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Quality by Design based Optimization of Spironolactone Immediate-Release Tablets.

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Abstract:

The development of pharmaceutical formulations demands a quality-driven approach to ensure therapeutic efficacy, safety, and patient compliance. This study focuses on the quality-based development of spironolactone immediate-release tablets, an essential medication for managing hypertension, heart failure, and hyperaldosteronism. A systematic approach incorporating Quality by Design (QbD) principles was employed to optimize the formulation and manufacturing processes.Critical quality attributes (CQAs) such as dissolution rate, disintegration time were identified through risk assessment and targeted for optimization. Key formulation variables, including binder concentration, lubrication level and disintegrant levels, were systematically varied using a design of experiments (DoE) approach. The optimized formulation demonstrated rapid disintegration and consistent drug release, meeting the predefined quality criteria. This study highlights the importance of a quality-driven development framework for achieving a robust and patient-centric spironolactone immediate-release tablet formulation. The findings underscore the potential of applying QbD principles to improve formulation efficiency, reduce development timelines, and ensure regulatory compliance, ultimately benefiting patients and the pharmaceutical industry. The target goals for each of the response variable were provided, which included enhancing of % drug release NLT 75% in 60 min and reducing disintegration time less than 8 min f3, f10 and f11 batches shoes maximum f2 factor with comparable disintegrant time.

Keywords: QbD, DoE, CQAs, CMAs, hyperaldosteronism.

Introduction-

Spironolactone, a potassium-sparing diuretic and aldosterone antagonist, is widely used in the treatment of conditions such as hypertension, heart failure, and primary hyperaldosteronism. Its therapeutic efficacy depends on achieving rapid and consistent drug release, which makes the development of an immediate-release tablet formulation critical for ensuring optimal patient outcomes. The growing emphasis on regulatory compliance and product quality in pharmaceutical development necessitates the adoption of advanced methodologies such as Quality by Design (QbD) [1,2,3,4].

QbD is a systematic, science-driven approach that focuses on identifying and understanding the critical quality attributes (CQAs) of a drug product and the critical process parameters (CPPs) that influence these attributes. By incorporating risk assessment tools and experimental design strategies [5, 6, 7, 8, 9], QbD ensures a robust formulation that consistently

meets predefined quality criteria. For spironolactone, key challenges in formulating immediate-release tablets include achieving rapid disintegration, consistent dissolution, and stability under varied storage conditions[10].

This study aims to develop a spironolactone immediate-release tablet using a quality-focused framework. Critical formulation and process parameters, such as the choice of excipients, binder concentration, and disintegrant levels[11, 12, 13, 14], are optimized to ensure rapid drug release and compliance with pharmacopeial standards. Furthermore, stability studies are conducted to evaluate the formulation's performance under accelerated and real-time conditions[15, 16].

By leveraging QbD principles, this research seeks to establish a robust, patient-centric formulation of spironolactone immediate-release tablets. The findings are expected to demonstrate the advantages of adopting a quality-driven approach in pharmaceutical development, including improved formulation efficiency, reduced production variability, and enhanced regulatory compliance.

The initiation of quality has been started in 1979- P. Crosby believe that Quality is Free in 1986 Motorola develops Six Sigma for reducing defects and improving quality and therefore customer compliance, in 1987- FDA's first Guideline on Process Validation has been implemented, and 1988- US DoD implements Total Quality Management, in 1991- J. Juran has given Quality by Design: the new steps for planning quality into goods and services, finally in 2005 ICH guideline QbD related drafts appear- ICH Q8-11 and at last in 2008- FDA's Guidance for Industry Process Validation a General Principles and Practices (Rev. 1, 2011) was given[17, 18, 19, 20, 21].

Materials & Methods- Spironolactone was obtained as a free sample from Zhejiang Langhua Pharmaceutical co., ltd, China, gifted from Ind-swift Ltd Chandigarh. Calcium sulfate dihydrate was obtained from Canton Laboratories Pvt Ltd, Vadodara; Povidone was obtained from G C Chemie Pharmie Ltd. Magnesium stearate was obtained from JR Drug Chem, Gujrat, Corn starch were obtained from Ingredion Incorporated, Maharashtra. Opadry was obtained as a free sample from Colorcon, Goa.

Method- A risk analysis was evaluated based on ICH Q9 to establish which variables and unit operations were likely to have the greatest impact on drug product quality. A risk assessment of the drug substance attributes was performed to evaluate the impact that each attribute could have on the drug product CQAs. The outcome of the assessment and the accompanying justification is provided as a summary in the pharmaceutical development report. The relative risk that each attribute presents was ranked as high, medium or low. The high risk attributes warranted further investigation whereas the low risk attributes required no further investigation. The medium risk is considered acceptable based on current knowledge. Further investigation for medium risk may be needed in order to reduce the risk. The same relative risk ranking system was used throughout pharmaceutical development and is summarized below table.

Table1 - Overview of Relative Risk Ranking System.

Low	Broadly acceptable risk. No further investigation is needed.
Medium	Risk is acceptable. Further investigation may be needed in order to reduce the risk.
High	Risk is unacceptable. Further investigation is needed to reduce the risk

Based upon the physicochemical and biological properties of drug substance, the initial risk assessment of drug substance attributes on drug product CQAs shown shown in below two tables provides the justification for the level of risk that was assigned to each attribute. Assay, degradation product and dissolution were identified as potential critical quality attributes that need to be investigated further.

Table 2- Initial risk assessment of the drug substance attributes.

Drug	**Drug Substance Attributes**

Product CQA	Solid state form	Particle Size distribution	Hygros-copicity	Solubility	Moisture content	Residual solvents	Process Impurity	Chemical Stability	Flow property
Assay	Low	Low	Low	Low	Low	Low	Low	Low	Low
CU	Low	Low	Low	Low	Low	Low	Low	Low	Low
Dissolution	Low	Low	Low	Low	Low	Low	Low	Low	Low
Impurity	Low	Low	Low	Low	Low	Low	Low	Low	Low

Initial Risk assessment of formulation variables & critical material attributes are as follows-

Table 3- Initial risk assessment of formulation variables & critical material attributes.

Drug Product CQA	Calcium sulfate dehydrate	Maize Starch	Povidone	Peppermint flavour	Magnesium Stearate
	Level	Level	Level	Level	Level
Assay	Low	Low	Low	Low	Low
Content Uniformity	Low	Low	Low	Low	Low
Impurity	Low	Low	Low	Low	Low
Dissolution	Low	High	High	Low	High

Implementation of DOE for the optimization of high risk Critical material attributes as Binder, Disintegrant and Lubricant.

The systematic optimization of spironolactone tablet USP 100 mg was carried out using 2^3 full Factorial Design using Design Expert® ver. 9.0 software (Stat-Ease Inc., Minneapolis, USA). Three most influential factors including disintegrant concentration, binder concentration and lubricant concentration were selected as independent variable for optimization at 2 levels low (-1) medium (0) and high (+1) because as the molecule is categorised to BCS II, where the solubility is low, it become important to use disintegrant in adequate concentration to achieve its peak plasma concentration as the dosage form design is immediate release. Total of 8

Experiments and 3 center points were suggested by selected design as shown in Table. % Drug release and disintegration time were analysed as dependent variable or responses. After putting the data in software, mathematical modelling was performed to analyse the results.

Manufacturing Process: same for all the batches only there is deviation in concentration of binder, disintegrant and lubricant.

1. Spironolactone, calcium sulfate dihydrate, maize starch were cosifted through sieve no 30. Sifted materials were mixed in high shear mixture.
2. Binder solution was prepared by dissolving Plasdone K29/32 in Purified water and kept aside till clear solution was prepared.
3. Binder solution and extra purified water was added to the dry mix of step no. 1 at slow impeller speed and granulated at fast speed of impeller and chopper.
4. Wet granules were milled through 9.5 mm using multimill and semidried in fluid bed dryer at inlet temperature set point 60ºC and high set point 65°C till target loss on drying was achieved.
5. The semi dried granules were passed through 30 ASTM and retained granules were milled through 2.00mm screen using multimill and further dried dried in fluid bed dryer at inlet temperature set point 60ºC and high set point 65°C till target loss on drying was achieved.

6. Dried granules were passed through sieve no. 30 and retained granules were milled through 1.00 mm screen.
7. Dried corn starch was sifted through sieve no. 60.
8. Magnesium stearate was sifted through sieve no 60.
9. Dried and sized granules were blended with sifted dried corn starch.
10. Lubricate the above blend with sifted magnesium stearate.
11. Lubricated blend was compressed in a rotary press using round shaped concave punch.

Table 4 - The systematic optimization of spironolactone tablet USP 100 mg was carried out using 2^3 full Factorial Design using Design Expert® ver. 9.0 software

		Factor 1	Factor 2	Factor 3	Response 1	Response 2
Std	Run	A:Binder	B:Disintegrant	C:Lubricant	Dissolution	Disintegration Time
		mg	Mg	mg	% Release	min
3	1	10	150	0	100	2
1	2	10	50	0	88	8
9	3	20	100	3	95	4
4	4	30	150	0	91	6
7	5	10	150	6	90	8
2	6	30	50	0	72	16
6	7	30	50	6	55	25
5	8	10	50	6	70	18
11	9	20	100	3	92	5
10	10	20	100	3	96	4
8	11	30	150	6	83	11

Table 5: Bill of material of formulation F1-F11-

Spironolactone Tablet usp 100mg Tablet Optimization											
Ingredient	% w/w Formulation										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Intragranular											
Spironolactone	100										
Maize starch	75	25	50	75	75	25	25	25	50	50	75
Calcium sulphate dehydrate	374	474	411	354	368	454	448	468	411	411	348
Binder											
Plasdone K29/32	10	10	20	30	10	30	30	10	20	20	30
P.W	q.s										
Extragranular											
Dried corn starch	75	25	50	75	75	25	25	25	50	50	75
Magnesium Stearate	0	0	3	0	6	0	6	6	3	3	6
Total Weight	634.0	634.0	634.0	634.0	634.0	634.0	634.0	634.0	634.0	634.0	634.0

q.s- Quantity Sufficient

Difference and Similarity Factor- Results obtained from the dissolution profile were fitted into equations (1) and (2) to determine the difference and similarity factors of the various batches compared to standard. Difference and similarity factors are model independent approach used to estimate the dissimilarity factor (f1) and similarity factor (f2) to compare the dissolution profile of optimized formulation (F5) with innovator product. The difference between the reference and test curve at each time point and is a measurement of the relative error between two curves. The FDA suggested that two dissolution profiles were declared similar if f2 value between 50-100 and f1 was 0-15.

$f1 = \{(\sum t=\ln |Rt-Tt|) / (\sum t=\ln Rt]) \times 100$ -- Equation (1)

$f2=50 \cdot \log \{(1+\ln \sum t=\ln (Rt-Tt)\ 2)-0.5\times 100\}$ -- Equation (2) Where,

f1: Difference factor; f2: Similarity factor; n: time points; Rt: cumulative percentage dissolved at time t for the reference; Tt: cumulative percentage dissolved at time t for the test.

Result and discussion-

Table 6- Justification for the risk assessment of the drug substance attributes-

Drug Substance Attributes	Drug Products CQAs	Justification	Plan of action to minimize the risk
Solid state form	**Assay**	Drug substance solid state form does not affect tablet assay and CU. The risk is low.	XRD data will be analyzed to prove that spironolactone form II remains unchanged in finish product.
	Content uniformity		
	Dissolution	Different polymorphic forms of the drug substance have different solubility and can impact tablet dissolution. Spironolactone polymorphic Form II is the most stable form and the DMF holder consistently provides this form. In addition, pre-formulation studies demonstrated that Form II does not undergo any polymorphic conversion under the various stress conditions tested. Thus, further evaluation of polymorphic form on drug product attributes was not conducted. The risk is low	
	Degradation products	Drug substance with different polymorphic forms may have different chemical stability and may impact the degradation products of the tablet. Spironolactone tablets contain the spironolactone crystalline form II, which is purer and most stable. The probability to convert stable form	

		to other forms is less, hence the risk is low.	
Particle Size Distribution (PSD)	**Assay**	A small particle size and a wide PSD may adversely impact blend flowability. In extreme cases, poor flowability may cause an assay and cu failure. But the method adopted during manufacturing is wet granulation which will minimize segregation. Risk is low.	Not applicable
	Content uniformity		
	Dissolution	The drug substance is a BCS class II compound; therefore, PSD can affect dissolution. But spironolactone used has particle size less than 10 micron will provide best solubility and therefore dissolution. The risk is low.	
	Degradation products	As the drug substance is unmilled. The risk is low	
Solubility	**Assay**	Solubility does not affect tablet assay, CU and degradation products. Thus, the risk is low.	Not applicable
	Content uniformity		
	Degradation products		
	Dissolution	Spironolactone exhibited low (~ 0.07mg/mL) and constant solubility across the physiological pH range. Drug substance solubility strongly impacts dissolution. But spironolactone used has particle size less than 10 micron which is vey fine will have highest solubility. The risk is low.	
	Assay	Moisture is controlled in the drug substance specification (NMT 0.5%). Thus, it is unlikely to	
	Content uniformity		
	Dissolution		

Moisture content		impact assay, CU and dissolution. The risk is low.	Not applicable
	Degradation products	The drug substance is not sensitive to moisture based on forced degradation studies. The risk is low.	
Flow property	**Assay**	Spironolactone has poor flow properties. In extreme cases, poor flow may impact assay and CU. But method adopted during manufacturing is wet granulation which will minimize segregation. Hence the risk is low	Not applicable
	Content uniformity		
	Dissolution	The flowability of the drug substance is not related to its degradation pathway or solubility. Therefore, the risk is low.	

Table 7- Justification for the risk assessment of formulation variables

Formulation Variables	**Drug Products CQAs**	**Justification**	**Plan of Action to mitigate the risk**
Calcium sulfate dehydrate	Assay	As calcium sulphate dihydrate is used as a diluent so it may not impact assay, CU, degredation, dissolution. The risk is Low	Not applicable
	Content Uniformity		
	Degradation products		
	Dissolution		
Maize Starch	Assay	Maize starch is used as a disintegrant in the product and will not impact assay and CU. Risk is low.	Selection of ratio of starch intrgranular: extragranular will be finalized during development and will be evaluated.
	Content Uniformity		
	Degradation products	As maize starch is used by innovator and there is no sign of incompatibility of drug substance with maize starch which is proved during compatibility study also. The risk is low.	
	Dissolution	Maize starch act as a disintegrant, the level of it can have high impact on dissolution. Risk is high.	
Povidone	Assay	Povidone can increase the the	

	Content Uniformity	flow of drug product therefore will aid in assay and CU. Risk is low	
	Degradation products	As povidone is used by innovator and there is no sign of incompatibility of drug substance with povidone which is proved during compatibility study also. The risk is low.	Not applicable
	Dissolution	Change in Level of povidone can impact dissolution. Risk is high	The effect of povidone concentration on dissolution profile will be evaluated during development.
Magnesium Stearate	Assay	Since the level of magnesium stearate used is low and its impact on flow is minimal, it is unlikely to impact assay and CU. The risk is low.	
	Content Uniformity		
	Degradation products	As Magnesium Stearate is used by innovator and there is no sign of incompatibility of drug substance with magnesium stearate. The risk is low.	Not applicable
	Dissolution	Over-lubrication due to excessive lubricant may retard dissolution. The risk is high.	The effect of magnesium stearate concentration on dissolution profile will be evaluated during development.

Table 8 - Physico-chemical characteristics of blend and tablets

Batch no	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Loss on Drying (at 105°C for till constant weight is achieved)	1.75% w/w	1.95 w/w	1.65 w/w	1.72 w/w	2.01 w/w	2.11 w/w	1.68 w/w	1.61 w/w	1.85 w/w	1.81 w/w	1.93 w/w
BD	0.70	0.61	0.58	0.58	0.58	0.55	0.53	0.7	0.68	0.72	0.74
TD	0.87	0.76	0.73	0.74	0.73	0.71	0.72	0.86	0.82	0.91	0.94
CI	19.54	19.74	20.54	21.62	20.55	22.53	26.38	18.60	17.07	20.87	21.27
HR	1.24	1.24	1.25	1.28	1.26	1.29	1.30	1.23	1.21	1.26	1.27
PSD of granules											
Seive											

30 ASTM	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
40 ASTM	18.00	23.09	24.00	13.00	21.09	22.98	23.02	11.03	13.10	16.28	28.00
60 ASTM	51.00	51.20	55.00	37.00	55.24	51.95	52.05	37.11	41.33	42.41	56.00
80 ASTM	60.00	65.26	68.00	51.00	67.30	67.93	67.07	60.18	62.50	62.51	65.00
100 ASTM	64.00	70.28	73.00	58.00	71.31	73.93	72.07	69.21	68.55	74.57	70.00
Below 100	99.66	99.76	99.36	100.00	100.10	99.96	100.10	99.46	100.02	100.10	98.42
Uncoated Tablets											
Average weight (mg)	634.0										
Hardness (N)	140-160 N										
Friability (%)	0.12% w/w	0.09 w/w	0.18 w/w	0.11 w/w	0.15 w/w	0.23 w/w	0.09 w/w	0.11 w/w	0.15 w/w	0.18 w/w	0.22 w/w
Thickness (mm)	5.10 – 5.18 mm										
Disintegration time (mins)	2 min	8 min	4 min	6 min	8 min	16 min	25 min	18 min	5 min	4 min	11 min

Table 9- Comparative dissolution profile of formulation f1-f11 using 0.1N HCl + 0.1% SLS 1000 ml, 75 rpm, USP II over innovator addactone.

Dissolution; 0.1N HCl + 0.1% SLS 1000 ml, 75 rpm, USP II												
TIME POINT	**INNOVATOR**	**TRIALS BY DESIGN EXPERT-**										
	W40914 (^{Pr}Aldactone*)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**
	% Release											
5	11	18	7	9	14	7	5	2	7	10	12	6
10	37	46	27	35	39	30	20	16	22	34	38	31
15	66	82	62	68	64	65	50	30	45	63	67	59
20	75	88	68	78	74	73	57	36	50	74	77	65
30	85	90	74	87	80	79	62	43	59	82	86	70
45	90	95	81	93	86	85	67	50	64	88	91	78
60	94	100	88	95	91	90	72	55	70	92	96	83
–	**f2 (similarity factor)**	**50.84**	**55.39**	**80.55**	**74.25**	**66.44**	**36.38**	**23.24**	**33.36**	**80.04**	**88.6**	**49.89**
	f1 (difference factor)	**13.32**	**11.14**	**3.275**	**4.37**	**6.332**	**27.29**	**49.34**	**30.79**	**3.275**	**1.965**	**14.41**

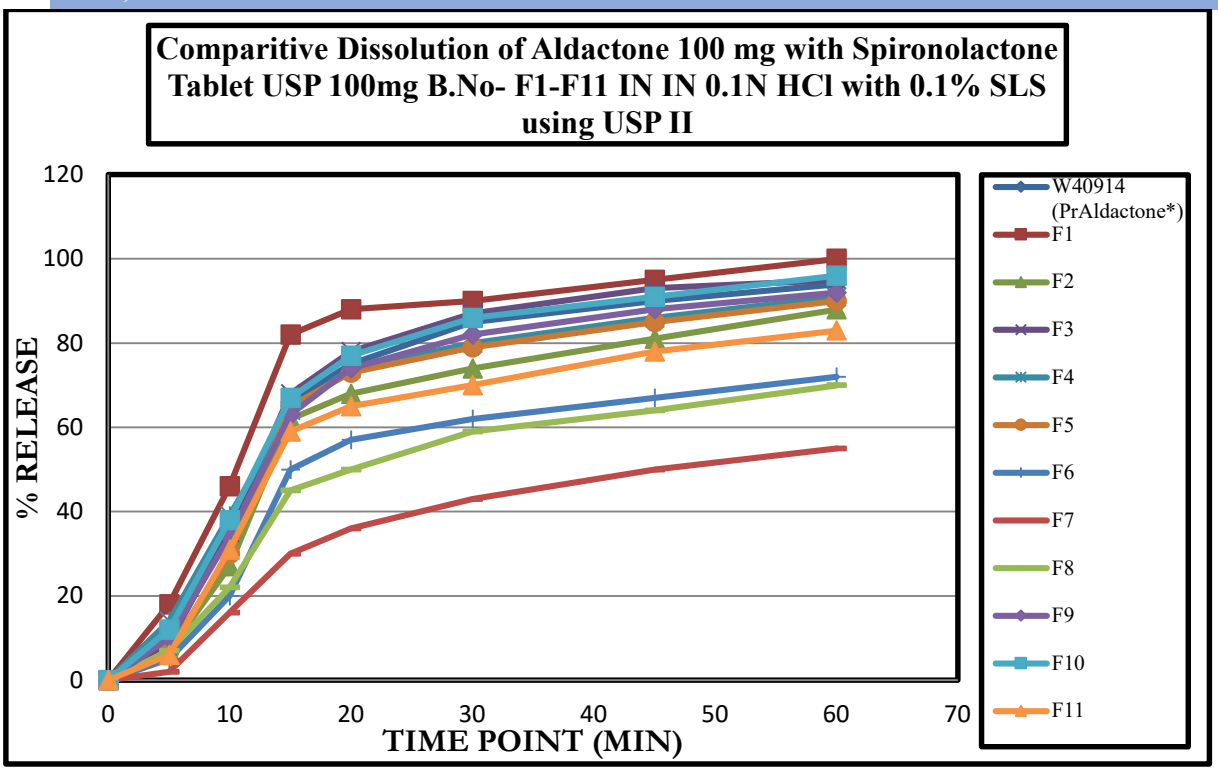

Figure 1- Comparitive Dissolution of Aldactone 100 mg with Spironolactone Tablet USP 100mg B.No- F1-F11 IN IN 0.1N HCl with 0.1% SLS using USP II.

Conclusion-as F2 of Formulation F3, F9 and F10 are more than 75% as the concentration was optimized to disintegrant- 100 mg, Binder- 20 mg and Lubricant- 3 MG.

ANOVA for selected factorial model-

Table 10- Response (Dissolution)-

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	1407.38	3	469.13	7.22	0.0151	significant
A-Binder	276.12	1	276.12	4.25	0.0782	
B-Disintegrant	780.13	1	780.13	12.01	0.0105	
C-Lubricant	351.13	1	351.13	5.40	0.0530	
Residual	454.81	7	64.97			
Lack of Fit	446.14	5	89.23	20.59	0.0470	significant
Pure Error	8.67	2	4.33			
Cor Total	1862.18	10				

Factor coding is **coded**.

Sum of squares is **Type III – Partial.** The **Model F-value** of 7.22 implies the model is significant. There is only a 1.51% chance that an F-value this large could occur due to noise. **P-values** less than 0.0500 indicate model terms are significant.

In this case B is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. The **Lack of Fit F-value** of 20.59 implies the Lack of Fit is significant. There is only a 4.70% chance that a Lack of Fit F-value this large could occur due to noise. Significant lack of fit is bad -- we want the model to fit.

Table 11- Fit Statistics

Std. Dev.	8.06		**R^2**	0.7558
Mean	84.73		**Adjusted R^2**	0.6511
C.V. %	9.51		**Predicted R^2**	0.4958
			Adeq Precision	9.2065

The **Predicted R^2** of 0.4958 is in reasonable agreement with the **Adjusted R^2** of 0.6511; i.e. the difference is less than 0.2. **Adeq Precision** measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 9.207 indicates an adequate signal. This model can be used to navigate the design space.

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.

Linear model was selected and the data-fitting with the model was analysed by ANOVA along with other parameters like p-value, coefficient of correlation (r2), adjusted r2, predicted r2 and predicted residual sum of squares. Optimized concentrations required for development of spironolactone tablet were identified by the numerical desirability function and graphical optimization technique

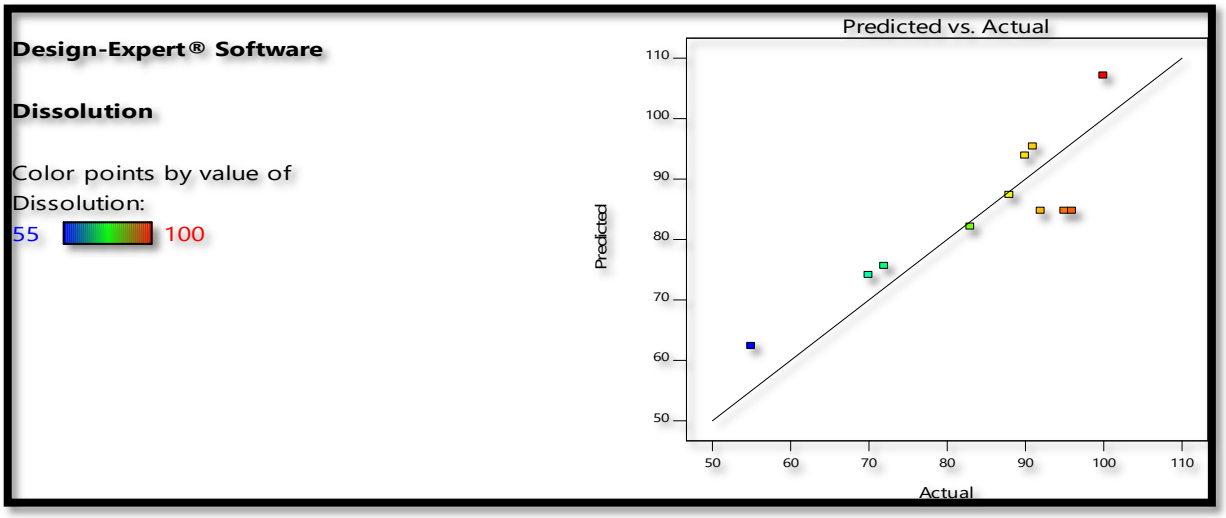

Figure2- predicted vs actual plot for dissolution over formulation impact**.**

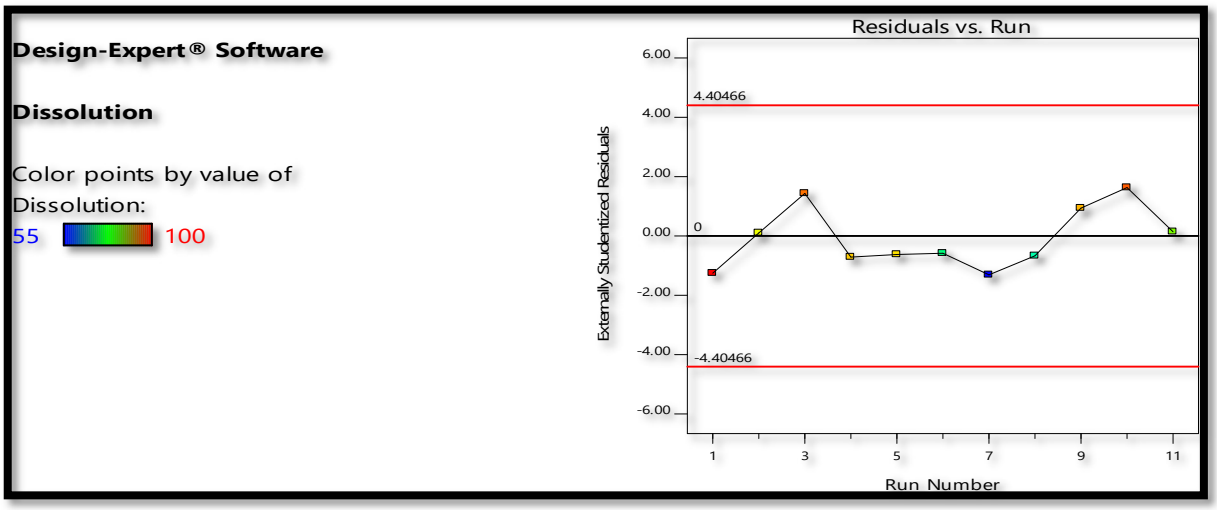

Figure 3- residual vs. run lot for formulation impact on dissolution.

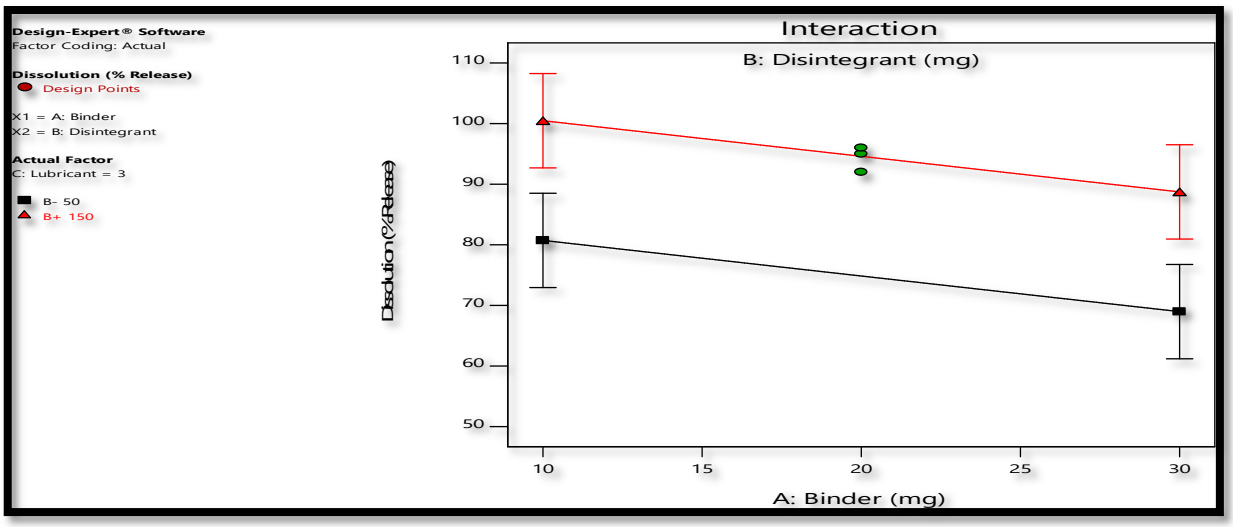

Figure 4- interaction effect of binder, disintegrant and lubricant concentration over dissolution.

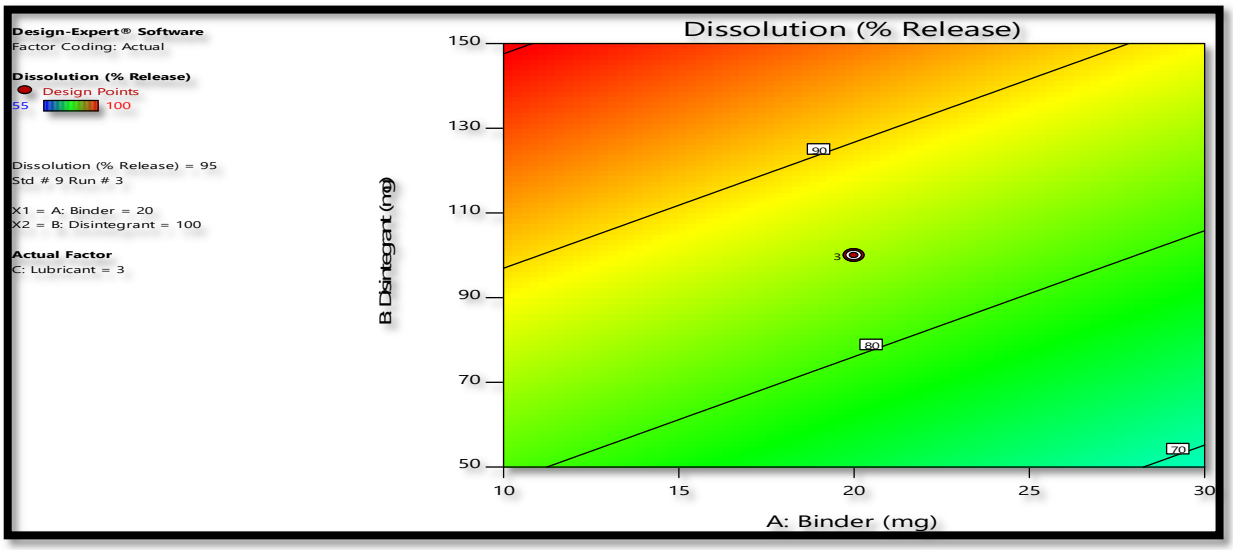

Figure 5- 2D Countour plot of binder, disintegrant and lubricant impact over dissolution profile.

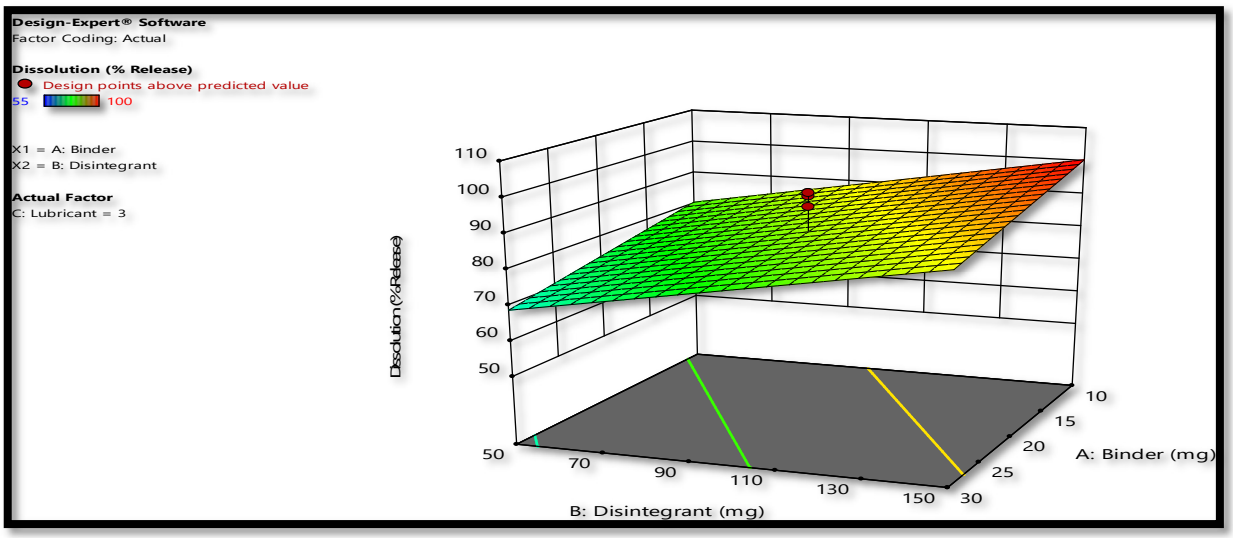

Figure 6- 3D response surface plots showing the impact of independent variable on dissolution.

ANOVA for selected factorial model-

Table 12- Response (Disintegration Time)-

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	373.00	3	124.33	6.34	0.0209	significant
A-Binder	60.50	1	60.50	3.09	0.1223	
B-Disintegrant	200.00	1	200.00	10.21	0.0152	
C-Lubricant	112.50	1	112.50	5.74	0.0477	
Residual	137.18	7	19.60			
Lack of Fit	136.52	5	27.30	81.91	0.0121	significant

Pure Error	0.6667	2	0.3333			
Cor Total	510.18	10				

Factor coding is **coded**.

Sum of squares is **Type III – Partial** the **Model F-value** of 6.34 implies the model is significant. There is only a 2.09% chance that an F-value this large could occur due to noise. **P-values** less than 0.0500 indicate model terms are significant. In this case B, C are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. The **Lack of Fit F-value** of 81.91 implies the Lack of Fit is significant. There is only a 1.21% chance that a Lack of Fit F-value this large could occur due to noise. Significant lack of fit is bad -- we want the model to fit.

Table 13- Fit Statistics

Std. Dev.	4.43		**R²**	0.7311
Mean	9.73		**Adjusted R²**	0.6159
C.V. %	45.51		**Predicted R²**	0.4531
			Adeq Precision	8.6158

The **Predicted R²** of 0.4531 is in reasonable agreement with the **Adjusted R²** of 0.6159; i.e. the difference is less than 0.2. **Adeq Precision** measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 8.616 indicates an adequate signal. This model can be used to navigate the design space.

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.

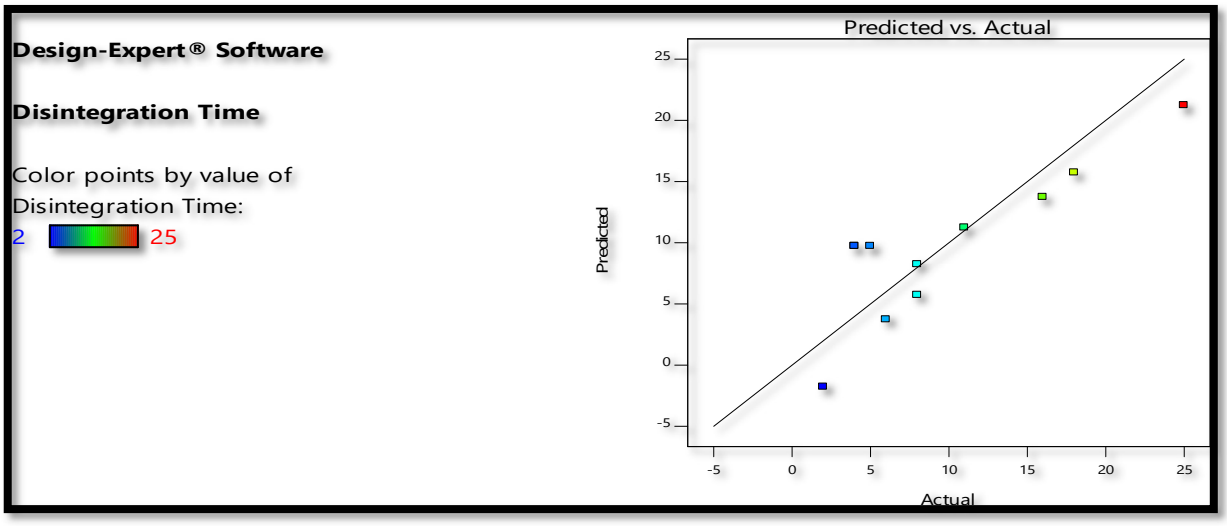

Figure 7- predicted vs actual plot for Formulations Impact on disintegration time.

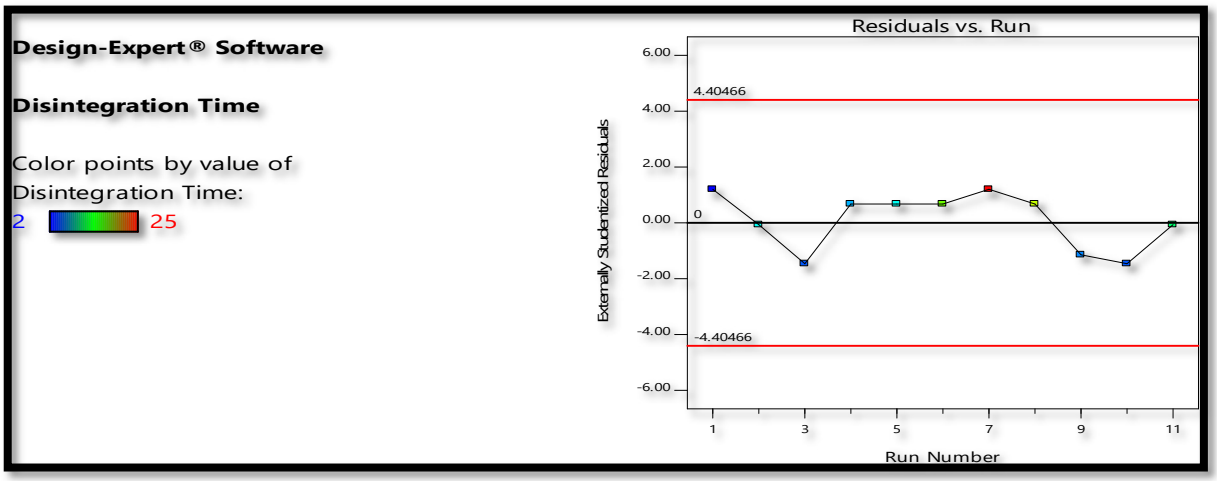

Figure 8- Residual vs Run plot for Formulations Impact on disintegration time.

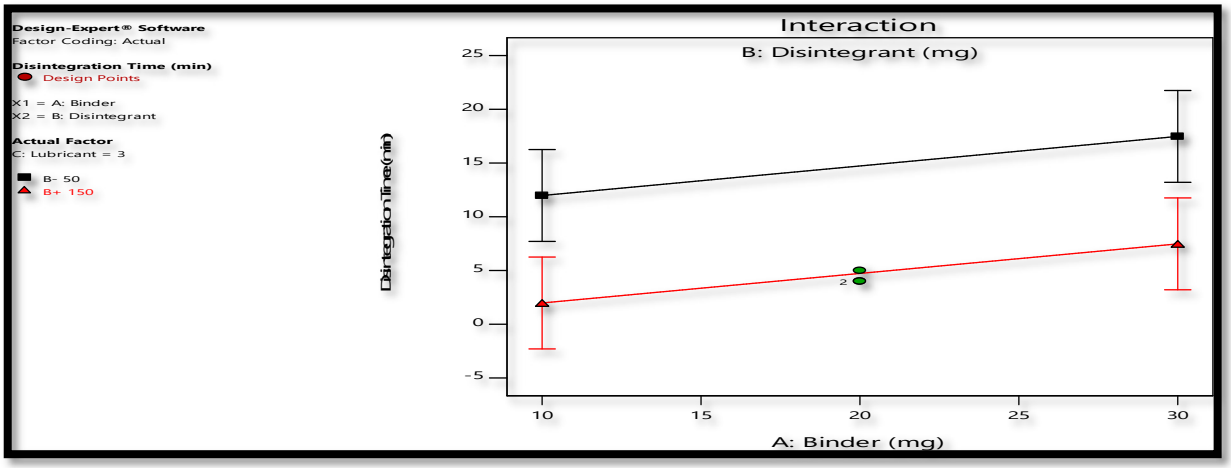

Figure 9- Interaction effect of disintegrant, binder and lubricant over disintegration time.

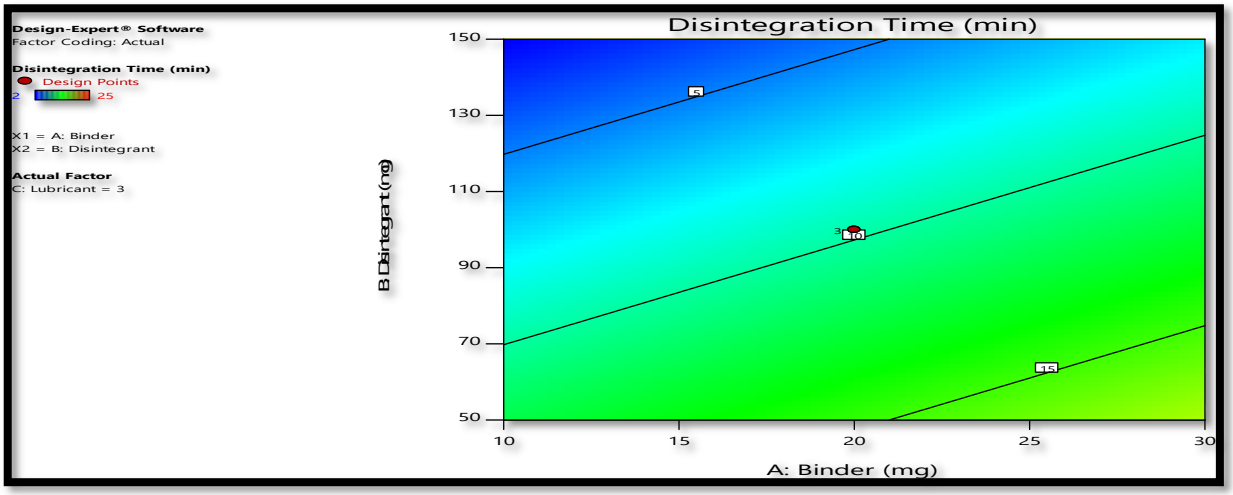

Figure 10- 2D countour plot of binder, disintegrant and lubricant concentration over disintegration time.

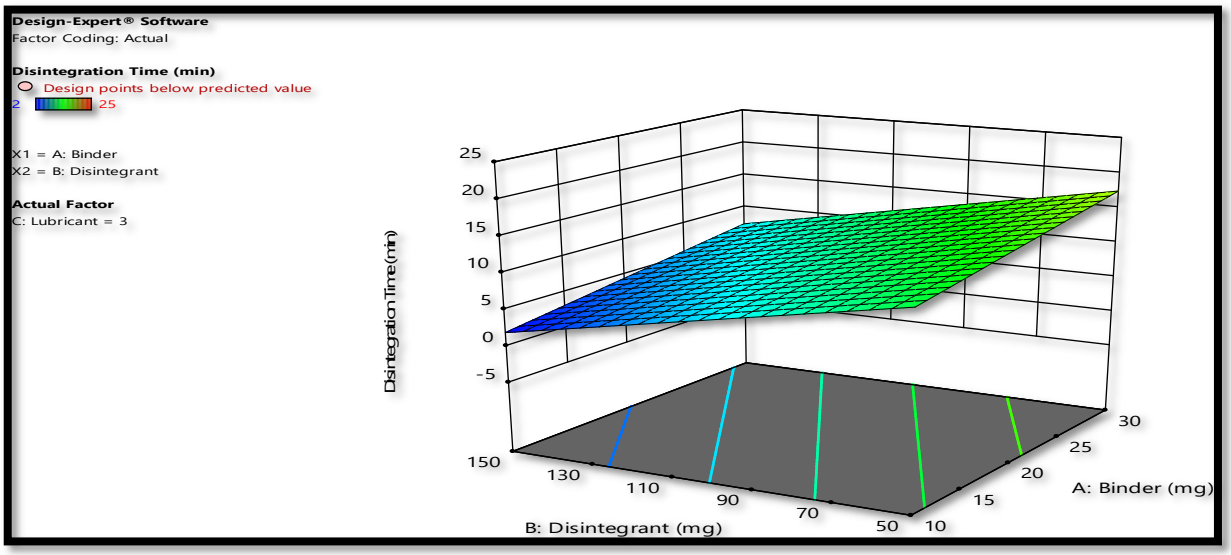

Figure 11- 3D response surface plots showing the impact of independent variable disintegrant binder and lubricant concentration on dependent variable disintegration time of spironolactone 100 mg tablet.

Equation 1 and 2 were obtained as the equations generated after the data modelling, which indicates that there is no interaction effect and curvilinear effect for both the response variables analysed (dissolution and disintegration). The parameters like coefficient of correlation were found good in the range between 0.78 (for dissolution) and 0.70 (for content uniformity), along with The Predicted R^2 in reasonable agreement with the Adjusted R^2 i.e., the difference is less than 0.2, Adequate Precision ratio greater than 4 is desirable and achieve with linear model showing significant model for use. Hence, this model can be used to navigate the design space. Moreover, the model diagnostic plots for the responses are illustrated Figure indicating good fitting of the data with the selected model.

Dissolution = +84.73 * A – 5.87 * B + 9.88 * C – 6.62 ……Eq 1

Disintegration =+9.73 * A+2.75 * B -5.00 * C +3.75……Eq 2

Factor-response Relationship and Response Surface Methodology-

Dissolution- Response surface analysis was carried out using 3D response surface plots and 2D contour plots, which explained the absence of interactions among the independent variables and their influence(s) on the response variables. The response surface analysis plots for dissolution Figure 7. The relationship between concentration of Binder and concentration of Disintegrant and the concentration of lubricant is shown in Figure 7. This indicated that there is no interaction effect as the plots are straight line in 3D response surface and has a significant impact on dissolution, where increase in the concentration of disintegrant and decrease in concentration of disintegrant and lubricant increases the drug release of tablet. However, impact of concentration of disintegrant and lubricant is much more significant that the impact of binder on % drug release as the p-value of disintegrant is 0.0105 as compare to p-value of binder 0.0782.

Disintegration- The response surface analysis plots for disintegration Figure 13. The relationship between concentration of Binder and concentration of Disintegrant and the concentration of lubricant is shown in Figure 13. This indicated that there is no interaction effect as the plots are straight line in 3D response surface and has a significant impact on disintegration, where increase in the concentration of disintegrant and decrease in concentration of binder and lubricant decreases the disintegration time of tablet. However, impact of concentration of disintegrant and lubricant is much more significant that the impact of binder on disintegration time as the p-value of disintegrant is 0.0152 as compare to p-value of binder 0.1223.

Prediction of Optimized Formulation-

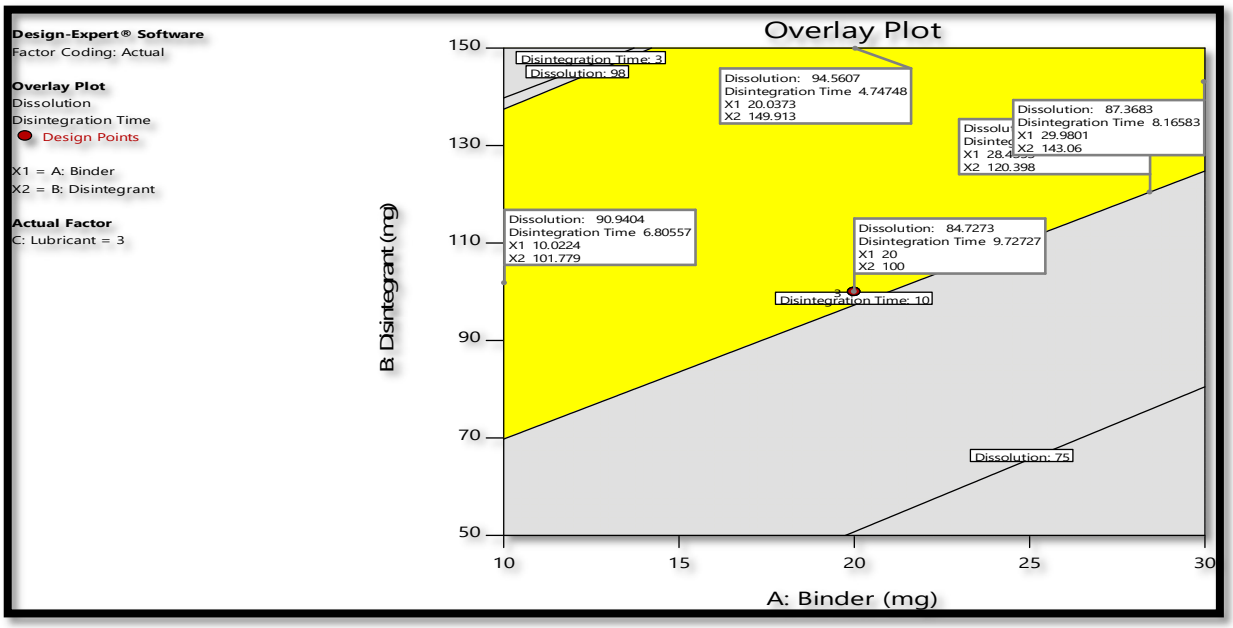

Figure 12- Overlay plot indicating yellow colour region as the optimized region and flagged point as the composition of spironolactone tablet.

Conclusion- The optimized formulation of spironolactone 100 mg tablet identified by numerical optimization with desirability function value closer to 1. The target goals for each of the response variable were provided, which included enhancing of % drug release NLT 75% in 60 min and reducing disintegration time less than 8 min. The overlay plot indicated the yellow colour region as the optimized region that working within this region will be considered to have response within specified limit along with the flagged point representing concentration of disintegrant, concentration of binder and finally concentration of lubricant, this also provide that the response specification of NLT 75% dissolution and NMT 8 min for disintegration time would be achieved when working in yellow region of design space.

Conflict of Interest- The authors have no conflicts of interest regarding this investigation.

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References-

1. Lionberger RA, Lee SL, Lee L, Raw A, Yu LX. Quality by design: concepts for ANDAs.AAPS J. 2008 Jun; 10(2):268–276. https://doi.org/10.1208/s12248-008-9026-7. Epub 2008 May 9. PMID: 18465252; PMCID: PMC2751376.
2. FDA Guidance for Industry and Review Staff: Target Product Profile – A Strategic Development Process Tool (Draft Guidance).
3. Q8 (R1): pharmaceutical development, revision 1, ICH harmonized tripartite guidelines. In: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. 2007.
4. Q9: quality risk management. ICH harmonized tripartite guidelines. In: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. 2006.
5. Q10: pharmaceutical quality system, ICH tripartite guidelines. In: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. 2007.

6. Huang J, Kaul G, Cai C, et al. Quality by design case study: an integrated multivariate approach to drug product and process development. Int J Pharm. 2009 Dec 1; 382(1–2):23–32. https://doi.org/10.1016/j.ijpharm.2009.07.031. Epub 2009 Aug 5. PMID: 19664698.
7. Khan A, Alam MS, Hasan R. Formulation and Evaluation of Equivalent Gastro-Resistant Acamprosate Calcium Tablet 333mg. Neuro Quantology. 2022; 20(10):10553-10570.
8. Khan A, Naquvi K J, Haider MH, Khan MA. Quality by design- newer technique for pharmaceutical product development. Intelligent Pharmacy, Volume 2, Issue 1, February 2024, Pages 122-129. https://doi.org/10.1016/j.ipha.2023.10.004.
9. Juran JM. Juran on Quality by Design: The New Steps for Planning Quality into Goods andServices. New York: The Free Press; 1992.
10. Jain S. Quality by design (QBD): a comprehensive understanding of implementation and challenges in pharmaceutical development. Int J Pharm Pharmaceut Sci. 2014;6:29–35.
11. Woodcock J. The concept of pharmaceutical quality. Am Pharmaceut Rev. 2004;7(6):10–15.
12. Leuenberger Hans, Puchkov Maxim, Krausbauer Etienne, Betz Gabrielle. Manufacturing pharmaceutical granules: is the granulation end-point a myth? Powder Technol Powder Technol. 2009;189:141–148. https://doi.org/10.1016/j.powtec.2008.04.005.
13. Sinica DP, Gholve SB, Ajgunde RR, Bhusnure OG, Thonte SS. Pelagia Research Library Analytical method development and validation by QbD approach – A review. 2015; 6(8):18–24.
14. Food and Drug Administration Office of Generic Drugs. Model Quality Overall Summary for IR Product; 2006. http://www.fda.gov/cder/ogd/OGD_Model-Qo S_IR_Product.pdf. Accessed March 31, 2006.
15. Lawrence X Yu. Pharm Res. 2008; 25(4):781–791.
16. Altan S, Bergum J, Pfahler L, Senderak E, Sethuraman S, Vukovinsky KE. Statistical considerations in design space development (Part I of III). Pharmaceut Technol. 2010; 34(7):66–70.
17. Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, Woodcock J. Understanding pharmaceutical quality by design. AAPS J. 2014 Jul;16(4):771-83. doi: 10.1208/s12248-014-9598-3. Epub 2014 May 23. PMID: 24854893; PMCID: PMC4070262.
18. Kulkarni RS and Behera AL: Formulation and Evaluation of Immediate Release Tablet of Valsartan. Int J Pharm Sci Res 2015; 6(2): 808- 15.
19. Anju govind, Manjunath B Menden, Ravikumar, Simila1, Mercy, Narayana Swamy VB. Formulation and Evaluation of Mouth Dissolving Tablets of Deflazacort. Asian J. Pharm. Tech. 2016; 6(2): 91-98.
20. Bhautik Kapadiya, Dipti Gohil1, Dinal Patel, Snehal Patel, Chintan Aundhia, Nirmal Shah, Kartik Pandya, Chainesh Shah. Formulation and Evaluation of Spironolactone Loaded Emulgel for Topical Application, J Pharm Sci Bioscientific Res. 2016. 6(5):740-752
21. Shamsuddin, Fazil M, Ansari SH, Ali J. Development and evaluation of solid dispersion of spironolactone using the fusion method. Int J Pharm Investig. 2016 Jan-Mar; 6(1):63-8.