

# Design and Optimization Fast Dissolving Tablets for Felodipine Using Response Surface Approach

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**Abstract:** The purpose of the current study was to use sodium starch glycolate and croscarmellose sodium to optimize fast-dissolving tablets (FDT) to successfully manage hypertension and angina pectoris utilizing the response surface technique. Felodipine is a highly effective calcium channel inhibitor. Because it dissolves so poorly in GI fluid, it has a restricted bioavailability when taken orally. The two independent variables under investigation were croscarmellose sodium (X1) and sodium starch glycolate (X2). Disintegration time (Y1) and time needed for 90% of dissolution (Y2) were the primary components or dependent variables. Utilizing the direct compression method, FDT formulations of felodipine were prepared. Nine trials were created and evaluated based on pharmaceutical product performance. Using statistical models, the FDT of Felodipine with quick disintegration (69 seconds) and maximum drug release (45.25 minutes) was successfully prepared. Results show that every formulation satisfies the acceptance standards, and the in-vitro dissolution profiles were subjected to kinetic modeling. The optimized formulation (F5) contained 6 mg of croscarmellose sodium and 6 mg of sodium starch glycolate, and it was comparable to the commercial formulation (PLENDIL-5) (similarity = 87.35, dissimilarity = 1.97). Formulation (F5) follows first order, whereas the release mechanism was found to be Fickian type ( $n = 0.449$ ). Consequently, the present investigation unequivocally shows the possible involvement in terms of quick breakdown and ideal drug release.

**Keywords:** Felodipine; super disintegrants; sodium starch glycolate; croscarmellose sodium; fickian.

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## 1. Introduction

Within the pharmaceutical market, fast-dissolving tablets (FDT) hold a special position. Oral dissolving tablets and melt-in-the-mouth pills were frequently used instead of FDT [1].

It is easy to get tablets that dissolve quickly; in only 60 seconds, they break down in the mouth. Depending on the manufacturing procedure, they exhibit modifications in normal organoleptic properties, such as improved palatability and masking sweetness or taste. They also display variations in quality control parameters such as stability, clinical outcome, drug release from formulation, and breaking index. Numerous methods, including the cotton candy process, granulation techniques, spray drying, molding, trituration, lyophilization/freeze drying, and named technologies (Durasolv, Orosolv) can be used to prepare FDTs [2].

Felodipine is an antihypertensive, anti-anginal, and member of the CCB (Blocker of Calcium Channel) class of medication. This drug has poor dissolution in GI fluid, resulting in low oral bioavailability, one of its primary problems. Therefore, in order to improve patient compliance by enhancing dissolution and preventing the first-pass effect, it is imperative to produce a fast-dissolving tablet for the selected drug [3-5].

The formulation scientist has a number of tools at their disposal to optimize the produced formulations with statistical significance. The response surface approach was the most extensively utilized statistical technique in both industry and academics out of all the tools available. The factorial/response surface approach, central composite approach, Box-Behnken approach, and other popular techniques fell under the aforementioned category [6-13].

Among the many manufacturing techniques available, direct compression tablets are unique in that they require less time, can be produced quickly, and save operational management costs [14].

When creating the Fast dissolving tablets for felodipine, an effort was made to achieve quick disintegration and optimize drug release from the formulation with the aid of combination super disintegrants at different quantities (sodium starch glycolate, or SSG, and croscarmellose sodium, or CCS).

## 2. Materials and Methods

### 2.1. Materials.

A gift sample of felodipine was obtained from Meditech Pharma Pvt Ltd in India. We purchased avicel, sodium starch glycolate, and sodium croscarmellose from National Scientifics in Guntur. We purchased more excipients from High Chemie Ltd. in Vadodara.

### 2.2. Methods.

#### 2.2.1. Design and development of rapid disintegrating formulations for felodipine.

The amounts needed for sodium starch glycolate and croscarmellose sodium to develop fast-dissolving Felodipine tablets were designated independent variables (X1, X2). The disintegration time and time needed for 90% drug dissolution was designated as the dependent variable (DT&t 90%). Using PCP Disso software, polynomial equations were developed for the dependent variables [15].

The three levels for X1 (CCS) were 4, 6, and 8 %. The X2 (SSG) levels were 4, 6, and 8 % (% based on the average weight of the formulation). As part of a 3<sup>2</sup>-factorial design, nine

different felodipine-dissolving tablet formulations were developed. The design layout is presented in Table 1.

**Table 1.** Formulae for the preparation of Felodipine fast dissolving tablets.

Formulation code	X <sub>1</sub>	X <sub>2</sub>
F <sub>1</sub>	1	1
F <sub>2</sub>	1	0
F <sub>3</sub>	1	-1
F <sub>4</sub>	0	1
F <sub>5</sub>	0	0
F <sub>6</sub>	0	-1
F <sub>7</sub>	-1	1
F <sub>8</sub>	-1	0
F <sub>9</sub>	-1	-1
CF <sub>1</sub>	-0.5	-0.5
CF <sub>2</sub>	+0.5	+0.5

### 2.2.2. Preparation of Felodipine fast dissolving tablets.

Fluoxetine FDT was produced using the direct compression method, as indicated by the formulae in Table 2.

**Table 2.** Formulae for the preparation of Felodipine fast dissolving tablets.

Name of Ingredients	Quantity of ingredients per tablet (mg)								
	F <sub>1</sub>	F <sub>2</sub>	F <sub>3</sub>	F <sub>4</sub>	F <sub>5</sub>	F <sub>6</sub>	F <sub>7</sub>	F <sub>8</sub>	F <sub>9</sub>
Felodipine	5	5	5	5	5	5	5	5	5
Avicel pH 102	37.5	38.5	39.5	38.5	39.5	40.5	39.5	40.5	41.5
Lactose	37.5	38.5	39.5	38.5	39.5	40.5	39.5	40.5	41.5
Croscarmellose sodium	8	8	8	6	6	6	4	4	4
Sodium starch glycolate	8	6	4	8	6	4	8	6	4
Talc	2	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Total Weight	100	100	100	100	100	100	100	100	100

To create a consistent, fine mix, all of the ingredients were sieved through 40 mesh (#40). Lubricants were added to the mixture above, filtered through #60, and well mixed. The aforementioned blends were compressed to yield FDT by utilizing an 8-station tablet minipress and 8 mm diameter circular punches. Tests for IPQC were run on the prepared tablets. Finished tablet formulations were moved to airtight, light-resistant containers for storage and further processing [13,16].

### 2.3. Evaluation of Felodipine fast dissolving tablets.

#### 2.3.1. Hardness.

It was carried out with the help of Monsanto Tablet Hardness Tester [17,18].

#### 2.3.2. Friability/durability.

Weighing twenty tablets, the cumulative initial weight (W<sub>0</sub>) was recorded. After four minutes of dedusting at a speed of 25 rpm using a Roche Friabilator, the tablets were weighed again and recorded as (W). The following equation was used to obtain the percentage of friability (% Friability ≤1).

$$\text{Friability (\%)} = (W_0 - W) / W_0 \times 100 \quad (1)$$

### 2.3.3. Assay.

Twenty tablets were selected, and they were evenly ground to solubilize the drug fully. 100 mg of felodipine powder was weighed, placed in a 100 mL volumetric flask with 60 mL of methanol, and sonicated for 10 minutes. After that, water was added to the methanolic solution to get it up to the required volume. The methanolic solution was diluted with water to make up the required volume. To dilute it in 100 mL of 0.1 N HCl, prepare a further 2 mL aliquot. The resultant solution's absorbance at 362 nm was measured using a UV-visible spectrophotometer.

### 2.3.4. Thickness.

It was measured with the help of vernier calipers [19].

### 2.3.5. Wetting time.

To test the wetting time of the tablets, they were placed on a Petri dish that contained paper that had been soaked in 5 milliliters of distilled water. The wetting time of the tablet was expressed in seconds.

### 2.3.6. In-vitro dissolution study.

900 milliliters of pH 6.8 buffer and a Lab-India dissolving test apparatus were used to assess Felodipine FDT for the drug release study in compliance with the monograph's suggested methodology. The absorbance of the materials was measured at 362 nm using a UV-visible spectrophotometer, and kinetic modeling was applied to the results [20-24].

### 2.3.7. Disintegration test.

This test was performed in accordance with the requirements of the modified disintegration test for tablets. In a cylinder with 10 #, just 2 ml of medium was permitted to go below the sieve. The disintegration time was recorded [13].

## 3. Results and Discussion

Felodipine Fast Dissolving Tablets were developed using a 3<sup>2</sup>-factorial response surface design. The formulation design is shown in Table 1. Time required for disintegration (DT) and 90% dissolve ( $t_{90\%}$ ) were chosen as dependent factors ( $X_1$ ,  $X_2$  respectively), while the amount needed for Croscarmellose sodium ( $X_1$ ) and Sodium starch glycolate ( $X_2$ ) to make fast-dissolving tablets were chosen as independent variables.

Using the direct compression approach, nine distinct formulations of fast-dissolving tablets of felodipine were developed, each with a different ratio of super disintegrants based on the formulas listed in Table 2.

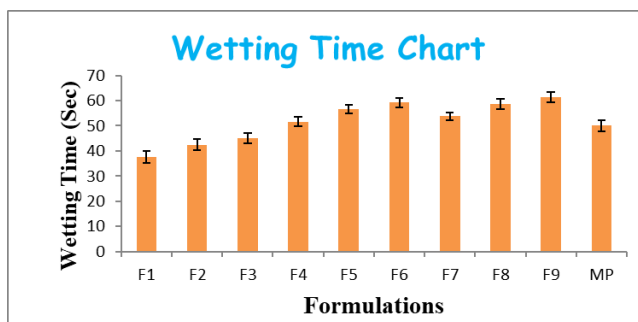
The produced formulations were subjected to performance tests for pharmaceutical products. The data is shown in Table 3.

It was found that all tablet formulations exhibited satisfactory mechanical strength and were less brittle. The consistency of weight and drug content of the manufactured tablets fell within acceptable limits.

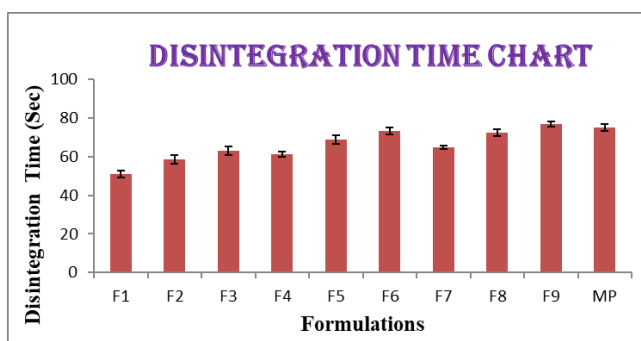
**Table 3.** Post-compression parameters.

S.No	Formulation Code	Hardness (kg/cm <sup>2</sup> )	Thickness (mm)	Friability (%)	Average weight (mg)	Drug content (%)	Wetting time (sec)	Disintegration time (sec)
1	F <sub>1</sub>	3.8±0.125	3.675±0.48	0.55±0.07	99.32±0.45	99.775±0.8	37.5±2.3	50.75±1.8
2	F <sub>2</sub>	3.75±0.225	3.65±0.04	0.45±0.065	99.85±0.95	99.525±2.05	42.5±2.2	58.35±2.2
3	F <sub>3</sub>	3.85±0.205	3.54±0.05	0.45±0.06	98.2±0.55	99.39±1.12	45±2.01	62.95±2.1
4	F <sub>4</sub>	4.05±0.33	3.705±0.495	0.5±0.06	100.04±1.1	100.5±1.35	51.65±1.9	61.15±1.5
5	F <sub>5</sub>	4±0.34	3.68±0.055	0.4±0.055	100.11±0.54	100.25±2.6	56.65±1.8	68.75±2.3
6	F <sub>6</sub>	4.1±0.32	3.57±0.065	0.4±0.005	99.18±0.89	100.115±1.67	59.15±1.7	73.35±1.9
7	F <sub>7</sub>	4±0.18	3.79±0.49	0.6±0.065	100.85±0.76	99.5±1.03	53.75±1.6	64.75±1.01
8	F <sub>8</sub>	3.95±0.19	3.765±0.05	0.5±0.06	100.81±0.15	99.25±2.28	58.75±2.0	72.35±1.9
9	F <sub>9</sub>	4.05±0.17	3.655±0.06	0.5±0.055	100.27±0.44	99.115±1.34	61.25±2.0	76.95±1.3

All the formulations showed wetting time in the range of 37±2.3 to 61.25±2 sec. All the formulations showed DT time in the range of 50.75±1.8 to 76.95±1.3 sec, and the same was represented in Figure 1-2.



**Figure 1.** Wetting time chart.



**Figure 2.** Disintegration time chart.

Dissolution profiles of Felodipine fast-dissolving tablets fit well with kinetic modeling. Results are presented in Table 4, and the same is shown in Figure 3-6.

**Table 4.** Statistical parameters.

S.NO	Formulation code	Statistical parameters											
		Zero-order			First order			Higuchi			Korsmeyer-peppas		
		a	b	r	a	b	r	a	b	r	a	b	r
1	F <sub>1</sub>	21.714	1.333	0.933	1.954	0.016	0.994	2.634	11.857	0.997	1.176	0.443	0.995
2	F <sub>2</sub>	24.439	1.450	0.927	1.984	0.023	0.994	3.414	12.959	0.995	1.226	0.438	0.994
3	F <sub>3</sub>	24.278	1.403	0.919	1.984	0.022	0.995	3.624	12.617	0.992	1.215	0.440	0.992
4	F <sub>4</sub>	20.960	1.336	0.937	1.958	0.016	0.995	2.000	11.846	0.997	1.153	0.456	0.995
5	F <sub>5</sub>	23.686	1.453	0.930	1.986	0.022	0.995	2.779	12.948	0.996	1.206	0.449	0.994
6	F <sub>6</sub>	23.525	1.406	0.922	1.986	0.021	0.995	2.990	12.605	0.993	1.194	0.451	0.991
7	F <sub>7</sub>	21.156	1.200	0.921	1.916	0.011	0.951	3.702	10.738	0.991	1.179	0.419	0.990
8	F <sub>8</sub>	23.928	1.314	0.916	1.915	0.014	0.963	4.530	11.828	0.991	1.230	0.416	0.991
9	F <sub>9</sub>	23.744	1.269	0.910	1.919	0.014	0.965	4.716	11.492	0.990	1.218	0.417	0.990

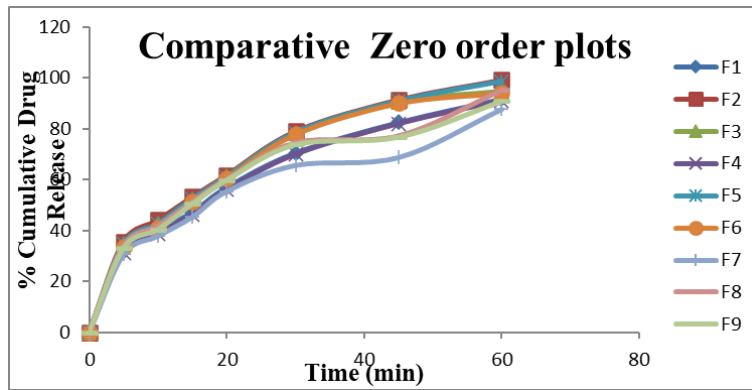


Figure 3. Comparative zero order plots.

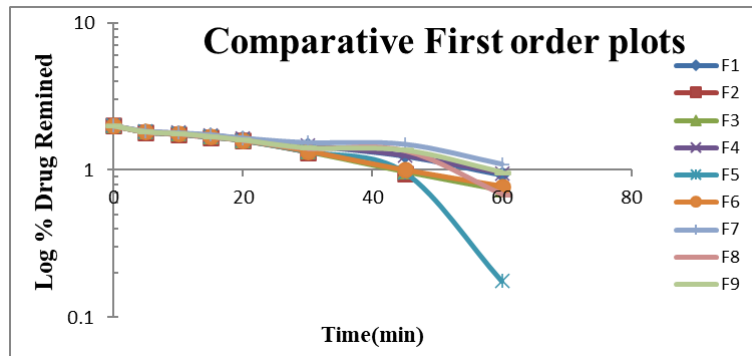


Figure 4. Comparative first-order plots.

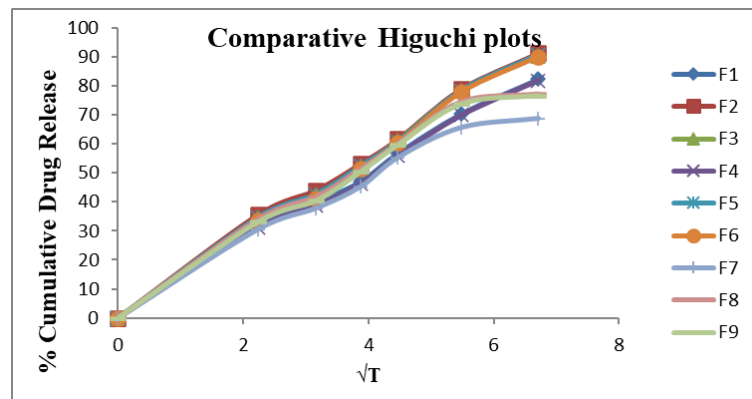


Figure 5. Comparative Higuchi plots.

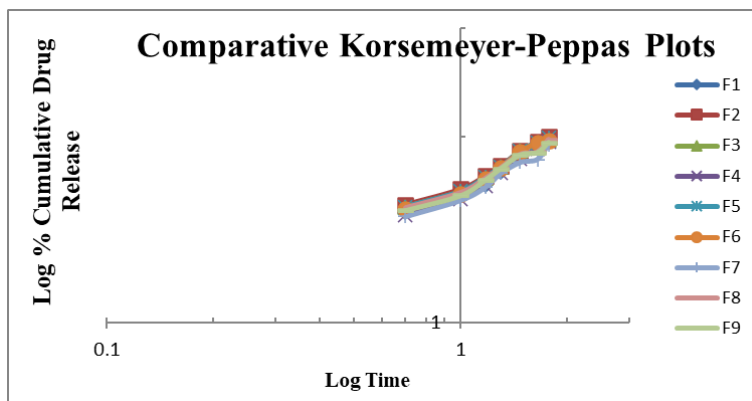


Figure 6. Comparative Korsmeyer-Peppas plots.

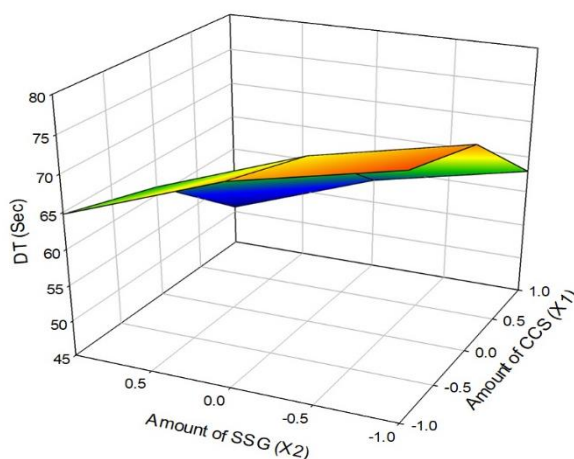
Felodipine-predicted rapid disintegration was accomplished using the right quantities of croscarmellose sodium and sodium starch glycolate. Table 5 provides a summary of the dissolution parameters. Response surface morphology (RSM) plots, shown in Figure 7-8, were

used to examine the combined impact of various polymer ratios on the drug delivery of divalproex sodium. Sigmaplot V13 was used to construct RSM graphs [25-27].

**Table 5.** Dissolution/kinetic parameters.

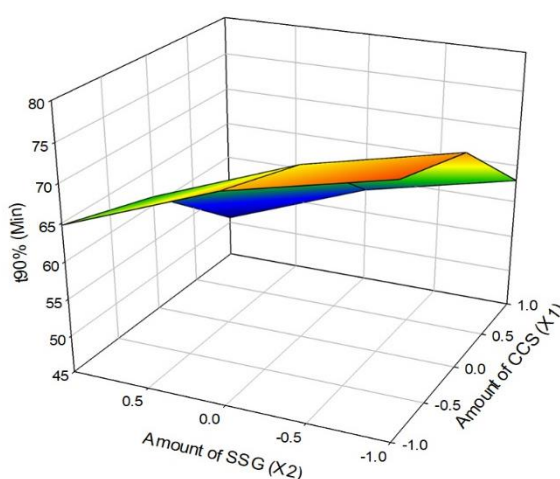
S.NO	Formulation Code	t <sub>10%</sub> (Min)	Kinetic parameters			
			t <sub>1/2</sub> (Min)	t <sub>90%</sub> (Min)	Wetting time (Sec)	Disintegration time (Sec)
1	F <sub>1</sub>	2.871	18.888	62.763	37.5±2.3	50.75±1.8
2	F <sub>2</sub>	2.030	13.357	44.384	42.5±2.2	58.35±2.2
3	F <sub>3</sub>	2.095	13.780	45.791	45±2.01	62.95±2.1
4	F <sub>4</sub>	2.904	19.108	63.495	51.65±1.9	61.15±1.5
5	F <sub>5</sub>	2.070	13.616	45.246	56.65±1.8	68.75±2.3
6	F <sub>6</sub>	2.133	14.032	46.627	59.15±1.7	73.35±1.9
7	F <sub>7</sub>	4.207	27.677	91.969	53.75±1.6	64.75±1.01
8	F <sub>8</sub>	3.226	21.225	70.531	58.75±2.0	72.35±1.9
9	F <sub>9</sub>	3.273	21.530	71.544	61.25±2.0	76.95±1.3

Response Surface Plot for DT



**Figure 7.** Response surface plot for disintegration time (DT).

Response Surface Plot for t<sub>90%</sub>



**Figure 8.** Response surface plot for time required for 90% dissolution (t<sub>90%</sub>).

F<sub>5</sub> is regarded as the best formulation among all batches (based on Desirability). F<sub>5</sub>, which contained 6 mg of Sodium starch glycolate and Croscarmellose sodium in equal amounts, produced promising dissolution characteristics that aid in achieving the study goal through rapid disintegration and quicker drug release.

Polynomial equations were developed to determine the predicted drug release parameter, and they are as follows:

$$Y1 = 65.484 - 7X1 - 6.1X2 - 3.4 X12 - 1.5X22 \quad (DT) \quad (2)$$

$$Y2 = 60.262 - 13.52X1 + 9.05 X2 - 0.863 X1X2 + 12.71 X12 + 10.32 X22 \quad (t_{90\%}) \quad (3)$$

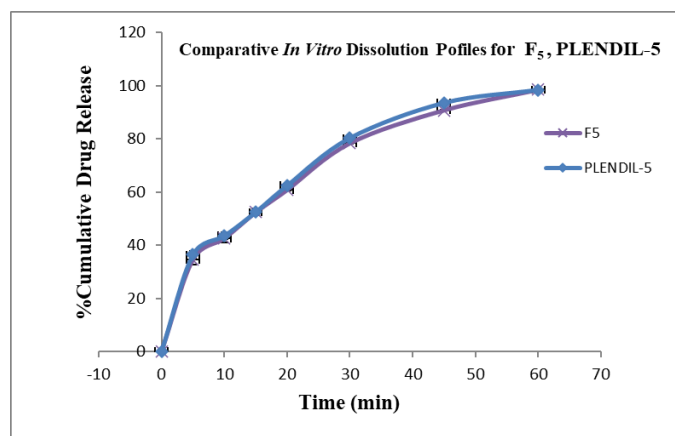
$X_1$ ,  $X_2$ ,  $X_1X_2$ ,  $X_{12}$ , and  $X_{22}$  were tested for their effects on disintegration time (DT) time required for 90% of dissolution ( $t_{90\%}$ ) using the factoring tool. The study's results claimed that two variable factors,  $X_1$ ,  $X_2$ , and  $X_1^2$ ,  $X_2^2$ , show the curve in an additive fashion and parallel to one another. In addition, the coded factor claims that a synergistic effect was observed in binate amount of constrained independent variables such as  $X_1^2$  and  $X_2^2$ .  $X_1$  and  $X_2$  alone could not effectively disintegrate as well as the drug release. Furthermore, the coded factor claims that a negative effect (antagonistic effect) was observed in amounts of constrained independent variables  $X_1X_2$  (-0.863) in the case of drug release. The combination of  $X_1$  and  $X_2$  in an equal ratio at 6 mg (mid-level) provides an appropriate release of the drug compared to the other level of formulations. The interaction between the CCS and SSG in the dissolution medium is most likely to have the maximum drug release. According to the theory, wicking swelling may take place at a rate equal to the moment of front between CCS and SSG. The same has been witnessed in Figure 7-8.

Comparative results for both original dissolution parameters as well as predicted parameters are shown in Table 6. Closeness was observed between the original and theoretical responses. It confirms that the developed equation was valid.

**Table 6.** Predicted vs actual responses for counter-check formulation.

Formulation code	Predicted value		Actual observed value	
	DT (Sec)	$t_{90\%}$ (min)	DT (Sec)	$t_{90\%}$ (min)
CF <sub>1</sub>	70.809	68.038	71.52	68.12
CF <sub>2</sub>	57.708	63.568	57.85	63.67

The *in-vitro* dissolution profile of F<sub>5</sub> was compared with that of Marketed product (PLENDIL-5) tablets, showing similarity  $f_2= 87.35$ ;  $f_1= 1.97$ , and the same was presented in Figure 9.



**Figure 9.** Comparative *in-vitro* dissolution profiles for f<sub>5</sub>, plendil-5.

#### 4. Conclusion

The current study focuses on the impact of super disintegrants, such as sodium starch glycolate and Croscarmellose sodium, on the development of Felodipine FDT. F<sub>5</sub> follows the

first-order type of kinetics, and the Higuchi-type model follows the mechanism of drug release, whereas the mechanism of drug release follows Fickian diffusion. The best formulation, F<sub>5</sub>, may be used for the effective management of Hypertension and Angina Pectoris.

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## Conflicts of Interest

The authors declare no conflict of interest.

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