RESEARCH ARTICLE

Formulation and Optimization of Fast Dissolving Tablets of Zidovudine

Somdutt Yadav*, Naresh Kalra, Pankaj Arora

Faculty of Pharmacy, Lords University, Alwar, Rajasthan, India.

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ABSTRACT

Fast-dissolving tablets (FDTs) have emerged as a prominent alternative to conventional oral dosage forms, particularly for drugs requiring rapid onset of action. This study aims to formulate and optimize fast-dissolving tablets of zidovudine, an antiretroviral medication used in the treatment of HIV/AIDS. The primary objective was to enhance patient compliance by ensuring the tablet disintegrates and dissolves quickly in the oral cavity without the need for water. Using various superdisintegrants like sodium starch glycolate and cross-carmellose sodium into, multiple formulations were prepared. The optimized formulation was evaluated based on pre-compression and post-compression parameters, including hardness, friability, disintegration time, dissolution profile, and drug content uniformity. The study found that the incorporation of superdisintegrants significantly improved the dissolution rate of zidovudine, thus offering a promising approach for patients with swallowing difficulties and ensuring better therapeutic efficacy.

Keywords: Fast dissolving tablets, Zidovudine, Antiretroviral medication, Therapeutic efficacy, superdisintegrants.

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INTRODUCTION

Fast-dissolving tablets (FDTs) of zidovudine are designed to improve the administration and efficacy of this antiretroviral medication used in the treatment of HIV. These tablets rapidly disintegrate in the mouth, allowing for quicker absorption and onset of action, which is crucial in managing viral load effectively.[1] The FDT formulation enhances patient compliance, particularly for those who have difficulty swallowing traditional tablets. Techniques such as direct compression and lyophilization are utilized to create these tablets, ensuring they dissolve within seconds. The convenience and effectiveness of zidovudine FDTs make them a valuable option in HIV therapy.[2,3]

The aim of present work is to formulate and evaluate fast-dissolving tablets of zidovudine to prevent mother to child transmission (MTCT) of HIV virus in perinatal infants.

Formulation of Fast Dissolving Tablets of Zidovudine

Utilising the direct compression approach, zidovudine fast-dissolving tablets have been produced. Formulations were created utilizing two distinct superdisintegrants, namely: Croscarmellose sodium and sodium starch glycolate.

The concentrations of the superdisintegrants were adjusted for each formulation. Within a glass mortar, combine the medication, the superdisintegrants, as well as co-compressed diluents Avicel-HFE 102 and CombiLac® by grinding them thoroughly. Combine the other excipients, such as talc, magnesium stearate, sodium saccharin, and lactose, in the specified order, and effectively obtaining that all materials are completely incorporated.[4,5]

Optimization of Fast Dissolving Tablet by Factorial Design

The zidovudine tablets have been produced employing the direct compression process, which is fast-solving. After precisely mixing the entire components, the mixture was strained through a 100-mesh sieve and subsequently incorporated into the medicinal product for approximately 15 minutes in a bag made from plastic. Lastly, lubricants for example talcum & magnesium stearate, has been incorporated to the powder combinations and stirred once more over five minutes. A single punching tablet press was utilized for compressing the active mixes into 650 mg tablets. The 3^2-factorial approach was implemented to generate the final formulation groups based on the outcomes of the initial batches. The quantities of co-processed additives (X1) as well as Superdisintegrant (X2) became the independent variables. Lower, middle, and highest values have been designated by the three levels chosen for each component (−1, 0, +1). The prior and post-compression characteristics of nine different formulation batches of fast-solving tablets were investigated. This medicine's fast-dissolving tablet formulations in 3^2 factorial patterns are presented into Table 1, along with their respective layouts and compositions.[6-8]

Author for Correspondence: yadavsomdutt1@gmail.com

Table :1 Design Layout of 3^2 Factorial Designs.

Formulation Batches				*X_1*	*X_2*
CSF1	CCF1	ACF1	ASF1	−1	−1
CSF2	CCF2	ACF2	ASF2	0	−1
CSF3	CCF3	ACF3	ASF3	1	−1
CSF4	CCF4	ACF4	ASF4	−1	0
CSF5	CCF5	ACF5	ASF5	0	0
CSF6	CCF6	ACF6	ASF6	1	0
CSF7	CCF7	ACF7	ASF7	−1	1
CSF8	CCF8	ACF8	ASF8	0	1
CSF9	CCF9	ACF9	ASF9	1	1
X_1 :- CombiLac®	X_1 :- CombiLac®	X_1 :- Avicel-HFE 102	X_1 :- Avicel-HFE 102		
X_2:- Sodium Starch Glycolate	X_2:- Crros Carmelose Sodium	X_2:- Crros Carmelose Sodium	X_2:- Sodium Starch Glycolate		

Where 1 is the highest value, −1 is the lower value, and 0 is the middle value for the factors X_1 & X_2

Y1 : Disintegration Time (60 Sec)

Y2 : $t_{90\%}$ (Percentage Release after 30 min)

Optimized Formulations

ANOVA was used to statistically analyze the resultant data, which was entered into Microsoft Excel (MS Excel) and also Minitab 21.2 (Trial Edition). The 3-D response surface approach was also used to analyze the data and find out how cross-carmelose sodium, sodium starch glycolate, Avicel-HFE 102, and CombiLac® affected the dependent variable.[9]

The answer was evaluated using a statistical model that included interactive and polynomial variables.

$$Y= b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2$$

Given that Y represents the dependent variable, b 0 represents the average of the 9 runs, followed by bi (b1, b2, b12, b11, and b22) are the predicted coefficients for the component Xi (X1, X2, X1 X2, X12, and X22). When we increase the value of one element from its lowest to its highest point, the average result is the major impact (X1 and X2). When two variables are changed at the same time, the response changes as shown by the interaction factor (X1 X2). The inclusion of the polynomial factors (X12, X22) allows for the investigation of nonlinearity.[10,11]

One optimisation technology that was used a grid point finding approach. Before looking for the measurements of the t90%, this approach requires first dividing the design space in to a grid and then trying to identify those values. The optimized formula is displayed in Table 2.[12]

Table 2: Optimizes formula table for all the formulations

Ingredients (mg per tablet)	*CSF*	*CCF*	*ACF*	*ASF*
Drug (Zidovudine)	300	300	300	300
CombiLac®	255	275	---	---
Avicel-HFE 102	---	---	214	221
Sodium Starch Glycolate	31.5	----	----	36
Cross Carmelose Sodium	---	25	23	---
Sodium saccharin	2.5	2.5	2.5	2.5
Mint flavor	0.5	0.5	0.5	0.5
Talc	1	1	1	1
Magnesium stearate	2	2	2	2
Camphor	4	4	4	4
Vanillin	4	4	4	4
Lactose	qs	qs	qs	qs
Total Weight	650	650	650	650

RESULTS AND DISCUSSION

Optimized Formulations

Two components were examined employing a full factorial design. The polynomial equations regarding disintegration time and t90% drug release was utilized to describe the impact of variables that were independent upon responses. After taking the magnitude of the coefficients into account, the regression equations derive their conclusions. The affirmative (+) symbol in the polynomial equation indicates that the response increases as the value increases, while the negative representation indicates that the response decreases as the value increases. Changing two variables at once alters the answer, as shown by the interaction terms.

Influence of independent variables on disintegration duration:

(Y1):

ACF:- $Y1=72.33333-22.3333X_1-35.3333X_2 + 6.25X_1X_2+ 1X_1^2+11X_2^2$ (1)

ASF:- $Y1=74-17\ X_1 -31.5\ X_2+2\ X_1X_2-1\ X_1^2+5.5\ X_2^2$ (2)

CCF: - $Y1= 78-13.666\ X_1-28.8333\ X_2-1\ X_1X_2-2\ X_1^2-0.5\ X_2^2$ (3)

CSF:- $Y1 =74-17.1667\ X_1-31.5\ X_2+1.75\ X_1X_2-0.5\ X_1^2+5.5\ X_2^2$ (4)

Our findings from the polynomial equations indicate that the disintegration time of component Y1 increases as the concentration decreases and that the disintegration time of factor X2 (SSG/CCS) decreases as the concentration increases. Figure 1-4 shows the contour plots as well as 3D surface model of formulation ACF, ASF, CCF and CSF of the independent variables X1 and X2, which are involved with the dependent variables Y1 (Disintegration Time) and Y2 (t90%). Significant effects were identified using ANOVA. The R2 values for batches ASF, ACF, CCF, and CSF vary from 0.994 to.0999. Table 3 shows the results of ANOVA of Batch ACF and Table 4 contains the summary output of coefficients of batch ACF. At that degree of probability ($p<0.05$), the result was determined to be significant since the obtained value of F is more than the crucial F-value. Predictions have been based on this model since it was shown to be statistically significant overall. t90% drug release and the effect of independent variables on the substance

(Y2):

ACF:-$Y2=87.56233+5.500167\ X_1+5.921833\ X_2+2.99975\ X_1X_2-0.3435\ X_1^2-1.0785\ X_2^2$ (5)

ASF:-$Y2 =86.84+5.79\ X_1+1.625\ X_2+0.31\ X_1X_2-0.53\ X_1^2+3.445\ X_2^2$(6)

CCF: $Y2 =85.68444+6.175\ X_1+2.458333\ X_2+1.05\ X_1X_2-1.17167\ X_1^2+4.108333\ X_2^2$ (7)

CSF:-$Y2=90.02111+2.71\ X_1+2.031667\ X_2+0.4775\ X_1X_2+1.218333\ X_1^2+1.958333\ X_2^2$ (8)

It was possible to provide a visual prediction of the formulation optimization for the necessary response using simple contour plots. The optimal formulation was determined through optimization using constraints such as desirability analysis. For ACF, it was found to be 214 mg of Avicel-HFE 102 and 23 mg of CCS. For ASF, it was 221 mg of Avicel-HFE 102 and 36 mg of SSG. Table 5 displays the result of ANOVA of batch ASf and Table 6 Contains the summary output coefficient of batch ASF. For CSF, it was 255 mg of CombiLac® and 31.5 mg of SSG. Finally, for CCF, it was 275 mg of CombiLac® and 25 mg of CCS. Table 7 shows the results of ANOVA of batch CCF and Table 8 contains the summary output of coefficients of batch CCF. With these exact amounts, the desired response was achieved. The optimized fast-solving zidovudine tablet recipe was used to ensure that these tablets were made using the optimal levels. Table 9 displays the results of ANOVA of batch CSF and Table 10 contains the summary output coefficients of Batch CSF.

Table 11 has the results of an evaluation of pre-compression parameters of final formulations. The tablets were assessed after the optimized FDT formulation was manufactured using the direct compression technique. The outcomes of

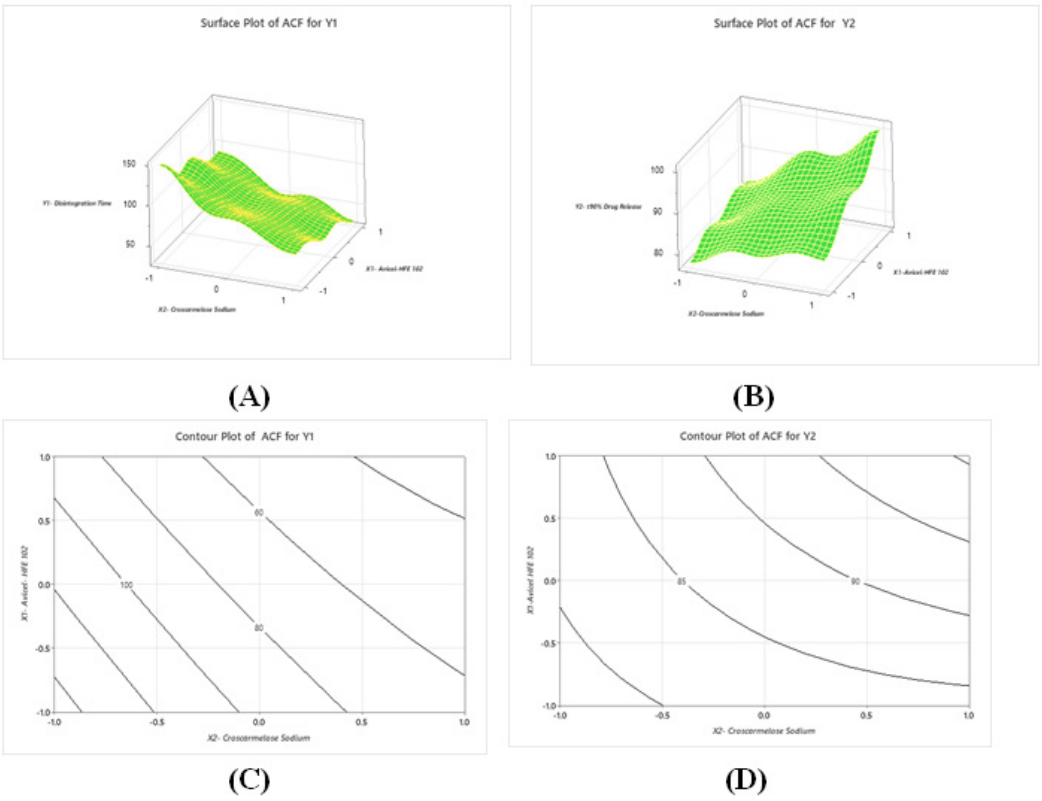

Figure 1: Shows 3D response surface plots and Contour plots of formulation ACF for the effect of super-disintegrates (X1) and co compressed diluents (X2) on the response Y1 (Disintegration Time)

Table 3: Results of ANOVA of Batch ACF

	df		*SS*		*MS*		*F*		*Significance F*		*R Square*	
	Y1	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*
Regression	5	5	10883.6	430.476	2176.72	86.0952	15672.36	6089247.51	8.04E-07	1.05E-10	0.999	0.999
Residual	3	3	0.41667	4.24E-05	0.13889	1.41E-05	15672.36					
Total	8	8	10884	430.476								

Table: 4 Summary output coefficients of Batch ACF

	Coefficients		*Standard Error*		*t Stat*		*P-value*	
	Y1	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*
b0	72.33333	87.56233	0.277778	0.002803	260.4	31242.51	1.24889E-07	7.23158E-14
b1	-22.3333	5.500167	0.152145	0.001535	-146.79	3582.975	6.97127E-07	4.79445E-11
b2	-35.3333	5.921833	0.152145	0.001535	-232.234	3857.662	1.76061E-07	3.84148E-11
b12	6.25	2.99975	0.186339	0.00188	33.54102	1595.539	5.82578E-05	5.42935E-10
b11	1	-0.3435	0.263523	0.002659	3.794733	-129.192	0.032119416	1.02253E-06
b22	11	-1.0785	0.263523	0.002659	41.74207	-405.628	3.02588E-05	3.30429E-08

p-values less than 0.0500 indicate model terms are significant & greater than 0.1000 indicate the model terms are not significant. ($E=10^{power}$)

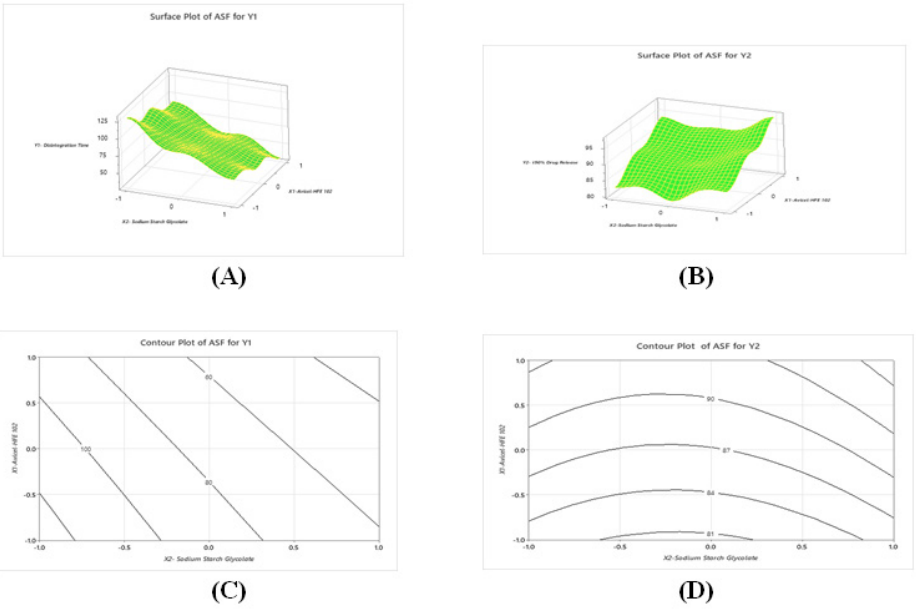

Figure 2: Shows 3D response surface plots and Contour plots of formulation ASF for the effect of super-disintegrates (X1) and co compressed diluents (X2) on the response Y1 (Disintegration Time)

Table 5: Results of ANOVA of Batch ASF

	df		*SS*		*MS*		*F*		*Significance F*		*R Square*	
	Y1	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*
Regression	5	5	7766	241.6706	1553.2	48.33412	5.96E + 31	2.03872E + 30	3.43E - 48	5.42E-46	0.999	0.999
Residual	3	3	7.82E - 29	7.11E - 29	2.61E - 29	2.37E-29						
Total	8	8	7766	241.6706								

($E=10^{power}$)

Table 6: Summary output coefficients of Batch ASF

	Coefficients		*Standard Error*		*t Stat*		*P-value*	
	Y1	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*
b0	74	86.84	3.81E-15	3.63E-15	1.94E+16	2.39E+16	3E-49	1.60971E-49
b1	-17	5.79	2.08E-15	1.99E-15	-8.2E+15	2.91E+15	4.07E-48	8.92386E-47
b2	-31.5	1.625	2.08E-15	1.99E-15	-1.5E+16	8.17E+14	6.39E-49	4.03672E-45
b12	2	0.31	2.55E-15	2.43E-15	7.83E+14	1.27E+14	4.59E-45	1.06817E-42
b11	-1	-0.53	3.61E-15	3.44E-15	-2.8E+14	-1.5E+14	1.04E-43	6.04565E-43
b22	5.5	3.445	3.61E-15	3.44E-15	1.52E+15	1E+15	6.24E-46	2.20142E-45

p-values less than 0.0500 indicate model terms are significant & greater than 0.1000 indicate the model terms are not significant. ($E=10^{power}$)

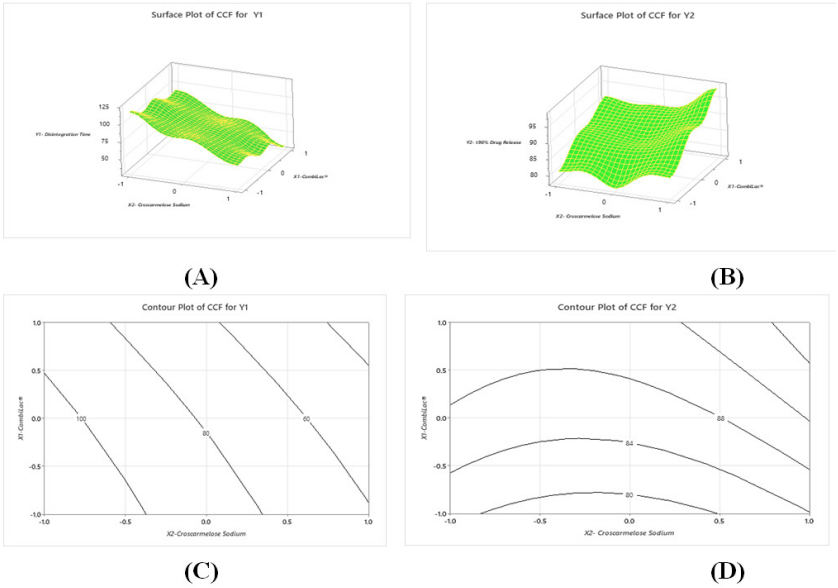

Figure: 3 Shows 3D response surface plots and Contour plots of formulation CCF for the effect of super-disintegrates (X1) and co compressed diluents (X2) on the response Y1 (DT)

Table 7: Results of ANOVA of Batch CCF

	df		*SS*		*MS*		*F*		*Significance F*		*R Square*	
	Y1	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*
Regression	5	5	6121.333	305.9566	1224.267	61.19132	5509.2	93.11961854	3.86E-06	0.001729	0.999	0.994
Residual	3	3	0.666667	1.971378	0.222222	0.657126						
Total	8	8	6122	307.928								

($E = 10^{power}$)

Table 8: Summary output coefficients of Batch CCF

	Coefficients		*Standard Error*		*t Stat*		*P-value*	
	Y1	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*
b0	78	85.68444	0.351364	0.60421	221.9919	141.8123	2.01571E-07	7.73128E-07
b1	-13.6667	6.175	0.19245	0.33094	-71.0141	18.659	6.15357E-06	0.000335995
b2	-28.8333	2.458333	0.19245	0.33094	-149.822	7.428345	6.55648E-07	0.005048501
b12	-1	1.05	0.235702	0.405317	-4.24264	2.590568	0.0239812	0.081034211
b11	-2	-1.17167	0.333333	0.573204	-6	-2.04407	0.009272715	0.133523472
b22	-0.5	4.108333	0.333333	0.573204	-1.5	7.167313	0.230583864	0.005594665

p-values less than 0.0500 indicate model terms are significant & greater than 0.1000 indicate the model terms are not significant. ($E=10^{power}$)

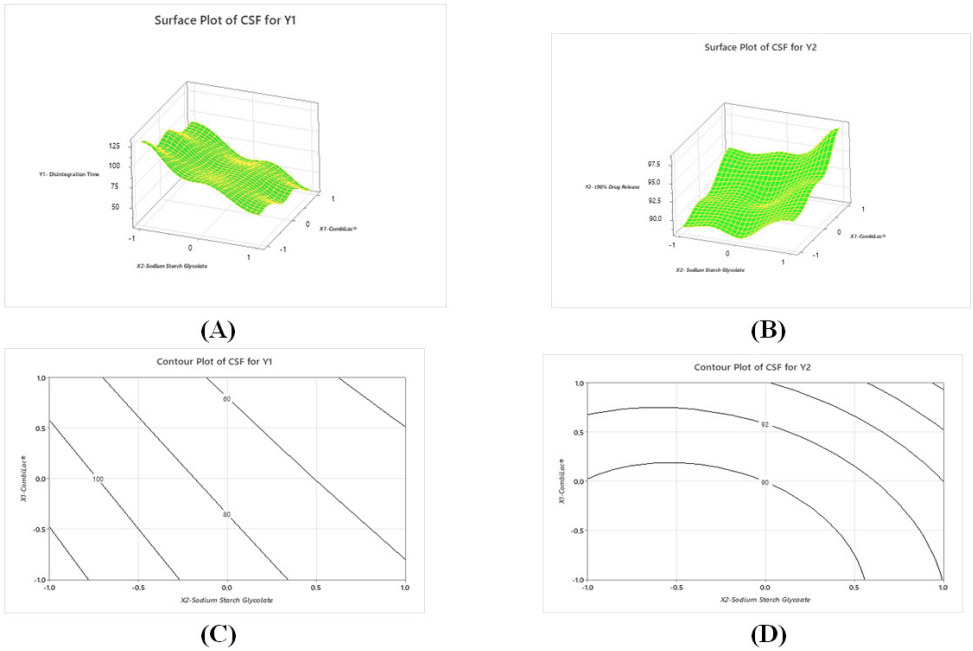

Figure 4: Shows 3D response surface plots and Contour plots of formulation CSF for the effect of super-disintegrates (X1) and co compressed diluents (X2) on the response Y1 (DT)

Table 9: Results of ANOVA of Batch CSF

	df		*SS*		*MS*		*F*		*Significance F*		*R Square*	
	Y1	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*
Regression	5	5	7794.917	80.5442	1558.983	16.10884	1516.849	561211.2	2.67E-05	3.75E-09	0.999	0.999
Residual	3	3	3.083333	8.61E-05	1.027778	2.87E-05						
Total	8	8	7798	80.54429								

Table 10: Summary output coefficients of Batch CSF

	Coefficients		*Standard Error*		*t Stat*		*p-value*	
	Y1	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*	*Y1*	*Y2*
b0	74	90.02111	0.755637	0.003993	97.93059	22543	2.35E-06	1.93E-13
b1	-17.1667	2.715	0.41388	0.002187	-41.4774	1241.299	3.08E-05	1.15E-09
b2	-31.5	2.031667	0.41388	0.002187	-76.1091	928.8789	5E-06	2.75E-09
b12	1.75	0.4775	0.506897	0.002679	3.452379	178.252	0.040866	3.89E-07
b11	-0.5	1.218333	0.71686	0.003788	-0.69749	321.5971	0.535694	6.63E-08
b22	5.5	1.958333	0.71686	0.003788	7.672344	516.9311	0.0046	1.6E-08

p-values less than 0.0500 indicate model terms are significant & greater than 0.1000 indicate the model terms are not significant. ($E=10^{power}$)

Table 11: Evaluation of Pre-compression Parameters of Final Formulations

Parameter	*CSF*	*CCF*	*ACF*	*ASF*
Bulk density (g/mL)	0.481 ± 023	0.484 ± 0.014	0.485 ± 0.021	0.514 ± 0.040
Tapped density (g/mL)	0.584 ± 0.013	0.548 ± 0.023	0.550 ± 0.020	0.587 ± 0.009
Angle of repose	20.30 ± 0.21	24.70 ± 0.13	21.30 ± 0.25	22.78 ± 0.32
Carr's index	17.6 ± 0.15	11.7 ± 0.25	16.6 ± 0.18	12.5 ± 0.21
Hausner ratio	1.21 ± 0.02	1.13 ± 0.01	1.20 ± 0.02	1.14 ± 0.01

Data are represented as mean ± SD (n=3).

Table 12: Evaluation of Postcompression Parameters of Final Formulations

Parameters	*CSF*	*CCF*	*ACF*	*ASF*
Hardness (kg/cm^2)	4.0 ± 0.25	4.2 ± 0.21	4.4 ± 0.23	4.0 ± 0.22
Friability (%)	0.9 ± 0.03	0.62 ± 0.05	0.31 ± 0.05	0.9 ± 0.04
Disintegration time (sec)	22 ± 06	25 ± 04	26 ± 05	20 ± 03
In vitro dispersion time (sec)	31 ± 02	24 ± 03	38 ± 02	24 ± 02
Wetting time (sec)	29 ± 01	26 ± 02	31 ± 01	24 ± 03
Water absorption ratio (%)	91.7 ± 0.09	131 ± 0.10	132 ± 0.13	126 ± 0.15

Data are represented as mean ± SD (n=3).

Table: 13 (A) Post Compression Evaluations of optimized Formulations

Formulationcode	*Hardness(kg/cm$^{3)}$*	*Thickness(mm)*	*Diameter (mm)*	*Drug content (%)*
CSF	4.2±0.05	4.01±03	10.07±0.05	95.74±125
CCF	4.4±0.05	4.01±0.02	10.01±0.05	96.21±1.68
ACF	4.3±0.05	4.01±0.03	10.02±0.05	96.69±1.05
ASF	4.6±0.05	4.02±0.03	10.01±0.05	96.21±2.04

Table 13 (B): Post Compression Evaluations of optimized Formulations

Formulation code	*Weight variation (mg)*	*Friability (%)*	*Wetting time (sec)*	*Water absorption ratio (%)*	*Disintegration time (sec)*
CSF	652.1±3.42	0.51±0.01	45±0.03	101±12	52±3
CCF	654.4±2.98	0.72±0.01	50±0.05	113±10	53±2
ACF	648.4±3.25	0.55±0.02	53±0.02	131±12	56±3
ASF	648.5±3.41	0.56±0.00	46±0.06	144±10	58±1

Table: 14 Dissolution Release Data of all optimized formulations

Time	*CSF*	*CCF*	*ACF*	*ASF*
2	64.7	59.5	68.2	60.8
5	71.7	67.405	72.8	74.8
10	79.11	76.09	78.4	79.4
15	84.03	81.96	84.9	83.4
20	89.25	88.3	88.8	86.7
30	91.08	90.9	91.84	90.5

the post-compression parameters of the final formulation are displayed in Table 12. To confirm the theoretical prediction, the optimized formulation was tested and the results were displayed in Tables 13(A) and 13(B). The dissolution release rate of optimized formulation was also observed and the result of dissolution release data of all optimized formulations has been presented in Table 14. The results, presented in Tables 13 and 14, were consistent across all four formulations. For each answer, we determined the percentage of errors (%) among the experimental and projected values and confirmed that they were all within the acceptable range. Consistent results between the model's predictions and experimental data demonstrate the reliability and applicability of the model.

CONCLUSION

Combining a factorial design with two co-processed diluents (CombiLac® and Avicel-HFE 102) and two superdisintegrants (Croscarmellose Sodium and Sodium Starch Glycolate), the tablets were manufactured utilizing the direct compression technique. We conclude that the factorial design technique allows us to produce an optimal formulation with little work and in the least amount of time. By combining numerical optimization with graphical optimization tools like overlay plots and desirability analysis, a stable, optimized formulation was created according to composition. The optimized formulation exhibited a water absorption ratio of 144, 131, 113 & 101%, disintegration time of 58, 56, 53, 52 Seconds, and t90% drug release of 97.56, 95.5, 97.9 & 96.08% within 30 minutes for ACF, ASF, CCF and CSF, respectively. The design's validity was validated by values that were close to predictions. It was shown that the optimized formulation was compatible and stable.

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