Research Article

Development of Delayed Release Rabeprazole Pellets Employing Quality by Design (QbD) Principles

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ABSTRACT

In the present study, delayed release pellets of Rabeprazole were developed using various principles of Quality by Design. Sugar spheres were drug layered, seal-coated, and enteric coated in a fluid bed coater to achieve delayed drug release. Based on previous knowledge and initial experimental data, failure mode and effect analysis method were further applied in the risk analysis for the parameters of pellets coating. Variables bearing highest RPN score (48) were screened as critical factors. Full factorial design (3^2) was employed to optimize Rabeprazole pellets selecting independent variables (% barrier coating and % enteric coating) and responses (% release at 2 hrs in acid media and % drug release at 15 minutes in buffer). Reduced multilinear regression equations had effectively translated the effect selected independent variables on critical quality attributes. Results of short term stability study indicated stable characteristics of developed formulation.

Keywords: Rabeprazole, Quality by Design, Risk assessment, Pellets.

INTRODUCTION

Quality by design (QbD) has become the answer to assist both industry and FDA to move towards a more scientific, risk based, holistic and proactive approach to pharmaceutical development. It encompasses designing and developing formulations and manufacturing processes which ensures predefined product specifications[1]. It identifies characteristics that are critical to quality from the perspective of patients, translates them into the attributes that the drug product should possess, and establishes how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics[2].

Rabeprazole sodium drug is a sodium salt of 2-((4-(3-methoxypropoxy)-3-methylpyridin-2-yl) methylsulfinyl)-1H-benzo[d]imidazole belongs to a class of proton pump inhibitors (PPIs).

It is approved for the healing of duodenal ulcers and erosive or ulcerative gastroesophageal reflux disease (GERD) and the treatment of pathological hypersecretory. Delayed release dosage form is best formulations which are used for drugs that are destroyed in gastric fluids or cause gastric irritation, or are absorbed preferentially in the intestine[3].

Multiple-unit sustained-release dosage forms, such as pellets can distributed in the gastrointestinal tract (GIT) homogeneously, which maximize drug absorption and reducing peak plasma fluctuations, risk of local GI tract irritation and dose dumping[4]. Thus, in the present study delayed release pellets of Rabeprazole were formulated using various principles of QbD.

MATERIALS AND METHODS

Materials

Rabeprazole was obtained from Cadila Pharmaceuticals Limited (Gujarat, India). Klucel LF was obtained from Ashlan (Wilmington, USA). Hypromellose phthalate (HP 55) was received from Shinetshu (Japan). Triethyl citrate was offered by cognis (Germany). Magnesium Oxide (SCORA, France), Talc (Luzenac) and empty hard gelatin capsule size 1 (ACG) were used as received.

Preparation of drug-loaded pellets

Sugar spheres were drug layered, seal-coated, and enteric coated in a fluid bed coater using ingredients shown in Table 1. Drug layering dispersion was prepared by dissolving a binder (Klucel LF, Hypromellose 3 cps), sodium hydroxide, magnesium oxide in water, followed by addition of drug. The drug dispersion was sieved through a 60# screen (250 µm) to remove any aggregates. The barrier coat dispersion (Table 1) was prepared and passed through a 60# screen and applied to the drug loaded beads. The seal-coated beads were then enteric coated, using Hypromellose phthalate (HP 55) and triethyl citrate (TEC) as the plasticizer. The enteric coating composition was prepared and applied on seal coated beads. The dispersion was passed through a 60# screen prior to application. Due to the small size of the beads, the spray rate, air flow, and product temperature were carefully monitored to ensure individual particle coating and to minimize potential agglomeration or electrostatic charge. The process parameters were as follows: rotational speed of plate: Inlet temperature (˚C): 40-60; Bed temperature (˚C): 30-40; Exhaust temperature (˚C):

30-40; Atomization air pressure (kg/cm^2): 1-3; Total pressure (kg/cm^2): 2-6; Peristaltic Pump rpm: 1-20.

Table.1: Formulation composition of RAB pellets

Ingredient	Quantity (mg)
Non pareil seeds (20/25 #)	90
Drug layering	
Rabeprazole	20
Hydroxy propyl cellulose USP-NF (Klucel LF)	7.5
Magnesium oxide	5
L-HPC LH 11	4
Dehydrated alcohol	350
Barrier coating	
Drug loaded pellets	126.5
Hydroxy propyl cellulose USP-NF (Klucel LF)	11
PEG 400	1.05
Talc	1.05
Dehydrated alcohol	120
Enteric coating	
Barrier coated pellets	**139**
Hypromellose phthalate (HP 55)	16.1
Talc	3.20
TEC	1.6
Acetone	Q.S.
Final composition	
Enteric coated pellets	160.53
Talc	0.47
Enteric coated lubricated pellets (mg) in empty hard gelatin capsule Size 1	161

Application of QbD principles

Risk assessment

Fish-bone diagram was constructed to identify the potential risks and corresponding causes. Based on previous knowledge and initial experimental data, failure mode and effect analysis (FMEA) method were further applied in the risk analysis for the parameters of pellets coating. Each variable (potential failure mode) was scored in terms of severity (S), detectability (D) and probability (P). More broadly, Severity is measure of the possible consequences of a failure mode affecting on the safety and efficacy of the final product. Detectability defined that a failure mode can be detected. The final parameter probability is considered as the occurrence probability or the likelihood of a failure. For each risk, S, D, P scores were multiplied together to produce a "Risk Priority Number" (RPN), RPN = S * D * P, which represents the overall magnitude of the risk. We ranked S, (1: No impact – have no influence on product quality, 2: Low impact – have little influence on product quality, 3: Moderate impact – have moderate influence on product quality, 4: High impact – have severe influence on product quality), D (1: Failure can be detected ever time., 3: Failure can be detected in some cases., 5: Failure cannot be detected) and P (1: Rare – failure is rare to happen., 3: Occasional – failure happens sometimes., 5: Frequent – failure is common to happen.). Maximum RPN of 100 and minimum RPN of 1 are possible. Any formulation variable or process parameter with an higher RPN was regarded as a potential critical factor, that is, potential risks are evaluated by subsequent process characterization studies since it possibly has a potential impact on CQAs and in consequence on product safety and efficacy, while factors with a lower RPN were eliminated from further study[5,6].

Application of 3^2 full factorial design (FFD)

After opting for the most important factors influencing the performance of the produced RAB pellets, a three-level, two factors, 3^2 full factorial design was employed. The selected independent variables were % barrier coat and % enteric coat. Both variables were studied at three levels (-1, 0, +1). Percentage drug release after 2 hrs in acidic media and % drug release after 15 minutes in buffer media were selected as dependent variables. According to the FFD matrix generated by Design-Expert software (Trial Version 7.1.6, Stat-Ease Inc., MN), a layout of 9 experiments was constructed. The applied FFD was further validated by standard error graph. Standard error graph is a contour plot showing the standard error of prediction for areas in the design space. These values are reflective of the design only, not of the response data. For acceptable criterion this graphs to have relatively low standard error (approximately 1.0 or lower) across the region of interest[7]. To verify the accuracy and robustness of the model, two different combinations were chosen at different levels of the selected factors within and outside of design space (DS). Formulations at those compositions were analyzed and further compared the observed responses with the predicted[8].

Determination of RAB

Concentrations of RAB in dissolution medium were quantified HPLC assisted by UV detector. A Novapak C18 (250 x 4.6mm, 5µ) column and a mobile phase comprising of phosphate buffer (pH 7.4) and acetonitrile in the ratio of 60:40 v/v were used. The flow rate was maintained at 1 ml/min.

Characterization of RAB pellets[9,10]

Physicochemical characterization

Loading of pellets into capsules

The pellets which are optimized after the trials were checked for the bulk density and were loaded into hard gelatin capsules size 1 with automatic capsule filling machine (Rimek formulations).

Weight variation test

Ten capsules were individually weighed and the contents were removed. The emptied capsules were individually weighed and the net weight of the contents was calculated by subtraction and the percent weight variation was calculated by using the following formula.

$$\text{Weight variation} = \frac{(\text{Wt of Capsule} - \text{Average weight})}{\text{Average wt of capsule}} * 100$$

Weight variation should not be more than 7.5 %.

Lock length

Ten individual capsules were taken from formulation trial batch and lock length was measured manually by using vernier calipers and average of ten capsules was noted.

Friability and Sphericity

A friability tester (CS-2, Tianjin, China) was used to tumble 10 g of pellets for 100 rpm. After friability testing, the pellets were sieved through a sieve. The weight of loss (F %) after testing was calculated as follows:

$$F\ (\%) = \frac{Wo - W}{Wo} * 100$$

Where, Wo is the initial weight of pellets before friability testing and W is the weight of pellets retained after friability testing. The testing was carried out in triplicate.

The one-plane-critical-stability (OPCS) was used to estimate the sphericity of the pellets[11]. The value of the OPCS was the angle between a horizontal plane and a tilted plane of maximum stability of the pellets staying on that plane. Each testing was carried out in triplicate.

In vitro drug release study

The RAB pellets were subjected to *in vitro* drug release for 6 hrs in a calibrated USP dissolution test apparatus (Electrolab, Model TDT 06-T, Mumbai, India) equipped with paddle employing 700 mL dissolution media (0.1 N HCl). The dissolution media was made basic after addition of 300 mL of 0.6M Tris buffer. The paddles were rotated at 100 rpm and the dissolution medium was maintained at a temperature of 37 ± 0.5°C throughout the experiment. Five ml aliquots were withdrawn and analyzed by HPLC method as mentioned above. Five ml of fresh dissolution medium was added after each withdrawal to maintain the volume of dissolution media. The study was carried out in triplicate.

Stability Studies

The optimized RAB pellets were charged for the accelerated stability studies as per ICH guidelines (40 ± 2°C and 75 ± 5% RH) for a period of 3 months in stability chambers (Model-TH 90 S, Thermolab, India). They were placed in flint vials and hermetically sealed with rubber plugs and aluminum caps. The samples were taken out at 30, 60 and 90 days and evaluated for the various physicochemical parameters[12-14].

RESULTS AND DISCUSSION

QTPP of RAB pellets and CQA identification

QTPP for RAB pellets are listed in Table 2. According to scientific prior knowledge and preliminary studies, % drug release at 2 hrs in acidic media and % drug release at 15 mins in buffer were selected as CQAs[15].

Table.2: QTPP for RAB pellets

Attribute	QTPP
Final Dosage form	Capsule
Type of core content	Pellets
Route of administration	Oral
Appearance	Spherical shape
Strength	20 mg
In vitro release	% drug release at 2 hrs in acidic media : 0-5%
	% drug release at 15 mins in basic media: Not less than 75%
Friability	<1.0%
Impurity	Below safety threshold
Assay	Acceptable limit
Content uniformity	Acceptable limit

Risk assessment

An Ishikawa diagram was plotted, in accordance with ICH Q8 R2 guideline, to identify an initial list of potential high risk factors that influenced the quality of the RAB pellets (Figure 1). It could be seen that four main causes (formulation, process, environmental and personnel factors) were identified. Figure 2 presents the results of risk analysis, which were achieved based on prior knowledge and preliminary study. It could be seen that three potential high risk variables (RPN=48) were identified. Then preliminary experiment was carried out to select the auxiliary excipients and non significant process parameters (data not shown). Further to understand the main, interactive and polynomial effect of these causative factors on selected CQAs, FFD was employed.

Application of 3^2 full factorial design

Table 3: Experimental runs obtained from FFD and responses

Run	X_1	X_2	Y_1	Y_2
1	-1	-1	11.22±.096	93.24±2.65
2	0	-1	9.22±0.82	90.75±3.27
3	1	-1	8.42±0.66	88.45±2.69
4	-1	0	7.46±0.37	85.74±3.63
5	0	0	6.9±0.82	84.5±3.52
6	1	0	6.66±0.53	82.92±4.01
7	-1	1	5.54±0.74	79.48±2.94
8	0	1	4.22±0.52	79.15±2.16
9	1	1	3.85±0.61	78.48±3.82

The experimental run with factors and corresponding responses were presented in Table 3. Y_1(%) varied from 3.85±0.61 to 11.22±.096. Y_2(%) varied from 78.48±3.82 to 93.24±2.65. The models explaining the effects of various factors on Y_1 and Y_2 were as follows:

$$Y_1= 6.73 -0.88X_1 -2.54 X_2 +0.28X_1X_2+0.41X_1^2+0.072X_2^2$$

$$Y_2= 84.44-1.44X_1-5.89 X_2+0.95X_1X_2-0.082X_1^2+0.54X_2^2$$

Statistical analysis exhibited that the most significant factor affecting Y_1 was X_2. Though, the factors X_1 also had negative effect on Y_1. The effect of X_2 on Y_1 was on negative, which further indicates that as the level of enteric coating is increased, initial release at 2 hrs in acidic stage is decreased.

Factor X_2 had significant negative effect on drug release at 15 minutes in buffer stage, which can be mathematically proved by regression equation of Y_2. As layer of enteric coating is increased on pellets, drug diffusion from inner core is retarded.

Though the terms bearing probability value (p) more than 0.05 (95% Confidence interval) (non-significant) were omitted from the full linear regression models and further reduced model were evolved to get accurate and significant information about the responses[18].

$$Y_1= 7.05-0.88X_1 -2.54 X_2$$

$$Y_2= 84.39-1.44X_1 -5.89 X_2+0.95X_1X_2+0.54X_2^2$$

Response surface plots relating the effect of factors X_1 and X_2 on selected CQAs (Y_1 and Y_2) are presented in figure.3. The main terms had significant effect on both Y_1 and Y_2, while interactive and polynomial terms had remarkable effect only on Y_2.

To confirm applicability of evolved reduced model equations, check-point batches F10 (with in design space; X_1=0.37, X_2=0.87) and F11 (outside of design space; X_1=0.24, X_2=0.12) were formulated. The theoretical and experimental responses of Y_1(%) and Y_2(%) for batch F10 were 4.40, 79.46 and 4.13±0.8, 81.34±3.27 respectively, whereas that of batch F11 were 6.24, 83.35 and 6.44±0.8, 80.69±2.58 respectively. The results confirmed predictive potential of the evolved models. Based on the results of *in vitro* drug release, batch F10 was considered as an optimized batch satisfying predetermined criteria in terms of % drug release at 2 hrs in acidic media and % drug release at 15 mins in basic media. Figure 4 depicts overlaid contour plot which shows dark region of interest.

Physical characterization

The values of bulk density and tapped density of RAB pellets were 0.589 and 0.643 g/ml respectively. The lock length value of capsule was 16.38 mm. The weight variation in final optimized formulation was 0.992±0.043%. The sphericity value of developed RAB pellets were nearer to the 1.

Short term stability study

An optimized formulation (F10) showed stable characteristics after short term stability study period. The results of the stability study are depicted in Table 5.

Table 4: Regression coefficients and p value for selected Y_1 and Y_2

Parameter	% Drug release at 2 hrs in acidic media (Y_1)		% Drug release at 15 mins in buffer media (Y_2)	
	Co efficient	p	Co efficient	p
X_1	-0.88	0.024	-1.44	< 0.0001
X_2	-2.54	0.001	-5.89	< 0.0001
X_1X_2	0.28	0.352	0.95	0.0004
X_1^2	0.41	0.33	-0.082	0.3518
X_2^2	0.072	0.85	0.54	0.0054

Table 5: Evaluation parameters for optimized batch subjected to stability study

Parameters	F10			
	Initial	1 month	2 months	3 months
Drug content (%)	98.66±0.085	99.74±0.022	99.56±0.019	99.92±0.103
Friability	0.82±0.014	0.78±0.026	0.89±0.063	0.75±0.022
Physical degradation	No	No	No	No
% Drug release after 2 hrs in acidic media	4.13±0.8	4.26±0.62	4.32±0.49	4.28±0.33
% Drug release after 15 mins in basic media	81.34±3.27	80.36±2.67	83.64±4.01	78.32±3.41

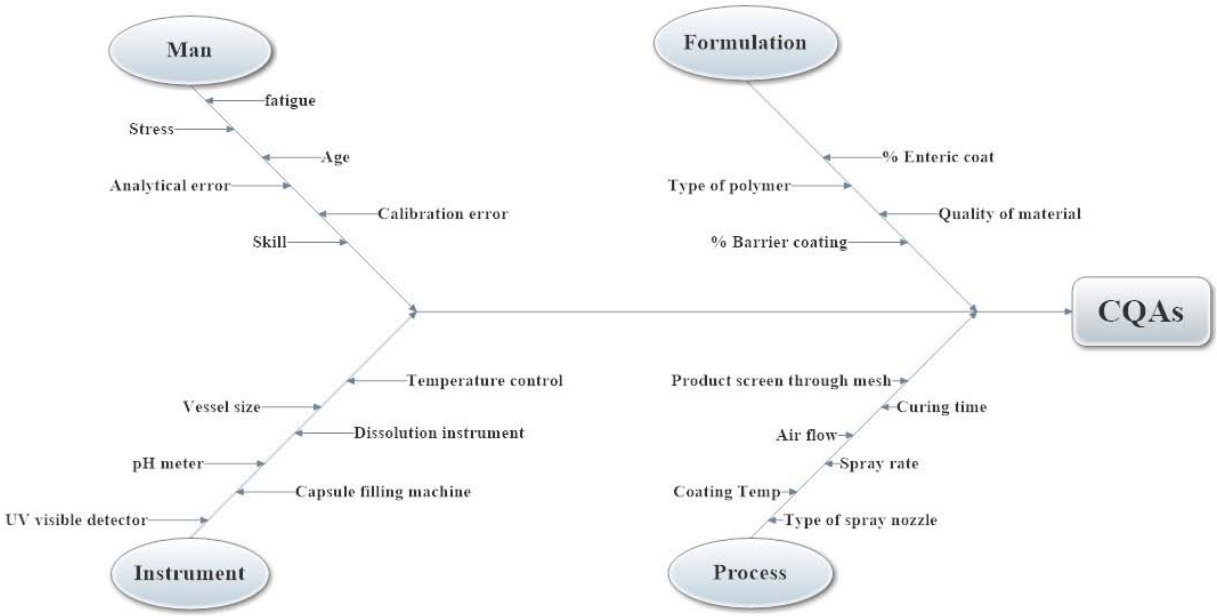

Figure.1: Fishbone diagram depicting factors that may have impact on the critical quality attribute (CQA) of the RAB pellets

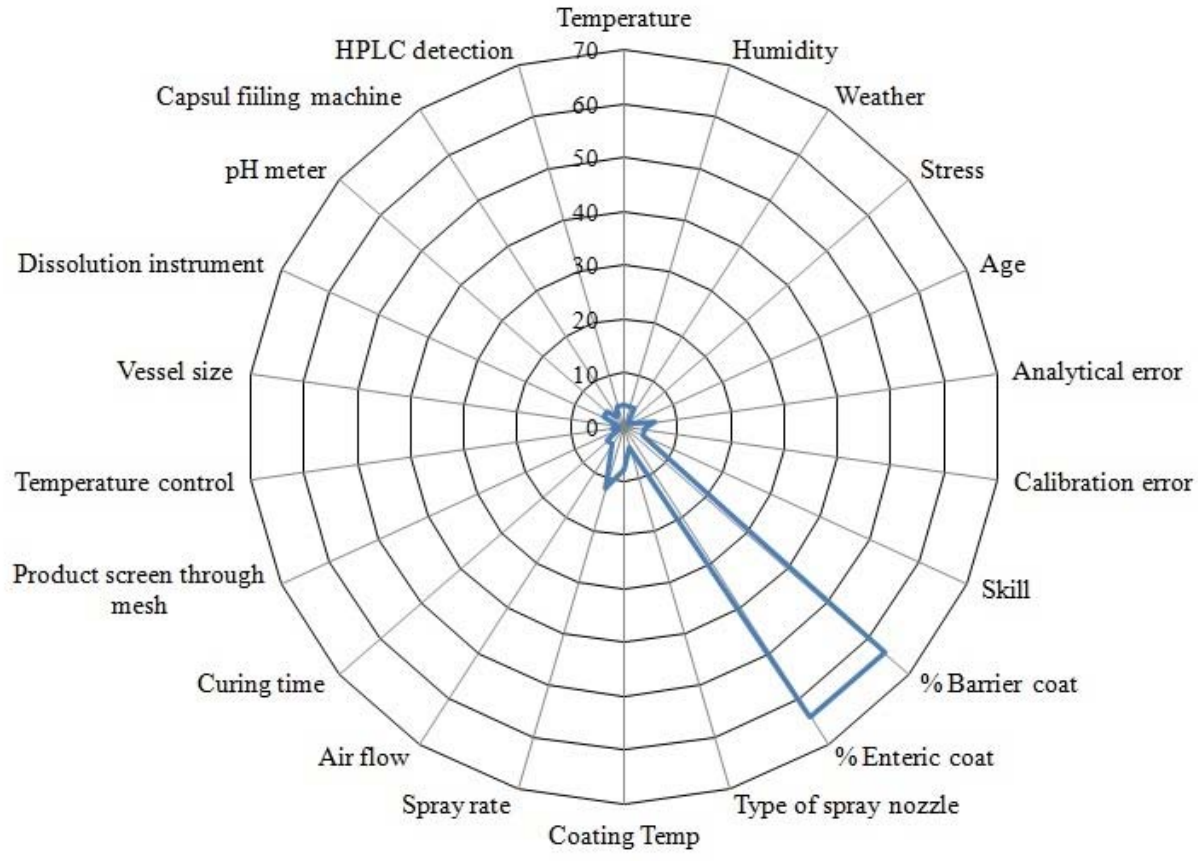

Figure 2: RPN score after FMEA risk assessment

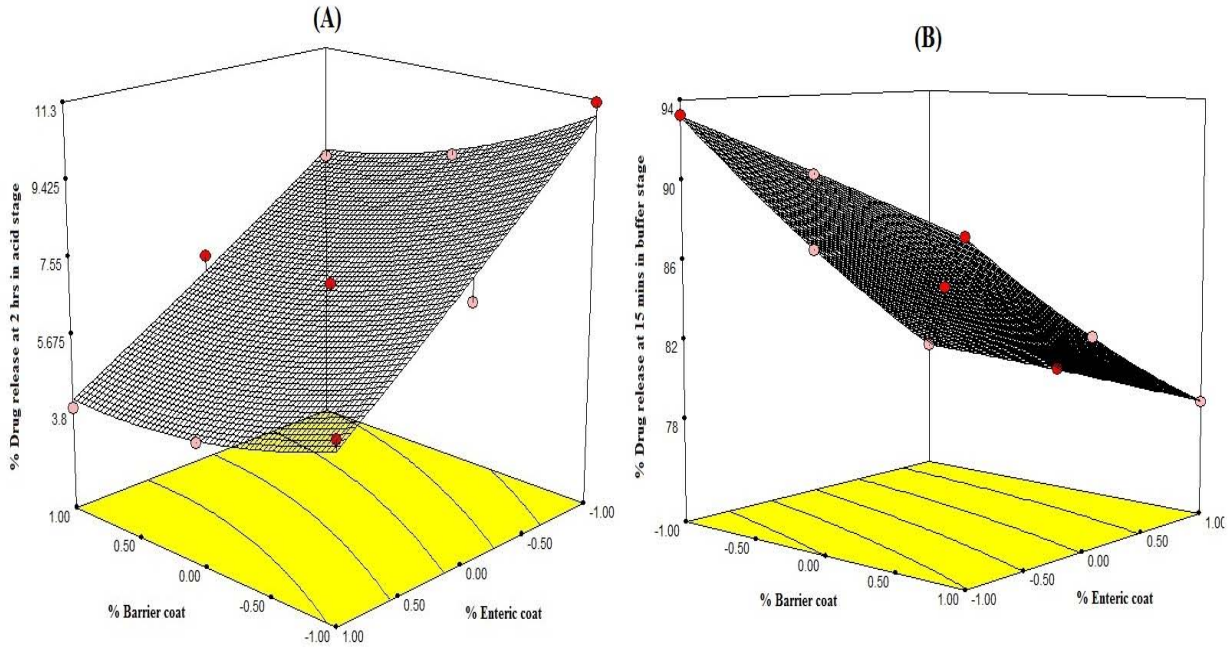

Figure 3: Response surface plots showing effect of X_1 and X_2 on Y_1(A) and Y_2(B)

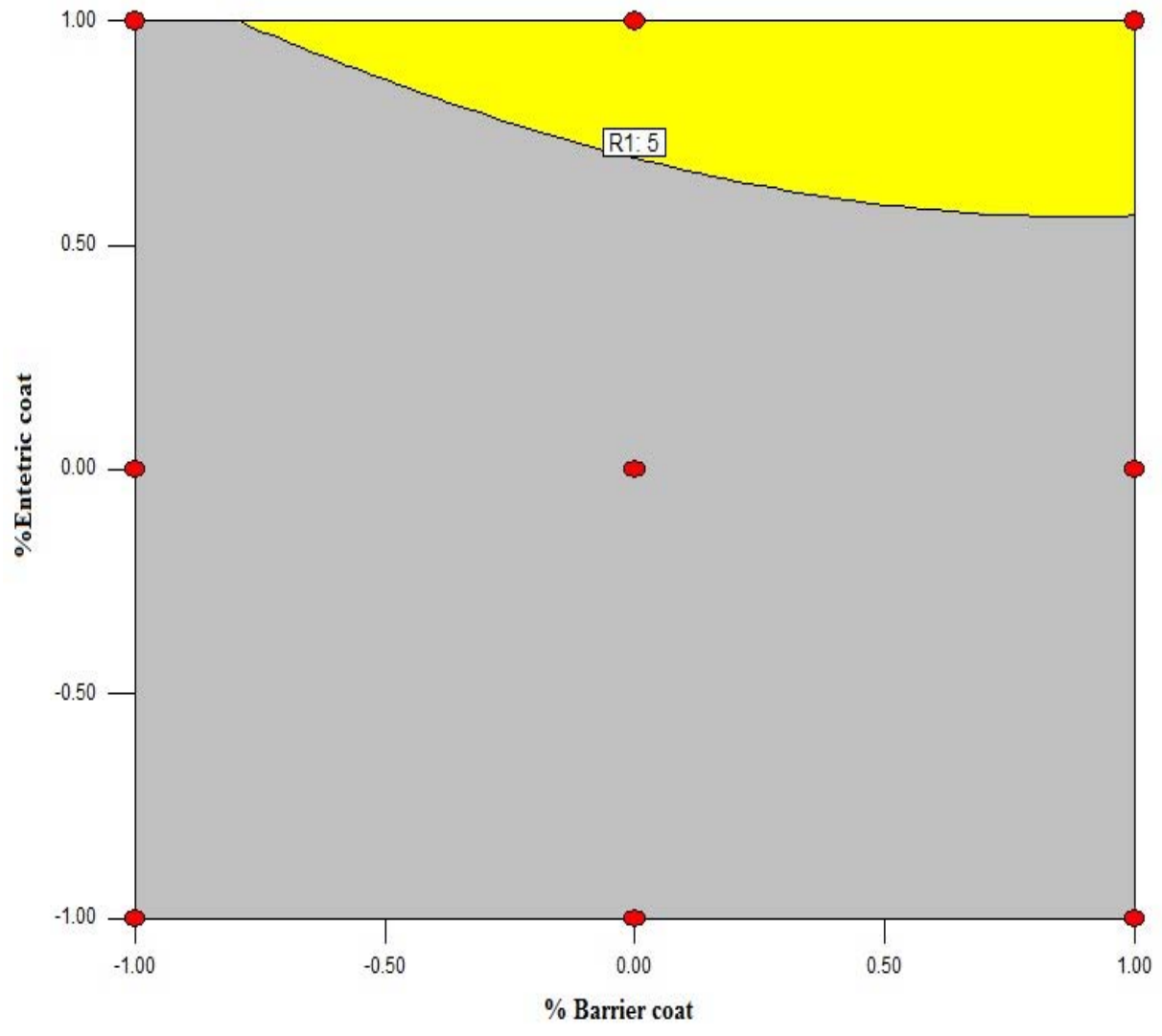

Figure 4: Overlaid contour plot

REFERENCES

1. Roy S, Quality by design: A holistic concept of building quality in pharmaceuticals, Int J Pharm Bio Res, 3, 2012, 100-108.
2. Lawrence XY, Pharmaceutical quality by design: product and process development, understanding, and control, Pharma res, 25, 2008, 781-791.
3. Kumar PS, Krishnan SN, Pavani S, Surendarnath Y, Formulation and Evaluation of Rabeprazole Sodium delayed release tablets, Sch Res Lib, 4, 2012, 287-296.
4. Hu L-D, Liu Y, Tang X, Zhang Q, Preparation and *in vitro*/*in vivo* evaluation of sustained-release metformin hydrochloride pellets, Eur J Pharm Biopharm, 64, 2006, 185-192.
5. Liu Y, Liu S, Dai Q, Design and evaluation of pH-independent pulsatile release pellets containing isosorbide-5-mononitrate, Chem Pharmaceut Bull, 57, 2009, 55-60.
6. Lionberger RA, Lee SL, Lee L, Raw A, Lawrence XY, Quality by design: concepts for ANDAs, The AAPS journal, 10, 2008, 268-276.
7. Parejiya PB, Barot BS, Patel HK, Shelat PK, Shukla A, Innovation of novel 'Tab in Tab' system for release modulation of milnacipran HCl: optimization, formulation and *in vitro* investigations, Drug Dev Ind Pharm, 39, 2013, 1851-1863.
8. Rathore AS, Saleki-Gerhardt A, Montgomery SH, Tyler SM, Quality by Design: Industrial case studies on defining and implementing design space for pharmaceutical processes (Part 2), Int BioPharm, 21, 2009, 213-218.
9. Petchimuthu S, Narayanan N, Uthirapathy S, Formulation of mebeverine hydrochloride MR pellets in capsules and comparative characterization against colofac MR capsules, Int J Pharm Ana Res, 3, 2014, 348-362.
10. Pharmacopoeia I, Indian Pharmacopoeia Commission Ghaziabad, India, 2, 2010, 786.
11. Bouwman AM, Bosma JC, Vonk P, Wesselingh JHA, Frijlink HW, Which shape factor (s) best describe granules?, Powder Tech, 146, 2004, 66-72.
12. Guideline IHT, Stability testing of new drug substances and products, Q1A (R2), Current Step, 4, 2003.
13. Ganesan V, Krishna Kanth VSVSP, Preparation and *in-vitro* evaluation of microballoon drug delivery system of telmisartan, Int J Pharmaceut Sci Drug Res, 5, 2013, 141-145.
14. George E, Mathews MM, Formulation and evaluation of topical gel containing hair growth promoters for the treatment of androgenic alopecia, Bull Pharm Res, 4, 2014, 1-8.
15. Kan S, Lu J, Liu J, Wang J, Zhao Y, A quality by design (QbD) case study on enteric-coated pellets: Screening of critical variables and establishment of design space at laboratory scale, Asian J Pharmaceut Sci Tech, 9, 2014, 268-278.

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