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Quality by design approach for optimizing the formulation properties of escitalopram oxalate Oro-dispersible tablets

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Abstract

The quality by design (QbD) approach was applied for optimizing the formulation of Escitalopram oxalate (ES) orodispersible tablets (ODTs) using Design-Expert Software. To Optimize ES-ODTs a quality target product profile was established in which critical quality attributes (CQAs) such as wetting time, dispersion time, disintegration time and drug release rates were defined and quantified. As critical formulation parameters (CFP) that were evaluated for their effect on the CQA. Percentage of Crospovidone (CP) and Croscaramellose (CCS) were choosen. Response surface methodology (RSM) such as Central Composite Design (CCD) was used to evaluate the effects of the CFPs on the CQAs of the final product. The main factor affecting disintegration, wetting time, dispersion time and release rate was the combination of CP and CCS. Disintegration time, wetting time and dispersion time were found to be sensitive to the percentage of CP and CCS. From the results a design space could be created. The results suggest QbD appears to be a useful approach for the rational design of ES-ODTs. The chosen model helps to visualize the different effects of the CFPs on the CQAs.

Keywords: QbD; Escitalopram oxalate: CQA; CFP; Orodispersible tablets; CCD

1 Introduction

Quality by design (QbD) is a systematic approach to optimize pharmaceutical preparations and to improve the control over and the quality of the production process. The QbD approach consistently yields a product with desired characteristics and built in quality[1]. The preferred tool for strategic drug development using the QbD approach is the establishment of a quality target product profile (QTPP)[2,3]. A QTPP starts with defining the critical quality attributes (CQAs) for the final product. A CQA can be defined as, physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality and thereby adequate performance and safety of the drug product when used[4]. A subsequent step of the QTTP is the identification of the critical formulation parameters (CFP) that influence the CQA. By combining the CQA and CFP a design space can be created. As long as the formulation and process variables remain within the design space, a product will be obtained that meets the quality requirements[4].

Orodispersible tablets (ODTs) are also called as orally disintegrating tablets, mouth dissolving tablets, rapid-dissolving tablets, fast-disintegrating tablets, fast-dissolving tablets. Recently, European Pharmacopoeia has used the term orodispersible tablets. This may be defined as uncoated tablets intended to be placed in the mouth where they disperse readily within 3 min before swallowing[5]. United States Pharmacopoeia has also approved these dosage forms as ODTs. Thus, ODTs are solid unit dosage forms like conventional tablets, but are composed of super disintegrants, which help them to dissolve the tablets within a minute in the mouth in the presence of saliva without any difficulty of swallowing. It offers several advantages with respect to its stability, administration without water, accurate dosing, easy manufacturing, small packaging size, and handling[6-9]. Its ease of administration in the population especially for pediatric, geriatric, or any mentally retarded persons makes it a very popular dosage form. Due to the presence of super

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disintegrants, it gets dissolved quickly, resulting in rapid absorption of drug which in turn provides rapid onset of action[10]. Since the absorption is taking place directly from the mouth, bioavailability of the drug increases[11]. Drugs present in orodispersible tablets are also not suffering from first pass metabolism. This type of drug delivery is becoming popular day by day due to its numerous advantages.

The aim of the present study was to apply QbD for the optimization of Escitalopram oxalate (ES) orodispersible tablets (ODTs) using the scientific expert system software Design-Expert trial version 13. The CQA in the present study were wetting time, dispersion time, disintegration time and t50. For every CQA Design-Expert gives a unique matrix of probabilities that helps to determine the best crossed model. The varied CFP in this study were super disintegrating agents Crospovidone (CP) and Croscaramellose (CCS). The other excipients and conditions were kept constant.

2 Material and methods

Escitalopram oxalate (ES) was obtained as gift sample from Caplin Point Laboratories, Chennai, Tamilnadu, India. Crospovidone, Croscaramellose, Microcrystalline cellulose (MCC), Mannitol and Lactose were procured from S.D. Fine Chemicals, Mumbai, India. All other ingredients used throughout the study were of analytical grade and were used as received.

2.1 Choice of design and experimental layout

The design space was calculated using the Design-Expert Software (version 13 trial, Stat ease). The choice of minimum and maximum values of CFPs (CP and CCS) were used for the study. A central composite design (CCD) was made for the response surface methodology (RSM) and the number of runs needed was calculated. The CFPs were varied over two levels (-1 low, +1 High) resulting in a setup of 10 runs which were performed randomly to prevent bias. Table 1 shows the ranges of CFPs applied and trial run generated keeping other excipients constant. To each run different variables were assigned by the program resulting in different plots, e.g. diagnostic and model response surface plot. For each run a different percentage of CP (X1), and CCS (X2) were applied. The best fitted models were assigned by Design-Expert Software and were chosen based on their significance using an analysis of variance (ANOVA) F-test[12].

Table 1 Ranges of CFPs (percentage CP and, percentage of CCS) as per CCD

Std order	Runs	% CP(mg)	% CCS (mg)	ES	MCC (mg)	Mannitol (mg)	Lactose (mg)	Total weight (mg)
		X1	X2					
10	1	12.5 (20)	12.5(20)	10	48	32	30	160
1	2	10 (16)	10(16)	10	48	32	38	160
3	3	10 (16)	15(24)	10	48	32	30	160
9	4	12.5(20)	12.5(20)	10	48	32	30	160
2	5	15(24)	10(16)	10	48	32	30	160
4	6	15(24)	15(24)	10	48	32	22	160
6	7	15(24)	12.5(20)	10	48	32	26	160
7	8	12.5(20)	10(16)	10	48	32	34	160
5	9	10(16)	12.5(20)	10	48	32	34	160
8	10	12.5(20)	15(24)	10	48	32	26	160

2.2 Fabrication of ES-ODTs

The trial runs of ES-ODTs were prepared by direct compression method (Batch size 40). The components as per table 1 were accurately weighed and mixed in a polybag for few minutes, the blend at that point was characterized for precompression parameters by performing angle of repose, tapped and bulk density, carr's index and hausner ratio before the compression process. After precompression characterization the blend was compressed by rotary tablet punching machine using 8 mm flat head punch. The obtained tablets were subjected to postcompression characterization by performing thickness, diameter, hardness, friability, weight variation, drug content and *in vitro* drug

release. Further the ES-ODTs were evaluated for CPQs such as wetting time, dispersion time, disintegration time and t50. The obtained data were analyzed by Design expert software to interpret the design space.

2.3 Evaluation

2.3.1 Evaluation of precompression parameters[13-17]

- **Bulk density (BD):** Weighed quantity 2 G of blend was introduced into a measuring cylinder. After determination of initial volume, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals and the tapping was continued until no further change in volume was noted. The determination was carried out in triplicate.

$$BD = \frac{M}{V_o}$$

BD- Bulk density (cm^3); M- Weight of powder (gm); Vo- bulk volume (cm^3)

- **Tapped density (TD):** Weighed quantity 2 G of blend was introduced into a measuring cylinder. After determination of initial volume, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals for 100 times. The tapped density is then obtained by dividing the weight of the sample in grams by the final volume in cm^3 of the sample contained in the cylinder.

$$TD = \frac{M}{V}$$

TD- Tapped density (cm^3); M- Weight of powder (gm); V- Tapped volume (cm^3)

- **Compressibility index:** Compressibility index was determined by placing the blend in a measuring cylinder and the volume (V_0) was noted before tapping, after 100 times tapping again volume (V) was recorded.

Compressibility index = $(1-\frac{V}{V_o})$ X 100

Where, V_0 - Volume of powder/granules before tapping.

V - Volume of powder/granules after 100 times tapping.

- **Carr's index:** The compressibility index of the powder blend was determined by carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's index is as below,

$$\text{Carr's index (\%)} = \frac{[(BD - TD) \times 100]}{TD}$$

Where, TD- Tapped density; BD- Bulk density

- **Hausner's ratio:** The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular blend.

$$\text{Hausner's ratio} = TD / BD$$

Where, TD = Tapped density; BD = Bulk density

- **Angle of repose (Θ):** The angle of repose is a parameter commonly used for the evaluation of interparticle force. The simplest method for the determination of the angle of repose was the poured angle. A funnel with a wide outlet was affixed at a distance of 10 cm above the bench, where a piece of paper is placed directly beneath the funnel. Powder was added while the funnel is closed. The contents flow through and collect on the paper. The diameter of the cone (D) and two opposite sides ($l_1 + l_2$) were measured with rulers. The angle of repose (θ) was calculated from the equation arc tan $[D/(l_1 + l_2)]$. The relationship between flow properties and angle

of repose had been established. When the angle of repose is less than 25 degrees, the flow is said to be excellent, on the other hand, if the angle of repose is more than 40 degrees, the flow is considered to be poor.

2.3.2 Evaluation of postcompression parameters[18-21]

- **Thickness and diameter:** The thickness and diameter of ES-ODTs were measured using digital Vernier calipers. In each case randomly selected 10 tablets were used for the test. Averages of ten readings were taken and the results were computed.
- **Uniformity of weight:** Individually twenty tablets of ES-ODTs were selected and weighed accurately. The average weight of individual tablet was compared for the determination of weight variation. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following and none deviates by more than twice that percentage.

  Tablets weighed 80 mg or less - Permissible deviation is 10%
  Tablets weighed <80 mg but >250mg - Permissible deviation is 7.5%
  Tablets weighed 250 mg or more - Permissible deviation is 5%
- **Drug content uniformity:** From each batch three randomly selected ES-ODTs were subjected for drug content uniformity test. In each case tablets were weighed accurately and powdered in a clean and dry glass mortar with pestle, powder equivalent to 5 mg of ES was transferred into 50 ml volumetric flask containing 50 ml of pH 6.8 buffer. The solution was shaken intermittently for 2 hr and then it was filtered, desired dilutions were made and analyzed using validated analytical method for drug content. Triplicate readings were taken and average was computed.
- **Hardness[11]:** The hardness test was performed to determine the driving force required to break the tablet over an applied pressure. The hardness was done using Monsanto hardness analyzer.
- **Friability:** Friability test was performed to determine the weight loss from the tablet and comparing the final weight with the original tablet. This test is important to obtain the surface resistance during the packaging and transport. The friability (F) of a sample of 20 ES-ODTs were measured using Roche fribilator. Twenty tablets were weighed, rotated at 25 rpm for 4 min. Tablets were reweighed after removal of fines (dedusted) and calculated the percentage of weight loss by using the below formula. Friability below 1% was considered acceptable.

$$F = \frac{(W_{initial}) - (W_{final})}{(W_{initial})} \times 100$$

2.3.3 Evaluation of CQAs

- **Wetting time:** Wattman filter paper was placed in a petri plate having an internal diameter 6.5 cm containing 1 ml of amaranth solution where the tablet was placed and the complete wetting time of the tablet was measured in seconds. Average of three tablets were recorded and computed.
- **Dispersion time:** The dispersion time was calculated via placing tablets in a watch glass containing 5 ml of pH 6.8 buffer. Three tablets from each formulation were randomly selected and dispersion time was measured.
- **Disintegration test (modified method):** *In vitro* disintegration time of ES- ODTs were carried out at (37±2) ºC in 10 ml of pH 6.8 buffer solution using a disintegration test apparatus. Disintegration time of 6 individual ES-ODTs were recorded and carried out at (37± 2) ºC in 900 ml of pH 6.8 buffer solution.
- ***In vitro* dissolution studies:** *In vitro* drug release studies for ES-ODTs were carried out using USP XXII dissolution apparatus type II at 50 rpm. The dissolution medium consisted of 500 ml of pH 6.8 buffer, maintained at 37 ± 0.5^{0}C. Samples were taken after fixed time intervals viz., 1, 2, 3, 5, 7, 10, 12, 15, 20 and 30 min, withdrawn samples (5 ml) were then filtered through 0.45 µm millipore syringe filters, and the concentration of drug in each sample was estimated by using validated analytical method. To maintain the sink conditions, 5 ml of fresh buffer solution was added to the medium immediately after sample collection.
- FTIR studies: The interaction between the drug and polymer was studied by FTIR. To produce a stable product, the drug and polymer must be compatible with one another. Drug and polymer interactions were studied by using FT-IR (Shimadzu, Japan model–8400S). FTIR spectral analysis of ES and OP-ES-ODTS were carried out, no change in peaks of OP-ES-ODTS compared to ES indicates the absence of interactions.

3 Results and Discussion

3.1 Precompression studies

The bulk density was found to be in the range of 0.6714 ± 0.01528 to 0.7823 ± 0.01155 g/cm^3; tapped density 0.535 ± 0.0041 to 0.613 ± 0.0032 g/cm^3; compressibility index value 14.2 ± 0.300 to 17.43 ± 0.060 and Hauser's value 1.68 ±

0.100 to 1.72 ± 0.020; angle of repose $24^0 43'$ to $26^0 54'$ for F1 to F10 design trial run batches of ES-ODTs, indicates good compressibility and flowability and can be used for direct compression.

3.2 Postcompression studies

The postcompression data were found to be in the range of 3.12 ± 0.01732 to 3.22 ± 0.01155 mm thickness; 8.02 ± 0.0002309 to 8.03 ± 0.0001732 mm diameter; 2.45 to 2.85 Kg/cm^2 hardness; 157.9 ± 1.1732 to162.5 ± 1.0434 mg weight variation; 0.75 to 0.81 % friability for design trial batches of ES-ODTs suggest the ODTs have desired mechanical strength, tablet integrity and uniform weight throughout the batches prepared. The drug content was in the range of 98.56 ± 1.231 to 99.15 ± 1.131 %, low SD values indicate drug distribution was uniform throughout the tablets.

3.3 CQAs studies within the design space

Critical quality attributes (CQA) for ES-ODTs a shorter wetting time (< 15 Sec), dispersion time (< 20), disintegration time (< 30 sec) and t50 (< 5min) are preferred and these limits were based on earlier experiments on ODTs[22]. The experimental results of CQAs properties were given in table 2, this data was further analyzed with Design-Expert Software. The software generated ANOVA data (table 3), model fit statistics data, polynomial equations to discuss the influence of CFPs on CQAs, further the data was interpreted with visualized measurement in support with Normality, Predicted vs actual, Contour, 3D surface and Interaction plots.

Table 2 Design trials with response table as per CCD

Design Trial Batches	CQAs			
	Wetting time (sec)	Dispersion time (sec)	DT (sec)	t50 (min)
F1	10.58	11.5	9	1.2
F2	15.32	13.25	12	3
F3	11.32	12.2	8	1.6
F4	10.65	11.25	8	1.3
F5	11.21	11.25	8	1.6
F6	9.45	10	6	1
F7	10.2	11.23	7	1.1
F8	12.25	12.31	10	2
F9	12.2	12.07	11	2.4
F10	10.12	11.58	7	1.2

Table 3 ANOVA data for all response

Model	Sum of Squares	df	Mean Square	F-value	p-value
Wetting time - Quadratic-model suggested					
Significant	24.32	5	4.86	37.53	0.0019
A-CP	10.61	1	10.61	81.90	0.0008
B-CCS	10.38	1	10.38	80.06	0.0009
AB	1.25	1	1.25	9.68	0.0358
A^2	0.8866	1	0.8866	6.84	0.0591
B^2	0.8440	1	0.8440	6.51	0.0632
Residual	0.5184	4	0.1296		
Lack of Fit-NS	0.5159	3	0.1720	70.19	0.0875

Pure Error	0.0025	1	0.0025		
Cor Total	24.84	9			
Dispersion time- 2F1 Model suggested					
Significant	4.34	3	1.45	20.73	0.0014
A-CP	1.69	1	1.69	24.13	0.0027
B-CCS	1.33	1	1.33	19.11	0.0047
AB	1.32	1	1.32	18.94	0.0048
Residual	0.4190	6	0.0698		
Lack of Fit-NS	0.3878	5	0.0776	2.48	0.4465
Pure Error	0.0313	1	0.0313		
Cor Total	4.76	9			
DT- Linear Model suggested					
Significant	30.17	2	15.08	47.28	< 0.0001
A-CP	16.67	1	16.67	52.24	0.0002
B-CCS	13.50	1	13.50	42.31	0.0003
Residual	2.23	7	0.3190		
Lack of Fit-NS	1.73	6	0.2889	0.5778	0.7637
Pure Error	0.5000	1	0.5000		
Cor Total	32.40	9			
T50 – Quadratic Model suggested					
Significant	3.66	5	0.7328	29.38	0.0030
A-CP	1.82	1	1.82	72.77	0.0010
B-CCS	1.31	1	1.31	52.39	0.0019
AB	0.1600	1	0.1600	6.42	0.0645
A^2	0.2519	1	0.2519	10.10	0.0336
B^2	0.0744	1	0.0744	2.98	0.1592
Residual	0.0998	4	0.0249		
Lack of Fit-NS	0.0948	3	0.0316	6.32	0.2826
Pure Error	0.0050	1	0.0050		
Cor Total	3.76	9			

3.3.1 Effect of factors on wetting time

ANOVA suggested Quadratic model, F-value of 37.53 implies the model was significant. There is only a 0.19% chance that F-value large could occur due to noise. P < 0.05 indicate model terms were significant and P > 0.10 indicate model terms were not significant. In this case CP, CCS, CP*CCS were significant model terms with non-significant Lack of fit. The regression R^2 of the linear model suggest 0.9791 (97.91 %) good positive correlation between the factors and stated response. The Predicted R^2 of 0.7700 was in reasonable agreement with the Adjusted R^2 of 0.9530; i.e. the difference is less than 0.2. The adequate precision measures the signal to noise ratio and ratio greater than 4 is desirable, here the ratio of 18.971 indicates an adequate signal. This model can be used to navigate the design space. The % CV describes the dispersion degree of data points around the mean values, a small CV value % 3.18 which is less than 10 denotes good reproducibility of the model. The actual response values were varied with small deviation with that of predicted values as shown in figure 1a. The polynomial equation was generated for actual factors. 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. The negative signs in the quadratic equation suggest significant second order model terms. The CP and CCS had indirect influence on the wetting time with positive intercept. The interaction terms CP * CCS had synergistic effect on the wetting time. The second order polynomial equation for wetting time was given as,

$$\text{Wetting time} = +68.27071 - 4.11771 * CP - 4.05171 * CCS + 0.089600 * CP * CCS + 0.098629 * CP^2 + 0.096229 * CCS^2$$

The relationship between factors vs response were shown in response surface plots viz., Contour, and 3D surface between factors vs response was shown in figure 1b,1c. The interaction plot (figure 1d) clearly suggest small interaction between the factors at high concentrations of CP under the influence of low concentrations of CCS and was further justified figure 1 as well as ANOVA data where CP and CCS has main effect whereas CP*CCS has interaction effect.

Wetting time in ODTs explained when tablet is exposed to an aqueous solution *in vitro* or *in vivo*, the fluid seeps into the tablet, causing the superdisintegrants present to expand in volume, which further facilitate disintegration. Wetting is a process of providing moisture required for a ODTs to disintegrate and dissolve. Here the ES-ODTs were prepared with combination of CP and CCS as super disintegrants and study the influence on wetting time. CP has a faster wetting time than CC, but CCS sodium has better wetting time than CP, shortest wetting time may be explained by a wicking mechanism that draws water into the tablet by capillary action, as well as CP superior hydration capacity. CP rapidly swells and disperses in water by capillarity nature facilitate disintegration. CCS has limited water solubility but higher degree of swelling up to 4-8 times of its initial volume, when the concentration of CCS was increased results no significant difference in wetting time. At higher concentrations of CP wetting time decreases as it forms gel and inhibit the water penetration but in combination with CCS increases the wetting time because of greater hydrophilicity of CCS. Wetting time is an important parameter in the evaluation of the disintegration of ODTs because disintegration rate is highly depends on the rate of tablet wetting process.

3.3.2 Effect of factors on dispersion time

ANOVA suggested 2FI model, F-value of 20.73 implies the model was significant. There is only a 0.14% chance that an F-value this large could occur due to noise. $P < 0.05$ indicate model terms were significant and $P > 0.10$ indicate model terms are not significant. In this case CP, CCS, CP*CCS are significant model terms with non-significant Lack of fit. The regression R^2 of the linear model suggest 0.9120 (91.20 %) good positive correlation between the factors and stated response. The Predicted R^2 of 0.8308 was in reasonable agreement with the Adjusted R^2 of 0.8680; i.e. the difference is less than 0.2. The adequate precision measures the signal to noise ratio and ratio greater than 4 is desirable, here the ratio of 13.2223 indicates an adequate signal. This model can be used to navigate the design space. The % CV describes the dispersion degree of data points around the mean values, a small CV value % 2.26 which is less than 10 denotes good reproducibility of the model. The actual response values were varied with small deviation with that of predicted values as shown in figure 2a. The polynomial equation was generated for actual factors. 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 centre of the design space. The negative signs in the quadratic equation suggest significant second order model terms. The CP and CCS has direct influence on the dispersion time with positive intercept. The interaction terms CP * CCS has antagonistic effect on the wetting time. The first order polynomial equation for dispersion time was given as,

$$\textbf{Dispersion time} = +2.30133 + 0.938 * CP + 0.961333 * CCS - 0.092 * CP * CCS$$

The relationship between factors vs response were shown in response surface plots viz., Contour, and 3D surface between factors vs response was shown in figure 2b, 2c. The interaction plot (figure 2d) clearly suggest small interaction between the factors at median concentrations of CP under the influence of median concentrations of CCS and was further justified figure 2d as well as ANOVA data where CP and CCS has main effect whereas CP*CCS has interaction effect.

3.3.3 Effect of factors on DT

ANOVA suggested linear model, F-value of 47.28 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. $P < 0.05$ indicate model terms are significant and $P > 0.10$ indicate model terms are not significant. In this case CP and CCS are significant model terms with non-significant Lack of fit. The regression R^2 of the linear model suggest 0.9311 (93.11 %) good positive correlation between the factors and stated response. The Predicted R^2 of 0.8373 is in reasonable agreement with the Adjusted R^2 of 0.9114; i.e. the difference is

less than 0.2. The adequate precision measures the signal to noise ratio and ratio greater than 4 is desirable, here the ratio of 20.4712 indicates an adequate signal. This model can be used to navigate the design space. The % CV describes the dispersion degree of data points around the mean values, a small CV value % 6.57 which is less than 10 denotes good reproducibility of the model. The actual response values were varied with small deviation with that of predicted values as shown in figure 3a. The polynomial equation was generated for actual factors. 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. The negative signs in the quadratic equation suggest significant second order model terms. The CP and CCS has indirect influence on the DT with positive intercept. The first order polynomial equation for DT is given as,

$$\mathbf{DT} = +24.43333 - 0.666667*CP - 0.600*CCS$$

The relationship between factors vs response were shown in response surface plots viz., Contour, and 3D surface between factors vs response was shown in figure 3b,3c. The interaction plot (figure 3d) clearly suggest no interaction between the factors and was further justified figure 2d as well as ANOVA data where CP and CCS has main effect on DT.

The DT time deceases with the increase in the concentration of CP and CCS it may be due to swelling and wicking properties of CP and CCS respectively and these results are in accordance with wetting time results, concludes that wetting is directly influence on the DT of ODTs. The mechanism could be better water penetration, swelling and bursting of the tablets. The fast disintegration time is important for identifying the tablets as ODTs, according to regulation recommendations. As a result, superdisintegrants are critical in shortening the time required for ODTs formulation disintegration.

3.3.4 Effect of factors on t50

ANOVA suggest Quadratic model, F-value of 29.38 implies the model was significant. There is only a 0.30 % chance that an F-value this large could occur due to noise. $P < 0.05$ indicate model terms were significant. In this case CP, CCS and CP^2 are significant model terms with non-significant Lack of fit. The regression R^2 of the linear model suggest 0.9735 (97.35 %) good positive correlation between the factors and stated response. The Predicted R^2 of 0.7777 is in reasonable agreement with the Adjusted R^2 of 0.9404; i.e. the difference is less than 0.2. The adequate precision measures the signal to noise ratio and ratio greater than 4 is desirable, here the ratio of 16.6219 indicates an adequate signal. This model can be used to navigate the design space. The % CV describes the dispersion degree of data points around the mean values, a small CV value % 9.63 which is less than 10 denotes good reproducibility of the model. The actual response values were varied with small deviation with that of predicted values as shown in figure 4a. The polynomial equation was generated for actual factors. 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 centre of the design space. The negative signs in the quadratic equation suggest significant second order model terms. The CP and CCS has indirect influence on the t50 with positive intercept. The second order polynomial equation for DT is given as,

$$\mathbf{T50} = + 24.09762 - 1.93429*CP -. 30095*CCS + 0.0320*CP*CCS + 0.52571*CP^2 + 0.028571*CCS^2$$

The relationship between factors vs response were shown in response surface plots viz., Contour, and 3D surface between factors vs response was shown in figure 4b,4c. The interaction plot (figure 3d) clearly suggest small interaction between the factors at high levels of CP and CCS and was further justified figure 4d as well as ANOVA data where CP and CCS has main effect and on CP^2 exponential effect on t50.

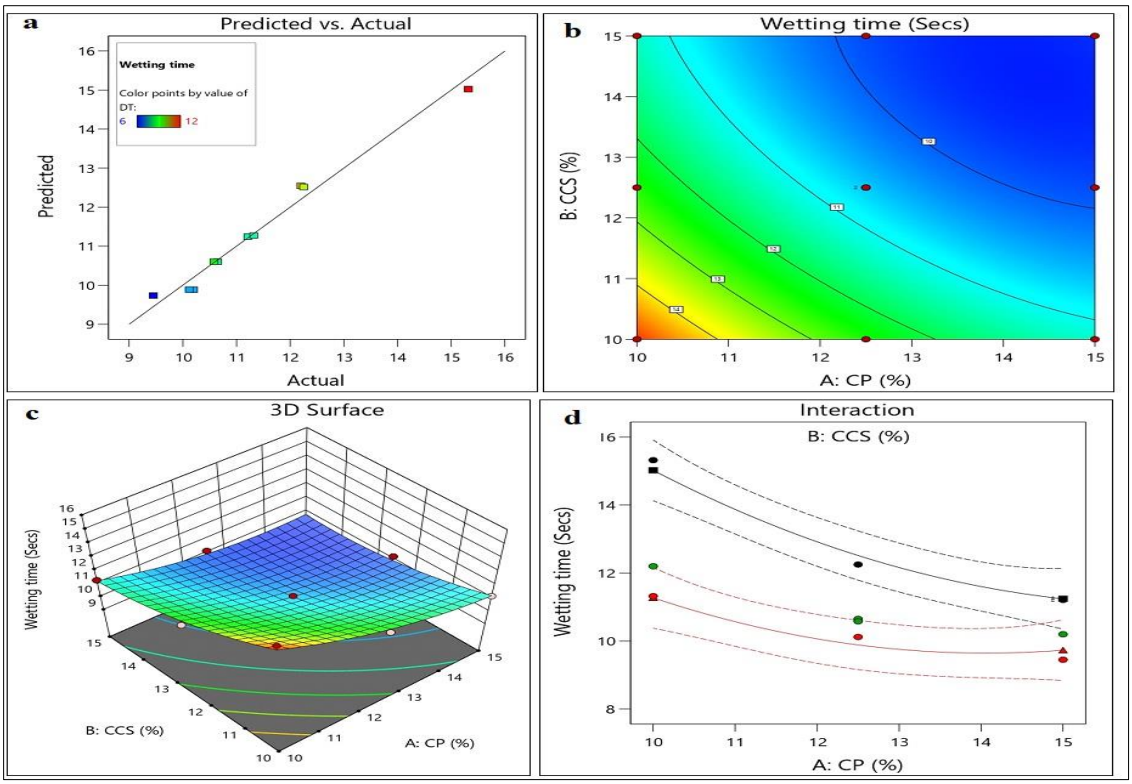

Figure 1 Graphical representation of factors influencing on response wetting time a) predicted vs actual b) contour c) 3D surface d) interaction

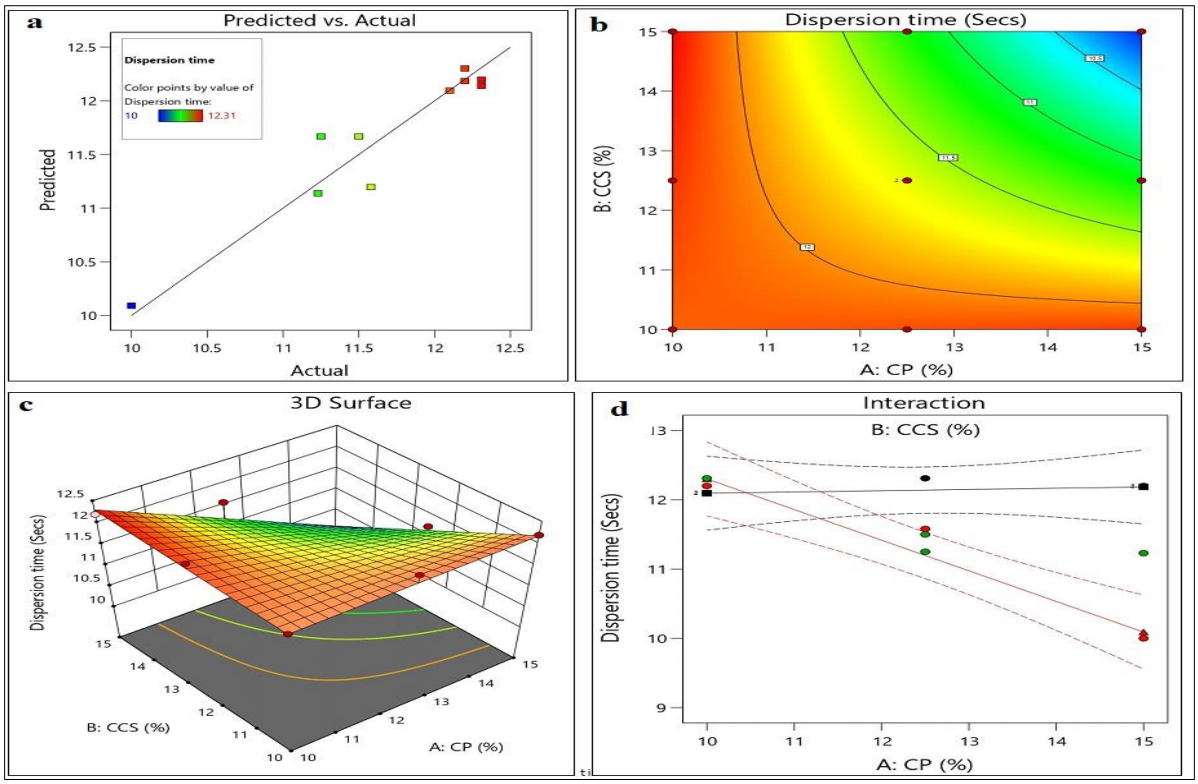

Figure 2 Graphical representation of factors influencing on response dispersion time a) predicted vs actual b) contour c) 3D surface d) interaction

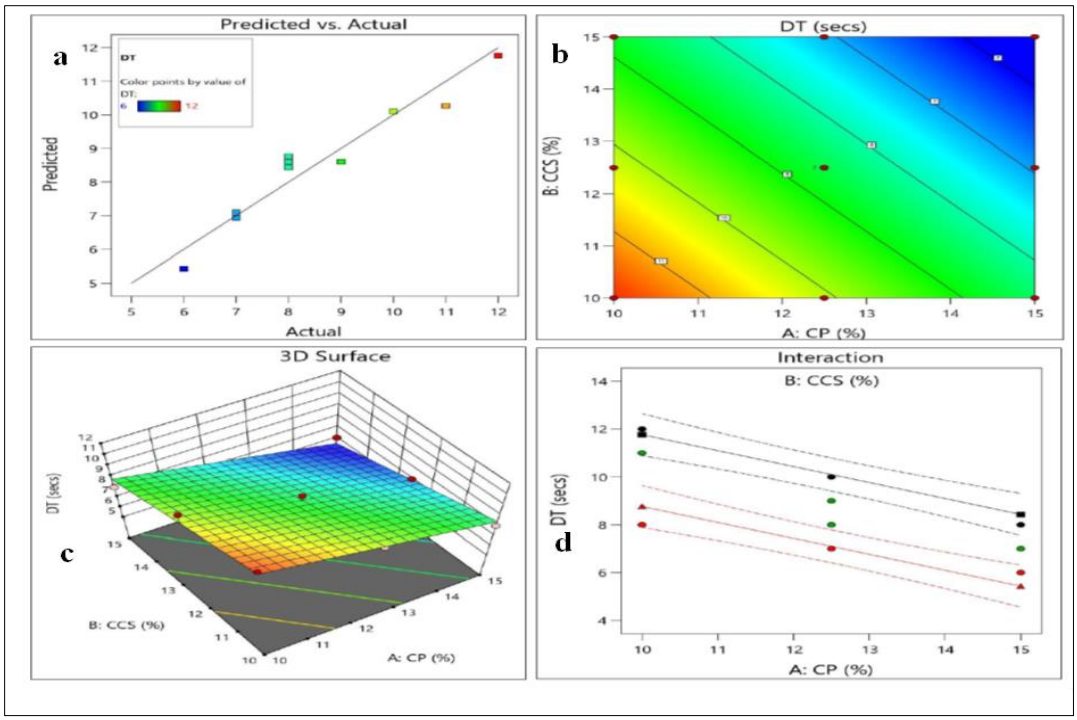

Figure 3 Graphical representation of factors influencing on response DT a) predicted vs actual b) contour c) 3D surface d) interaction

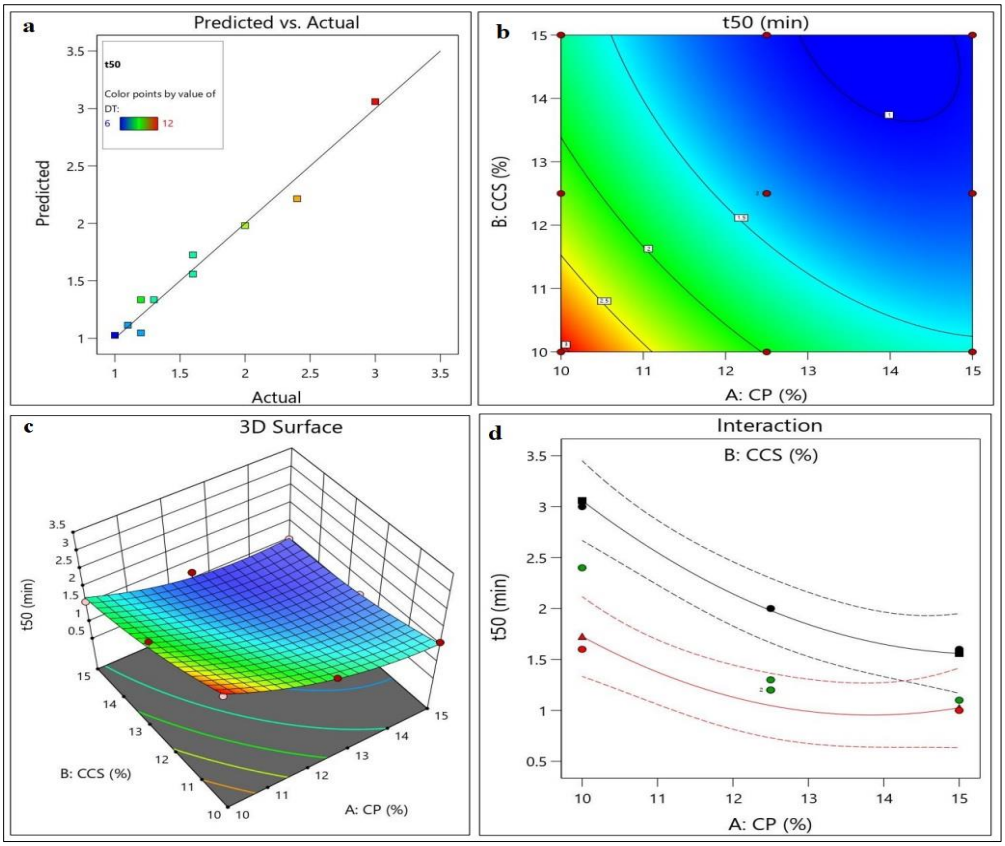

Figure 4 Graphical representation of factors influencing on response t50 a) predicted vs actual b) contour c) 3D surface d) interaction

3.4 Model justification

The normal probability plot of residuals showed for all test that residuals fell approximately along a straight line as shown in figure 5 indicating that the CQAs data were normally distributed. To statistically analyze the CQAs wetting time, dispersion time, DT and t50 a quadratic model, 2FI. Linear and quadratic model were used respectively. The ANOVA F test indicated a high degree of significance ($p < 0.01$) for all chosen models.

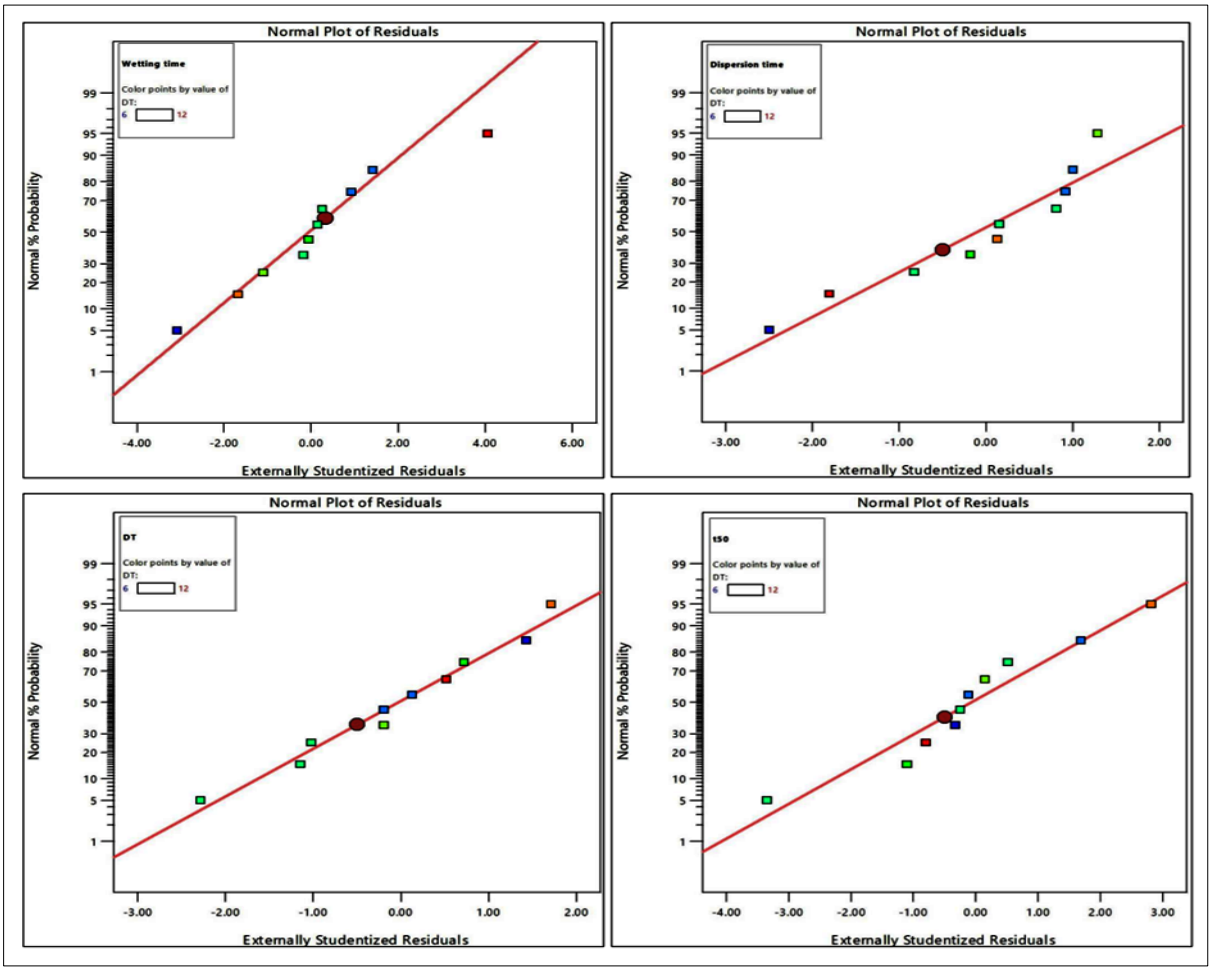

Figure 5 Normal probability plot of residuals for all CQAs

3.5 Design space

To calculate the design space the criteria of the CQAs were set to either a minimum or maximum or range. The CQAs were set maximize for wetting time, minimize for dispersion time, minimize for DT and in range for t50. Fix the CFPs in minimize the X_1 (CP) and maximize X_2 (CCS). Based on this, Design Expert 13 suggested nine formulation to be tested as shown in table 4. Among them formulation 1 is selected for validation based on two sided conformation at 95% CI as possible solution with high degree of desirability supported with overlay plot as shown in figure 6.

Table 4 Design space with CQAs set at the preferred values

Number	CP	CCS	Wetting time	Dispersion time	DT	t50	Desirability
1	10.563	15.000	10.852	11.793	8.391	1.516	0.491
2	10.543	15.000	10.866	11.798	8.404	1.523	0.491
3	10.532	15.000	10.874	11.802	8.412	1.527	0.491
4	10.598	15.000	10.828	11.783	8.368	1.504	0.491
5	10.504	15.000	10.894	11.809	8.431	1.537	0.491

6	10.655	15.000	10.790	11.768	8.330	1.485	0.491
7	10.733	15.000	10.738	11.746	8.278	1.459	0.490
8	10.904	15.000	10.628	11.699	8.164	1.405	0.488
9	14.763	15.000	9.694	10.637	5.592	1.000	0.270

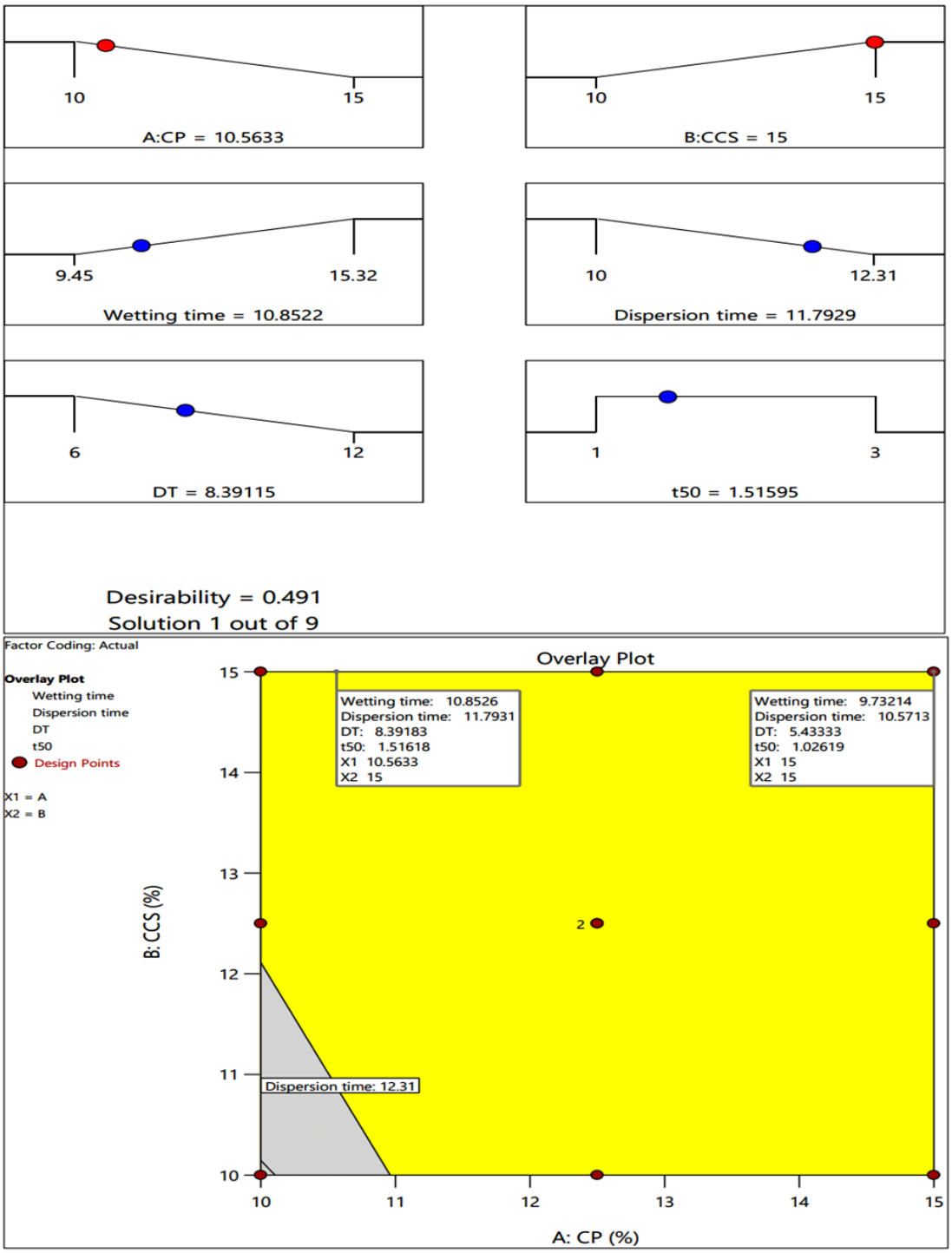

Figure 6 Degree of desirability supported with overlay plot

Table 5 Formula of ES-OP-ODTs as per CCD along with validation design space

ES-OP-ODTs		CQAs	Two sided 95% CI Predicted CQAs Mean ± SD	Experimental CQAs
Ingredients	**Amount mg**			
ES	10	Wetting time Sec	10.8522±0.359993	11
CP	17	Dispersion time Sec	11.7929±0.402018	12
CCS	24	DT Sec	8.39115±0.564843	9
MCC	48	t50 Min	1.51595±0.157926	1.9
Mannitol	32			
Lactose	29			
Total weight	160			

3.6 Validation of design space

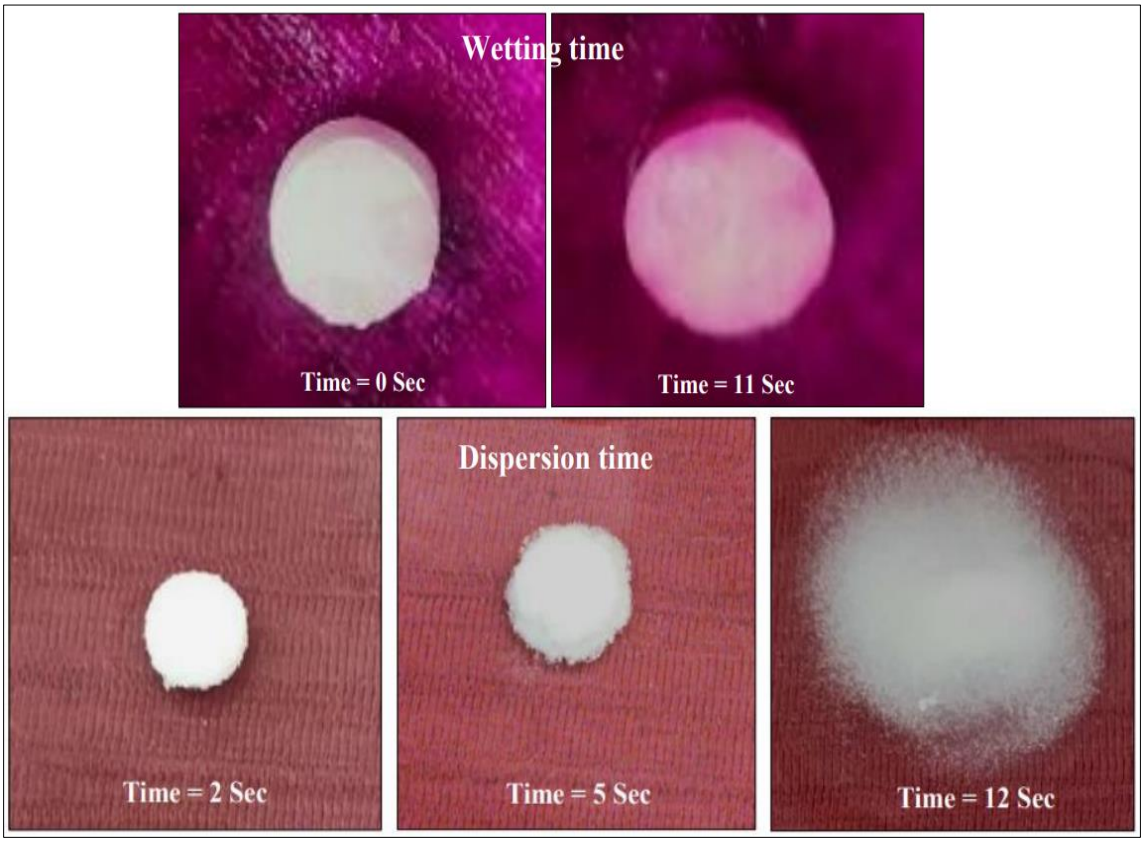

Figure 7 Wetting time and dispersion time of OP-ES-ODTs

The OP-ES-ODTs generated as per CCD was formulated experimentally by direct compression method. The formulated OP-ES-ODTs was evaluated for drug-excipient interaction, drug content, precompression, postcompression, *in vitro* drug release and CPQs. The relevant data and profiles were given in table 5 and figures 7, 8. The FTIR study confirms all the characteristic bands of ES appeared in OP-ES-ODTs indicates no interaction between SIT and added polymers (figure 9). The precompression data such as bulk density 0.6824 ± 0.02228 g/cm^3; tapped density 0.5231 ± 0.0123 g/cm^3; compressibility index value 15.1 ± 0.212; Hauser's value 1.88 ± 0.12; angle of repose 23^{0}23'for OP-ES-ODTs indicates good compressibility and flowability and can be used for direct compression. The drug content was found to be 98.96 ± 1.001 % with low SD values indicate the drug is uniformly distributed within the OP-ES-ODTs. The postcompression data was found to be 3.09 ± 0.01123 mm thickness; 8.02 ± 0.000132 mm diameter; 2.65 Kg/cm^2 hardness; 161.9 ± 1.1232 mg weight variation; 0.72 % friability suggest the OP-ES=ODTs have desired mechanical strength, tablet integrity and uniform weight throughout the batches prepared. The experimental results of CQAs were validate and ratified with

predicted CQAs data as shown in table 5 and figure 7, 8. The results clearly indicates the DoE studies can be used to study the influence of two factor on all CQAs. Validation of the predicted values of responses was performed by comparing with the experimental data, which indicated high degree closeness between the predicted and experimental values of the CQAs and confirmed excellent prognostic ability of the employed mathematical model. *In vitro* drug release of OP-ES-ODTs was conducted in phosphate buffer pH 6.8 to simulate salivary pH. The complete drug release was observed within 15 minutes and CQAs (t50) was found to be 1.9 min. The best fit model was found to be Hixan crowel with R value of 0.9989 and mechanism of drug release follows first order with R value of 0.9989.

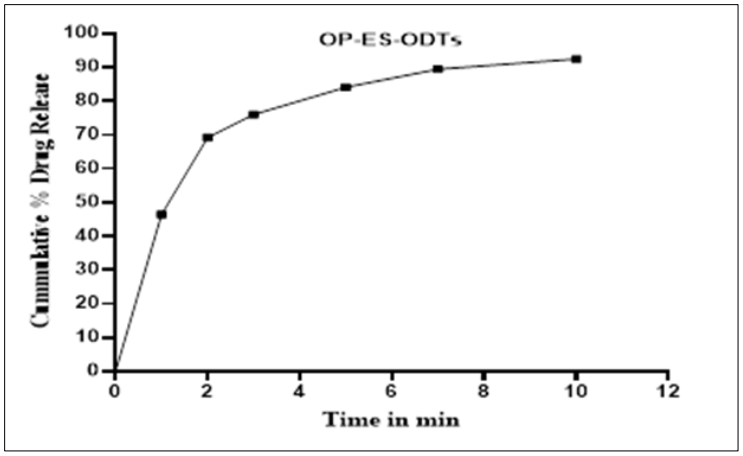

Figure 8 *In vitro* dissolution profile of OP-ES-ODTs

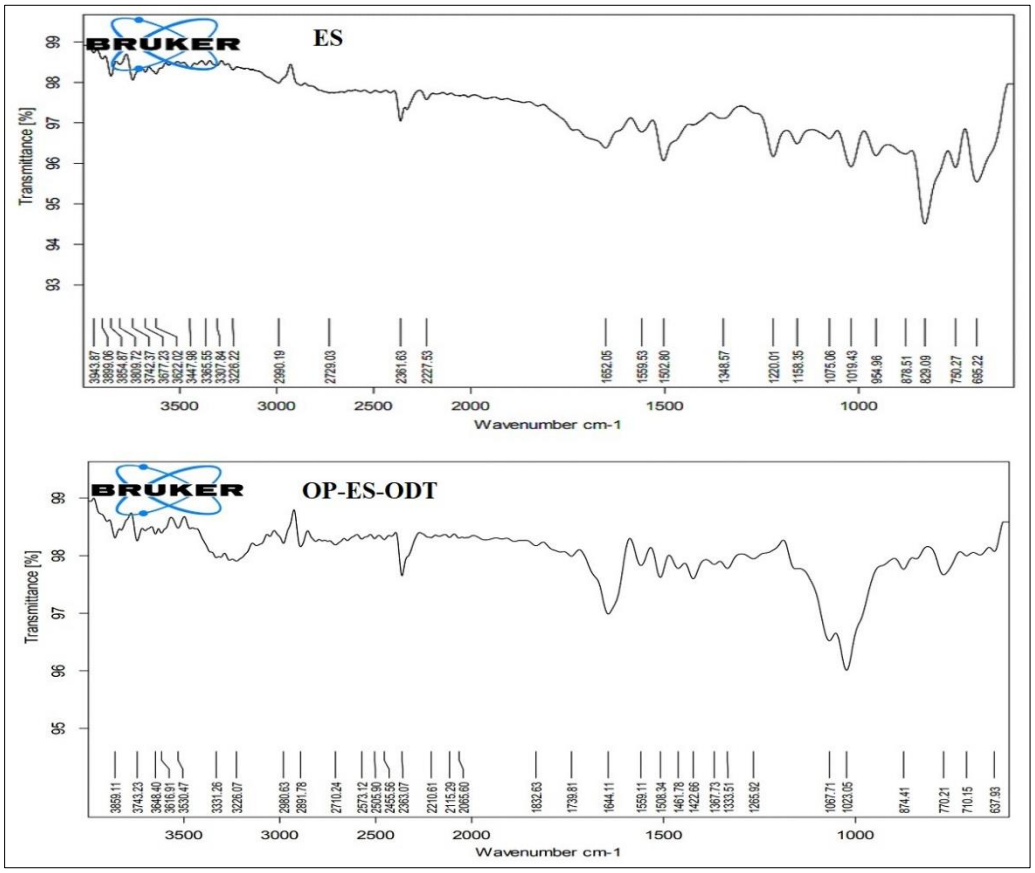

Figure 9 Comparative FTIR spectra of ES and OP-ES-ODT

4 Conclusion

The CCD model helps to visualize the different effects of the CFPs on the CQAs. The main factor influencing wetting time, dispersion time, Disintegration time and t50. Median percentage Crospovidone and high percentage of Croscaramellose maximize the wetting time, minimizes the dispersion time and DT and desired drug release and the results were validated and ratified within the design space. To the best of our knowledge this is the first study in which QbD is applied to experimental optimized ODTs. QbD appears to be a useful approach for the rational design of ES-ODTs

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

There are no conflicts of interest.

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