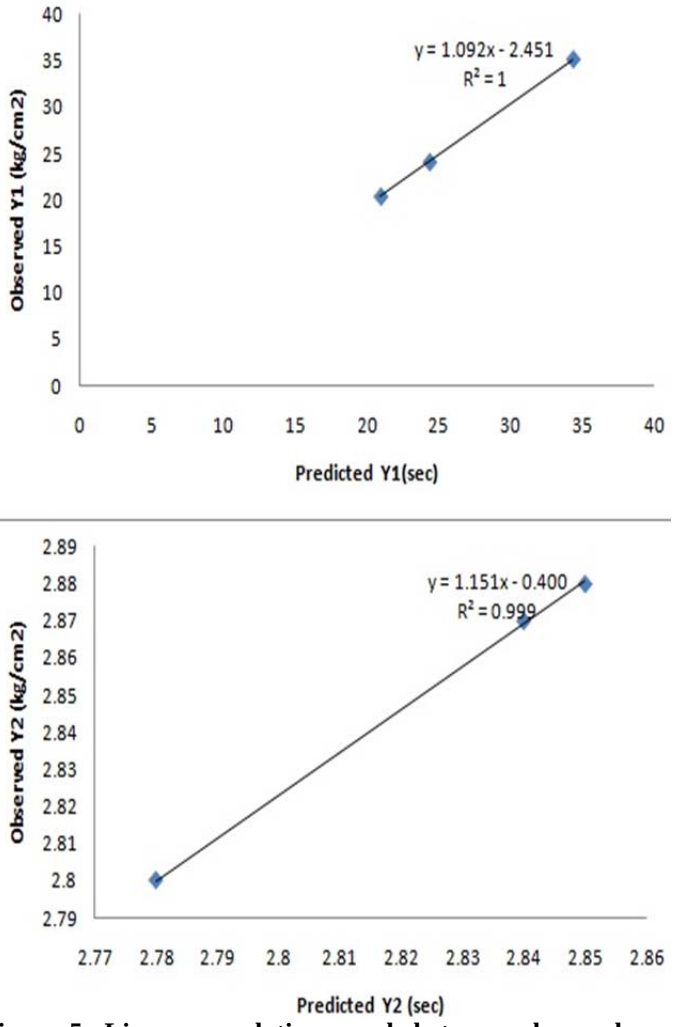

Figure 5: Linear correlation graph between observed and predicted value of response Y1 (Disintegration time) and response Y2 (Hardness).

Optimisation of independent variables

The numerical optimisation of fast dissolving tablets based on desirability approach is performed to obtain the levels of factor X1 and X2, which disintegrate rapidly with optimum hardness. The constraints, optimized level of factors and predicated responses are shown in table 6. Optimum amount of disintegrating agent and lubricant was found to be 4.15 mg and 1.57 mg, respectively. Optimized fast disintegrating tablets showed disintegration time of 22.35 (predicted), 22.12 ±3.2 (observed) seconds with hardness value of 3.00 (predicted), 3.08 ±0.31 (observed) kg/cm^{-2}.

Validation of the model

To determine the validity of generated mathematical model, formulations corresponding to optimum independent variable (factor) along with three additional random check point covering the entire range of experimental design were prepared. Responses were estimated for each one of these test runs, by use of the generated mathematical model (predicated value) and by the experimental processes (Actual value) (table 7). A high value of correlation coefficient r^2 (> 0.9) as well as lower value of percentage predication error, indicating validity and high predicative ability of response surface method (Fig.5).

CONCLUSION

In this study quality by design approach was used to optimise a fast dissolving tablet. The optimized formulation containing sodium starch glycolate (4.15 mg) and magnesium stearate (1.57 mg) showed rapid disintegration and optimum hardness, which was closed to the predicated value. Thus the quality by design can be a reliable approach for optimization of fast dissolving tablets.

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