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Pharmaceutical Sciences **Research Article……!!!**

FORMULATION AND OPTIMIZATION OF MOUTH DISSOLVING TABLET OF DULOXETINE HCl

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KEYWORDS:

Duloxetine Hcl, Solvent evaporation, fast dissolving tablet, In vitro dissolution studies.

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ABSTRACT

In present study, Mouth dissolving tablets of Duloxetine Hydrochloride was prepared using direct compression method. The main objective of the study is prepared the tablet by co process superdisintegrant technique for rapid release of the drug to overcome the symptoms of depression. Central composite design was used to optimized the tablets .Sodium starch glycolate (X_1) and crosspovidone (X_2) were selected as independent variables. The Disintegrating time, Friability and Hardness were selected as dependent variable. The Prepared tablets were evaluated for Hardness, disintegration time, friability, Weight Variation, drug content, wetting time, in vitro drug release. Drug-excipient interaction was investigated by FTIR Study. from results obtained it can be concluded that F6 formulation showed a maximum of 95% in vitro drug release with disintegration time of 15 seconds.

1. INTRODUCTION:

The oral route of drug administration is the most important method of administration of drug for systemic effect. Its ease of administration, pain avoidance and various advantages over other routes is the reason that the oral route achieved such recognition. But the most evident drawback of oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patient's incompliance particularly in case of pediatric and geriatric, bedridden, nauseous patients. An improved interest has been addressed to oral solid dosage forms designed for quick availability of therapeutic dose.[1] Mouth dissolve products (tablets and films) may show greater patient acceptability and convenience. Mouth dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking of water or chewing .[2] After disintegrating in mouth, enhanced the clinical effect of drug through pre-gastric absorption from mouth pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is considerably greater than those observed from conventional tablet dosage form.[3]In today scenario MDT_S are more preferred for patients suffering from disease like anta acids ;muscle relaxants ;hypertension; depression; nausea and vomiting(generally occur in patients who are following chemotherapy ,radiation therapy and surgery); heart attack etc. During the past decades the FDT technology makes tablet dissolve or disintegrate in mouth without the need of water has drawn great deal of attention. The tablet disintegrate in to the smaller granules or melt in the mouth from hard solid structure to a gel like structure allowing by pateints .The disintegration time varies from the few seconds to more than a minute[4]. MDT_s are not only formulated for pateints who have the swallowing problem, but also are ideal for active people. Mouth dissolving tablet are those when put on the tongue disintegrate instantaneously releasing the drug which dissolve or disperse in the saliva. The Faster the drug into the solution, quicker the absorption and onset of clinical effect [5]. It has been reported that difficulty in swallowing is common among all age group and more specific with paediatric ,geriatric population along with institutionalized pateints and patient with the nausea ,vomiting, motion sickness[6].

1.2 Salient features of mouth dissolving tablet

- Ease of Administration to the patient who cannot swallow, such as the elderly, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- Rapid dissolution and absorption of the drug, which will produce the quick onset of action.

- Good mouth feel property helps to change the perception of medication as a bitter pill, particularly in the pediatric patient.
- Beneficial in cases such as the motion sickness and sudden allergic attack where an ultra-rapid onset of action required.
- No need of water to swallow the dosage form, which is the highly convenient feature for patients who are traveling and do not have immediate access to water[7][8][9].

2. MATERIAL AND METHODS:

2.1 MATERIALS

Duloxetine was obtained as gift sample from (Concern pharma, Ludhiana) Micro crystalline cellulose & sodium starch glycolate and crosspovidone (DFE Pharma, Bangalore), magnesium stearate, spray dried lactose and talc (S D Fine Limited, Mumbai).

2.2 METHODS

2.2.1. OPTIMIZED CONCENTRATION OF SUPERDISINTEGRANT FOR MOUTH DISSOLVING FORMULATION

The 3^2 factorial designs was used for the optimization of mouth dissolving tablets of Duloxetine hydrochloride (Design Expert8.0.7.1). The two independent factors, concentration of Sodium Starch Glycolate (X1) and concentration of Crosspovidone (X2) were set to three different levels and experimental trials were performed for all thirteen possible combinations. The dependent responses measured were disintegration time, friability, and Hardness. The experimental design with corresponding formulation was given in Table1.

Table 1: Optimized Concentration of Superdisintegrant

Factors	Levels		
	(-1) Low	(0) Medium	(1) High
Sodium Starch glycolate	2	3.5	5
Crosspovidone (w/w)	2	3.5	5

Formulation code	X_1	X_2
AF1	2	5
AF2	3.5	3.5
AF3	3.5	3.5
AF4	5.6	3.5
AF5	3.5	5.6
AF6	3.5	3.5
AF7	1.37	3.5
AF8	5	2
AF9	3.5	3.5
AF10	3.5	1.37
AF11	2	2
AF12	5	5
AF13	3.5	3.5

2.2.2 Preparation of co processed super disintegrant by solvent evaporation

Sodium starch glycolate and crosspovidone was used as the super disintegrants. It helps in improving the disintegration and dissolution rate of the tablet. Co processed super disintegrant was prepared by using the following steps mentioned below:

Step: 1 A Blend of Sodium starch Glycolate and crosspovidone mixed in different ratio**.**

Step: 2 The 10 ml of ethanol was added in the mixture in 250 ml capacity beaker.

Step: 3 Then the mixture was stirred continuously till most of ethanol evaporated.

Step: 4 After this the wet mass was granulated through the #44 mess sieve.

Step: 5 The granules were dried in the hot air oven at 60^{o}C for 20 minutes.

Step: 6 The dried Granules were stored in the air tight container for further use.

2.2.3. Preparation of mouth dissolving tablets:

Mouth dissolving tablets of Duloxetine were prepared by direct compression method, using sodium starch Glycolate and crosspovidone as the co processed super disintegrants, and microcrystalline cellulose, Lactose, Talc and Magnesium Stearate. All the ingredients were weighed and kept separately. Then the weighed ingredients were mixed in geometrical order with weigh Duloxetine Hcl and blend together to get uniform mixture. Then tablets were compressed by using Compression machine. The formulation of tablets was given in Table2.

TABLE 2: Formulation of Mouth Dissolving Tablet

FC	F1	F2	F3	F4	F5	F6	F7
Drug(Duloxetine)	20	20	20	20	20	20	20
SSG	3	5.25	5.25	8.45	5.25	5.25	1.95
CSP	7.5	5.25	5.25	5.25	8.45	5.25	5.25
MCC	56.75	56.75	56.75	55.15	55.15	56.75	58.40
Spray Dried Lactose	56.75	56.75	56.75	55.15	55.75	56.75	58.40
Talc	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3
Total weight	150	150	150	150	150	150	150

F8	F9	F10	F11	F12	F13
20	20	20	20	20	20
7.5	5.25	5.25	3	7.5	5.25
3	5.25	1.95	3	7.5	5.25
56.75	56.75	56.75	59	54.50	56.75
56.75	56.75	56.75	59	54.50	56.75
3	3	3	3	3	3
3	3	3	3	3	3
150	150	150	150	150	150

3. EVALUATION OF POWDER BLEND

a. Determination of Angle of Repose:

The flow property was determined by angle of repose which is maximum angle that can be attained between the free surfaces of powder heap with its horizontal plan. The formula for calculating angle of repose was:

$$\Theta = \tan h/r$$

Values of θ less than 25^{o}C indicate Excellent flow property to the powder and value between 30-40^{o}C indicates Poor flow. Table 3 shows the angle of repose and type of flow.

Table3.Angle of repose and type of flow

S.No	Angle of Repose (Θ)	Type of flow
1.	<25	Excellent
2.	25-30	Good
3.	30-40	Poor
4.	>40	Very Poor

b. Bulk Density:

Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of the powder (M) was determined. The bulk density was calculated using the formula:

$$\rho b = M/Vb$$

c. Tapped Density

The measuring cylinder containing known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and weight (M) of the blend was measured. The tapped density (ρt) was calculated using the formula:

$$\rho t = M/ Vt$$

d. Compressibility Index:

The simplest way for measurement of flow of powder is its compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I) which is calculated as follow:

$$I = \rho t - \rho b / \rho t \times 100$$

e. Hausner's Ratio (%):

Hausner's ratio indicates the flow property of mixed powders. This ratio can be measured by the following equation.[10] The range of Hausner ratio was given in Table 4.

Hausner's ration = **ρ tapped /ρbulk**

Table 4: Range of Hausner ratio

S.NO	Hausner's Ratio	Property
1.	0-1.25	Free flowing
2.	1.25-1.6	Cohesive powder

4. EVALUATION OF MOUTH DISSOLVING TABLET

1. General Appearance:

The general appearance of a tablet, its visual identification and over all 'elegance' is essential for consumer acceptance. Therefore tablets were evaluated for its organoleptic properties.

2. Weight variation test:

I.P. procedure for weight Variation was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. [11].The % weight variation of each individual tablet from the average weight is calculated by the given formula

$$\% \text{ Weight variation} = \frac{\text{Average weight of 20 tablets - Individual weight of each tablet}}{\text{Average weight of 20 tablet}} / 100$$

3. Thickness:

The thickness was measured by placing tablet between two arms of the Vanier callipers. Five tablets were taken and their thickness was measured.

4. Hardness:

The limit of hardness for the FDT is usually kept in a lower range to facilitate early disintegration in the mouth. The hardness of the tablet was measured by Monsanto tablet hardness tester. It is expressed in kg or pound [12].

5. Friability:

Friability is to measure the extent of tablet breakage during physical stress conditions like Packing, transportation etc. A sample of randomly selected 6 tablets was evaluated for friability using Roche friabilator at 25 rpm for 4 minutes. The % weight loss is calculated by measuring the total weight of 6 tablets before and after the operation [13].

A formula for calculating the % weight loss is given below:

$$F=(1-Wi/Wf)*100$$

Where, W_i is the weight of the tablets before the test and W_f is the weight of the tablet after the test.

6. Disintegration test:

The test was carried out on six tablets using digital tablet disintegration test apparatus (Micro process based-Electro lab).Phosphate buffer at 37^{o}C ± 2^{o}C was used as a disintegration media and time for complete disintegration of each table were calculated. **.**

7. Wetting Time

The wetting time of the tablets was measured using a very simple process. Five circular tissue papers of 10cm diameter were placed in a Petri dish with a 10cm diameter. Ten millilitres of water containing a water soluble dye (crystal violet) was added to the Petri dish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablet was noted as the wetting time.

8. In vitro Dissolution studies:

Randomly selected 6 tablets were subjected to drug release studies using the beaker, in dissolution medium volume of 100 ml was used and a temperature of 37±0.5^{o}C was maintained. 1 ml of the sample was collected for every 1 minutes interval till 8 minutes and replaced with 1 ml of fresh buffer solution. [14]

9**. Drug content**:

Ten tablets were powdered and blend equivalent to 20 mg of Duloxetine hydrochloride was weighed and dissolved in suitable quantity of phosphate buffer pH 6.8. The solution was filtered through 0.45 mm membrane filter and drug content was analysed using UV Spectrophotometer (UV- 1700 PharmaspecShimadzu) at 243 nm. [15].

5. RESULT AND DISCUSSION

Table5. Pre-Compression Parameter of Duloxetine Mouth Dissolving Tablets

Formulation code	Angle of Repose	Bulk density	Tapped density	Compressibility Index	Hausner Ratio

F1	26.25±0.89	0.515±0.007	0.610±0.008	15.58±0.005	1.20±0.550
F2	25.96±0.44	0.523±0.009	0.615±0.009	14.95±0.008	1.14±0.655
F3	26.35±0.89	0.518±0.006	0.612±0.006	15.35±0.009	1.16±0.390
F4	26.35±1.78	0.517±0.005	0.613±0.004	15.68±0.006	1.19±0.795
F5	27.15±1.34	0.548±0.10	0.617±0.010	14.93±0.007	1.195±0.780
F6	25.15±0.65	0.522±0.008	0.611±0.006	14.58±0.004	1.12±0.530
F7	29.55±0.50	0.545±0.012	0.618±0.011	11.81±0.010	1.24±0.850
F8	28.25±0.75	0.535±0.011	0.614±0.005	12.95±0.0012	1.21±0.950
F9	25.20±0.35	0.516±0.004	0.619±0.003	15.36±0.011	1.14±1.20
F10	26.25±0.89	0.519±0.015	0.616±0.012	15.65±0.014	1.17±1.30
F11	29.75±0.15	0.521±0.014	0.620±0.014	15.55±0.015	1.24±1.50
F12	28.30±0.75	0.529±0.013	0.622±0.010	14.95±0.017	1.20±0.450
F13	26.10±0.35	0.533±0.005	0.620±0.011	14.30±0.004	1.15±0.350

*All the readings were in triplicate (n=3)

The values of angle of repose for all the formulations was found between 25.15°±0.65 to 29.75°±0.15.The bulk density and tapped density of blend for all the formulations were determined and used to calculate Carr's index and Hausner's ratio. The values for both the parameters were found in range indicating the optimum flow properties of the formulation blend. The results of Precompression parameter were recorded in Table 5**.** On the basis of these parameters, tablets were compressed and characterized for weight variation, thickness, hardness, friability and disintegration time. The weight of tablets was found between 146.34±0.602 to 152.13±0.620 mg. The percentage deviation for all the tablet formulations was found to be within the specified limits and hence all the formulations complied with the test for weight variation. The tablets from all batches showed acceptable thickness values in range 2.43±0.384 to 2.90±0.066 mm. The hardness of the tablets were found to be ranging between 3.06±0.230 to 3.29±0.130 kg/cm^2. The friability of all the formulations was evaluated using Roche friabilator. It was observed in range (0.330±0.025 to 0.710±0.020) indicating that the friability was within the prescribed limits. The tablets showed variation in the values of disintegration time due to different concentration of superdisintegrant in the formulations ranging from 15±0.178 to 72±0.176 seconds. The wetting time of tablet is ranges from 35±3.45 to 83±3.51.The all observation were given Table 6.

Table 6.Observation of Evaluation Parameters of mouth dissolving Tablets

Parameter	F1	F2	F3	F4	F5	F6	F7
Weight Variation	147.4± 1.78	148.56± 0.89	152.13± 0.60	150.93± 0.38	147.34± 0.67	149.33± 0.53	148.4± 0.731
Thickness	2.60± 0.121	2.53± 0.022	2.76± 0.089	2.86± 0.061	2.90± 0.066	2.67± 0.295	2.60± 0.357
Hardness	3.25± 0.156	3.21± 0.090	3.21± 0.200	3.14± 0.250	3.13± 0.150	3.21± 0.300	3.29± 0.130
Friability	0.653± 0.050	0.645± 0.065	0.630± 0.69	0.390± 0.040	0.370± 0.032	0.634± 0.070	0.705± 0.075
Disintegration time (sec)	36± 1.78	16± 0.047	18± 0.626	22± 0.636	26± 0.536	15± 0.178	70± 0.646
Wetting time	61±6.02	83±3.51	40±3.55	68±2.55	78±3.76	58±4.77	77±5.72

*All the readings were in triplicate (n=3)

F8	F9	F10	F11	F12	F13
149.56±0.264	151.33±0.502	150.33±1.45	146.34±0.620	148.56±0.740	149.66±0.250
2.60± 0.447	2.43± 0.384	2.67± 0.536	2.56± 0.393	2.89± 0.268	2.76± 0.232
3.26± 0.100	3.21± 0.170	3.29± 0.190	3.28± 0.220	3.06± 0.230	3.21± 0.100
0.654± 0.082	0.644± 0.030	0.706± 0.035	0.710± 0.020	0.330± 0.025	0.658± 0.038
40± 0.804	16± 0.616	22± 0.185	72± 1.76	36± 0.620	17± 0.656
36±6.45	66±2.22	74±3.51	59±3.80	35±3.45	63±4.80

*All the readings were in triplicate (n=3)

Table7. In vitro Release of the drug (F1 to F6)

Time	In Vitro Drug Release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	54.33	67.33	67.55	60.45	58.45	68.45
2	61.88	72.55	73.66	68.45	64.33	74.52

3	67.33	78.66	79.56	74.18	70.22	80.40
4	73.44	85.55	82.78	78.45	74.42	87.66
5	77.76	88.15	85.45	80.42	77.26	90.47
6	81.12	90.12	87.15	82.14	80.14	92.15
7	82.14	92.16	90.15	86.15	84.15	93.88
8	82.19	93.15	91.45	88.15	86.36	95.88

In vitro Release of drug (F7 to F13)

Time	In Vitro Drug Release						
	F7	F8	F9	F10	F11	F12	F13
0	0	0	0	0	0	0	0
1	50.55	53.25	67.35	60.45	49.66	54.33	66.35
2	58.63	59.69	71.55	68.45	57.45	61.88	70.55
3	65.45	64.55	77.66	74.18	64.23	67.33	75.45
4	70.85	73.45	84.55	77.56	69.36	73.44	78.25
5	72.78	75.45	85.45	79.25	70.22	74.44	80.35
6	75.12	80.85	87.89	82.36	72.22	77.24	82.39
7	78.45	81.45	90.65	84.16	74.55	81.77	86.88
8	79.23	83.65	94.23	86.22	76.22	85.36	92.96

In vitro drug release of Duloxetine HCl tablet was determined in phosphate buffer pH 6.8. At a predetermined interval of 1 minutes, 1 ml of samples were withdrawn, filtered through what man filter paper and absorbance of solution was checked by UV spectrophotometer at 243 nm. The percentage drug released was determined from standard curve and observations are recorded in Table 7.

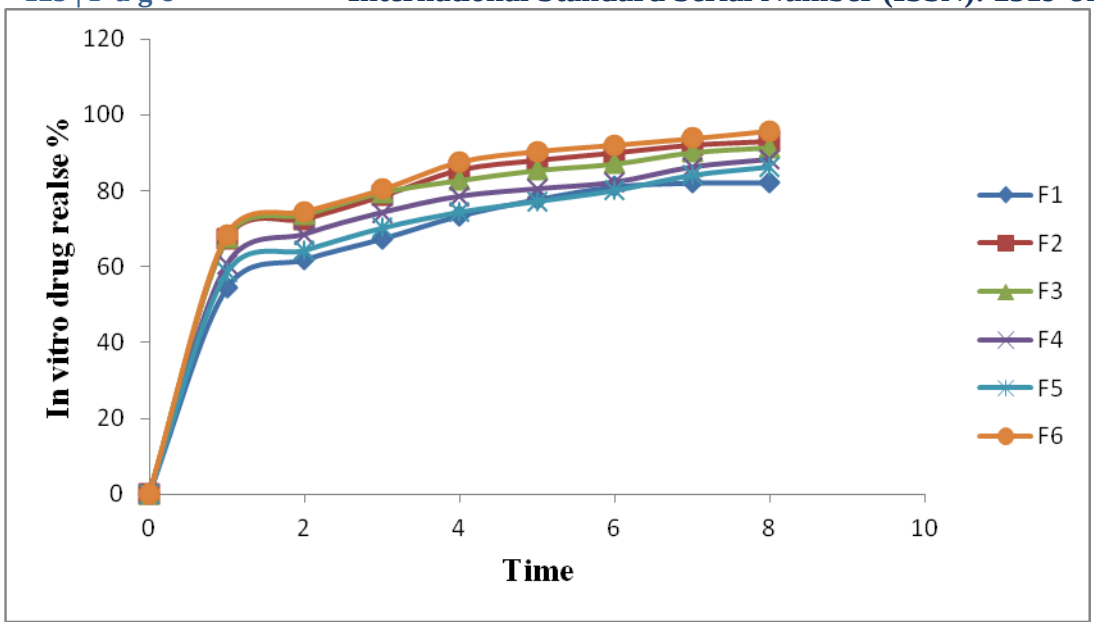

Figure 1: % In vitro drug release (F1 to F6)

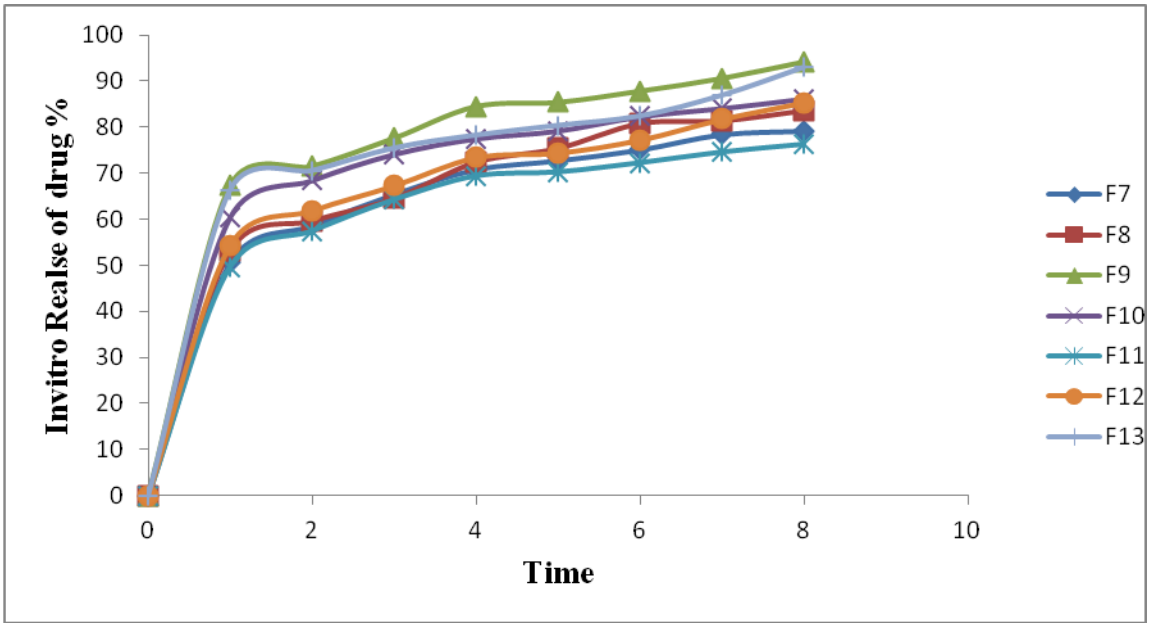

Figure 2: %In vitro Drug release (F7 to F13)

Table 8. %Drug content of duloxetine

Formulation	Drug content
F1	80
F2	94
F3	92
F4	88
F5	86
F6	96
F7	75
F8	79
F9	94
F10	88
F11	74
F12	80
F13	95

Drug content of all the formulation was determined spectrophotometrically and all the formulations were found to have more than 96% of drug content shown in table 8.

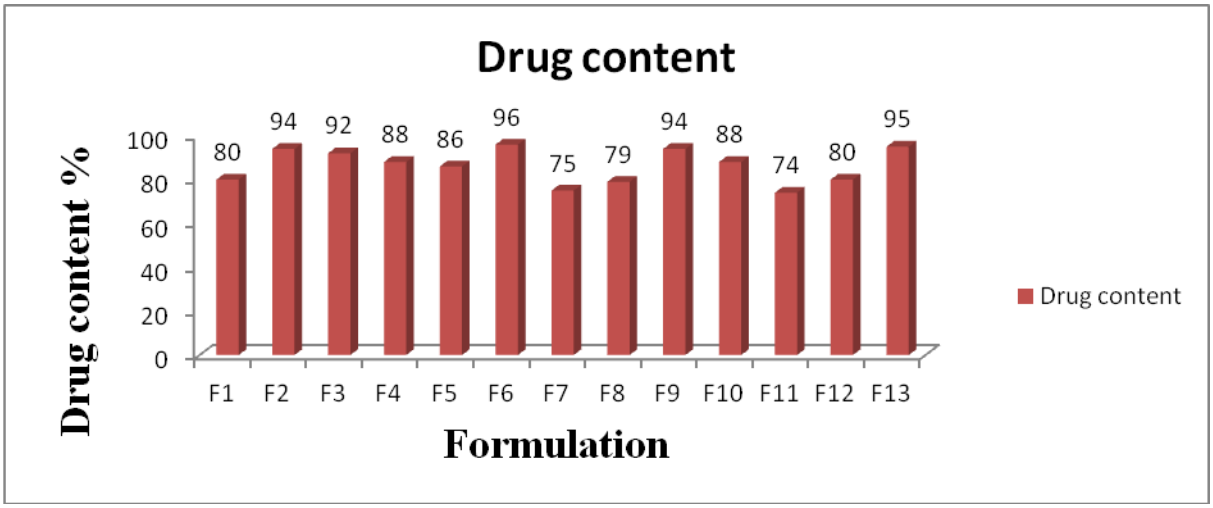

Figure 3: % of Drug content Release

6. OPTIMIZATION OF DEPENDENT VARIABLE

Each formulation (AF1-AF13) showed distinct Disintegration time, fraibility, hardness as given in Table 9**.**

Table 9.Optimization of Depended variable

Factors	Levels		
	(-1) Low	(0) Medium	(1) High
Sodium Starch Glycolate (w/w)	2	3.5	5
Crosspovidone (w/w)	2	3.5	5

Formulation code	X_1	X_2	Disintegration time	Friability	Hardness
AF1	2	5	36	0.653	3.25
AF2	3.5	3.5	16	0.645	3.21
AF3	3.5	3.5	18	0.630	3.21
AF4	5.6	3.5	22	0.390	3.14
AF5	3.5	5.6	26	0.370	3.13
AF6	3.5	3.5	15	0.634	3.21
AF7	1.37	3.5	70	0.705	3.29
AF8	5	2	40	0.654	3.26
AF9	3.5	3.5	16	0.644	3.21
AF10	3.5	1.37	22	0.706	3.29
AF11	2	2	72	0.710	3.28
AF12	5	5	36	0.330	3.06
AF13	3.5	3.5	17	0.658	3.21

6.1. Response Disintegration time

$Y1=+35.00 +5.15A -0.4268B -0.5000AB -6.75 A^2 -13.25 B^2$

(R^2 Value =0.9998)

After ANOVA estimation, the quadratic model of F-value is 9962.97 implies the model is significant p-value <0.0001. The 2D contour plot and 3D surface response plot in figure 4 and 5 showed the effect of different independent variables on Disintegration time**.** The Disintegration

time of the optimized mouth dissolving tablet was increases as the amount of superdisintegrant is increases.

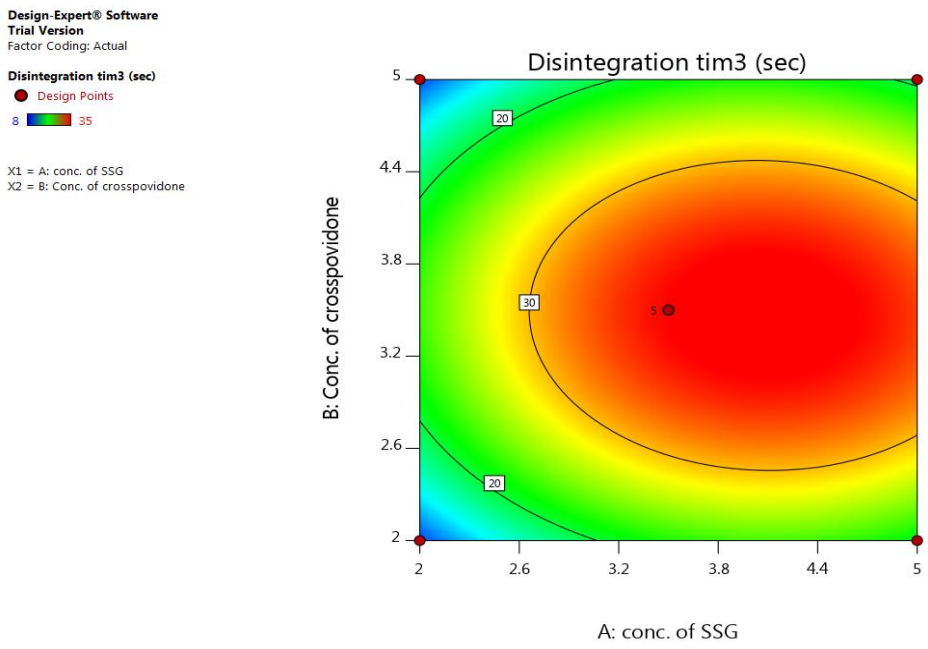

Figure 4: 2D Contour Plot Showing Effect of Superdisintegrants Concentration

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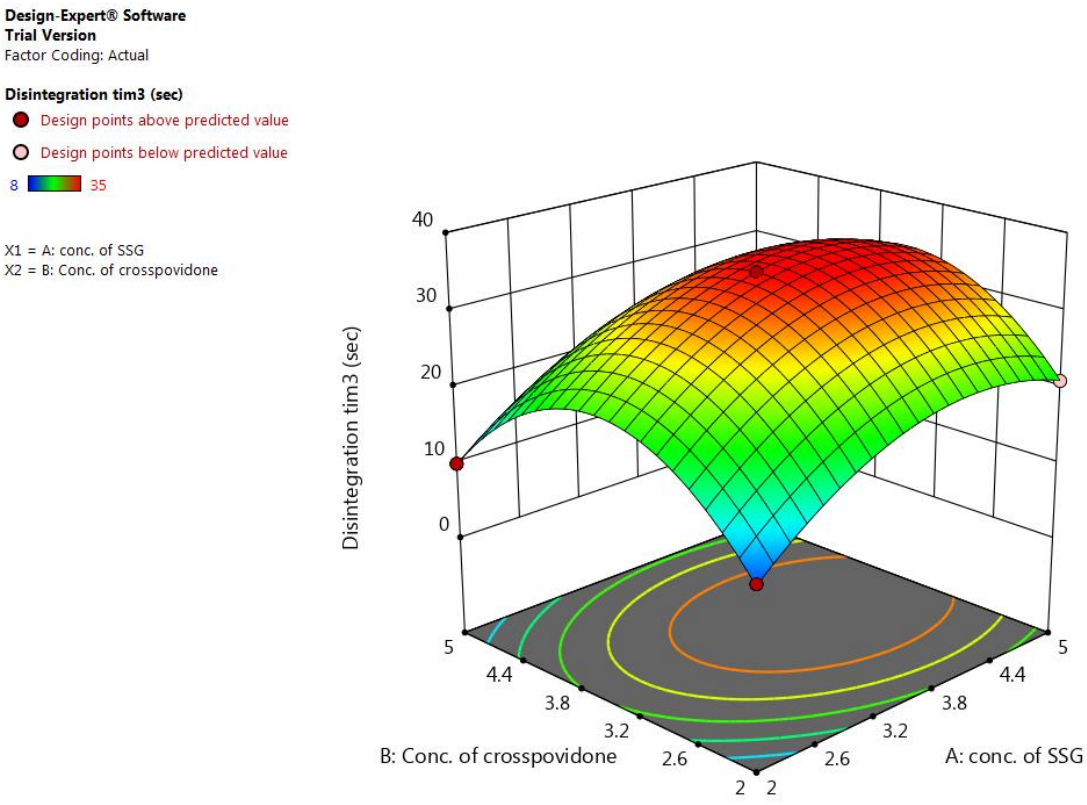

Figure 5: 3D Surface Response Plot Analysis

Table 10: ANOVA for Response Surface Quadratic Model

S.No	Source	Sum of squares	Df	Mean square	F value	p-value
1	**Model**	1614.54	5	322.91	9962.97	<0.0001
2	**Conc. Of SSG**	212.32	1	212.32	6550.77	<0.0001
3	**Conc. Of Crosspovidone**	1.46	1	1.46	44.96	0.0003
4	**AB**	1.0000	1	1.0000	30.85	0.0009
5	**A^2**	316.96	1	316.96	9779.33	<0.0001
6	**B^2**	1221.30	1	1221.30	37681.94	<0.0001
7	**Residual** Lack of fit Pure error	0.2269 0.2269 0.0000	7 3 4	0.0324 0.0756 0.0000		
8	**Core Total**	1614.77	12			

Table 10 shows the results of the analysis of variance (ANOVA), which was used to generate mathematical models. The high values of correlation factor for Disintegration time indicate a good fit i.e. good agreement between the dependent and independent variables.

6.1.1. Experimental value (Actual value v/s Predicted value) for Disintegration time

Table 11: Comparison Between Actual and Predicted Value

S.No.	Conc. of SSG	Conc. of crosspovidone	Disintegration Time		
			Actual value	Predicted value	Residual
1	2	5	10.00	9.92	0.0784
2	3.5	3.5	35.00	35.00	0.0000
3	3.5	3.5	35.00	35.00	0.0000
4	5.6	3.5	29.00	28.79	0.2145
5	3.5	5.6	8.00	7.90	0.1036
6	3.5	3.5	35.00	35.00	0.0000
7	1.37	3.5	14.00	14.21	-0.2145
8	5	2	21.00	21.08	-0.0784
9	3.5	3.5	35.00	35.00	0.0000
10	3.5	1.37	9.00	9.10	-0.1036
11	2	2	10.00	9.78	0.2249
12	5	5	19.00	19.22	-0.2249
13	3.5	3.5	35.00	35.00	0.0000

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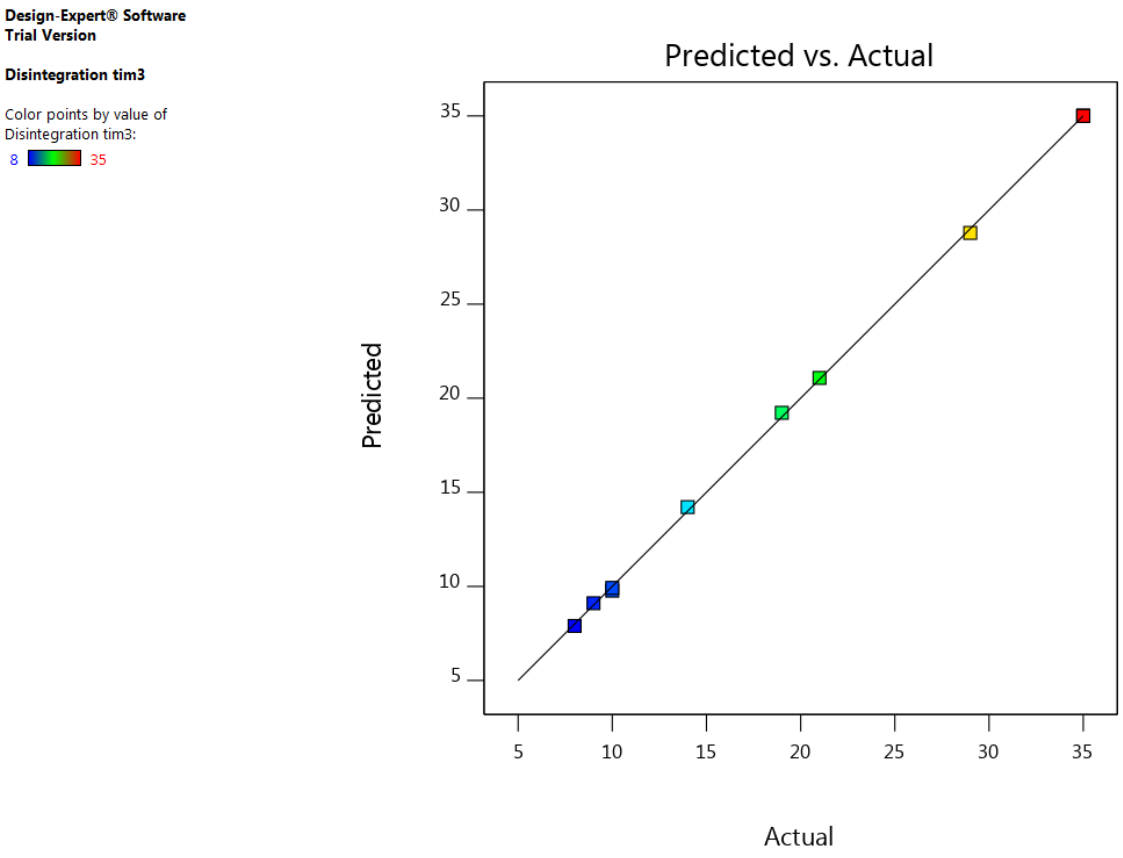

Figure 6: comparison of actual value and predicted value of Response 1

6.2. Response 2: Friability

$Y1=+0.6530 +0.0039 A -0.0101 B +0.0225 AB +0.0003 A^2 +0.0003 B^2$

(R^2 Value =0.9999

After ANOVA estimation, the quadratic model of F-value is 27240.84 implies the model is significant p-value <0.0001. The 2D contour plot and 3D surface response plot in figure 7 and Figure 8 showed the effect of different independent variables on Friability. The friability of optimized mouth dissolving tablet was decreases as the concentration of super disintegrant was increases.

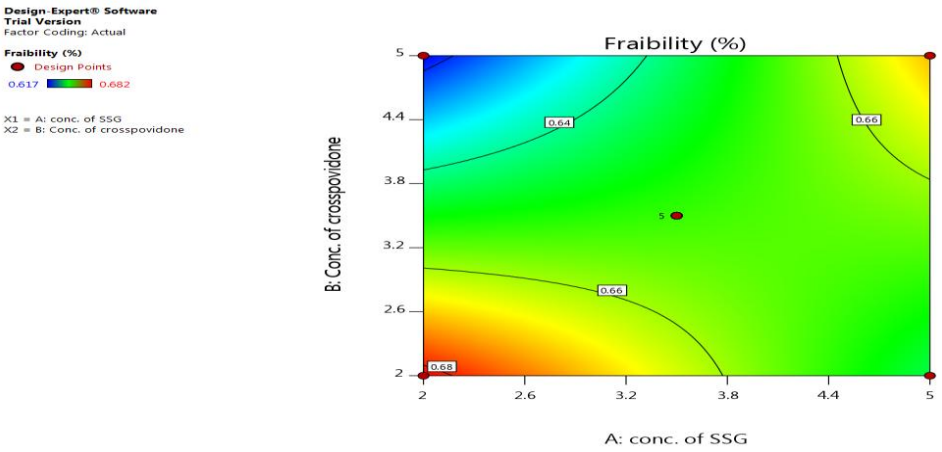

Figure 7: 2D Contour Plot Showing Effect of Superdisintegrants Concentration

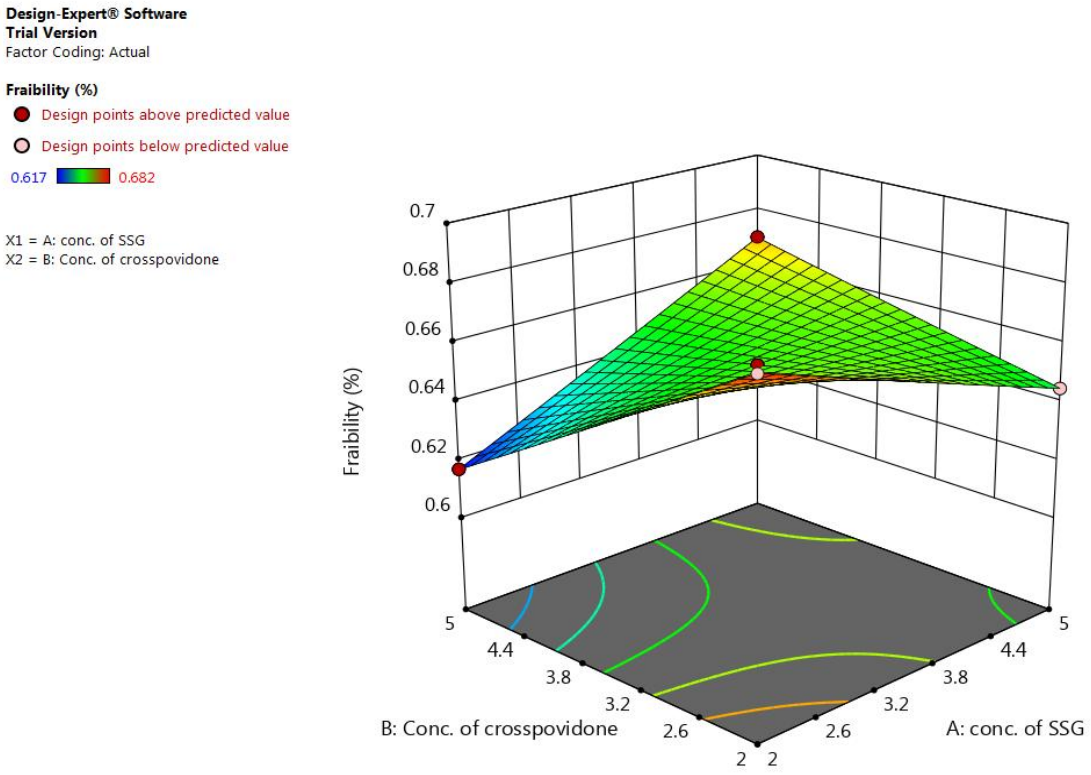

Figure 8:3D Surface Response Plot Analysis

Table 12: ANOVA for Response Surface Quadratic Model

S. No.	Source	Sum of Squares	Df	Mean Square	F-value	p-value
1.	**Model**	0.0030	5	0.0006	27240.84	<0.0001 significant
2.	**A-Conc. of SSG**	0.0001	1	0.0001	5707.26	<0.0001
3.	**B-Conc. of crosspovidone**	0.0008	1	0.0008	37614.44	<0.0001
4.	**AB**	0.0020	1	0.0020	92847.22	<0.0001
5.	**A^2**	4.348	1	4.348	19.93	0.0029
6.	**B^2**	4.348	1	4.348	19.93	0.0029
7.	**Residual**	1.527	7	2.18		
	Lack to fit	1.527	3	5.089		
	Pure error	0.0000	4	0.0000		
8.	**Core Total**	0.0030	12			

Table 12 shows the results of the analysis of variance (ANOVA), which was used to generate mathematical models. The high values of correlation factor for Friability indicate a good fit i.e. good agreement between the dependent and independent variables.

6.2.1. Experimental value (Actual value v/s Predicted value) for Friability

Table 13: Comparison between Actual and Predicted Value

S.No.	Conc. Of SSG	Conc. of crosspovidone	Friability		
			Actual Value	Predicted value	Residual
1	2	5	0.6170	0.6169	0.0001
2	3.5	3.5	0.6530	0.6530	0.0000
3	3.5	3.5	0.6530	0.6530	0.0000
4	5.6	3.5	0.6590	0.6591	-0.0001
5	3.5	5.6	0.6390	0.6392	-0.0002
6	3.5	3.5	0.6530	0.6530	0.0000
7	1.37	3.5	0.6480	0.6479	0.0001
8	5	2	0.6450	0.6451	-0.0001
9	3.5	3.5	0.6530	0.6530	0.0000
10	3.5	1.37	0.6680	0.6678	0.0002
11	2	2	0.6820	0.6822	-0.0002
12	5	5	0.6700	0.6698	0.0002
13	3.5	3.5	0.6530	0.6530	0.0000

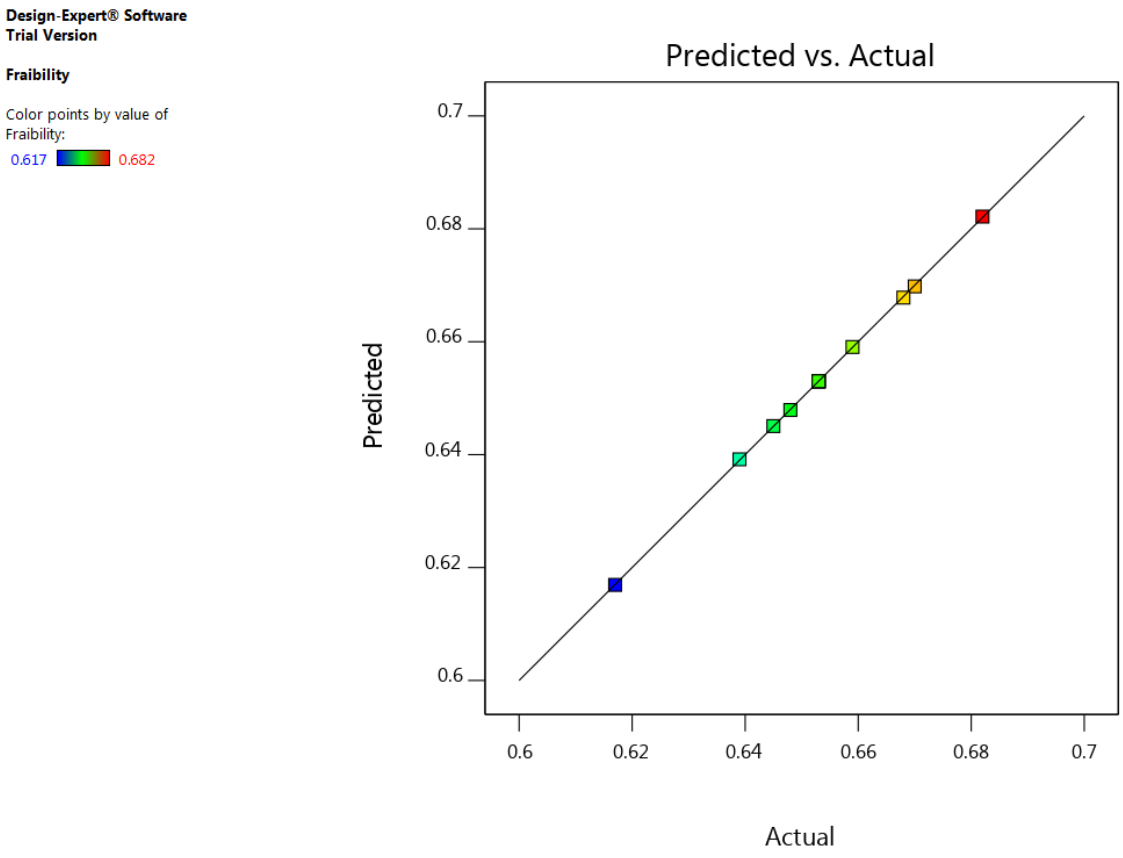

Figure 9: Comparision of actual value and predicted value of Response 2

6.3Response 3: Hardness

$Y1=+3.21 -0.0528 A 0.0570 B -0.0425 AB +0.0025 A^2 +0.0000 B^2$

(R^2 Value =0.9999

After ANOVA estimation, the quadratic model of F-value is 33773.09 implies the model is significant p-value <0.0001. The 2D contour plot and 3D surface response plot in figure 10 and figure 11 showed the effect of different independent variables on Hardness. The hardness of optimized tablets was not significantly affected by use of superdisintegrants.

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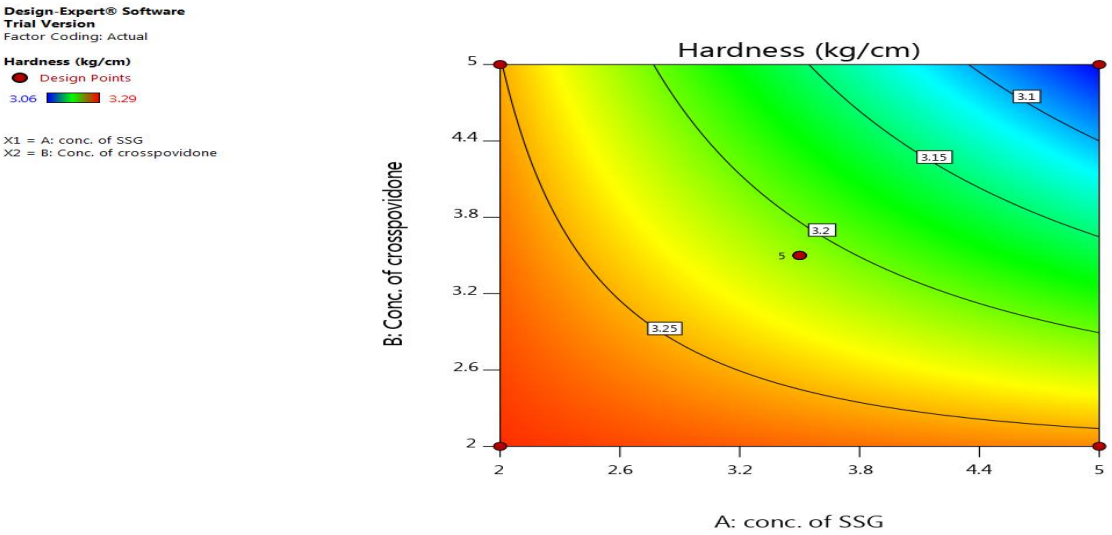

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Figure 10 : 2D Contour Plot Showing Effect of Superdisintegrants Concentration

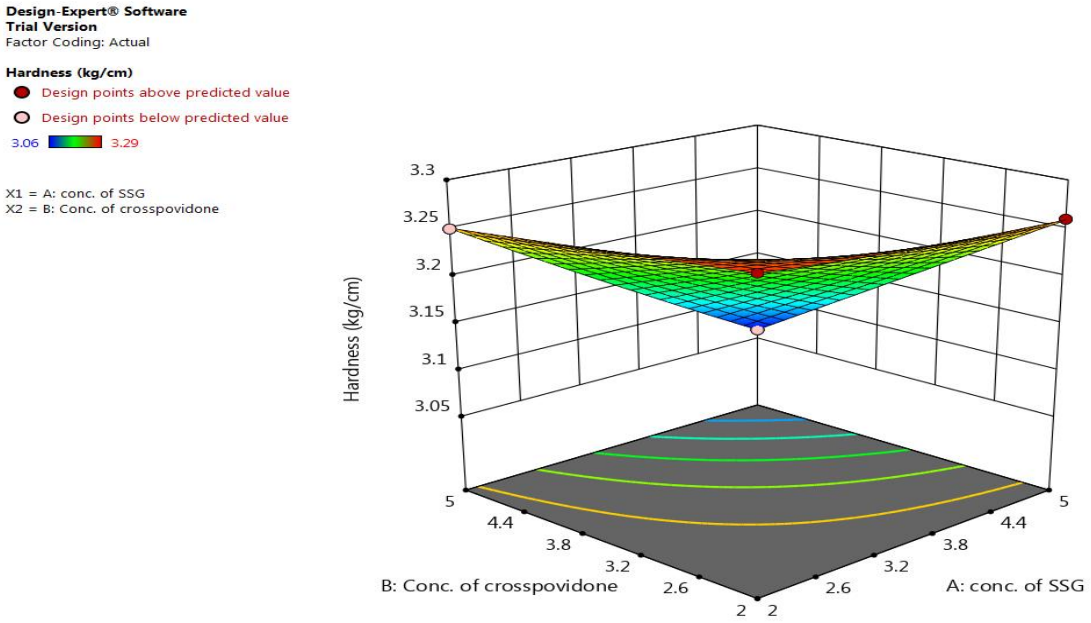

Figure 11:3D Surface Response Plot Analysis

Table 14: ANOVA for Response Surface Quadratic Model

S. No.	Source	Sum of Squares	Df	Mean Square	F-value	p-value
1.	**Model**	0.0556	5	0.0111	33773.09	<0.0001
2.	**A-Conc. of SSG**	0.0223	1	0.0223	67691.02	<0.0001
3.	**B-Conc. of crosspovidone**	0.0260	1	0.0260	79083.56	<0.0001
4.	**AB**	0.0072	1	0.0072	21956.46	<0.0001
5.	**A^2**	0.0000	1	0.0000	132.13	<0.0001
6.	**B^2**	0.0000	1	0.0000	0.0000	1.0000
7.	**Residual**	2.303	7	3.291		
	Lack to fit	2.303	3	7.678		
	Pure error	0.0000	4	0.0000		
8.	**Core Total**	0.0556	12			

Table 14 shows the results of the analysis of variance (ANOVA), which was used to generate mathematical models. The high values of correlation factor for Hardness indicate a good fit i.e. good agreement between the dependent and independent variables.

6.3.1. Experimental value (Actual value v/s Predicted value) for Hardness

Table 15: Comparison between Actual and Predicted Value

S.No.	Conc. of SSG	Conc. of crosspovidone	Hardness		
			Actual Value	Predicted value	Residual
1	2	5	3.25	3.25	-0.0007
2	3.5	3.5	3.21	3.21	0.0000
3	3.5	3.5	3.21	3.21	0.0000
4	5.6	3.5	3.14	3.14	-0.0004
5	3.5	5.6	3.13	3.13	0.0007
6	3.5	3.5	3.21	3.21	0.0000
7	1.37	3.5	3.29	3.29	0.0004
8	5	2	3.26	3.26	0.0007
9	3.5	3.5	3.21	3.21	0.0000
10	3.5	1.37	3.29	3.29	-0.0007
11	2	2	3.28	3.28	0.0002
12	5	5	3.06	3.06	-0.0002
13	3.5	3.5	3.21	3.21	0.0000

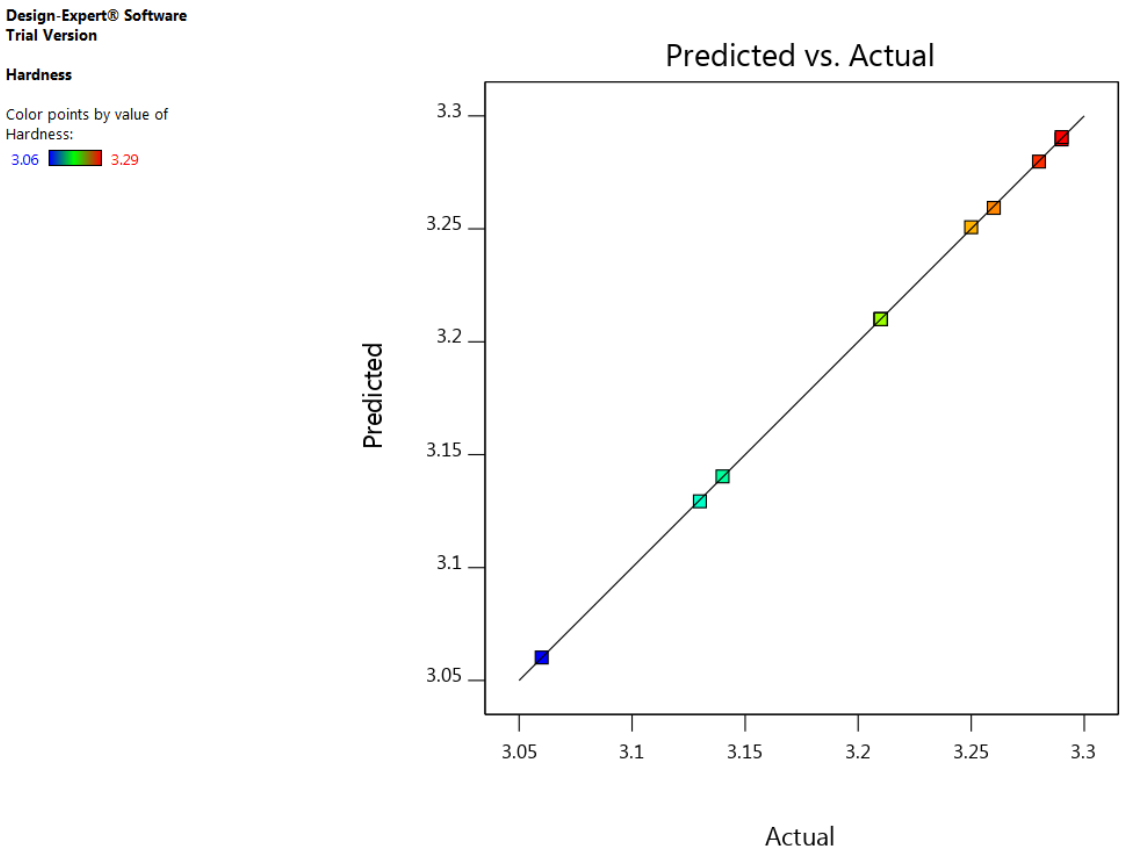

Figure 12: Comparison of actual value and predicted value of Response 3

7. CONCLUSION

The main aim of the present study was to develop mouth dissolving Tablet of Duloxetine for the treatment of depression. The Tablets were prepared by using Sodium Starch glycolate and crosspovidone by the solvent evaporation method. Mouth dissolving Tablet of Duloxetine was successfully designed and developed by direct compression method and it is suitable for quick onset of action, improved patient compliance. The F6 was found to be best formulation with disintegration time of 15 seconds and 95% of In vitro drug release.

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