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Research Article

Quality by Design (QbD) approach to optimize the formulation of Multiunit Particulate System (MUPS).

C Pradeep Kumar Reddy*

Graviti Pharmaceuticals Private Limited, Survey No. 621/E & 621/EE, Isnapur Village, Patancheru Mandal, Sangareddy - 502307, Telangana, India.

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***Corresponding author E-mail address:** pradeepkr@gravitipharma.com*

ABSTRACT
The objective of this study was to develop and evaluate a MUPS formulation intended for treatment digestive tract ulcers.Work involves evaluation of different formulations of esomeprazole magnesium having enteric polymer and plasticizers to understand impact on dissolution. A three-factor, two-level, full factorial design was used to investigate the influence of Eudragit L 100 55, Diethyl phthalate and Polyethylene glycol 6000 of the coating composition on the response, i.e., dissolution. Eudragit L 100-55 and Diethyl phthalate had a significant influence on dissolution, while Polyethylene glycol 6000 within studied level showed non-significant impact. Graphical analysis from pare to chart and half normal plots, enabled identification of variables active on the selected responses. The optimized formulation comprised of Eudragit L-100-55: 46.42mg/tablet, Diethyl phthalate: 6.14mg/tablet and Polyethylene glycol 6000: 0.71mg/tablet showed acid resistance and a desired release of Esomeprazole magnesium. Gastro-resistant MUPS formulation has been successfully developed for Esomeprazole Magnesium.

KEYWORDS
Gastro esophageal reflux disease, Esomeprazole magnesium, Design of Experiments, Multi unit particulate system

1. INTRODUCTION

Gastroesophageal reflux disease (GERD) is a major digestive health problem due to its ever high and increasing incidence and because it is the cause of serious complications. The management of patients with refractory GERD (rGERD) is a major clinical challenge for gastroenterologists. Proton pump inhibitors (PPIs) have steadily become the mainstay in treatment of acid-related disorders. Proton pump inhibitors inhibit the gastric H+/K+-ATPase via covalent binding to cysteine residues of the proton pump. All proton pump inhibitors must undergo acid accumulation in the parietal cell through protonation, followed by activation mediated by a second protonation at the active secretory canaliculus of the parietal cell. The relative ease with which these steps occur with different proton pump inhibitors underlies differences in their rates of activation, which in turn influence the location of covalent binding and the stability of inhibition.[1, 2, 3]

Esomeprazole is useful for inhibiting gastric acid secretion and has gastric mucosa-protective activity. In a more general sense, esomeprazole may be used for preventing and treating gastric acid related disorders in mammals, including man, e.g., gastroesophageal reflux disease, gastritis, gastric ulcer, duodenal ulcer, etc. Esomeprazole is susceptible to degradation/transformations in acidic reacting media. The stability of esomeprazole is also affected by moisture, heat, organic solvents, and to some degree by light. Formulation of such compound is a challenge as it issusceptible to degradation and/or transformations in both acid and neutral media. The decomposition of these acid labile compounds can be due to acid catalyzed reactions. One technique that is commonly used involves coating the acid-labile compound in pellets form, with an enteric polymer coating. This enteric coating is insoluble in aqueous acidic conditions and soluble in aqueous neutral to alkaline conditions. However, if the enteric coating material itself is acidic, that will cause the decomposition of the acid- labile compound. In order to avoid such problems, an inert barrier/intermediate coating was included (not acidic) in-between the core and enteric coating. [4, 5, 6, 7]

Experimental design and statistical modeling are essential tools for the development and understanding of complicated formulations and processes variables which will have direct impact on drug product CQA's. Design of experiment (DoE) approach can be used to understand impact of formulation variables. Further it allows efficient experimentation covering a large number of factors which are varied together over a set of experiments, in contrast with the traditional approach of varying each factor while keeping other factors constant, which may fail to identify any interactions between these factors.[8,9,10]

In current study, a computer-aided optimization technique using a three factor, two-level, full factorial design was used to investigate the effect of three formulation variables, i.e., concentration of Eudragit L 100-55, Diethyl phthalate and Polyethylene Glycol 6000.

2. MATERIALS & METHODS

2.1. Materials

Materials Esomeprazole Magnesium was obtained as a gift sample from Hetero Drugs. Sugar Spheres obtained from Hanns G. Werner GmbH + Co. KG. Ludipress LCE and PVP K-30, PVP K 90, Poloxamer 188, Crospovidone (Kollidon CL-F) was gifted from BASF. Prosolv SMCC

HD 90, Prosolv SMCC 90 and Sodium stearyl fumarate were obtained from JRS Pharma. PEG 6000 was obtained from Sigma Aldrich. Ethocel 7cps and Hypromellose 3cps gifted from Dow Chemicals. Magnesium stearate obtained from Peter Greven. Meglumine obtained from Merck. All the chemicals and reagents were of analytical reagent (AR) grade and used without further purifications.[11]

2.2. Methods

2.2.1. Preliminary formulation evaluation

2.2.1.1. Preparation of over coated Pellets

Initially two different formulations were evaluated with different polymers with their different concentration. Preparation process involves seal coating of sugar spheres followed by Drug loading involving drug and binder. Further barrier coating was done on drug loaded pellets followed by Enteric coating layer. For Enteric coating, Polymer Eudragit L 100 55, plasticizer Diethyl phthalate and PEG 6000 were evaluated at different concentration. Talc was used as anti-tacking agent in enteric coating. After enteric coating, pellets were over coated with Hypromellose 3cps with talc as anti-tacking agent (Table 1).All steps were carried out using Fluid Bed Coater (G.P.C.G 1.1).

2.2.1.2. Preparation of lubricated blend

All extra granular excipients were sifted through 30mesh (Table 1). Esomeprazole Magnesium over coated pellets with Prosolv SMCC HD 90 were co-sifted through 30 mesh, labelled as co-sift I. Crosspovidone, PEG 6000 and 1/2th quantity of ludipress LCE were sifted through30 mesh and labelled as co-sift II. Aerosil with remaining quantity of ludipress LCE were sifted through 30mesh, labelled as co-sift III. Initial pre-sifted Prosolv SMCC 90 added to double cone blender followed by co-sift I, co-sift II, co-sift III and mixed for 10 min with 10rpm.

2.2.1.3. Compression

Tablets were compressed using Protab 21station compression machine having unit weight as per given in table 1 using 19.3*9.7mm, oval shaped punches.

Table 1. Preliminary Compositions evaluated for Esomeprazole Magnesium MUPS Tablets.

S. No.	Raw Materials	Formulation 1	Formulation 2
		mg/Tablet	**mg/Tablet**
Seal Coating			
1	Sugar spheres	32.00	32.00
2	Ethyl cellulose 7cps	1.28	1.28
3	Magnesium stearate	0.32	0.32
4	Methanol	q.s.	q.s.
5	Methylene chloride	q.s.	q.s.
	Weight of Seal Coated pellets	**33.28**	**33.60**
Drug Loading			
6	Esomeprazole magnesium(Amorphous)	45.76	45.79
7	Poloxamer 188	4.00	-
8	Povidone K 30	6.69	13.00
9	Meglumine	4.0	4.00

10	Methanol	q.s.	q.s.
Weight of drug loaded pellets		**93.73**	**96.39**
Barrier Coating			
11	Povidone k 90	13.26	6.795
12	Magnesium oxide light	7.90	4.08
13	Magnesium stearate	7.05	3.614
14	Methanol	q.s.	q.s.
Weight of Barrier coated pellets		**121.94**	**110.88**
Enteric Coating			
15	Eudragit L 100 55	64.87	47.56
16	Diethyl phthalate	7.45	5.46
17	Polyethylene Glycol 6000	0.97	0.71
18	Talc	62.79	46.02
19	Methanol	q.s.	q.s.
Weight of Enteric coated pellets		**258.02**	**210.63**
Over coating			
20	Hypromellose 3cps	8.41	42.12
21	Talc	2.10	10.53
22	Methanol	q.s.	q.s.
Weight of Over coated pellets		**268.53**	**263.28**
Lubrication			
23	Ludipress LCE	217.88	280.96
24	Prosolv SMCC HD 90	135.00	135.00
25	Prosolv SMCC 90	135.00	135.00
26	Polyethylene Glycol 6000	70.00	70.00
27	Crospovidone	20.00	20.00
28	Sodium stearyl fumarate	6.00	6.00
29	Colloidal silicon dioxide (Aerosil 200)	4.00	4.00
Weight of Lubricated Blend		**856.41**	**914.24**

2.3. Optimization of formulation variables (Enteric coating stage) and Experimental design

A number of preliminary experiments were conducted to determine the critical formulation variables by which the formulation resulted in quality of MUPS. Design Expert software (Version 11.0) was used in our study for generation and evaluation of the statistical experimental design. A Three-factor, two-level, full factorial design was employed for the optimization procedure. The Eudragit L 100-55 (X1, mg/tab), Diethyl phthalate (X2, mg/tab) and Polyethylene Glycol 6000(X3, mg/tab) were selected as the independent variables, whereas Drug release in 0.1N HCl at 2hrs (Y1), and drug release in pH 6.5 simulated intestinal fluid at 15 min (Y2) were chosen as the dependent variables. Table 2 summarizes these formulation variables with corresponding levels and the responses studied, whereas experimental formulations are listed in Table 3.

Table 2. Three Factors, two level Full Factorial Experimental Design: Factors selected and responses measured.

Factors	Levels of factors used in formulation optimization studies		Responses to be studied
	-1	**+1**	
Concentration of Eudragit L 100-55(X1, mg/tab)	37.56	57.56	Y1: Drug release in 0.1N HCl at 2hrs
Concentration of Diethyl phthalate (X1, mg/tab)	4.56	6.56	Y2: Drug release in pH 6.5 simulated intestinal fluid at 15 min.
Concentration of Polyethylene Glycol 6000(X3, mg/tab)	0.66	0.76	

Table 3. Esomeprazole Magnesium MUPS tablet Enteric coating formulation variables as per 2^3 Full Factorial Experimental Design.

Run	Concentration of Eudragit L 100 55 (X_1)	Concentration of Diethyl Phthalate (X2)	Concentration of Polyethylene Glycol 6000 (X3)
RUN 1	37.56	6.56	0.76
RUN 2	57.56	4.56	0.66
RUN 3	57.56	4.56	0.76
RUN 4	37.56	4.56	0.66
RUN 5	37.56	4.56	0.76
RUN 6	57.56	6.56	0.76
RUN 7	57.56	6.56	0.66
RUN 8	37.56	6.56	0.66
RUN 9	47.56	5.56	0.71

2.4. Dissolution studies

Dissolution studies were performed using Electrolab dissolution apparatus (Model: EDT-14 LX) in two stages. Dissolution in acidic condition i.e., 0.1N HCl for 2 hrs with volume 500 mL, USP apparatus II (Paddle) and temperature 37±0.5^{o}C followed by dissolution in pH 6.5, simulated intestinal condition for 45 min with volume 500 mL, USP apparatus II (Paddle) and temperature 37±0.5^{o}C.

2.5. Statistical Analysis

Design Expert software (Version 11.0) was used for generation of polynomial models, including interaction terms for all response variables using multiple linear regression analysis. Polynomial

models together with interaction terms were generated for all the response variables by means of multiple linear regression analysis. The influence of various formulation variables and their interaction with each of the responses are represented graphically. In order to validate the polynomial equations, one optimum checkpoint and three random checkpoints were selected by intensive grid search, performed over the entire experimental domain. Values were predicted for each formulation variable using a mathematical model developed for the optimized formulation and three additional random checkpoints covering the entire range of the experimental domain. These predicted values were compared with the resulting experimental values and the percentage bias was calculated.[12]

3. RESULTS AND DISCUSSION

3.1. Preliminary formulation evaluation

Based on preliminary studies carried out for different formulations, faster dug release observed in Simulated gastrointestinal fluid pH for formulation 2 (Table 4) with polymer Eudragit L 100 55 (47.56mg/tablet), Plasticizer Diethyl 5.46 mg/tablet and PEG 6000 (0.71mg/tablet) concentration. Dissolution results shown in Table 4 and Fig 1. drug release observed in Acid media for both formulations were less than 10%.

3.2. Optimization of formulation variables (Enteric coating stage) and Experimental design

Based on initial risk assessment performed, Enteric coating considered as critical step which will have impact on DP-CQA dissolution. Higher concentration of enteric coating polymer may lead to slower drug release and vice versa. Higher concentration of Plasticizer concentration may lead to faster release. Therefore, optimization was carried out to understand impact on Drug release. Details for 9 experimental design batches and responses observed shown in Table 5. Compression process and variables also have impact on DP-CQA dissolution and were optimized. [11]

Table 4. Dissolution Results for Formulation Trials.

Time (min)	Formulation Trial 1		Formulation Trial 2	
	% Drug Release (Min, Max)	**% RSD**	**% Drug Release (Min, Max)**	**% RSD**
Media	Acid stage: 0.1N HCl for 2 hrs with volume 500 mL, USP apparatus II (Paddle) and Temperature 37±0.5^{o}C			
	2 hrs	15.4	5	12.8
Media	Buffer stage: pH 6.5, simulated intestinal condition for 45 min with volume 500 mL, USP apparatus II (Paddle) and temperature 37±0.5^{o}C			
05	11	13.26	24	9.63
10	19	8.45	40	6.21
15	48	5.22	70	2.16
20	76	3.17	92	1.11
30	89	2.11	97	0.83
45	97	2.03	97	0.67

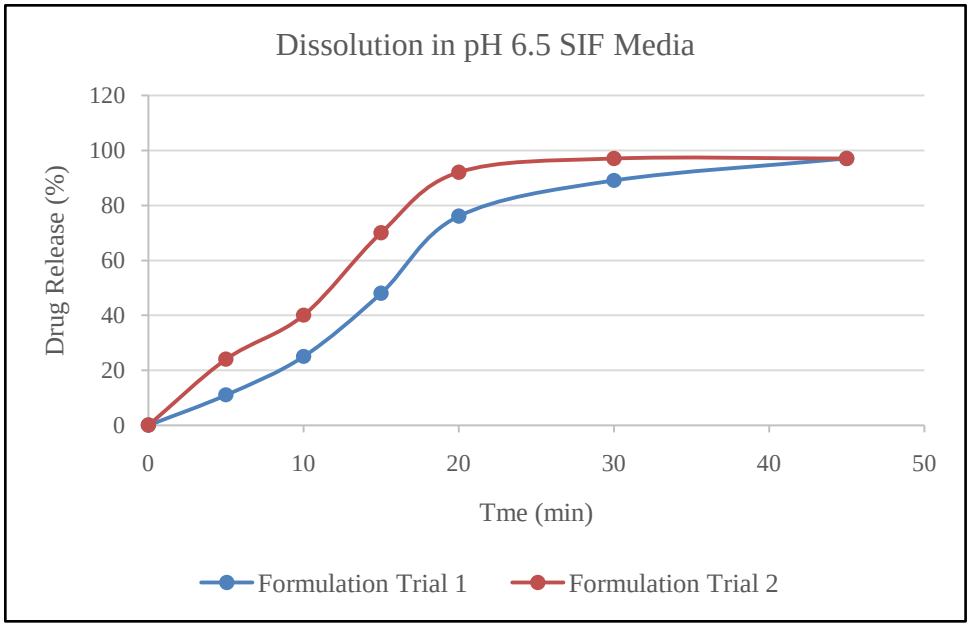

Figure 1. Dissolution profile for Esomeprazole Magnesium MUPS formulations.

Table 5. Result data for 9 experimental batches of Esomeprazole Magnesium MUPS tablet as per 2^3 Full Factorial Experimental Design.

Run	Formulation variables			Response	
	Concentration of Eudragit L 100 55 (X_1)	**Concentration of Diethyl Phthalate (X2)**	**Concentration of Polyethylene Glycol 6000 (X3)**	**Drug release in 0.1N HCl at 2hrs (%)**	**Drug release in Simulated intestinal fluid at 15 min (%)**
RUN 1	37.56	6.56	0.76	10	64
RUN 2	57.56	4.56	0.66	3	69
RUN 3	57.56	4.56	0.76	7	65
RUN 4	37.56	4.56	0.66	2	72
RUN 5	37.56	4.56	0.76	7	65
RUN 6	57.56	6.56	0.76	2	70
RUN 7	57.56	6.56	0.66	7	66
RUN 8	37.56	6.56	0.66	1	71
RUN 9	47.56	5.56	0.71	4	67

3.3. Factorial design

Experiments were carried out to determine the mathematical relationship between the formulation variables acting on the system and the response of the system. The statistical evaluation of experimental outcomes was processed with Design Expert software (Version 11.0) to find the optimum levels.

A first order polynomial regression equation that fitted the data is as follows:

$$\mathbf{Y} = b0 + b1\,X1 + b2\,X2 + b12X1\,X2 + b13X1\,X3 + b23X2\,X3 + b123X1\,X2\,X3 \textbf{……. (1)}$$

Here b0 is the arithmetic mean of all the quantitative outcomes of the eight experimental runs; b1–b3 are the estimated coefficients from the observed experimental values of Y for X1, X2, and X3. The interactions terms Xi XjXk (i, j, and k = 1, 2, and 3) shows how the change in response occurs when two or more factors are simultaneously changed. The equation represents the quantitative effect of factors upon the each of the responses. A positive sign in front of the terms indicates a synergistic effect while a negative sign indicates an antagonistic effect of the factors. The significance of the model was estimated by applying analysis of variance (ANOVA) at the 5% significance level. A model was considered significant if the P value was less than 0.05.

3.4. Evaluation of Effect of Formulation Variables on selected Responses and ANOVA analysis

Note: In equation formulation Variables Eudragit L 100-55, Diethyl phthalate and Polyethylene Glycol 6000 indicated as A, B & C respectively.

3.4.1. Response Y1: Drug release in 0.1N HCl at 2hrs (%)

Enteric coating was employed in formulation to avoid drug release in stomach having pH 1.2 - 3.0 and to prevent degradation of drug at lower pH conditions. Therefore, all formulation batches were evaluated in 0.1N HCl at 2hrs for drug release to mimic GIT condition.

$$\textbf{Y1:}\ \text{Drug release in 0.1N HCl} = +4.75 - 2.50 * A - 1.00 * B \textbf{……(2)}$$

From equation it is observed that Enteric polymer Eudragit L 100-55 and Diethyl phthalate have negative effect on drug release in 0.1N HCl. Increase in concentration of Eudragit L 100-55 and Diethyl phthalate leads to decrease in drug release. Pareto chart (Fig.2a), also shows that concentration of Eudragit L 100-55 t-limit is above Bonferroni limits showing certainly significant whereas Diethyl phthalate showed limits above t-limit showing possibly significant. Half normal plot (Fig. 2b) showed both variables are away from line showing significant impact on evaluated response. Other individual factor Concentration of PEG 6000 and combination effects found non-significant (Fig.2a, 2b).

3.4.2. Response Y2: Drug release in pH 6.5 simulated intestinal fluid at 15 min.

Eudragit L 100-55 used as enteric coating polymer which will dissolves above pH 5.5. Once the pellets come in contact with higher pH in GIT, polymer will get dissolve and drug will get released. To simulate *in-vivo* conditions, dissolution was performed in pH 6.5 simulated intestinal fluid and drug release evaluated at 15 min.

$$\textbf{Drug release in SIF 15 min} = +67.38 - 4.13 * A - 2.13 * B \textbf{……(3)}$$

From equation it is observed that enteric polymer Eudragit L 100-55 and Diethyl phthalate have negative effect on drug release in SIF pH 6.5 media. Increase in concentration of Eudragit L 100-55 and Diethyl phthalate leads to decrease in drug release. Pareto chart (Fig.2c), shows that concentration of Eudragit L 100-55 and Diethyl phthalate t-limit is above Bonferroni limits showing certainly significant whereas Polyethylene glycol 6000 and combination effects showed values below t-limit showing non-significant. Half normal plot showed both variables are away from line showing significant impact whereas other factors near to line showed non-significant impact on evaluated response (Fig.2d).

3.5. Optimization using regression analysis and validation of mathematical model

With the help of above mentioned mathematical models, Formulation variables were optimized keeping the constraints in range to have design space. The optimum calculated concentrations for formulation variables were

X1 Concentration of Eudragit L 100 55:46.42mg/tablet

X2: Concentration of Diethyl Phthalate: 6.14 mg/tablet

X3: Concentration of Polyethylene Glycol 6000**:**0.71 mg/tablet

The experiments were carried out according to the formulation variables obtained after applying constraints, and the optimum solution with formulation variables was evaluated for its considered responses. Results obtained for responses are shown in Table 6. In order to evaluate the reliability of the mathematical model developed, three additional checkpoints were taken, and estimated using a generated model covering the entire experimental domain. Table 6 gives the levels of variables of optimum formulation and three random checkpoints with their experimental values, predicted values, and the percent bias.

For the optimum solution Formulation variables (Table 6), Y1 Experimental was 4.50 (Y1 predicted, 4.44; percent bias, 1.33%), Y2 Experimental was found to be 68.0 (Y2 predicted, 66.60; percent bias, 2.06) in the current study indicate the robustness of the mathematical model. Based on above optimization studies, risk for the evaluated formulation variables reduced High to low.

Table 6. The experimental and predicted values for evaluated responses Y1 and Y2 along with percentage prediction error observed for optimum run (1) and random runs (2, 3 and 4).

Number	Concentration of Eudragit L 100 55 (X_1)	Concentration of Diethyl Phthalate (X2)	Concentration of PEG 6000 (X3)	Response variables	Predicted Values (%)	Experimental values	#Bias (%)
1.	46.42	6.14	0.71	Y1	4.44	4.50	1.33
				Y2	66.60	68.0	2.06
2.	44.24	5.62	0.68	Y1	5.51	5.30	-3.96
				Y2	68.61	66.0	-3.95
3.	50.08	6.26	0.74	Y1	3.42	3.47	1.44
				Y2	64.85	65.0	0.23
4.	49.40	6.23	0.67	Y1	3.62	3.60	-0.55
				Y2	65.19	65.0	-0.29

Notes: #Bias (%) = (experimental value-predicted value)/experimental value × 100

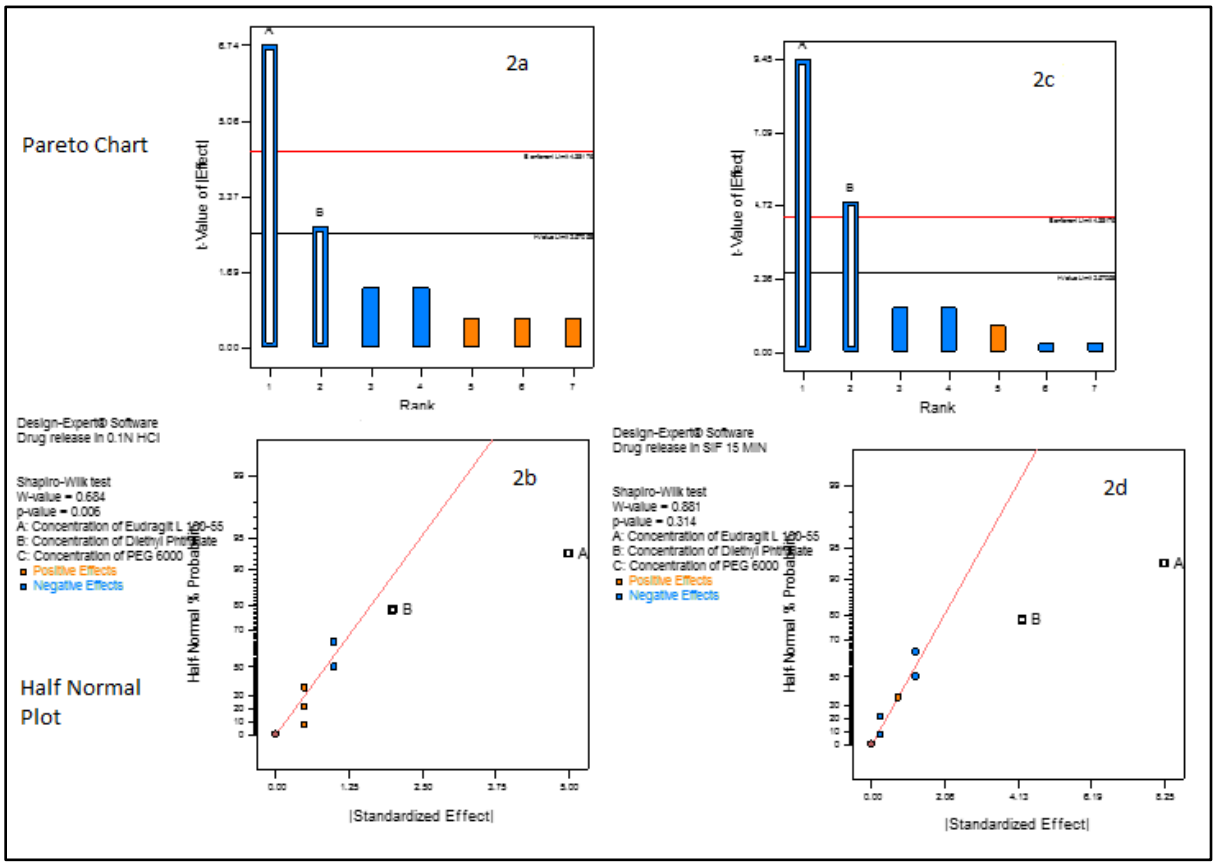

Figure 2. a) Graphical analysis by pareto chart for Drug release in 0.1N HCl at 2hrs (%)
b) Graphical analysis by Half Normal Plot for Drug release in 0.1N HCl at 2hrs (%)
c) Graphical analysis by pareto chart for Drug release in pH6.5 SIF, at 15min (%)
d) Graphical analysis by Half Normal Plot for Drug release in pH6.5 SIF, at 15min (%)

4. CONCLUSION

Formulation optimization of Esomeprazole MUPS at Enteric coating stage was carried out using a three-factor, two-level, full factorial design. This allowed rapid evaluation and identification of the formulation variables in determining the desired responses. The impact of varying the levels of concentration of Eudragit L 100-55, Diethyl phthalate and Polyethylene Glycol 6000 on independent variables Viz. Drug release in 0.1N HCl at 2hrs (Y1), and drug release in pH 6.5 simulated intestinal fluid at 15 min (Y2) was investigated. ANOVA analysis showed all models for selected responses were significant. The mathematical model for each of the responses developed using multiple regression analysis quantitatively describes the influence of the selected variables on the responses under investigation. Regression analysis showed R^2 values more than 0.90 which indicates that the model explains all the variability of the response data around its mean. For optimized run, observed responses were in close agreement with the predicted values, indicating excellent predictability of the optimization procedure. The formulation with optimized formulation variables showed Drug release in 0.1N HCl at 120min:

4.50% and Drug release in pH 6.5 SIF at 15min: 68% in the current study indicate the robustness of the mathematical model. From above studies, it is concluded that a quality Esomeprazole MUPS tablet was successfully evaluated using QbD approach for Enteric coating formulation variables.

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