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Research Article

A Mechanistic Approach of QbD for the Preparation and Evaluation of Immediate Release Tablet Containing Mycophenolate Mofetil and Prednisolone

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ABSTRACT
The aim of present study is to develop an optimized formulation as immediate release tablet containg Mycophenolate mofetil (250mg) and Prednisolone (5mg) using Quality by Design (QbD) concept. According to QbD, the Target product profile (TPP) was developed in which values of critical quality attribute of the product was predicated. Formulation variables and process variables were selected for initial risk assessment of the product, and for this purpose two design layouts were prepared using design expert software 8. The responses were the final evaluation parameters for the tablets, were disintegration time (Y1), dissolution times for MMF (Y2) and Prednisolone (Y3). To select the one good design layout predicted Vs actual results were compared by graphical analysis. Design layout 1 was selected for further data analysis to understand the effect of variables on CQA of product. Some statistical model (sequential mode of sum squares, model summary statics design, ANOVA) were applied on the data of both the design layouts and also draw the perturbation plot contours plot and 3D contours plot. The optimized batch containing Croscarmellose sodium (2.75% w/w), Polyvinylpyrrolidone K-30 (2.75% w/w), Aerosil (0.55 %w/w) and mixing time 45 minutes, as per design expert software, was finally validated.

Keywords: Quality by Design (QbD), Mycophenolate mofetil (MMF), Prednisolone, immediate release tablets, Target product profile (TPP), formulation variables, and process variable.

INTRODUCTION

Tablets are the most preferred dosage form because of the convenience of self-administration, compactness, stability and easy manufacturability (Sandeep N *et al*, 2013). Most of the pharmaceutical industries are currently making tablets but they work with the manufacturing processes and operating procedures that are inefficient, time consuming, inflexible and outdated. This creates barrier to the development of new formulations, delays their marketing and chances of recalls are more. FDA is now taking initiative to enrol the sound scientific principles that involve prior identification of the loop holes in the manufacturing and operating procedures that provide hindrance in the development of safe, efficacious and effective product with better therapeutic value (Yu LX, 2008). QbD is a vast term and can be applied to any process or a step of process, analytical method, dosage form whether generic or new chemical entity to fulfill the objectives cited. Due to its importance and success in pharmaceutical fields, the concept is also shifting to other fields. It's because all the fields focus on cost, quality and timelines.9 The concept of QbD has been originated from the combination of ICH guidelines ICH Q8 (Pharmaceutical Development), Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality System) (Adam S *et al*, 2011, Lionberger RA *et al*, 2008). Q8 addresses collection of necessary knowledge, and Q9 addresses applying the collected knowledge to manage risk. Q10 addresses the need for systems to maintain the process, the facility and, ultimately, product quality throughout the product lifecycle (Somma R *et al*, 2008). Implementation of these three concepts defines QbD – a modern systematic approach for the pharmaceutical product development as it involves predefined objectives, involves product and process understanding, monitoring all the critical steps based on sound science and quality risk management. It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives. Hence it is a concept that follows quality should not be tested but should be built into the product (ICH Q10, 2008). Chronic kidney disease is a global public health problem of growing proportions. End-Stage Renal Disease (ESRD) is defined as permanent loss of the kidneys ability to filter wastes from the circulatory system. Renal transplantation is now widely considered the treatment of choice for patients with ESRD

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due to improved short- and long-term survival benefits than the dialysis treatment. Unfortunately, the survival rates of transplant are lesser due to the rejection of the allograft by the self-defensive mechanism of the body. So, there is a need to prepare the body before the transplantation as well as after to allow the incorporation of the allograft. For this immunosuppressants are used that follow different mechanism of action to prevent the rejection of the transplanted organ. Therapy of renal transplantation has always been given in the combination form. Combination therapy have various advantages over monotherapy such as problem of dose-dependent side effects is minimized, a low dose combination of two different agents reduces the dose-related risk, the addition of one agent may counteract some deleterious effects of the other, using low dosage of two different agent minimize the clinical and metabolic effects that occur with maximal dosage of individual component of the combined tablet (Kalble T *et al*, 2005, Mitchell DC *et al*, 2010). Mycophenolate mofetil (Wishart D, 2005) (Figure1) is a white or off white crystalline powder, it's molecular formula is C23H31NO7, molecular weight is 433.49 and IUPAC name is 2-(morpholin-4-yl) ethyl(4E)-6-(4-hydroxy-6- methoxy-7-methyl-3- oxo-1,3-dihydro-2-benzofuran-5-yl)-4- methylhex-4-enoate. It is used as immunosuppressant, antineoplstic agent, enzyme inhibitors and dermatologic agents. It is extensively bound to protein so bioavailability is 94% (mycophenolic acid) and $t_{1/2}$ is 18 hrs. Mycophenolate mofetil is an ester of mycophenolic acid (MPA). When taken orally MMF is converted by hepatic esterase to MPA. Mycophenolic acid is a nonnucleoside, non-competitive reversible inhibitor of inosine-5-monophosphate dehydrogenase (IMPDH). This is the rate-limiting enzyme in de novo synthesis of guanosine nucleotides preferentially in T and B lymphocytes and inhibits their proliferation, thereby suppressing cell-mediating immune responses and antibody formation (Fujiyama N *et al*, 2012, Laccarino L *et al*, 2007). Predinisolone (Figure 1) is white crystalline powder, its molecular formula is C21H28O5, Molecular weight is 360.44 and IUPAC name is (1S,2R,10S,11S,14R,15S, 17)-14,17-dihydroxy-14-(2-hydroxyacetyl)-2,15 dimethyltetracycloheptadeca-3,6-dien-5-one. Its protein binding is 90%, bioavailability is 80-100% and biological half-life is 18-36 hrs. Prednisolone is a synthetic corticosteroid that mimics the action of cortisol (hydrocortisone), the naturally-occurring corticosteroid produced in the body by the adrenal glands (FDA, cellcept, 2012, Liverani E *et al*, 2012, Sagcal-Gironella AAP *et al*, 2011).

MATERIAL AND METHODS

Micophenolate mofitil was received from Biocon (Bangalore, India), predinisolone, microcryatalline cellulose, crosscarmilose sodium were from Jackson pharmaceutical (Amritsar, India). PVK-30 and magnesium stearate, were received from Qualikem laboratories (Mumbai, India) and aerosil was from central Drug House (p), India. All other chemicals were of analytical grade.

Selection of QTPP, CQA and CCP

QbD implementation requires a thorough understanding of the relationship between the critical quality attributes (CQAs) and the clinical properties of the product, leading to successful product development with predefined quality attributes (QTPP). A CPP is a process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. The selected CQA, QTPP and CPP for the formulation are described in Table I.

Risk assessment and design space

Once the CQA's and CPP's are defined risk assessment is done. Risk assessment is a valuable science based process that help in identifying which material attributes and process parameters will eventually have an effect on CQA's (Bala I. *et al*, 2014). Then design space is constructed which is a multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. The independent variables for this study were concentration of superdisintegrants(A), grnulting agent(B), glidants(C) and mixing time (D) whereas dependent variables are disintegration time for tablet(Y1), dissolution time for MMF(Y2) and dissolution time for predinisolone(Y3) (Table II). For thorough risk assessment of critical material and process attributes Box-Behnken design (Design expert software 8) was selected with 29 experiments to carry out for applying DOE as shown in [Table III].

Preparation of granules

The excipients were selected according to the individual monograph of drugs i.e. excipients that are used for the preparation of the individual tablets of MMF and Prednisolone and those found more correlated according to physical compatibility test were used for the preparation of granules. The Box-Behnken design was constructed using design expert software 8 and granules were prepared according to the runs to know the effect of the variables. The granules were prepared by wet granulation method. The excipients microcrystalline cellulose, CCS/SSG (divided into intragranular and extragranular part) and PVP K-30 and drugs were passed through sieve no.40 and aerosil and magnesium stearate were passed through sieve no. 60. The excipients and drugs (except extragranular part of superdisintegrant) were mixed and granulation was done with isopropyl alcohol. The wet mass was passed through sieve no. 30 and granules were obtained. Granules were air dried because of the volatile nature of isopropyl alcohol. Then glidant (aerosil) and lubricant (magnesium stearate) was added along with extragranular part of superdisintegrant (CCS/SSG).

Evaluation of granules flow properties

The prepared granules were evaluated for parameters such as bulk density, tap density, compressibility index, Hausner's ratio and angle of repose as per the pharmacopoeial specification.

Tablet Compression

The tablets were prepared by compressing the granules formulated as per design layouts and were evaluated for

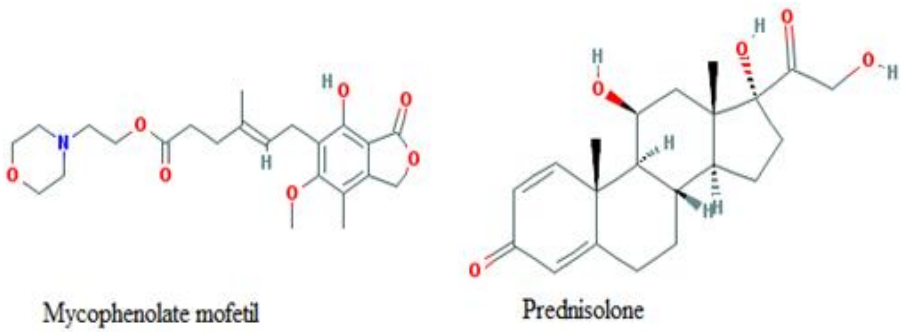

Figure 1: Structure of Mycophenolate mofetil and prednisolone.

Table 1: Selected CQA, QTPP and CPP for the formulation.

S. No.	CQA	QTPP	CPP
1.	Appearance	White to off- white, round shaped TABLEIts	Concentration of formula ingredients and mixing time
2.	Assay	95 to 105 % for both drugs	
3.	Disintegration time	Not more than 15 minutes	
4.	Dissolution tine	Not less than 85 % in 30 minutes for MMF and not less than 75 % in 45 minutes for Prednisolone	

Table 2: Factors for Design layout 1 and design layout 2.

Design layout 1				Design layout 2			
Factor	Description	Low	High	Factor	Description	Low	High
A	CCS (%)	0.5	5	A	SSG (%)	2	8
B	PVK-30(%)	0.5	5	B	PVK-30(%)	0.5	5
C	Aerosil(%)	0.1	1	C	Aerosil(%)	0.1	1
D	Mixing time (minutes)	30	60	D	Mixing time (minutes)	30	60

Note: % was in w/w

the initial parameters. Hardness and friability were considered as initial parameters for the evaluation of tablets, disintegration and dissolution studies were considered as the main parameters. The design of experiment was applied to for the analysis of main parameters and to see the effect of variables on them. The prepared tablets were evaluated for following parameters.

Evaluation of tablets

The tablets were evaluated for weight variation, hardness, friability, disintegration time and drug content. The drug content was calculated for the final batch. It was done by adding the amount equivalent to dose strength i.e 255.63 mg in 100 ml of volumetric flask from the crushed powder. Then the Prednisolone was estimated by taking the absorbance at the selected wavelengths of the simultaneous estimation by 1/10th dilution and MMF by 1/100th dilution (Kaur J *et al*, 2014)

In-Vitro dissolution studies

It was done by using USP apparatus II in 0.1 N HCl (pH 1.2) as the medium maintained at 37± 2ºC, at 50 rpm. Sampling was done at 5, 10,15,30,45 and 60 minutes. For the final batch the dissolution was carried out using USP apparatus II at 50 and 75 rpm respectively as per guidelines of dissolution testing of immediate release tablets for new chemical entity.

RESULT AND DISCUSSION

Evaluation of granules

The granules for different formulations were evaluated for their physical properties. The values are shown in Table IV. Most of the batches have shown good flow property.

Evaluation of tablets

All the batches of tablets were produced under similar conditions to avoid processing variables. The weight variation and thickness of all formulations were found within acceptable limits as per official specifications. The values of friability, hardness, disintegration and dissolution are given in Table V for design layout 1. In the similar way the friability, hardness, disintegration, dissolution time for mmf and dissolution time for predinisolone ranged within 0.5-2.02 %, 3.75-6 Kg/cm2, 58-98 sec., 15-45 min, 10-45 min respectively for design layout 2.

Interpretation of data

Hardness and friability was found to be in range for both the designs. The batches that are failed in friability (range is 0.5-1.0%), could not fit better in design. Disintegration time and dissolution time were analysed by design of experiment software to get the best possible batches out of all the designed batches. A total of 29 experiments were carried out to study the effect of formulation and process variable affecting disintegration and dissolution time of tablets. Response data is summarised in Table V. The selection of good design layout out of two was based on the predicted v/s actual result analysis (Figure 2). The predicted v/s actual results for both the designs were compared for each response and it was concluded that

Table 3: Design runs of design layout 1 and layout 2.

Run	Runs for design layout 1				Runs for design layout 2			
	Factor A (%)	Factor B (%)	Factor C (%)	Factor D (minutes)	Factor A (%)	Factor B (%)	Factor C (%)	Factor D (minutes)
1	2.75	2.75	0.55	45	5	0.5	0.1	45
2	2.75	2.75	0.55	45	2	2.75	1	45
3	2.75	2.75	0.1	30	8	5	0.55	45
4	2.75	0.5	0.1	45	5	5	0.55	30
5	2.75	2.75	1	60	2	2.75	0.55	30
6	2.75	0.5	0.55	60	5	0.5	1	45
7	0.5	2.75	0.55	60	5	2.75	0.55	45
8	2.75	2.75	0.55	45	5	5	1	45
9	5	0.5	0.55	45	2	2.75	0.1	45
10	2.75	2.75	0.55	45	8	2.75	0.1	45
11	2.75	2.75	0.1	60	8	2.75	1	45
12	2.75	2.75	0.55	45	5	0.5	0.55	60
13	0.5	5	0.55	45	5	2.75	0.55	45
14	2.75	5	0.55	30	8	2.75	0.55	60
15	2.75	5	0.1	45	8	2.75	0.55	30
16	0.5	2.75	0.55	30	8	0.5	0.55	45
17	5	2.75	0.55	60	2	2.75	0.55	60
18	5	5	0.55	45	5	2.75	0.1	30
19	0.5	2.75	0.1	45	5	2.75	0.55	45
20	5	2.75	1	45	5	2.75	1	30
21	0.5	0.5	0.55	45	5	5	0.1	45
22	5	2.75	0.55	30	5	5	0.55	60
23	2.75	5	1	45	5	0.5	0.55	30
24	0.5	2.75	1	45	5	2.75	0.55	45
25	2.75	0.5	1	45	2	5	0.55	45
26	2.75	5	0.55	60	5	2.75	1	60
27	2.75	0.5	0.55	30	2	0.5	0.55	45
28	2.75	2.75	1	30	5	2.75	0.1	60
29	5	2.75	0.1	45	5	2.75	0.55	45

Note: % was in w/w

design layout1 gave better results that has CCS as superdisintegrant in the formulation. The selection of model for further analysing the responses of design layout1 was based on the Sequential Model Sum of Squares, lack of fit test, Model summary statistics. The Prob> F value of P>0.001, low standard deviation, high R-sqaured value and lower Predicated Residual Error Sum of Square (PRESS) value suggested to select quardratic model for analysing both the responses. The details are mentioned in Table VI and Table VII. ANOVA was applied to confirm the adequacy of the model (Model Prob>F should be less than 0.05). It also helped to identify the significant factors that were affecting the responses. The significant model terms that affected the responses were factor A (CCS) and factor B (PVP K-30). The details of ANOVA are provided in Table VIII. The Pre R-squared value was found to be in close agreement with Adjusted R- squared value.

Perturbation plots

When the response shows a steep curvature it means that the factor is sensitive to the response. It was observed from perturbation plots (Figure 3) that factor A (CCS) and factor B (PVP K-30) were sensitive to responses. Whereas factor C (Aerosil) do not showed any steep curve. It was also noted the factor D (Mixing time) was not showing effect on response Y1 and Y2 but it had some effect on response Y3. When the graphs were analysed then the combination of effect of factor A with D and B with D didn't showed any major predictions. So the plot that showed maximum effect was of factors A and B.

Contour plots

It was concluded from Figure 4 that as the concentration of factor A (CCS) increased and concentration of factor B (PVP K-30) decreased the response Y1 and Y2 decreased whereas response Y3 decreased when concentration of factor A (CCS) and factor B (PVP K-30) decreased but the effect was not significant.

3D Contour plots

The effect of factors was also studied with 3D contour plots. It showed that when the concentration of factor A (CCS) increased and concentration of factor B (PVP K-30) decreased response Y1 and Y2 decreased whereas response Y3 decreased when concentration of factor A (CCS) and factor B (PVP K-30) decreased but the effect was not significant, as shown in Figure 5. This is because as the binder concentration decreased the granules would be loosely held, on the other side superdisintegrant helped to break the particles as soon as they come in contact with the medium.

Overlay plot

The optimisation was done with graphical method and the

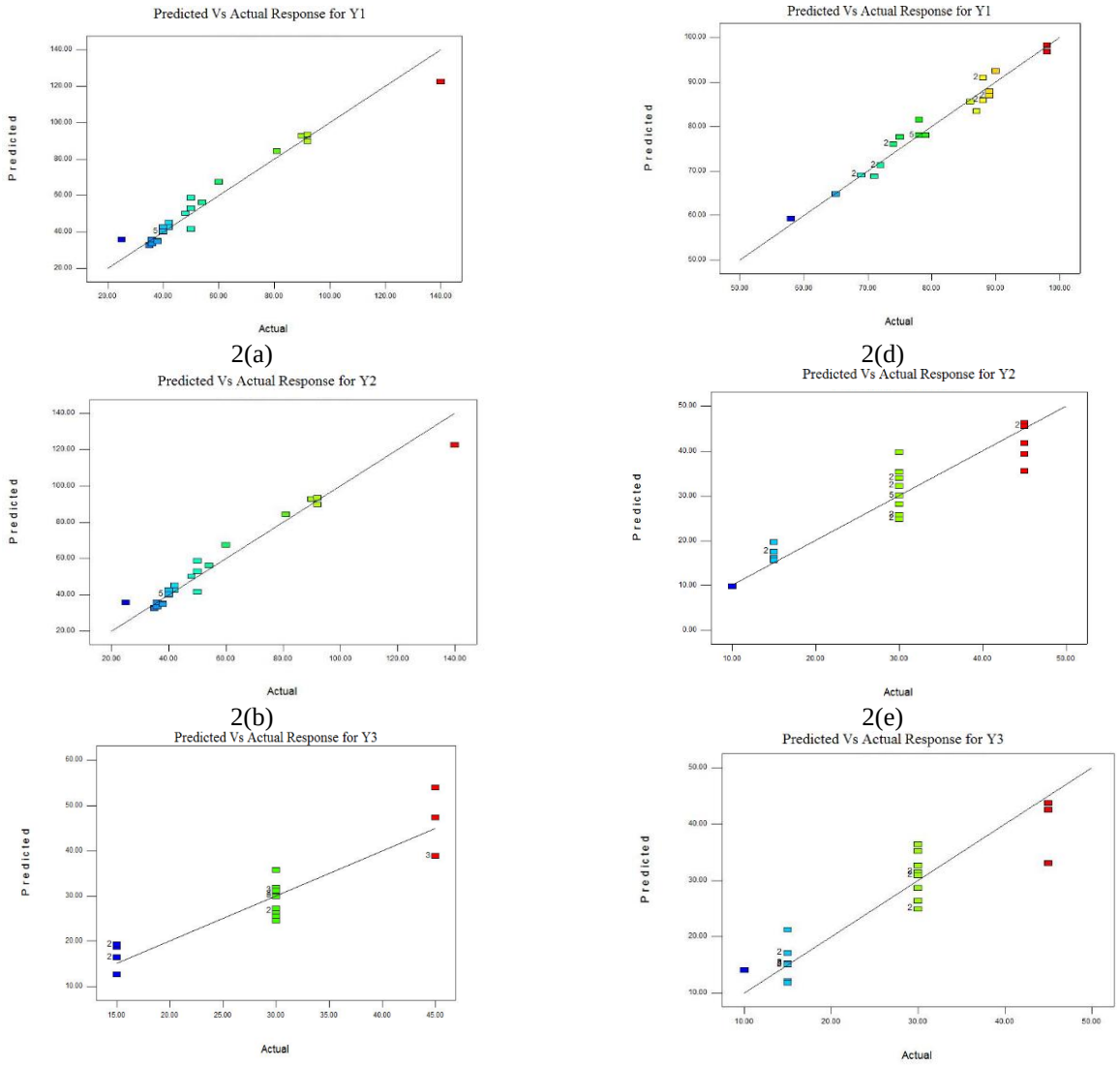

Figure 2: Predicted v/s actual for response for design layout 1(Figure 2a, 2b and 2c) and design layout 2(FIGURE 2d, 2e and 2f).

Table 4: Evaluation parameters of granules for design layout 1 and design layout 2.

Name of parameter	Angle of repose	Bulk density (gm/cm^3)	Tap density (gm/cm^3)	Carr's index	Hausner's ratio
Range for design layout 1	19.21°- 26.09°	0.405-0.469	0.450-0.527	6.02-16.47	1.06-1.19
Range for design layout 2	18.28°- 25.46°	0.389-0.463	0.471-0.550	6.02-16.27	1.06-1.19

overlay plot represented that batch which was best among all the batches (Figure 6).

Validation of optimized batch

The optimized batch of design layout1 was compressed in the tablets form. The ingredients of tablet were (mycophenolate mofetil (250 mg), prednisolone (5 mg), Croscarmellose sodium (2.75% w/w), Polyvinylpyrrolidone K-30 (2.75% w/w), Aerosil (0.55 %w/w), Microcrystalline cellulose (29.2%), Magnesium stearate (1%) and mixing time 45 minutes. Weight variation, hardness and friability tests were passed for the tablets. Disintegration time was 42 seconds which was under limit. Drug contents were 100.19% and 96.22% for mycophenolate mofetil and prednisolone respectively in the formulation.

In vitro dissolution studies

It was carried according to the dissolution guidelines for new chemical entity. Dissolution study was carried out at two different rpm i.e. 50 rpm and 75 rpm. At 75 rpm both the drug showed good dissolution profile. Dissolution profile of mycophenolate mofetil (Figure 7) shown 70% of the drug release within 5 minutes and rest of the drug

Table 5: Evaluation of tablets for design layout 1.

Run	Hardness (kg/cm^2)	Friability (%)	Disintegration time (seconds)	Dissolution time for MMF (minutes)	Dissolution time for Prednisolone (minutes)
1	6	0.5	40	30	30
3	5	0.76	42	30	30
4	5	0.76	35	15	15
5	5	0.72	40	15	15
6	4	0.6	38	10	15
7	5	0.5	81	30	15
9	4	0.6	25	10	30
11	4	0.76	40	15	15
13	5.5	0.9	140	45	30
14	6	0.5	54	45	45
15	5.5	0.89	50	30	30
16	6	0.5	90	45	30
17	5	0.76	35	10	30
18	4	0.63	38	30	45
19	5	0.76	92	45	30
20	5.5	0.5	36	10	45
21	5	1.26	60	45	30
22	4	0.75	35	15	45
23	5.5	0.62	50	30	30
24	5.5	0.5	92	45	30
25	4	0.6	50	15	15
26	5.5	0.9	48	30	30
27	4	0.6	38	15	30
28	6	0.5	42	30	30
29	5.5	0.67	36	15	45

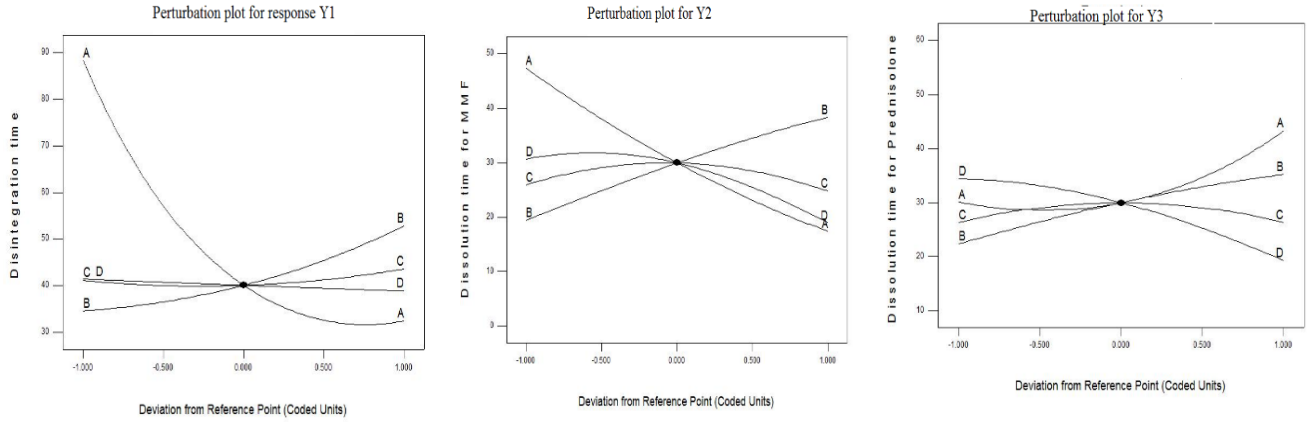

Figure 3: Perturbation plots for effect of individual factors on response Y1, Y2, Y3 of design layout 1.

Table 6: Summary of Sequential Mode Sum of Squares for design layout 1.

Source	Sum of Squares			df			Mean Square			F- Value			P- Value		
	Y1	Y2	Y3	Y1	Y2	Y3	Y1	Y2	Y3	Y1	Y2	Y3	Y1	Y2	Y3
	Sequential Model Sum of Squares														
Linear	47.31	35.89	14.53	4	4	4	11.83	8.97	3.63	18.08	31.99	10.8	<0.0001	<0.0001	<0.0001
2FI	2.57	1.6	0.45	6	6	6	0.43	0.27	0.07	0.59	0.94	0.18	0.7362	0.4933	0.9798
Quadratic	10	2.86	4.56	4	4	4	2.5	0.72	1.14	11.17	4.42	5.21	0.0003	0.0161	0.0088
Cubic	2.99	1.75	0.93	8	8	8	0.37	0.22	0.12	15.95	2.57	0.33	0.0016	0.1331	0.9273
Residual	0.14	0.51	2.14	6	6	6	0.02	0.08	0.36	-	-	-	-	-	-
Total	1487	775	855	29	29	29	51.28	26.72	29.48	-	-	-	-	-	-

Table 7: Summary of Model Summary Statistics for design layout.

Source	S.D			R-Squared			Adjusted R-Squared			Predicted R-Squared			PRESS		
	Y1	Y2	Y3	Y1	Y2	Y3	Y1	Y2	Y3	Y1	Y2	Y3	Y1	Y2	Y3
	Model Summary Statistics														
Linear	0.81	0.53	0.58	0.75	0.842	0.642	0.709	0.815	0.583	0.627	0.764	0.442	23.46	10.04	12.61
2FI	0.85	0.53	0.65	0.791	0.879	0.662	0.675	0.654	0.475	0.391	0.654	-0.11	38.36	14.74	25.15
Quadratic	0.47	0.40	0.47	0.95	0.946	0.864	0.9	0.693	0.728	0.713	0.693	0.219	18.05	13.05	17.65
Cubic	0.15	0.29	0.60	0.15	0.988	0.906	0.997	0.944	0.559	0.678	-0.73	-12.6	20.26	73.68	307.57

Table 8: Summary of ANOVA for design layout 1.

Source	Sum of Squares			df			Mean Square			F- Value			P- Value		
Model	Y1	Y2	Y3	Y1	Y2	Y3	Y1	Y2	Y3	Y1	Y2	Y3	Y1	Y2	Y3
	59.88	40.36	19.54	14	14	14	4.28	2.88	1.4	19.11	17.81	6.38	<0.0001	<0.0001	0.0007
CCS	41.26	22.16	3.55	1	1	1	41.26	22.16	3.55	184.35	136.91	16.23	<0.0001	0.6282	0.0012
PVP K-30	5.81	9.49	4.41	1	1	1	5.81	9.49	4.41	25.98	58.65	20.15	0.0002	0.038	0.0005
Aerosil	0.11	0.042	-3.55	1	1	1	0.11	0.04	-3.6	0.5	0.26	-1.62	0.4925	0.3553	1
Mixing	0.12	4.19	6.57	1	1	1	0.12	4.19	6.57	0.55	28.89	30.02	0.4691	0.618	<0.0001
Residual	3.13	2.27	3.06	14	14	14	2.13	0.16	0.22	-	-	-	-	-	-
Lack of fit	3.13	2.27	3.06	10	10	10	0.22	0.23	0.31	-	-	-	-	-	-
Pure error	0	0	0	4	4	4	0.31	0	0	-	-	-	-	-	-

slowly releases within 15 minutes. After that the drug profile got steady state. Like this Prednisolone drug release profile (Figure 8) shown 75% of drug release within 5 minutes and rest of the drug release within 15 minutes.

CONCLUSION

It was concluded from the study that superdisintegrant concentration and binder concentration are the critical parameters that significantly affects the CQA of the formulation. The perturbation plots proved that glidant (Aerosil) had no significant effect. Mixing time showed some deviations in the perturbation plots but the effect was not significant. As this was just an initiative towards the approach there is a wide scope to study the effect of other variables including individual effect of API's and other process parameters. Individual effect of API's may include effect of particle size, stability and purity. Process parameters may include effect of compression force etc.

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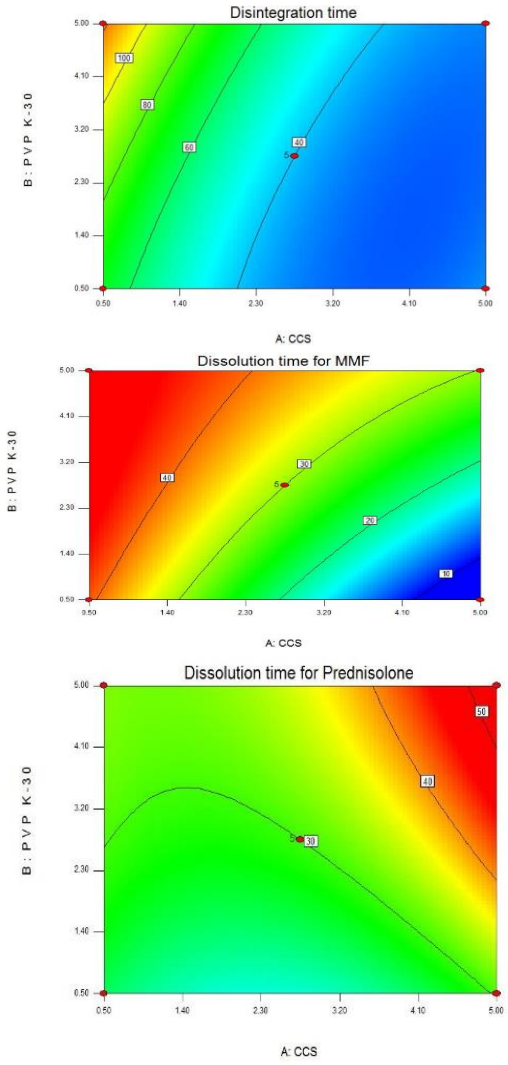

Figure 4: Contour plots for the effect of CCS (A) and PVP K-30 (B) on disintegration time(Y1), dissolution time for MMF (Y2) and dissolution time for prednisolone (Y3)for design layout 1.

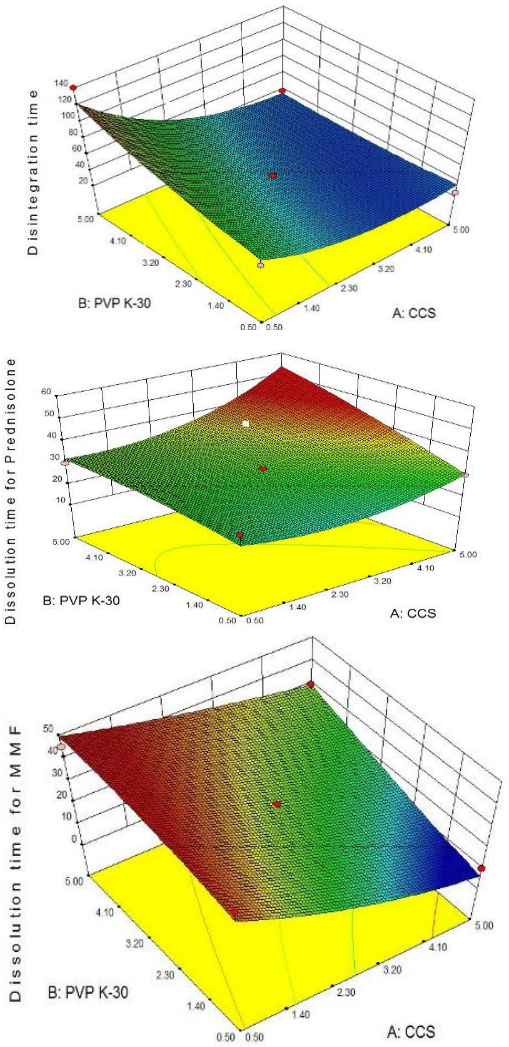

Figure 5: 3D Contour plot showing the effect of CCS (A) and PVP K-30(B) on Disintegration time (Y1) Dissolution time for prednisolone(Y2) Dissolution time for MMF(Y3) and for design layout 1.

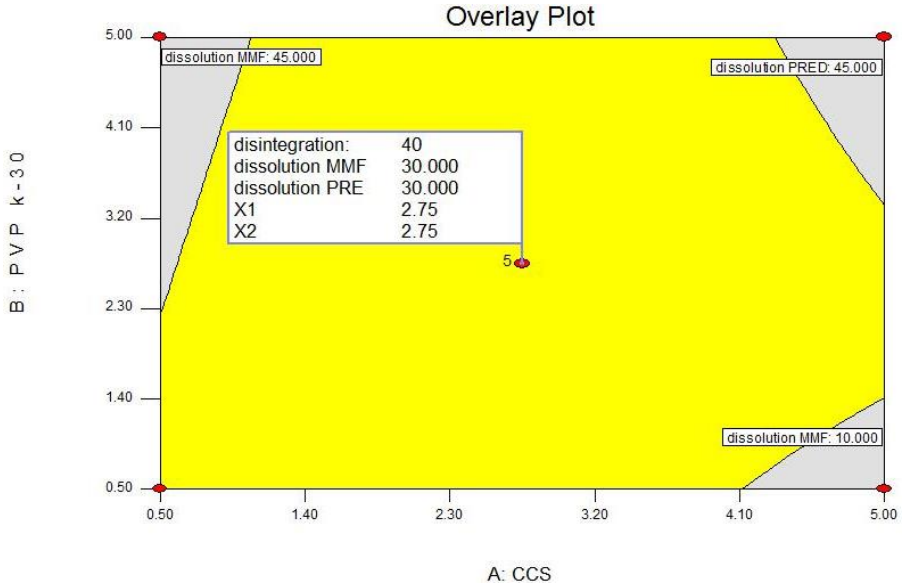

Figure 6: Overlay plot showing the optimised batch for design layout 1.

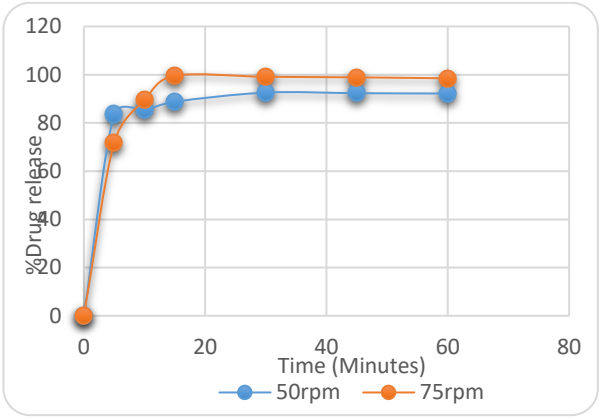

Figure 7: Dissolution profile of MMF.

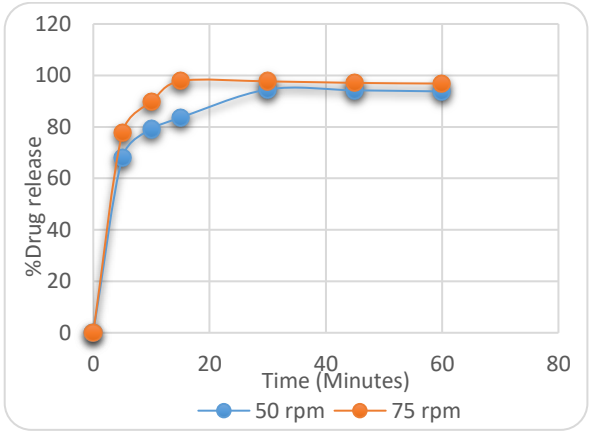

Figure 8: Dissolution profile of Prednisolone.

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