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Original Article

Formulation Development and Evaluation of Fast Dissolving Tablets of Bisoprolol Fumarate using Response Surface Technique

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ABSTRACT

Objectives: The purpose of the current study was to develop and evaluate Fast Dissolving Tablets (FDT) for the successful management of hypertension and heart failure utilizing the response surface technique. Bisoprolol Fumarate is a highly effective cardio selective beta-blocker. **Materials and Methods:** 12 Fast Dissolving Formulations were developed for Bisoprolol fumarate using various various concentrations of super disintegrants. Among all, The Formulation F_6 showed promising results were considered for further optimization studies as per 3^2 factorial design. The two independent variables under investigation were Lactose (X_1) and Magnesium stearate (X_2). % Friability (Y_1), Wetting time (Y_2), Disintegration time (Y_3), and % Drug release at the end of 10^{th} min (Y_4) were the primary components, or dependent variables. Utilizing the Direct Compression method, FDT formulations of Bisoprolol Fumarate were prepared. Nine trials were created and evaluated as per Pharmaceutical Product Performance. **Results:** The FDT of Bisoprolol Fumarate with quick disintegration (69 sec) and maximum drug release (45.25 min) was successfully prepared using statistical models. Results show that every formulation satisfies the acceptance standards, and the *in vitro* dissolution profiles were subjected to kinetic modeling. **Conclusion:** Based on the desirability, SF_5 formulation contained 8 mg of Lactose and 2 mg of Magnesium stearate, was considered as optimsed one. Formulation (SF_5) follow zero order kinetics, whereas release mechanism found to be non-fickian diffusion, super case transport (n=1.043) consequently, the present investigation unequivocally shows the possible involvement in terms of quick breakdown and ideal drug release.

Keywords: Bisoprolol Fumarate, Super disintegrants, Magnesium stearate, Lactose, Non-Fickian diffusion, Super case transport.

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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 in place of FDT.[1]

It is easy to get tablets that dissolve quickly; in only 60 sec, they break down in the mouth. They exhibit modifications in normal organoleptic properties, such as improved palatability and masking sweetness or taste, depending on the manufacturing procedure. 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, moulding, trituration, lyophilization/freeze drying, named technologies (Durasolv, Orosolv) can be used to prepare FDTs.[2]

When it comes to treating people with essential hypertension, beta-blockers are an essential part of treatment. One of the cardio selective beta-blockers used to treat angina, arrhythmias, hypertension, and coronary heart disease is bisoprolol. Studies have demonstrated that when compared to propranolol, atenolol, and metoprolol, bisoprolol fumarate is more successful in lowering high blood pressure. When it comes to treating people with essential hypertension, beta-blockers are an essential part of treatment. One of the cardio selective beta-blockers used to treat angina, arrhythmias, hypertension, and coronary heart disease is bisoprolol. Studies have demonstrated that when compared to propranolol, atenolol, and metoprolol, bisoprolol fumarate is

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more successful in lowering high blood pressure.[3-5] 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 for performing quicker action against hypertension.

The formulation scientist has a number of tools at their disposal to optimize the produced formulations with statistical significance. Response surface approach was the most extensively utilized statistical technique in both industry and academics out of all the tools available. The aforementioned group included the factorial/response surface approach, central composite approach, Box-Behnken approach, and other well-known methods.[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]

In order to achieve quick disintegration and optimize drug release from the formulation, different super disintegrants were used in different quantities (such as croscaramellose sodium, crospovidone, and sodium starch glycolate) and lactose and magnesium stearate were used for final optimization when creating the Fast dissolving tablets for Bisoprolol Fumarate.

MATERIALS AND METHODS

Materials

A gift sample of Bisoprolol Fumarate was obtained from Merck Ltd., India. We purchased Avicel, Magnesium stearate, and sodium croscarmellose from Aman Scientifics, Vijayawada. We purchased other excipients from High Chemie Ltd., Vadodara.

Methods

Formulation of Fast Dissolving Tablets for Bisoprolol Fumarate

Fast-dissolving tablets containing bisoprolol fumarate were made using the direct compression process. Twelve formulations in total were produced. Following their individual passage through a #60 sieve and collection, the materials were compressed into tablets using a RIMEK 8 station tablet compression machine. The tablets were then lubricated with talc and magnesium stearate. The formulas were shown in Table 1. The ready-made tablets were used to undertake IPQC tests. The completed tablet compositions were transferred to light-resistant, airtight containers so they could be stored and processed further.

Design and Optimization of Rapid Disintegrating Formulations for Bisoprolol Fumarate

It is ideal to create a pharmaceutical formulation that is acceptable in the shortest amount of time while requiring the fewest man-hours and raw materials. Pharmaceutical formulations are typically generated by adjusting One Factor at a Time (OFAT). Formulation F_6 is taken into consideration for a subsequent optimization step based on the quality control criteria. To develop fast-dissolving Bisoprolol Fumarate tablets, the amounts of lactose and magnesium stearate required were identified as independent variables (X_1, X_2). The dependent variable (DT & $t_{90\%}$) were chosen as the disintegration time and the time required for 90% drug drug release. Polynomial equations were derived for the dependent variables using PCP Disso.[15]

For X1 (lactose), there were three levels: 6, 8, and 10 mg. The amounts of magnesium stearate (X2) were 1, 2, and 3 mg. Nine distinct Bisoprolol Fumarate fast dissolving tablet formulations were developed utilizing the direct compression method as per of a 3^2 factorial design. The design arrangement was shown in Table 2.

Evaluation of Bisoprolol Fumarate fast dissolving tablets

Hardness

The Monsanto Tablet Hardness Tester was used to assist with it.

Friability/Durability

The cumulative beginning weight (W_0) was measured using twenty tablets. After 4 min of dedusting with a Roche Friabilator set to 25 rpm, the tablets were weighed again and recorded as (W). To find the proportion of friability (% Friability ≤ wa utilize the following formula.

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

Assay

After choosing twenty tablets, the drug was thoroughly dissolved by grinding each one equally. After weighing and adding 60 mL of methanol to a 100 mL volumetric flask containing 100 mg of bisoprolol fumarate powder, the mixture was sonicated for 10 min. After that, water was added to the methanolic solution to get it up to the required volume. After that, water was added to the methanolic solution to get it up to the necessary volume. Make another 2 mL aliquot out of it to dilute it in 100 mL of 0.1 N HCl. The absorbance of the resulting solution at 220 nm was determined with a UV-visible spectrophotometer.

Thickness

Vernier calipers were used to measure Thickness.

Wetting time

The tablets were put on a petridish with paper that had been soaked in 5 mL of distilled water to measure the wetting time of the tablets. The tablet's wetting time was given in seconds.

In vitro Dissolution Study

In accordance with the recommended approach in the monograph, Bisoprolol Fumarate FDT for the drug release study conducted using 900 mL of pH 6.8 buffer in a Lab-India

Tablet dissolution test apparatus (DS-8000, Paddle type, 50 rpm speed). The samples were collected at predetermined intervals. A UV-Visible spectrophotometer was used to measure the collected samples absorbance at 220 nm. Kinetic modeling was applied to the results.[16-21]

Disintegration test

This test was conducted in compliance with the modified tablet disintegration test specifications. Only 2 mL of the media were allowed to pass through the sieve in a cylinder with a 10 #. The duration of disintegration was noted.[1]

RESULTS AND DISCUSSION

Bisoprolol Fumarate Fast Dissolving Tablets were developed using vaious amounts of super disintegrating agents such as crospovidone, croscaramellose sodium, sodium starch glycolate etc., along with Lactose, Mannitol, Microcrysatlline cellulose as diluent mixture. Using the direct compression approach, 12 distinct formulations of Bisoprolol Fumarate fast-dissolving tablets were developed, each with a different concentration of super disintegrants and based on the formulas listed in Table 1. All formulations showed good results in terms of Hardness, Friability, Weight Variation, Drug Content. It was found that all tablet formulations exhibited a satisfactory mechanical strength and was less brittle. The consistency of weight and drug content of the manufactured tablets fell within acceptable limits. The comparative results for all Post compression parameters were presented in Figures 1A, 1B. The cumulative Drug Release for all formulations were found to be within the range of 99.03-99.95 at the end of 15 Min. The comparative dissolution profiles for all formulations was presented in Figure 2. The dissolution data was fitted to kinetic modeling and results were summarised in Table 3. Formulation F_6 performed promisive characterstics for desired quick disntegration and satisfactory needs for FDT. Hence It

Table 1: Formulae for the Preparation of Bisoprolol Fumarate Fast dissolving tablets.

Name of Ingredients	Quantity of Ingredients per each Tablet (mg)											
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
Bisoprolol Fumarate	5	5	5	5	5	5	5	5	5	5	5	5
Mannitol	55	55	55	55	55	55	55	55	55	55	55	55
Micro Crystalline Cellulose	26	24	22	26	24	22	26	24	22	26	24	22
Lactose	8	8	8	8	8	8	8	8	8	8	8	8
Crospovidone	2	4	6	-	-	-	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	2	4	6	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	2	4	6	-	-	-
PVP K-30	-	-	-	-	-	-	-	-	-	2	4	6
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2
Total Weight	100	100	100	100	100	100	100	100	100	100	100	100

Table 2: Design Layout for the Optimisation of Bisoprolol Fumarate FDTs.

Formulation Code	Coded Values		Quantity in mg	
	X_1	X_2	X_1	X_2
SF_1	-1	-1	6	1
SF_2	0	-1	8	1
SF_3	+1	-1	10	1
SF_4	-1	0	6	2
SF_5	0	0	8	2
SF_6	+1	0	10	2
SF_7	-1	+1	6	3
SF_8	0	+1	8	3
SF_9	+1	+1	10	3
CSF_1	-0.5	-0.5	7	1.5
CSF_2	+0.5	+0.5	9	2.5

Table 3: Kinetic Parameters.

Sl. No.	Formulation Code	Kinetic Parameters											
		Zero order			First order			Higuchi			Korsmeyer-peppas		
		a	b	r	a	b	r	a	b	r	a	b	r
1	F_1	0.961	6.752	1.000	2.334	0.114	0.785	22.29	28.454	0.960	0.783	1.039	1.000
2	F_2	0.899	7.098	0.998	2.496	0.157	0.802	23.49	29.978	0.960	0.796	1.049	1.000
3	F_3	2.823	7.467	0.982	2.385	0.154	0.926	22.78	32.265	0.967	0.839	1.060	0.993
4	F_4	1.469	6.996	0.998	2.401	0.133	0.828	23.38	29.404	0.956	0.802	1.030	0.999
5	F_5	0.911	7.352	0.995	2.597	0.188	0.839	24.40	31.088	0.958	0.817	1.043	0.998
6	F_6	6.335	7.574	0.964	2.651	0.265	0.906	20.79	33.183	0.962	0.924	1.005	0.989
7	F_7	0.526	6.823	1.000	2.300	0.109	0.840	22.31	28.843	0.962	0.776	1.057	0.999
8	F_8	0.510	7.345	0.994	2.403	0.144	0.893	24.23	31.159	0.960	0.797	1.068	0.998
9	F_9	3.228	7.524	0.980	2.451	0.174	0.922	22.66	32.545	0.966	0.862	1.043	0.994
10	F_{10}	0.589	7.091	0.996	2.300	0.113	0.871	23.62	30.132	0.964	0.739	1.112	0.998
11	F_{11}	0.226	7.060	0.996	2.399	0.136	0.786	22.90	30.078	0.967	0.767	1.090	0.998
12	F_{12}	0.869	7.116	0.997	2.478	0.157	0.817	22.48	30.329	0.968	0.824	1.038	0.999

Table 4: Predicted vs Actual Responses for Counter Check Formulation.

Formulation Code	Predicted value				Actual observed value			
	Y_1	Y_2	Y_3	Y_4	Y_1	Y_2	Y_3	Y_4
CSF_1	0.589	55.23	75.27	115.55	0.601	55.81	76.21	116.24
CSF_2	0.375	47.23	56.61	82.03	0.381	47.91	56.75	82.54

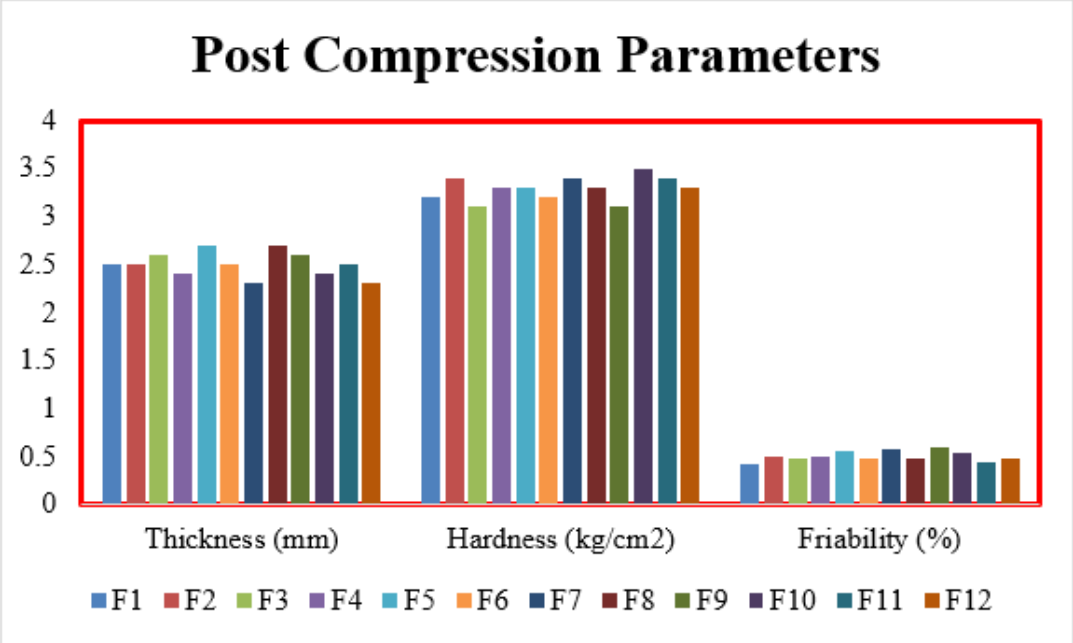

Figure 1A: Thickenss, Hardness, Friability.

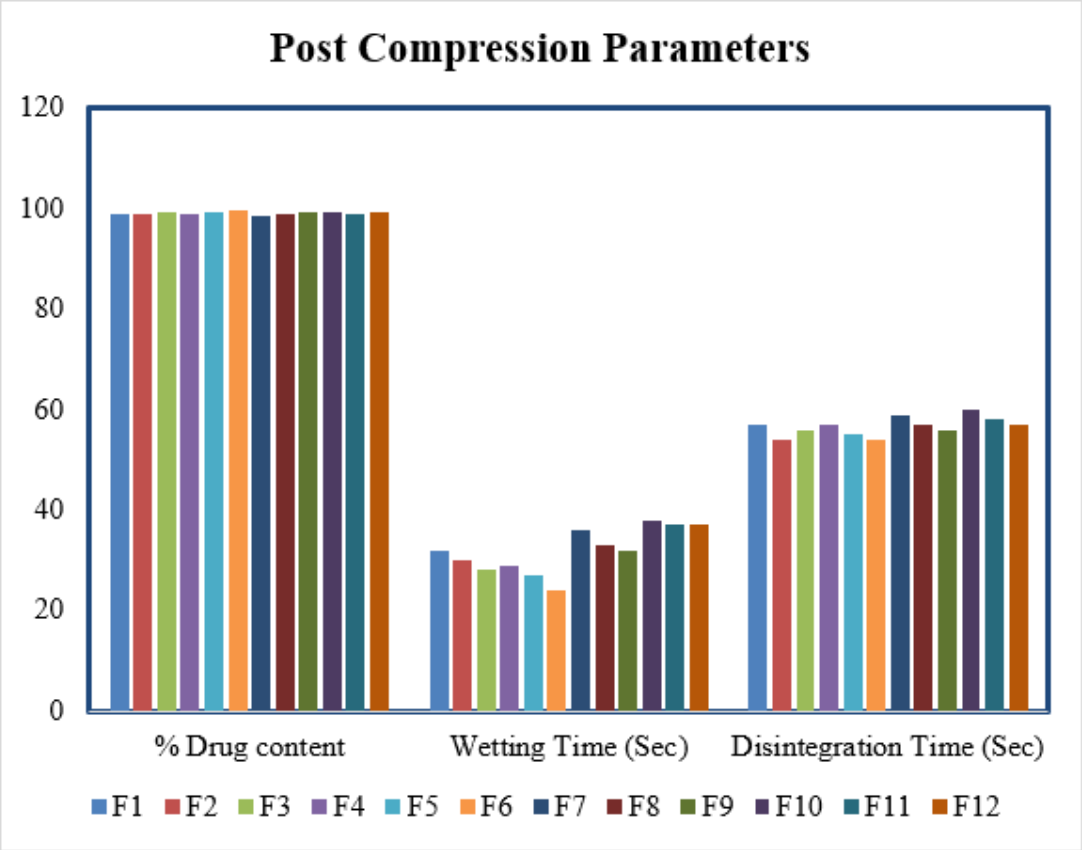

Figure 1B: Drug Content, Wetting Time, Disintegration Time.

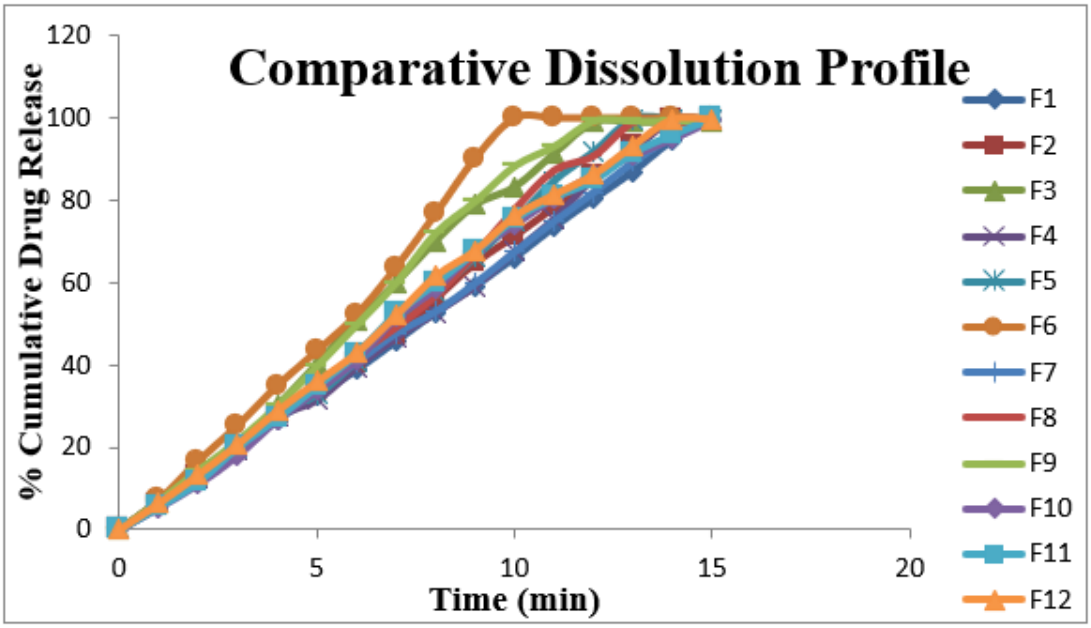

Figure 2: Comparative Dissolution Profile.

was further processed for optimzation process as per 3^2 factorial design technique.

% Friability, Wetting Time (Sec), Disintegration Time (Sec), % Drug release at the end of 10 min were chosen as dependent factors (Y_1, Y_2, Y_3, Y_4 respectively), while the amount needed for Lactose (X_1) and Magnesium stearate (X_2) to make fast dissolving tablets were chosen as independent variables.

Using the direct compression approach, 9 distinct formulations of Bisoprolol Fumarate fast-dissolving tablets were developed, each with a different ratio of super disintegrants and based on the formulas listed in Table 2.

The wetting time for each formulation ranged from 23 to 63 sec. The DT time for each formulation ranged from 45 to 74 sec and the same was represented as Figures 3 and 4.

With the appropriate amounts of lactose and magnesium stearate, the fast disintegration that Bisoprolol Fumarate predicted was achieved. Figures 5 (a-d) displays Response Surface Morphology (RSM) plots that were used to analyze the combined effect of independent variables on dependent variables. Using Sigmaplot V13, RSM graphs were created.[13-15]

Based on desirability, SF5 is thought to be the best formulation of all the batches. With its 8 mg of lactose and 2 mg of magnesium stearate, SF5 demonstrated encouraging dissolving properties that help the study reach its objective by facilitating faster drug release and disintegration.

To calculate the anticipated drug release parameter, polynomial equations were developed and they looked like this:

$Y_1 = 0.489-0.047X_1-0.167X_2+0.028X_1X_2-0.18\ X_1^2+0.124X_2^2$ (% Friability).

$Y_2 = 45.45-14.17X_1+6.17X_2+8.75X_1X_2+8.17\ X_1^2+6.17X_2^2$ (Wetting Time).

$Y_3 = 62-18.83X_1+0.17X_2+5.75X_1X_2+9.5\ X_1^2+0.5X_2^2$ (Disintegration Time).

$Y_4 = 98.95-33.13X_1-0.39X_2-0.352X_1X_2-0.158\ X_1^2-0.138X_2^2$ (Drug Release at the end 10 Min).

Using the factor tool, the impacts of X_1, X_2, X_1X_2, X_1^2, and X_2^2 were evaluated with respect to % Friability, Wetting Time (WT), Disintegration Time (DT), and % Drug Release at the end of 10 min. The study's findings indicated that the two variable factors, X_1, X_2, and X_1^2, X_2^2, exhibit the curve in a parallel and additive manner. Moreover, the coded factor states that a binate amount of restricted independent variables, like X_1^2 and X_2^2, showed a synergistic effect. X_1 and X_2 by themselves were unable to dissolve the medication release as well. Additionally, the coded component states that in the case of medication release, levels of constrained independent variables X_1X_2 (-0.352) showed a negative effect (antagonistic effect). In comparison to the other level of formulations, the combination of X_1 and X_2 in an equal ratio at the mid-level provides a suitable release of drug. The highest drug release occurs most often when lactose and magnesium stearate interact in the dissolving liquid. Wicking theory suggests that swelling could occur at a pace equivalent to

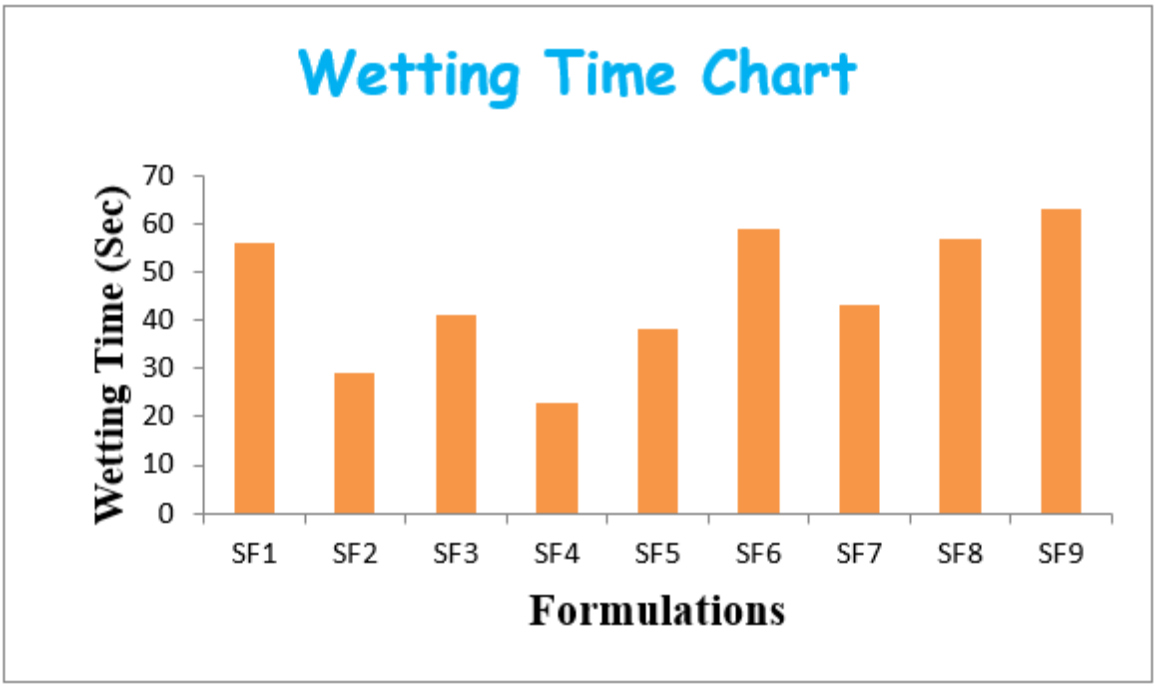

Figure 3: Wetting Time Chart for Factorial Batches.

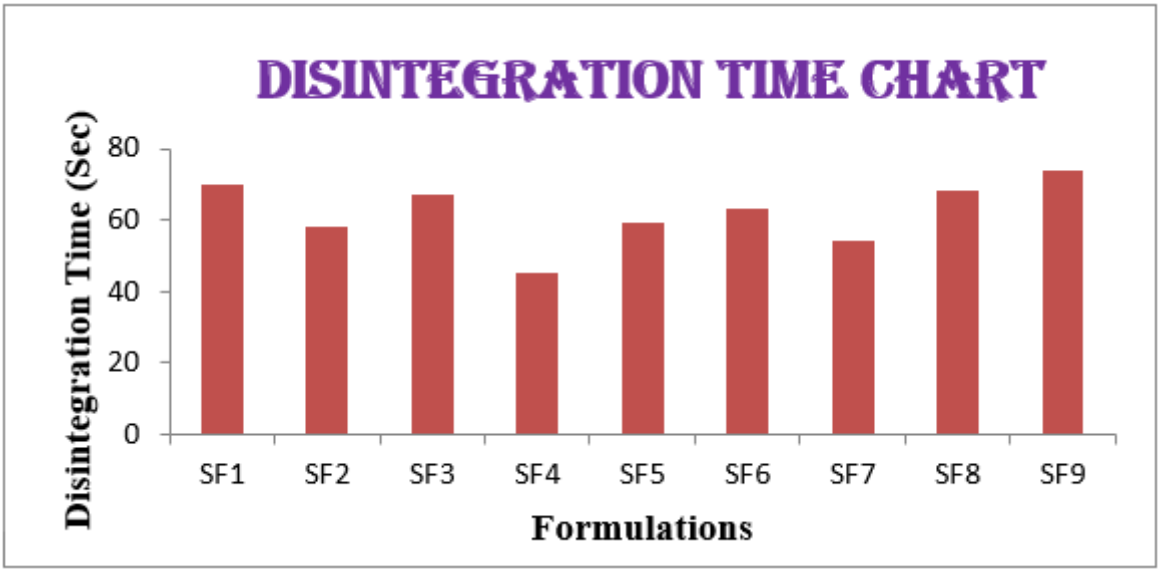

Figure 4: Disintegration Time Chart for Factorial Batches.

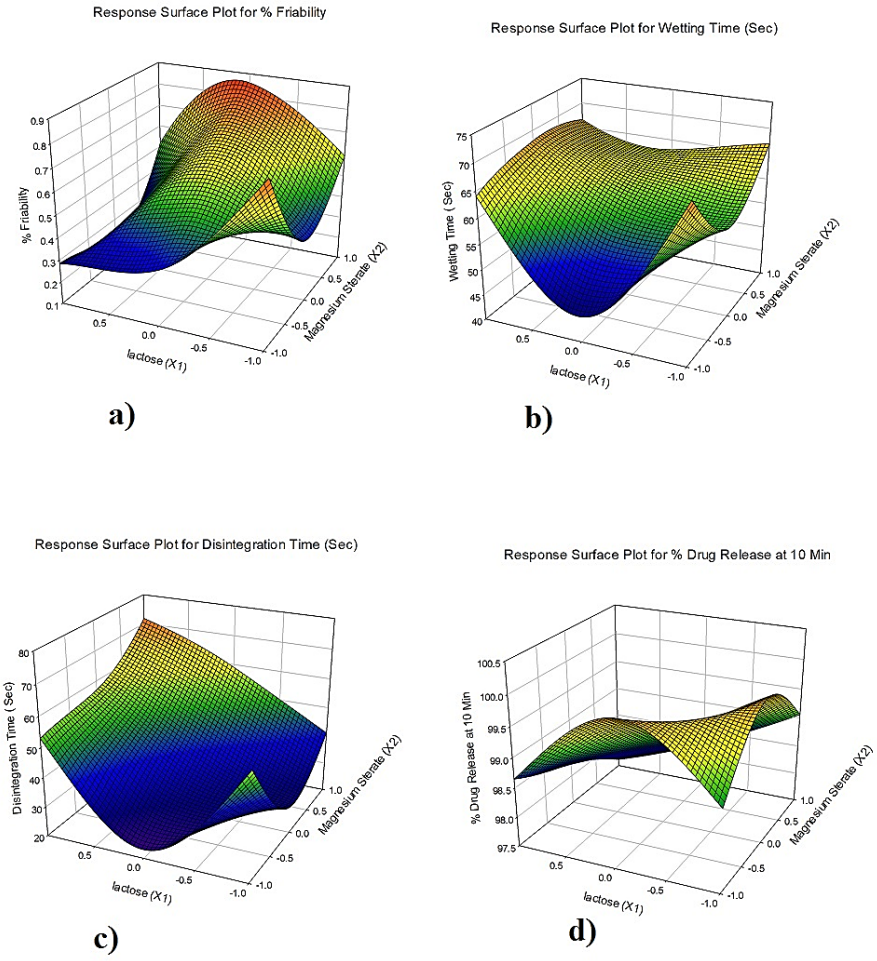

Figure 5: Response Surface Morphology Plot for a) % Friability (Y_1); b) Wetting Time (Y_2); c) Disintegration Time (Y_3); d) % Drug Release at End of 10 min (Y_4).

the moment of front between magnesium stearate and lactose. The same has been witnessed in Figure 5.

Table 4 displayed comparison results for the original dissolution parameters and the anticipated values (Predicted). There was a close relationship found between the theoretical and original answers. It validates the validity of the developed equation.

CONCLUSION

The current study examines the effects of employing superdisintegrants, lubricants, and diluents, such as lactose, magnesium stearate, and croscarmellose sodium, on the development of bisoprolol fumarate FDT. The Final Best (Optimized) Formulation among all is SF_5. It uses a Higuchi type model with zero order kinetics, however the drug release mechanism uses a non-fickian diffusion super case transport mechanism. Angina pectoris and hypertension can be effectively managed with the use of the optimal SF_5 formulation.

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ABBREVIATIONS

FDT: Fast Dissolving Tablet; **FD:** Factorial Design; **OFAT:** One Factor at a Time; **nm:** Nano Meter; **rpm:** Revolutions per Minute; **mg:** Milligram; **mL:** Milliliter; **%CDR:** Percentage cumulative drug release; **DT:** Disintegration time; **WT:** Wetting time.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

This Current study meticulously optimizes the factors/ independent variables on the response/dependent variables for the development of Bisoprolol fumarate fast dissolving tablets for the effective management of Hypertension using response surface technique. Through systemic experimentation, the current research investigation identifies the composotion of lactose, magnesium stearate, directly impacting the tabletting properties. Furthermore, the investigation reveals lactose 8 mg and Magnesium stearate 2 mg produced promising desired release characteristics. This strategic approach elucidates the interplay between factors in facilitating improved rates of diffusion and improved therapeutic outcomes.

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