

**FORMULATION AND OPTIMIZATION OF MOUTH DISSOLVING  
TABLET OF DULOXETINE HCl****Neerav Kumar Barsiwal<sup>a\*</sup>, Rajni Bala<sup>a</sup>, Naresh Singh Gill<sup>b</sup>**<sup>a</sup>Department of Pharmaceutics, Rayat Institute of Pharmacy, Railmajra, SBS Nagar<sup>b</sup>Department of Pharmaceutical chemistry, Rayat Institute of Pharmacy, Railmajra, SBS Nagar.**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<sub>1</sub>) and crosspovidone (X<sub>2</sub>) 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.<sup>[1]</sup> 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.<sup>[2]</sup> 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.<sup>[3]</sup> In today scenario MDTs are more preferred for patients suffering from disease like antacids; 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 into the smaller granules or melt in the mouth from hard solid structure to a gel like structure allowing by patients. The disintegration time varies from the few seconds to more than a minute<sup>[4]</sup>. MDTs are not only formulated for patients who have the swallowing problem, but also are ideal for active people. Mouth dissolving tablets 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<sup>[5]</sup>. It has been reported that difficulty in swallowing is common among all age group and more specific with paediatric, geriatric population along with institutionalized patients and patient with the nausea, vomiting, motion sickness<sup>[6]</sup>.

### 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<sup>[7][8][9]</sup>.

## 2. MATERIAL AND METHODS:

### 2.1 MATERIALS

Duloxetine was obtained as gift sample from (Concern pharma, Ludhiana) Micro crystalline cellulose & sodium starch glycolate and croscopolidone (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<sup>2</sup> 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 (X<sub>1</sub>) and concentration of Croscopolidone (X<sub>2</sub>) 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        |
| Croscopolidone (w/w)    | 2              | 3.5            | 5        |
| Formulation code        | X <sub>1</sub> | X <sub>2</sub> |          |
| 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°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    |
|----------------------------|-------|-------|-------|-------|-------|-------|-------|
| <b>Drug(Duloxetine)</b>    | 20    | 20    | 20    | 20    | 20    | 20    | 20    |
| <b>SSG</b>                 | 3     | 5.25  | 5.25  | 8.45  | 5.25  | 5.25  | 1.95  |
| <b>CSP</b>                 | 7.5   | 5.25  | 5.25  | 5.25  | 8.45  | 5.25  | 5.25  |
| <b>MCC</b>                 | 56.75 | 56.75 | 56.75 | 55.15 | 55.15 | 56.75 | 58.40 |
| <b>Spray Dried Lactose</b> | 56.75 | 56.75 | 56.75 | 55.15 | 55.75 | 56.75 | 58.40 |
| <b>Talc</b>                | 3     | 3     | 3     | 3     | 3     | 3     | 3     |
| <b>Magnesium stearate</b>  | 3     | 3     | 3     | 3     | 3     | 3     | 3     |
| <b>Total weight</b>        | 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  $\theta$  less than 25°C indicate Excellent flow property to the powder and value between 30-40°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 ( $\Theta$ ) | Type of flow |
|------|------------------------------|--------------|
| 1.   | <25                          | Excellent    |
| 2.   | 25-30                        | Good         |
| 3.   | 30-40                        | Poor         |
| 4.   | >40                          | Very Poor    |

#### b. Bulk Density:

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

$$\rho_b = M/V_b$$

#### c. Tapped Density

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

$$\rho_t = M/ V_t$$

**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:

$$I = \frac{p_t - p_b}{p_t} \times 100$$

**e. Hausner's Ratio (%):**

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

Hausner's ration =  $\frac{\rho_{\text{tapped}}}{\rho_{\text{bulk}}}$

**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.<sup>[11]</sup> The % weight variation of each individual tablet from the average weight is calculated by the given formula

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

**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<sup>[12]</sup>.

**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 <sup>[13]</sup>.

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

$$F=(1-W_i/W_f)*100$$

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  $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$  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  $37 \pm 0.5^{\circ}\text{C}$  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. <sup>[14]</sup>

#### 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 Pharmaspec Shimadzu) at 243 nm. <sup>[15]</sup>.

### 5. RESULT AND DISCUSSION

**Table5. Pre-Compression Parameter of Duloxetine Mouth Dissolving Tablets**

| Formulation code | Angle of Repose | Bulk density | Tapped <u>density</u> | Compressibility Index | Hausner Ratio |
|------------------|-----------------|--------------|-----------------------|-----------------------|---------------|
|------------------|-----------------|--------------|-----------------------|-----------------------|---------------|

|            |            |             |             |              |             |
|------------|------------|-------------|-------------|--------------|-------------|
| <b>F1</b>  | 26.25±0.89 | 0.515±0.007 | 0.610±0.008 | 15.58±0.005  | 1.20±0.550  |
| <b>F2</b>  | 25.96±0.44 | 0.523±0.009 | 0.615±0.009 | 14.95±0.008  | 1.14±0.655  |
| <b>F3</b>  | 26.35±0.89 | 0.518±0.006 | 0.612±0.006 | 15.35±0.009  | 1.16±0.390  |
| <b>F4</b>  | 26.35±1.78 | 0.517±0.005 | 0.613±0.004 | 15.68±0.006  | 1.19±0.795  |
| <b>F5</b>  | 27.15±1.34 | 0.548±0.10  | 0.617±0.010 | 14.93±0.007  | 1.195±0.780 |
| <b>F6</b>  | 25.15±0.65 | 0.522±0.008 | 0.611±0.006 | 14.58±0.004  | 1.12±0.530  |
| <b>F7</b>  | 29.55±0.50 | 0.545±0.012 | 0.618±0.011 | 11.81±0.010  | 1.24±0.850  |
| <b>F8</b>  | 28.25±0.75 | 0.535±0.011 | 0.614±0.005 | 12.95±0.0012 | 1.21±0.950  |
| <b>F9</b>  | 25.20±0.35 | 0.516±0.004 | 0.619±0.003 | 15.36±0.011  | 1.14±1.20   |
| <b>F10</b> | 26.25±0.89 | 0.519±0.015 | 0.616±0.012 | 15.65±0.014  | 1.17±1.30   |
| <b>F11</b> | 29.75±0.15 | 0.521±0.014 | 0.620±0.014 | 15.55±0.015  | 1.24±1.50   |
| <b>F12</b> | 28.30±0.75 | 0.529±0.013 | 0.622±0.010 | 14.95±0.017  | 1.20±0.450  |
| <b>F13</b> | 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  $25.15^{\circ}\pm 0.65$  to  $29.75^{\circ}\pm 0.15$ . 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  $146.34\pm 0.602$  to  $152.13\pm 0.620$  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  $2.43\pm 0.384$  to  $2.90\pm 0.066$  mm. The hardness of the tablets were found to be ranging between  $3.06\pm 0.230$  to  $3.29\pm 0.130$  kg/cm<sup>2</sup>. The friability of all the formulations was evaluated using Roche friabilator. It was observed in range ( $0.330\pm 0.025$  to  $0.710\pm 0.020$ ) 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  $15\pm 0.178$  to  $72\pm 0.176$  seconds. The wetting time of tablet is ranges from  $35\pm 3.45$  to  $83\pm 3.51$ . 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              |
|----------------------------------|-----------------|-----------------|----------------|-----------------|-----------------|-----------------|-----------------|
| <b>Weight</b>                    | 147.4±          | 148.56±         | 152.13±        | 150.93±         | 147.34±         | 149.33±         | 148.4±          |
| <b>Variation</b>                 | 1.78            | 0.89            | 0.60           | 0.38            | 0.67            | 0.53            | 0.731           |
| <b>Thickness</b>                 | 2.60±<br>0.121  | 2.53±<br>0.022  | 2.76±<br>0.089 | 2.86±<br>0.061  | 2.90±<br>0.066  | 2.67±<br>0.295  | 2.60±<br>0.357  |
| <b>Hardness</b>                  | 3.25±<br>0.156  | 3.21±<br>0.090  | 3.21±<br>0.200 | 3.14±<br>0.250  | 3.13±<br>0.150  | 3.21±<br>0.300  | 3.29±<br>0.130  |
| <b>Friability</b>                | 0.653±<br>0.050 | 0.645±<br>0.065 | 0.630±<br>0.69 | 0.390±<br>0.040 | 0.370±<br>0.032 | 0.634±<br>0.070 | 0.705±<br>0.075 |
| <b>Disintegration time (sec)</b> | 36±<br>1.78     | 16±<br>0.047    | 18±<br>0.626   | 22±<br>0.636    | 26±<br>0.536    | 15±<br>0.178    | 70±<br>0.646    |
| <b>Wetting time</b>              | 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±<br>0.447  | 2.43±<br>0.384  | 2.67±<br>0.536  | 2.56±<br>0.393  | 2.89±<br>0.268  | 2.76±<br>0.232  |
| 3.26±<br>0.100  | 3.21±<br>0.170  | 3.29±<br>0.190  | 3.28±<br>0.220  | 3.06±<br>0.230  | 3.21±<br>0.100  |
| 0.654±<br>0.082 | 0.644±<br>0.030 | 0.706±<br>0.035 | 0.710±<br>0.020 | 0.330±<br>0.025 | 0.658±<br>0.038 |
| 40±<br>0.804    | 16±<br>0.616    | 22±<br>0.185    | 72±<br>1.76     | 36±<br>0.620    | 17±<br>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.

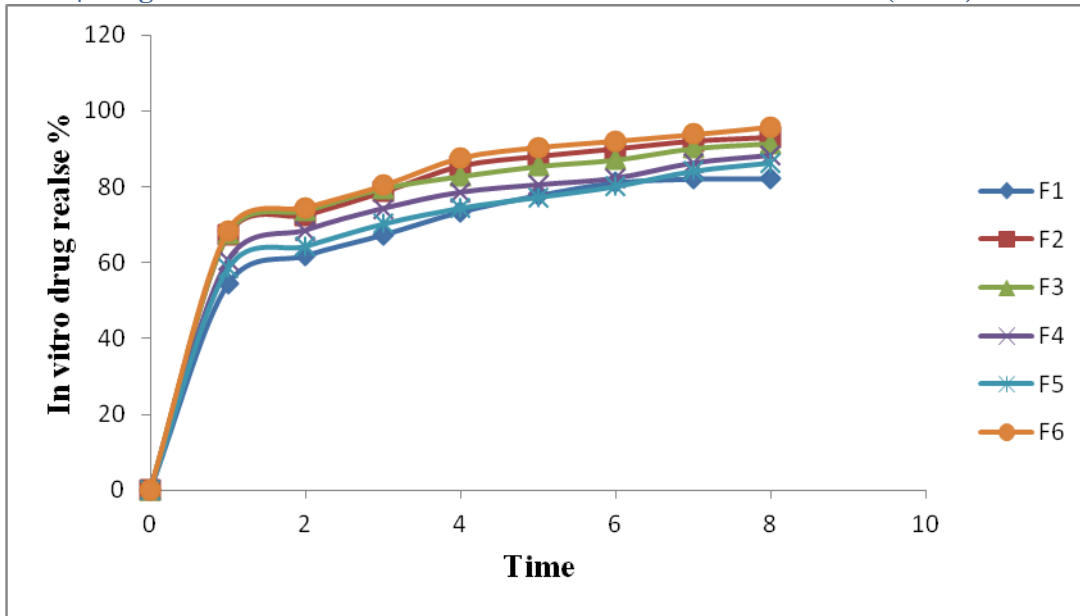


Figure 1: % In vitro drug release (F1 to F6)

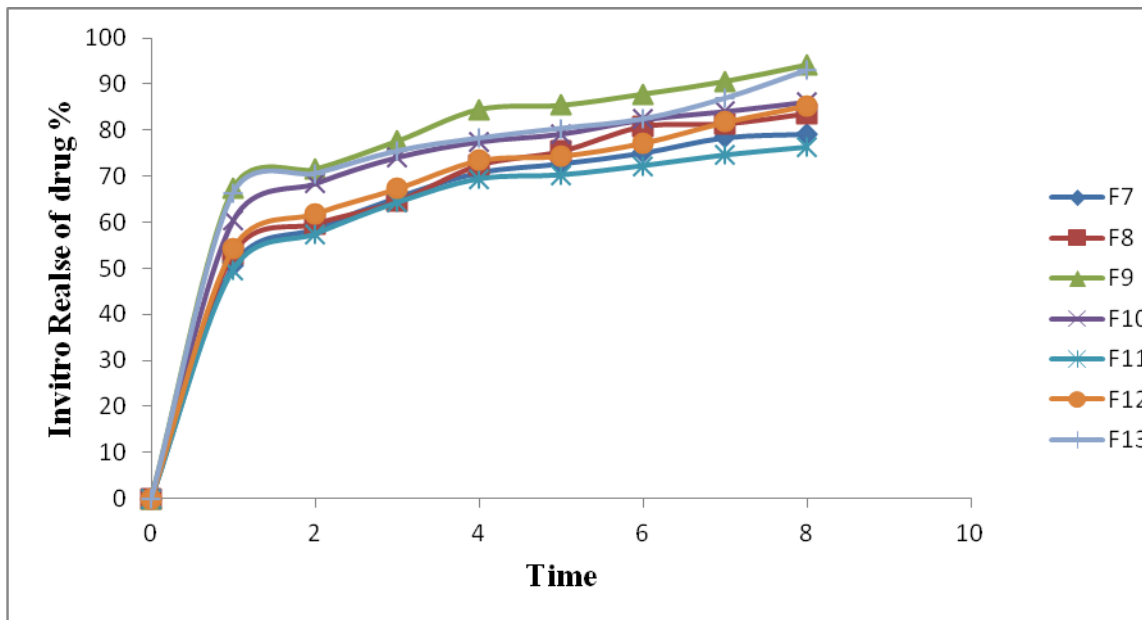


Figure 2: %In vitro Drug release (F7 to F13)

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.

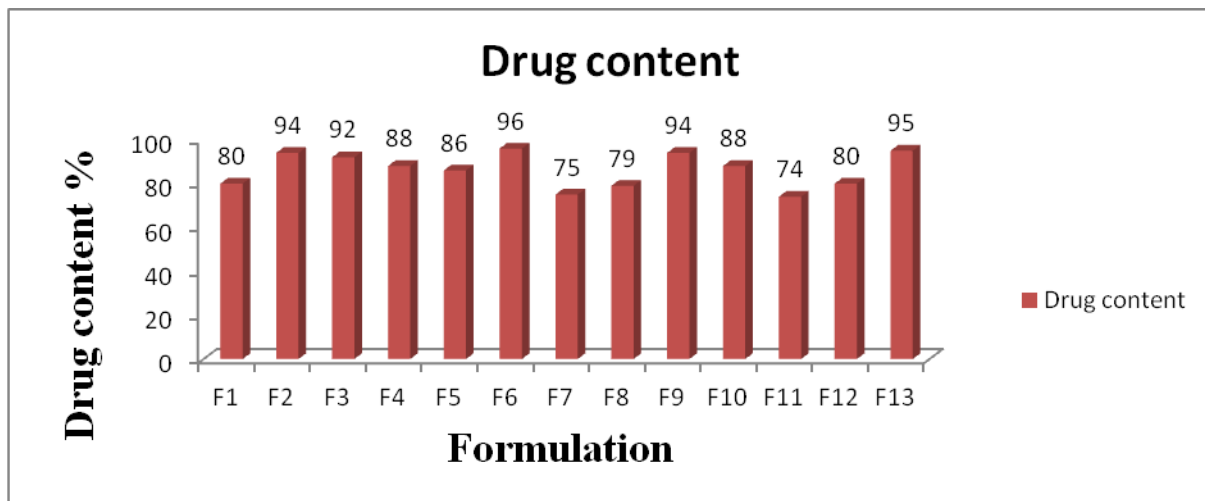


Figure 3: % of Drug content Release

## 6. OPTIMIZATION OF DEPENDENT VARIABLE

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

**Table 9. Optimization of Depended variable**

| Factors                       | Levels         |                |             | Disintegration time | Friability | Hardness |
|-------------------------------|----------------|----------------|-------------|---------------------|------------|----------|
|                               | (-1)<br>Low    | (0)<br>Medium  | (1)<br>High |                     |            |          |
| Sodium Starch Glycolate (w/w) | 2              | 3.5            | 5           |                     |            |          |
| Crosspovidone (w/w)           | 2              | 3.5            | 5           |                     |            |          |
| Formulation code              | X <sub>1</sub> | X <sub>2</sub> |             |                     |            |          |
| 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     |

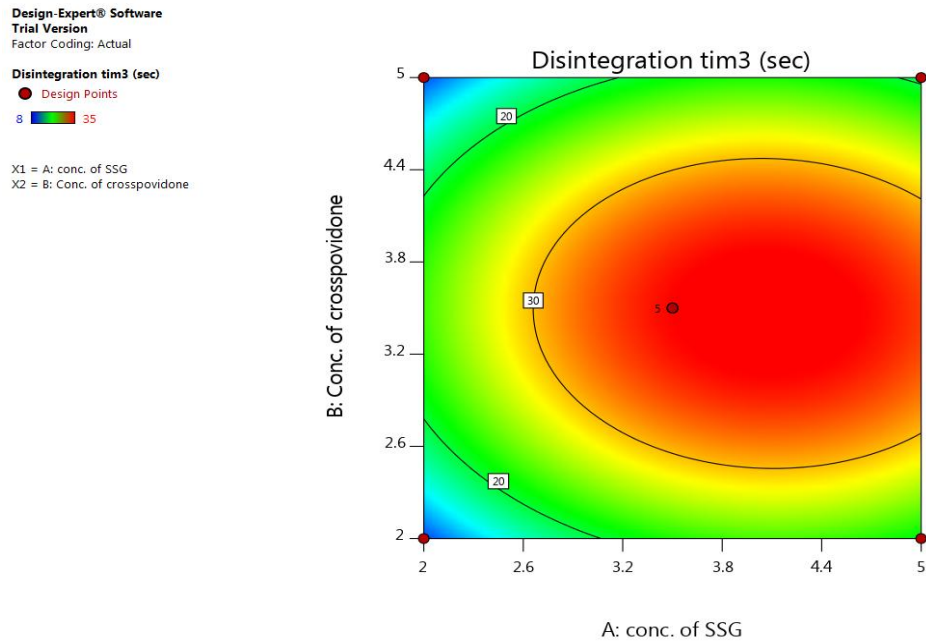
### 6.1. Response Disintegration time

$$Y_1 = +35.00 + 5.15A - 0.4268B - 0.5000AB - 6.75 A^2 - 13.25 B^2$$

(R<sup>2</sup> 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**

Design-Expert® Software

Trial Version

Factor Coding: Actual

Disintegration tim3 (sec)

● Design points above predicted value

○ Design points below predicted value

8  35

X1 = A: conc. of SSG

X2 = B: Conc. of crosspovidone

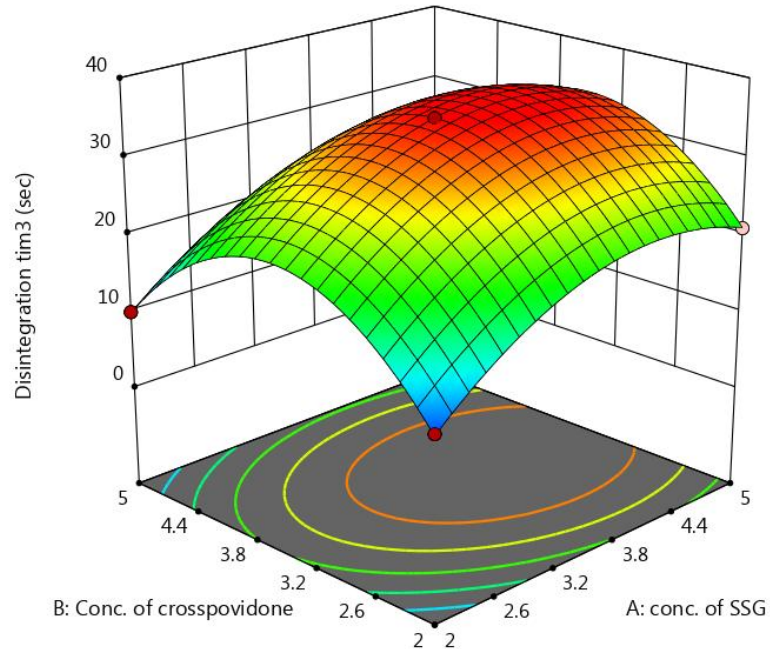


Figure 5: 3D Surface Response Plot Analysis

Table 10: ANOVA for Response Surface Quadratic Model

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

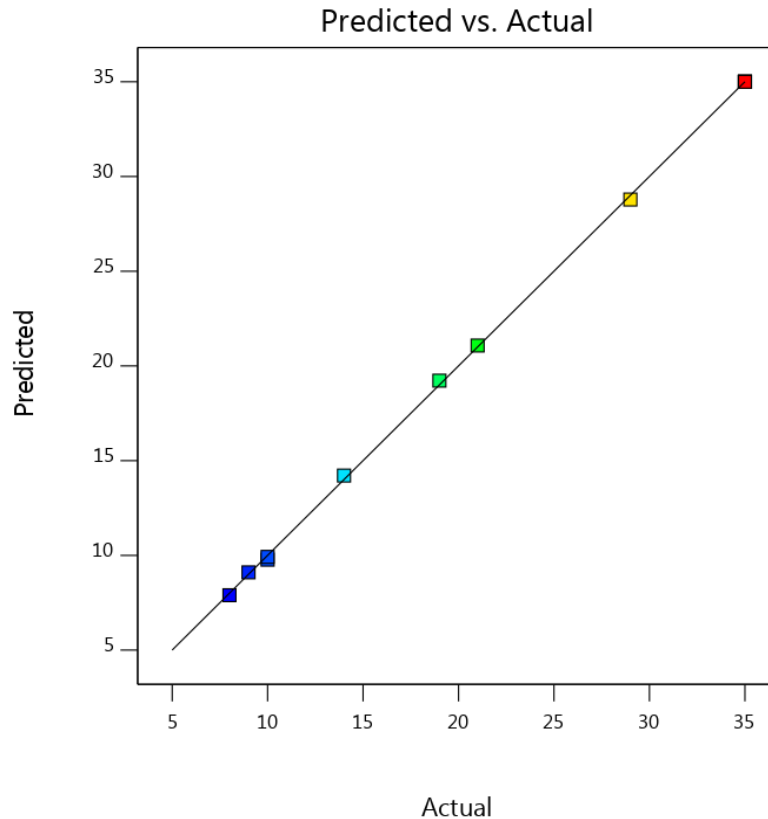


Design-Expert® Software  
Trial Version

Disintegration tim3

Color points by value of  
Disintegration tim3:

8  35



**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<sup>2</sup> 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.

Design-Expert® Software  
 Trial Version  
 Factor Coding: Actual  
**Fraibility (%)**  
 ● Design Points  
 0.617 0.682  
 X1 = A: conc. of SSG  
 X2 = B: Conc. of crosspovidone

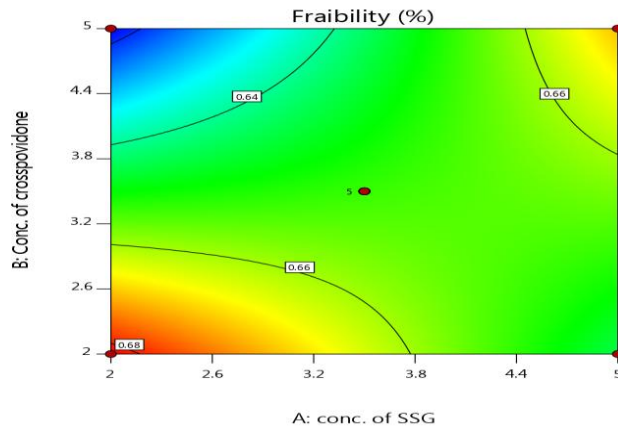


Figure 7: 2D Contour Plot Showing Effect of Superdisintegrants Concentration

Design-Expert® Software  
 Trial Version  
 Factor Coding: Actual  
**Fraibility (%)**  
 ● Design points above predicted value  
 ○ Design points below predicted value  
 0.617 0.682  
 X1 = A: conc. of SSG  
 X2 = B: Conc. of crosspovidone

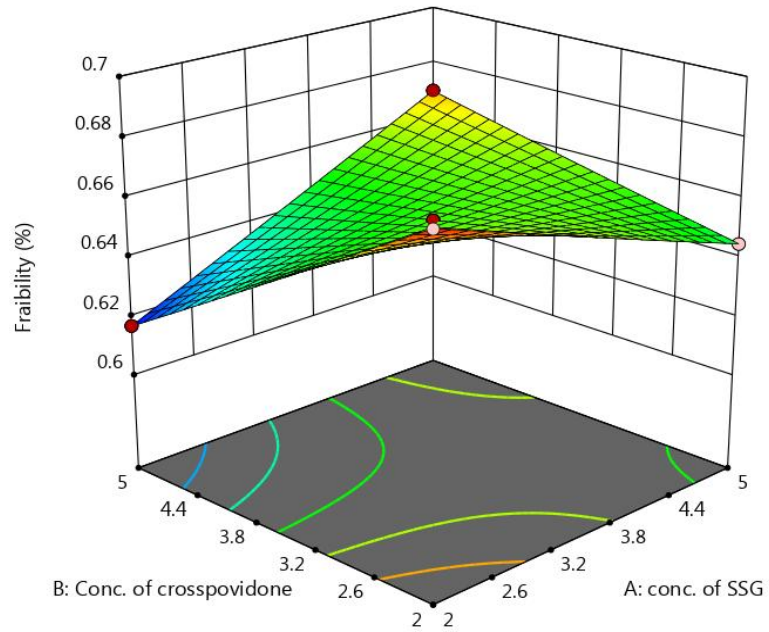


Figure 8:3D Surface Response Plot Analysis

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 <sup>2</sup>           | 4.348          | 1  | 4.348       | 19.93    | 0.0029              |
| 6.     | B <sup>2</sup>           | 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

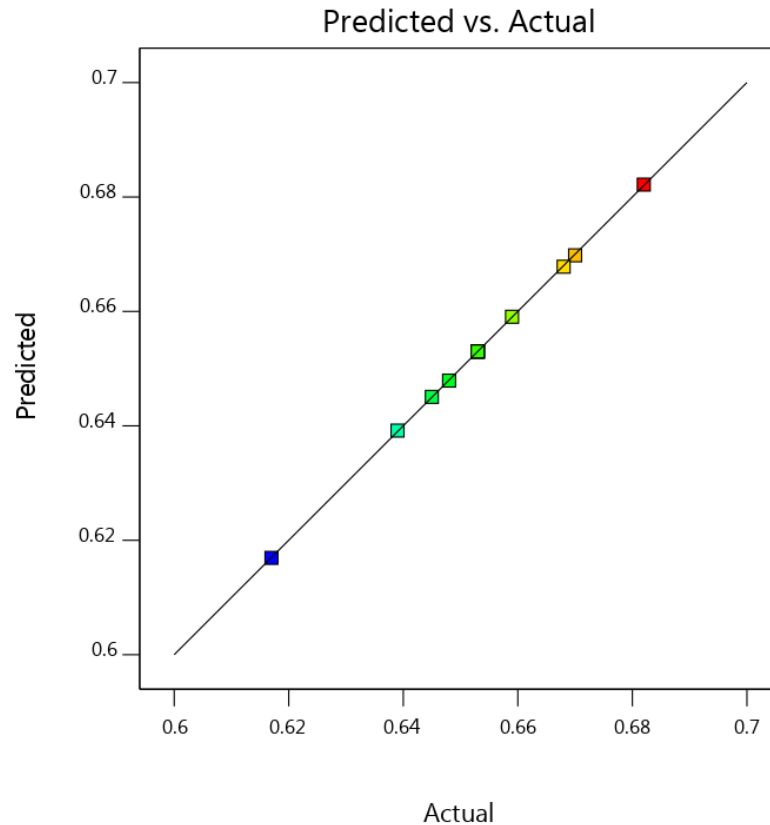
| S.No. | Conc. Of SSG | Conc. of crosspovidone | Friability   |                 |          |
|-------|--------------|------------------------|--------------|-----------------|----------|
|       |              |                        | Actual Value | Predicted value | Residual |
| 1     | 2            | 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   |

Design-Expert® Software  
Trial Version

#### Fraibility

Color points by value of  
Fraibility:

0.617  0.682



**Figure 9: Comparison of actual value and predicted value of Response 2**

### 6.3 Response 3: Hardness

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

(R<sup>2</sup> 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.

Design-Expert® Software  
 Trial Version  
 Factor Coding: Actual

Hardness (kg/cm)  
 ● Design Points  
 3.06 3.29

X1 = A: conc. of SSG  
 X2 = B: Conc. of crosspovidone

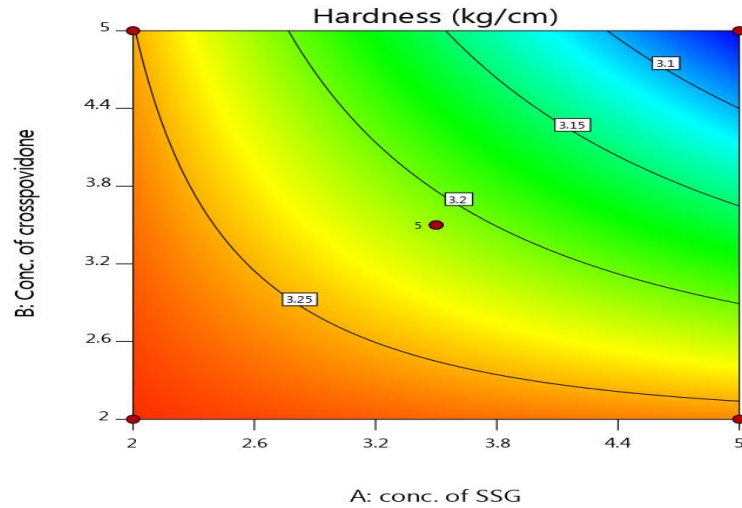


Figure 10 : 2D Contour Plot Showing Effect of Superdisintegrants Concentration

Design-Expert® Software  
 Trial Version  
 Factor Coding: Actual

Hardness (kg/cm)  
 ● Design points above predicted value  
 ○ Design points below predicted value  
 3.06 3.29

X1 = A: conc. of SSG  
 X2 = B: Conc. of crosspovidone

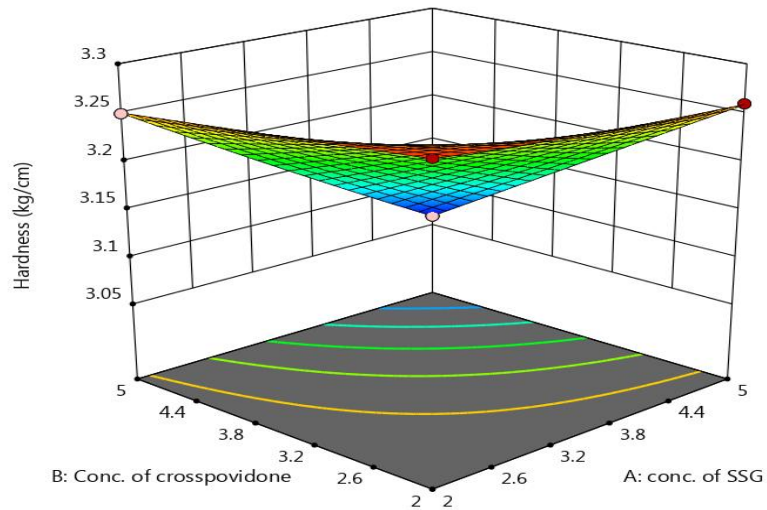


Figure 11:3D Surface Response Plot Analysis

Table 14: ANOVA for Response Surface Quadratic Model

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

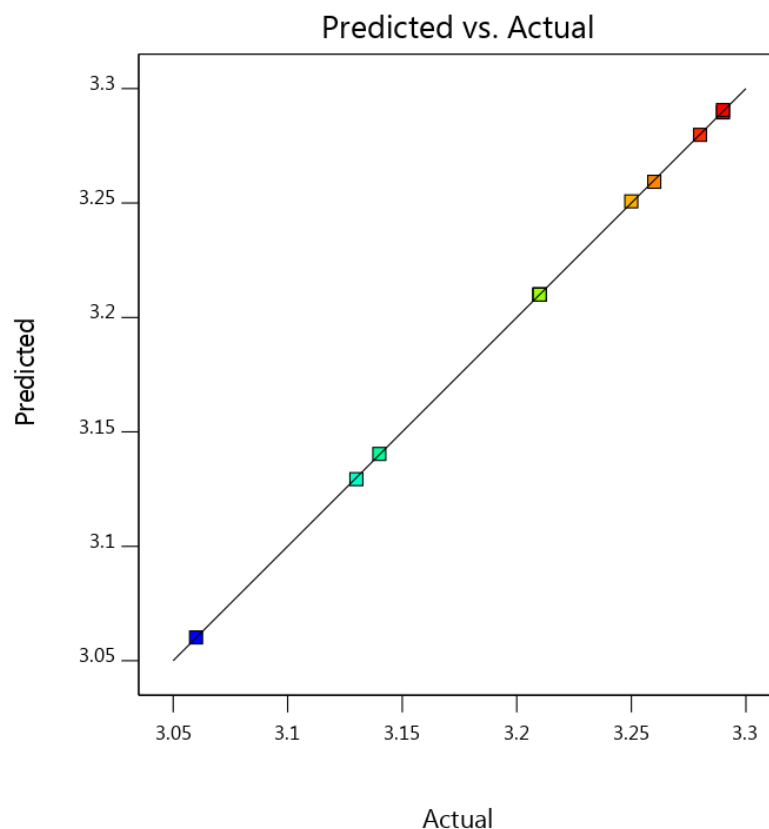
| S.No. | Conc. of SSG | Conc. of crosspovidone | Hardness     |                 |          |
|-------|--------------|------------------------|--------------|-----------------|----------|
|       |              |                        | Actual Value | Predicted value | Residual |
| 1     | 2            | 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   |

Design-Expert® Software  
Trial Version

Hardness

Color points by value of  
Hardness:

3.06  3.29



**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 croscopolidone 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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