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PREPARATION OF PELLETS OF BOSENTAN BY EXTRUSION SPHERONIZATION-SCREENING STUDY OF PROCESS PARAMETERS BY PLACKETT-BURMAN DESIGN

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ABSTRACT

The study was aimed to find out the significant factors affecting the particle size during a pellatization by plackett and Burman design. The pellets were made with the help of extrusion spheronization method. The screening study with the help of plackett and Burman design will help the experimenter to exclude the less significant factors at the early stage of the research. As this design consist of extremely less number of experiments, the time, cost of study will be less and further studies were made smooth and efficient. Seven different factors were identified and included in this screening study which was expected to have some effect on the percentage yield of pellets having particle size 1mm. 8 experimental runs were carried out and with the help of ANOVA and regression analysis the significant factors were identified. The model linearity and validity were checked and a reduced polynomial equation was suggested for the easy understanding of the effect of different factors on the percentage yield of pellets size of 1mm. Pareto chart ,term effect plot and actual Vs fitted plot were constructed and studied.

INTRODUCTION

Extrusion is a well-known processing technology that has been developed over the last century and spans many diverse industrial fields. Extrusion can be simply defined as the process of forming a new material (the extrudate) by forcing a material through an orifice or die under controlled conditions.[1, 2, 3, 4]. The process of preparing spherical granules of approximately 1mm in diameter by extrusion/spheronization (E/S) was introduced during the late 1960s. It involves forming the powder into a wet mass, which is forced through a restricted area (extrusion) to form strands of extrudate that are broken into short lengths and rounded by placement on a rotating plate within a cylinder. The main objective of the extrusion spheronization is to produce pellets/spheroids of uniform size with high drug loading capacity [4, 5]. Extrusion spheronization is a multiple process of wet mass extrusion followed by spheronization to produce uniform size spherical particles, called as spheroids, pellets, beads or matrix pellets depending upon the material as well as process used for extrusion spheronization**.** The particle size range should be as narrow as possible. The optimum size of pellets for pharmaceutical use is considered to be between 600 and 1000mm. Pellets should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating. Statistically designed experiments or DoE are widely used nowadays mainly because of its systematic approach, reduced number of runs, more reliable results , and the use of polynomial equations and graphs for better understanding of the process. DoE experiments proceeds with mainly three steps: Screening studies, Factor influence studies and Optimization. Screening study is normally done very early stages in the life of the project in order to simplify the problem and thus enable the experimenter to make use of his resources in more detailed examinations and optimization of the principal factors. The objective of a screening study is ***not*** to obtain complete and exact numerical data on the properties of a system to allow a full description, but rather to be able to answer "yes" or "no" (or "perhaps") to some simple questions about whether or not certain factors have an effect.[6,7,8] In this experiment we have tried to find out the significant factors which are affecting the percentage yield of desired particle size during the extrusion Spheronization process with the help of Plackett and Burman design. The model drug selected was bosentan is a dual endothelin receptor antagonist (ET-A&ET-B) used in the treatment of pulmonary artery hypertension (PAH).

MATERIALS AND METHODS

Bosentan was obtained as a gift sample from alembic Pharmaceuticals, Microcrysatline cellulose, lactose, cross povidone, polyvinyl pyrolidine were obtained from Loba Chem (Mumbai, India).

Preparation of pellets of Bosentan [9, 10, 11,13,14,15]

Accurately Weigh all the ingredients and mix them with sufficient quantity of PVP K30 dissolved in sufficient quantity of the ethanol in a mortar to form semisolid paste having thick consistency. The different ingredient used for the preparation of the pellets were shown in the Table 1 .The coherent mass was placed in the extruder and forced through the sieve screeen where it was formed extrudes of uniform shape and size. The wet extruders were collected. The extrudates were put in to the spheronizer where a gridded disc breaks them in to smaller particles and rounds them in to pellets .The Extrusion spheronization assemble was shown in the Figure 1and the total process was diagrammatically represented in the Figure 2 .

Table 1: Ingredients for the preparation of pellets

Ingredient	Quantity (%)
Bosentan	30%
MCC	60%
LACTOSE	20%
Cross povidone	3%
PVP K30	Q S
Water	Q S

Magnesium stearate and talc was added to the spheronizer during the spheronization stage.

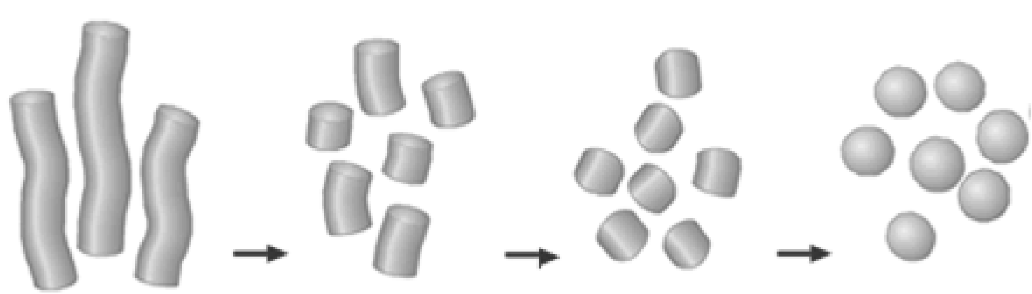

Fig. 1: Pelletization stages

Fig.2: Assemble of the extrusion spheronization apparatus

Screening study of process parameters affecting the percentage yield of pellets of desired size [6, 7, 8]

The size of the pellets was so important in the process of pellatization. Usually pellets of 0.5-1.5 mm were advised and prepared. In this experiment we kept the pellets size 1mm as the optimum size. The different factors were identified which are affecting the particle size as amount of binder, amount of water, granulation time, Spheronization load, spheronization speed, Extruder rate and spheronization time. Plackett and Burman design was selected for the screening study. The polynomial equation suggested for the effect of process parameters on the particle size of the pellets was written as follows,

$$Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_4X_4 + \beta_5X_5 + \beta_6X_6 + \beta_7 X_7 + \varepsilon$$

Particle size measurement

Particle size of the pellets was determined using sieving analysis. The 14/16 sieves were used for the study. The pellets retain on the sieve no 16 will having a particle size of 1.168 – 0.992 mm. The amount of specific size produced for each formulation was found out as percentage yield.

RESULT AND DISCUSSION

The bosentan pellets were prepared with the help of extrusion spheronization method. The ingrediens used for the preparation was shown in the Table 1. Particle size of the pellets was considered to be one of the important parameter to be optimized during the formulation of the pellets. Many factors will contribute to the particle size of the pellets. Different factors identified to influence the particle size of the pellets were shown in the Table 2. A screening study was performed to find out the significant factors affecting the particle size during the extrusion spheronization process using Plackett and Burman design. The different limits of each factors selected for the study was shown in the Table 2.

Table 2 .Different factors and the limits selected for the screening study

Factors	Units	Designation	Lower limit	Upper limit	Dependant variable
Amount of binder	%	X1	0.5	1	Particle size (1mm)
Amount of water	%	X2	40	50	
Granulation time	min	X3	1	5	
Spheronization load	Kg	X4	1	5	
Spheronization Speed	RPM	X5	500	1500	
Extruder rate	RPM	X6	10	70	
Spheronization time	min	X7	1	6	

The different formulations F1 – F8 was made according to the Placket and Burman design. The design table and the levels of the factors selected in the original units were given in the Table 3. The design table and the levels of the factors selected in the coded units were given in the Table 4. The particle size of the formulation F1 – F8 was determined using sieve analysis. The percentage amount of pellets having 1mm size was determined for each formulation. The percentage amount of pellets having particle size of 1mm was considered as the dependant variable for the Placket and Burman design. The significant level selected for the study was 5%. Percentage amount of particle size of 1mm for formulation F1 –F8 were shown in the Table 4.

Table 3: Design matrix of Plackett and Burman design (in actual values)

Formulation	Factors						
	X1	**X2**	**X3**	**X4**	**X5**	**X6**	**X7**
F1	0.5	40	1	5	500	70	6
F2	1	40	1	1	1500	10	6
F3	1	50	1	1	500	70	1
F4	0.5	50	5	1	500	10	6
F5	1	40	5	5	500	10	1
F6	0.5	50	1	5	1500	10	1
F7	0.5	40	5	1	1500	70	1
F8	1	50	5	5	1500	70	6

Table 4: Design matrix of Plackett and Burman design (in coded values)

Formulation	Factors						
	X1	**X2**	**X3**	**X4**	**X5**	**X6**	**X7**
F1	-1	-1	-1	+1	-1	+1	+1
F2	+1	-1	-1	-1	+1	-1	+1
F3	+1	+1	-1	-1	-1	+1	-1
F4	-1	+1	+1	-1	-1	-1	+1
F5	+1	-1	+1	+1	-1	-1	-1
F6	-1	+1	-1	+1	+1	-1	-1
F7	-1	-1	+1	-1	+1	+1	-1
F8	+1	+1	+1	+1	+1	+1	+1

ANOVA and the regression studies were performed to find out the coefficients and the significance of the factors on the percentage amount of pellets of 1mm particle size. The regression analysis was shown in the table 5. From the regression analysis the corresponding effect and coefficient of each factor were found out. It was seen that the factors, amount of water, amount of binder, spheronization speed, spheronization load and spheronization time were found to be significantly affecting the particle size of the pellets at 5% significant level. The quantity of the effect of each factor was shown in the Table 5. it was found that among the significant factors all other factors except amount of water had a positive effect on the particle size. The coefficient of each factors were also shown in the Table 5. Graphical representation of the factors in terms of the pareto chart was given in the Figure 3 .From the graph also it was evident that amount of water, amount of binder, spheronization speed, spheronization load, spheronization time were significantly affecting the particle size (T value > 2.152) . The Extrusion rate and granulation time has little effect on the particle size (T value < 2.152). The polynomial equation representing the Y response can be written as,

$$Y = 56.375 + 5.625 X_1 - 3.875 X_2 – 0.125 X_3 + 4.375X_4 + 2.375X_5 + 1.125 X_6 + 1.875 X_7$$

By eliminating the non significant factors from the model, the reduced model can be written as,

$$Y = 56.375 + 5.625 X_1 - 3.875 X_2 + 4.375X_4 + 2.375 X_5 + 1.875 X$$

From the screening study it was evident that amount of binder and water, Spheronization load, and spheronization speed were having a greater effect on the particle size as the coefficient values a larger than the others.

Table 5: Regression analysis

Regression Information							
Term	**Effect**	**Coefficient**	**Standard Error**	**Low CI**	**High CI**	**T Value**	**P Value**
Intercept		56.375	0.5	54.7838	57.9662	112.75	1.54E-06
A:Amount of binder	11.25	5.625	0.5	4.0338	7.2162	11.25	0.0015
B:Amount of water	-7.75	-3.875	0.5	-5.4662	-2.2838	-7.75	0.0045
C:Granulation time	-0.25	-0.125	0.5	-1.7162	1.4662	-0.25	0.8187
D:Spheronization load	8.75	4.375	0.5	2.7838	5.9662	8.75	0.0031
E:Spheronization Speed	4.75	2.375	0.5	0.7838	3.9662	4.75	0.0177
F:Extruder rate	2.25	1.125	0.5	-0.4662	2.7162	2.25	0.1099
G:Spheronization time	3.75	1.875	0.5	0.2838	3.4662	3.75	0.0331
Curvature		6.625	0.866	3.8689	9.3811	7.6499	0.0046

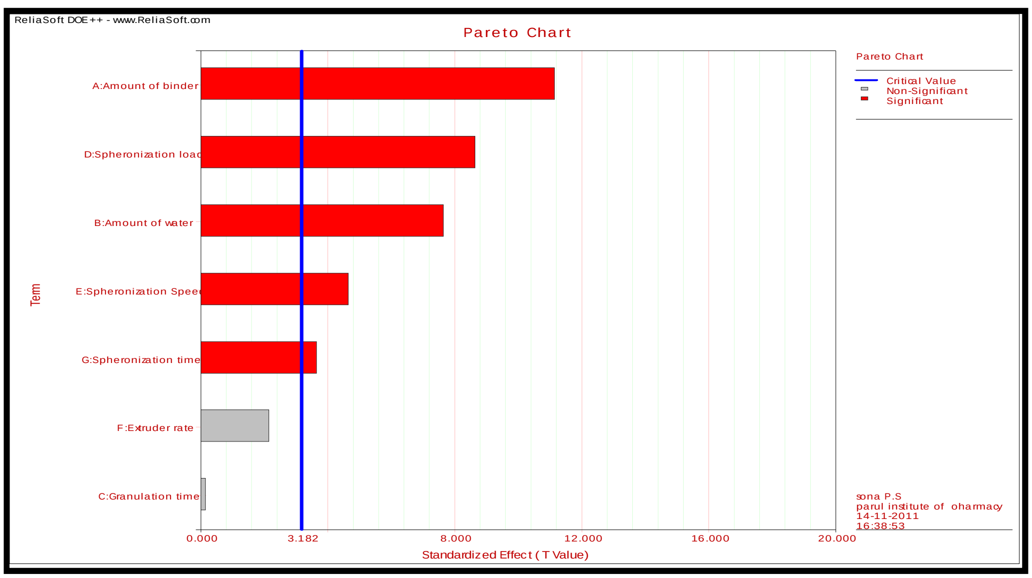

Fig.3: Pareto chart

From the ANOVA table it was confirmed that the main effect and the model predicted were significant at 5 % level. There was also some indication that some curvature effect was present in the response. So a 3 level design would be adequate for the further studies. The R^2 value and the R_{adj} from the ANOVA suggest the model validity and the absence of lack of fit. Table 6.

Table 6: ANOVA analysis

ANOVA Table					
Source of Variation	**Degrees of Freedom**	**Sum of Squares [Partial]**	**Mean Squares [Partial]**	**F Ratio**	**P Value**
Model	8	726.9167	90.8646	45.4323	0.0048
Main Effects	7	609.875	87.125	43.5625	0.0051
Curvature	1	117.0417	117.0417	58.5208	0.0046
Residual	3	6	2		
Pure Error	3	6	2		
Total	11	732.9167			
S =	1.4142				
R-sq =	99.18%				
R-sq(adj) =	97.00%				

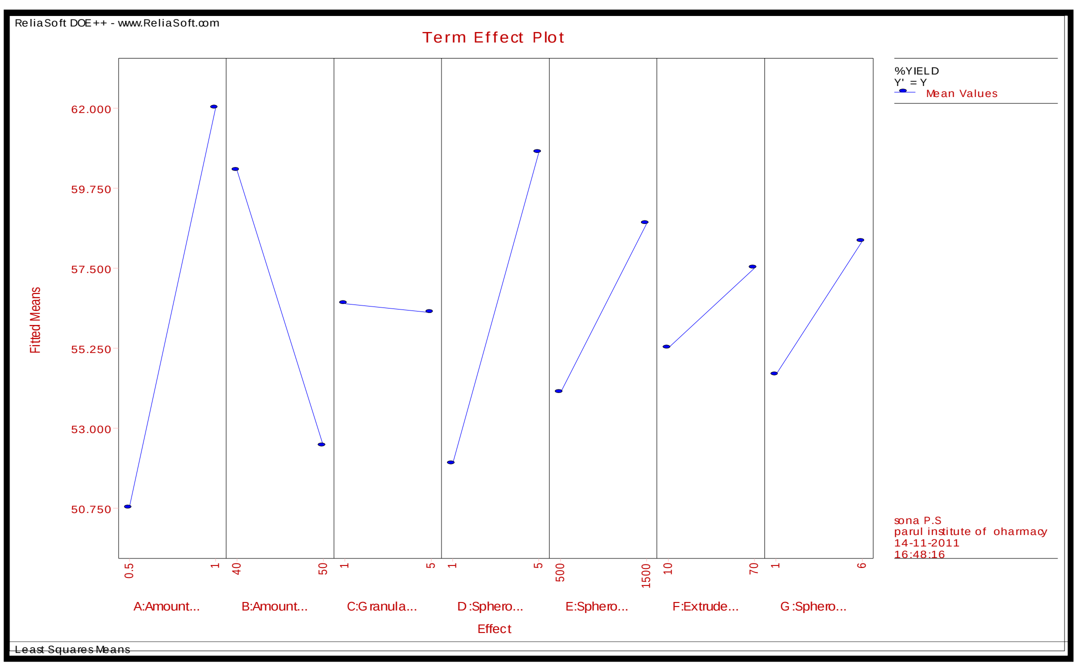

Fig.4 :Term effect

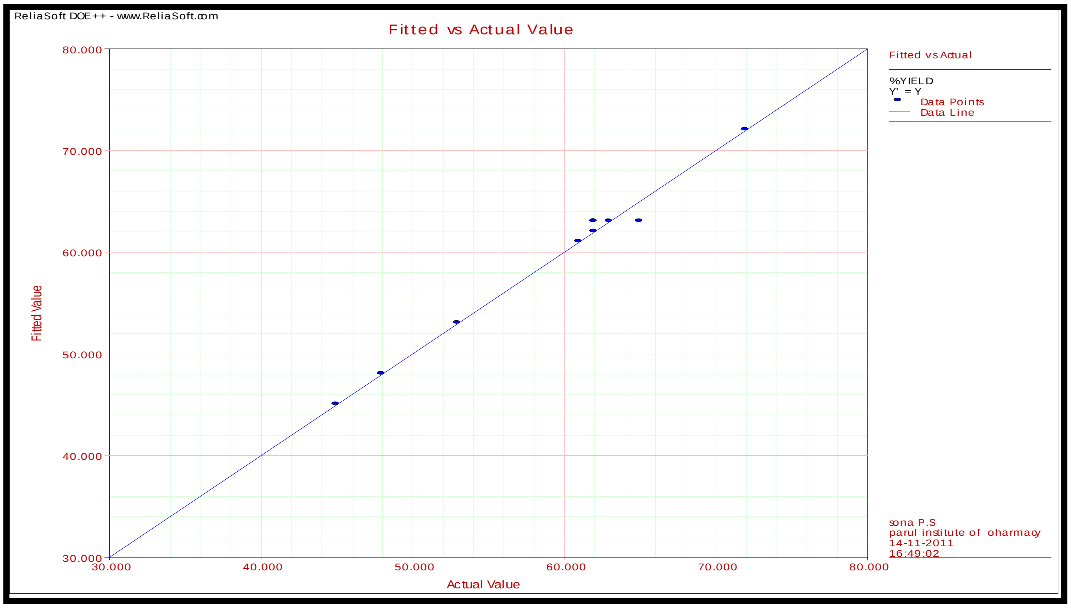

Fig. 5: Fitted Vs Actual value plot

Individual factor effect on the percentage yield of 1mm particle size was also shown in the Figure 4. The fitted Vs actual value graph was also constructed and studied Figure 5. It was found that there were no much variations in the fitted value as well as the actual values.

CONCLUSION

A Placket and Burman design was used as a screening tool for finding out the factors affecting the yield of 1mm particle size of pellets in the extrusion spheronization experiment. Seven factors were studied and analyzed and critical factors were identified. The model validity and linearity was checked and proved. The result of the screening study will be helpful for the successful optimization of particle size of the pellets in an extrusion spheronization.

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