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Advances in Bioresearch

ORIGINAL ARTICLE

Formulation and evaluation of effervescent tablets by DOE

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ABSTRACT
The present study focuses on the formulation and optimization of effervescent cefdinir tablets to enhance drug release and disintegration efficiency. A combination of fumaric acid, tartaric acid, and sodium bicarbonate was employed to achieve rapid effervescence and dissolution. The optimization was carried out using the Box-Behnken design to evaluate the impact of critical formulation variables. UV spectroscopic analysis confirmed a linear calibration curve at 287 nm and 290 nm. FTIR and DSC studies indicated no significant interactions among the formulation components, confirming their compatibility. The inclusion of xanthan gum prolonged the floating time, while the combination of fumaric and tartaric acids significantly reduced disintegration time, enhancing the formulation's performance. The in vitro drug release study followed a diffusion-mediated mechanism, best fitting the Higuchi model, suggesting a controlled release profile. The optimized formulation demonstrated improved stability and dissolution characteristics, making it a promising approach for enhancing cefdinir bioavailability. Accelerated stability studies confirmed the robustness of the formulation under various storage conditions. The effervescent system improved patient compliance by offering ease of administration and rapid onset of action. This study highlights the potential of effervescent technology in improving the therapeutic efficacy of poorly soluble drugs.
Keywords*: Effervescent tablets, Cefdinir, Box-Behnken design, Drug release, FTIR, DSC, Higuchi model, Bioavailability, Optimization, Stability, Patient compliance, Effervescent technology.*

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INTRODUCTION

Rapid drug delivery methods are widely recognized due to their ease of production, compact size, and convenience for self-administration. However, conventional solid dosage forms, such as tablets and capsules, pose a significant challenge for patients who have difficulty swallowing, leading to poor compliance [1]. Fast-dispersible tablets (FDTs) offer an effective alternative, catering not only to individuals with dysphagia but also to those with active lifestyles who require convenient medication intake.Fast-disintegrating tablets dissolve rapidly—often within seconds—upon placement on the tongue, eliminating the need for water. As the tablet comes into contact with saliva, it disintegrates, releasing the active pharmaceutical ingredient (API), which is then absorbed through the gastrointestinal tract (GIT) [1]. The U.S. Food and Drug Administration (FDA) defines FDTs as "a solid dosage form containing medicinal substances that disintegrates rapidly, usually within seconds, when placed on the tongue." Similarly, the European Pharmacopoeia recognizes the term "fast-dispersible tablet" to describe formulations that dissolve quickly before being swallowed [1-3]. These tablets are also referred to as quick-dissolving, rapid-melt, fast-dispersible, or fast-disintegrating tablets[2]. Cefdinir, a Biopharmaceutical Classification System (BCS) Class IV drug, exhibits both low solubility and low permeability, significantly limiting its bioavailability. Class IV drugs dissolve slowly in the aqueous environment of the gastrointestinal tract, reducing their absorption and therapeutic efficacy. However, enhancing the dissolution rate of such drugs can significantly improve their bioavailability, making FDT formulations a promising strategy for optimizing drug delivery [4-7].

MATERIAL AND METHODS

Preparation of tablets

Direct compression technique

The drug, polymers, and other excipients were thoroughly added to a double cone mixture after being weighed individually (Minipress –II, Karnavathi Engineering Ltd., India) and allowed to sit for 15 minutes before being sieved through a 60# sieve. Using a rotating tablet compression machine (RIMEK Mini Press II, make: Karnavathi Engineering, India), the powder was compressed to produce tablets with a 10 mm diameter. A lubricant called magnesium stearate was utilized. Granules' flow and compressibility properties were assessed before compression [4].

Experimental Design

Box Behnken design studies were conducted to investigate the effects of parameters found during exploratory trials on the different qualities of effervescent tablets. The response surface plots were created using Design Expert® software (trial version 7.1.2, Stat-Ease, Inc., Minneapolis, MN) to visually represent the impact of each element on the response. Three amounts were chosen as independent variables: X1, X2, and X3 shown in Tab. These were the amounts of fumaric acid, tartaric acid, and sodium bicarbonate. Disintegration time, carbon dioxide content, and percentage of medication release after five minutes were the dependent response variables that were measured [6-8]. The table 1 displays the composition of design batches as well as the degrees of independent variables in both coded and actual form. The following is the polynomial equation that was produced by design:

Yi=b0+b1X1+ b2X2+ b3X3+ b12X1X2+ b23X2X3+ b13X1X3 +b11X1 2 + b22X2 2 + b33X3 2 (1)

Yi is the dependent variable; X1, X2, and X3 are the independent variables; b0 is the intercept; and b1, b2, b3, b12, b23, b13, b11, b22, and b33 are the regression coefficients. For every batch, three copies were produced and evaluated. After taking into account the dependent variable findings of the experimental design batches, the optimal formulation was chosen. An optimized batch will be defined as one that has a lesser disintegration time and a higher carbon dioxide and drug release within 5 minutes.

Table 1: Experimental design of Cefdinir formulations

Independent variables	Levels		
	Low	Medium	High
Sodium bicarbonate (X1)	50	75	100
Tartaric acid (X2)	20	30	40
Fumaric acid (X3)	30	40	50
Dependent variables			
Y1= Disintegration time			
Y2= Drug release after 5 min			
Y3= swelling studies			

Post-compression physicochemical evaluation of Cefdinir tablets

Visual examination

The created tablets were examined visually to check for common tablet flaws. The tablets had a similar size, shape, and color and were smooth [8].

Weight variation

The following formula was used to get the percent weight variation.

$$\%\,Weight\,Variation = \frac{Average\ weight - Individual Weight}{Average\ weight} X\ 100$$

Hardness Test

It was decided how hard the tablet was by a Monsanto hardness tester (kg/cm^2)

Friability

The tablets' friability was assessed using the Roche friability test instrument.

$$Friability = \frac{Initial weight - Final Weight}{initial\ weight} X\ 100$$

Uniformity of drug composition

Ten pills were coarsely ground into a powder, and then 70 milliliters of methanol were poured into a 100-milliliter volumetric flask after the equivalent of 100 mg had been weighed out. After quivering the flask for five minutes, the volume was adjusted with methanol and clarified via Whatman filter paper having a pore size of 0.45 µm. After that, it was appropriately diluted and examined at 279 nm by a UV Spectrophotometer (Shimadzu UV-1700). The calibration curve was used to compute the amount [9-11].

Studies on buoyancy in vitro

The duration of the dosage form's continuous stay in the medium is known as the total floating time (TFT), However, floating lag time (FLT) refers to the amount of time it takes a tablet to reach the surface. The in vitro buoyancy was calculated using the floating lag time approach as reported by Rosa et al. (1994). The tablets and 100 milliliters of 0.1N HCl were added to a 250-millilitre beaker [5-7].

Swelling

After weighing each produced tablet independently (W0), 50 mL of 0.1N HCl was added to a Petri plate. An incubator maintained at 37±0.5 ºC was used to store the Petri plates. When removing the tablets from the petri dish and reweighing (Wt), predetermined intervals were noted. To obtain the % swelling index (Wu), the following formula was applied.

$$\%WU=W0(Wt-W0/W0)\times 100$$

Where:

Wt – Mass of tablet at time t,

Wo – Mass of the tablet before immersion.

In vitro dissolution studies (Rosa et al., 1994)

Using a USP-Type II paddle apparatus (Electrolab TDT 08L), the release of medicines from the produced floating tablets was investigated. A drug release profile was tested in 900 milliliters of 0.1N HCl at a temperature of 37±0.5°C and 100 revolutions per minute. Up to 12 hours, 5 mL of samples were taken out at regular intervals. The samples were substituted with a corresponding volume of dissolving medium and passed through Whatman filter paper of 0.45 µm. Using a Shimadzu UV 1700 UV spectrophotometer, the materials were appropriately diluted and examined at 265.5 nm (FAM), 279 nm (LAF), and 314 nm (FAM) [4, 12].

Study of Drug Release Kinetics

Using the information gathered from in-vitro release tests, the following kinetic models were plotted to determine the drug release kinetics of the drug. (Higuchi equations, first order, and zero order). Using Korsmeyer Peppas equations, the mechanism of Drug release from the tablets was ascertained [13-16].

RESULTS

Organoleptic characteristics

Table 2 presents the organoleptic characterization of the drug, comparing observed results with reported standards. The drug exhibited a white to light yellow color, was odorless, and appeared as a crystalline powder, all consistent with standard specifications. These attributes confirm the drug's purity and stability, with no signs of contamination or degradation. The melting point, a key parameter for assessing thermal stability and purity, further supports its identity when aligned with the reported standard [17-20].

Table 2: Organoleptic characterization of drug

Identification test	Observed results	Reported standard
Color	white to light yellow	white to light yellow
Odor	Odourless	Odourless
Appearance	Crystalline powder	Crystalline powder

Melting point (MP)

The observed melting point of the drug (170.25 ± 1.35°C) closely aligns with the reported standard range (168-170°C), indicating its purity and consistency, as shown in Table 3.

Table 3: The melting point of the drug

Observation	Avg. M.P	Reported standard
170.25±1.35 ^{0}C	169.51±1.34 ^{0}C	168-170 ^{0}C
168.47±1.24 ^{0}C		
169.83±1.09 ^{0}C		

Solubility

The solubility of Cefdinir varies across different solvents and buffers, with the highest solubility observed in phosphate buffer pH 6.8 (17.85 mg/mL), making it freely soluble. In other solvents like water, ethanol, methanol, chloroform, and dichloromethane, Cefdinir remains sparingly soluble, with solubility values ranging from 0.75 to 12.34 mg/mL shown in table 4.

Table 4: The solubility of Cefdinir

Solvents/Buffers	Solubility (mg/mL)	Solubility
Water	8.83±5.69	Sparingly soluble
Ethanol	12.34±0.24	Sparingly soluble
Methanol	10.64±0.69	Sparingly soluble
Chloroform	8.96±0.13	Sparingly soluble
dichloromethane	1.06±0.002	Sparingly soluble
Phosphate buffer pH 1.2	0.75±1.87	Sparingly soluble
Phosphate buffer pH 6.8	17.85±0.95	Freely soluble

Determination of absorption maxima in Methanol

The UV-absorption spectrum of Cefdinir shows a prominent **λmax at 287 nm shown in figure1 with methanol.**

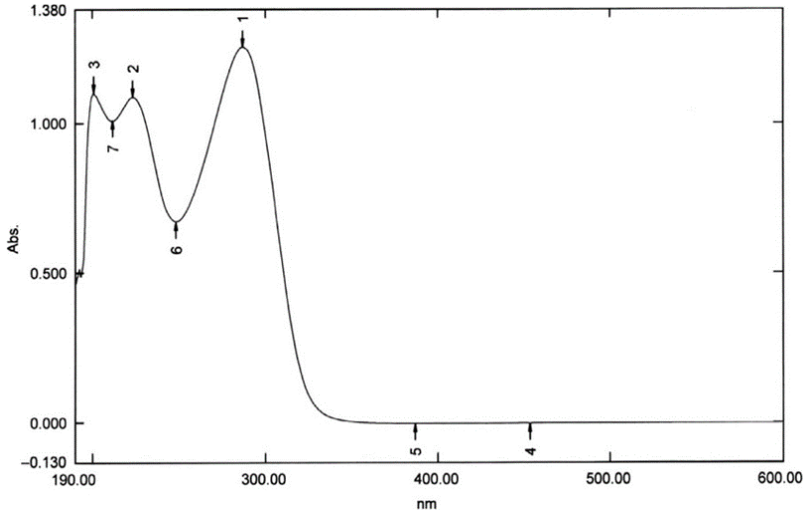

Figure 1: Absorption maxima of Cefdinir in Methanol

Calibration curve of methanol in water

The calibration curve of Cefdinir in water at **λmax = 287 nm** demonstrated a linear relationship between concentration and absorbance, confirming adherence to Beer-Lambert's law shown in figure 2 and table 5.

Table 5: Absorption maxima of Cefdinir in methanol

Concentration (µg/mL)	Absorbance
0.0	0
2.0	0.198±0.02
4.0	0.301±0.06
6.0	0.527±0.08
8.0	0.716±0.07
10.0	0.906±0.05

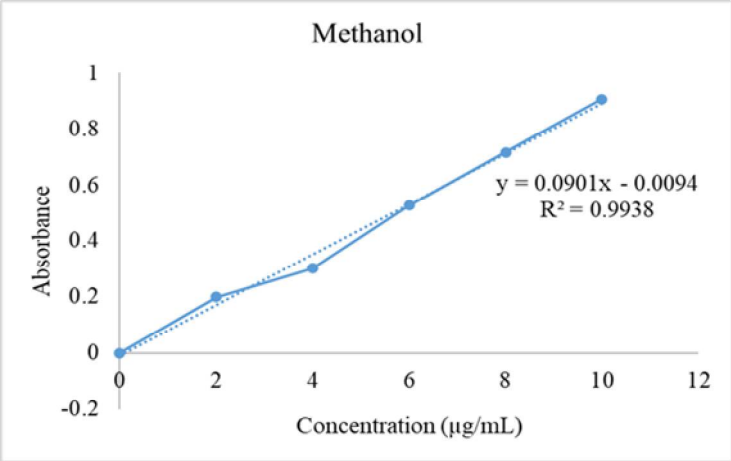

Figure 2: Calibration curve of Cefdinir in Water (λmax-287 nm)

FTIR Spectroscopy

Figure 3 represents the FTIR spectrum of the pure drug Cefdinir, illustrating the characteristic functional group vibrations and confirming its structural integrity through spectral analysis.

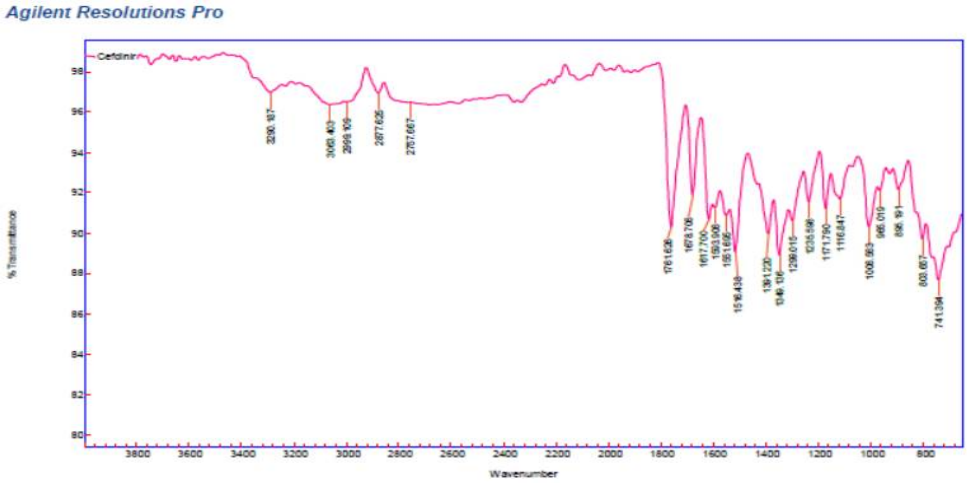

Figure 3: FTIR spectrum of Pure drug (Cefdinir)

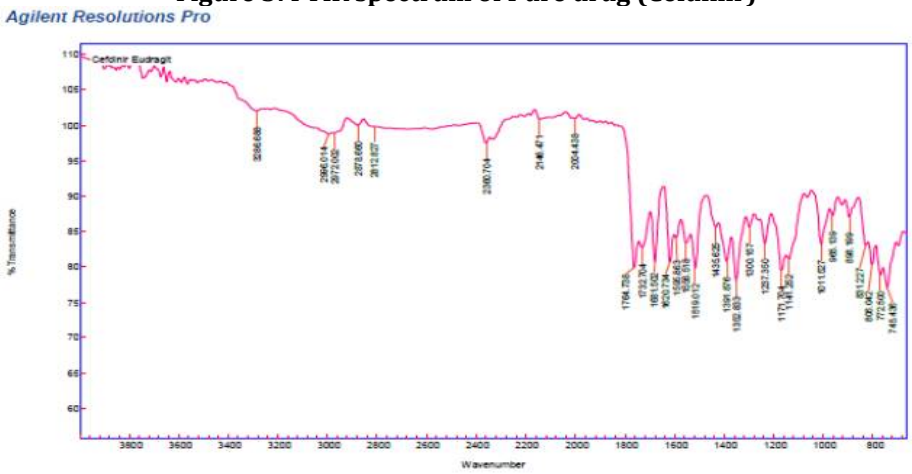

Figure 4: FTIR spectrum of physical mixture

Figure 4 represents the FTIR spectrum of the physical mixture, demonstrating that there are no significant peak changes. This indicates the absence of any notable interactions between the constituent components, confirming their compatibility.

Pre-compressional parameters

The micromeritic properties of cefdinir tablets were evaluated based on various pre-compressional parameters, including bulk density, tapped density, angle of repose, Carr's index, and Hausner's ratio shown in table 6. These pre-compressional parameters indicate that the powder blends of cefdinir tablets possess suitable flow and compressibility properties, making them suitable for further processing into tablet formulations [21-25].

Table 6: Micromeritic properties of cefdinir Tablets

F. Code	Bulk density (g/cm3)	Tapped density (g/cm3)	Angle of repose (θ)	Car's index (%)	Hausner's Ratio
F1	0.476±0.58	0.555±0.60	14.23±0.72	1.16±0.61	27.12±0.28
F2	0.487±0.69	0.587±0.59	17.03±0.63	1.20±0.63	28.16±0.30
F3	0.521±0.63	0.601±0.61	13.31±0.70	1.15±0.51	28.19±0.61
F4	0.499±0.75	0.592±0.57	15.70±0.62	1.18±0.55	25.64±0.52
F5	0.496±0.59	0.591±0.58	16.07±0.59	1.19±0.63	26.19±0.59
F6	0.501±0.72	0.602±0.61	16.61±0.60	1.20±0.59	26.20±0.48
F7	0.512±0.60	0.600±0.53	14.66±0.63	1.17±0.65	29.20±0.64
F8	0.515±0.64	0.612±0.62	15.84±0.64	1.18±0.58	28.16±0.59
F9	0.510±0.65	0.609±0.57	16.25±0.69	1.19±0.65	27.82±0.52
F10	0.499±0.59	0.598±0.63	16.55±0.58	1.19±0.62	26.47±0.55

F11	0.498±0.65	0.597±0.49	16.58±0.61	1.19±0.59	25.97±0.68
F12	0.500±0.62	0.594±0.50	15.81±0.54	1.18±0.54	26.74±0.70
F13	0.512±0.59	0.618±0.52	17.15±0.57	1.20±0.49	28.19±0.72
F14	0.500±0.60	0.601±0.53	16.80±0.59	1.20±0.56	27.90±0.78
F15	0.499±0.63	0.597±0.57	16.41±0.63	1.19±0.55	26.08±0.81
F16	0.489±0.59	0.598±0.62	18.22±0.51	1.22±0.26	26.15±0.85
F17	0.490±0.61	0.596±0.64	17.78±0.50	1.21±0.28	27.34±0.59

Formulation of cefdinir floating tablets

The experimental design shown in table 7 for the formulation of cefdinir floating tablets involved 16 different standard trials, each with varying levels of three independent variables. Results provide insights into the influence of the formulation components on the floating behavior, drug release kinetics, and swelling characteristics of the cefdinir floating tablets. Further statistical analysis and optimization studies can help identify the best formulation with the desired characteristics [26-29].

Table 7: Experiment design of cefdinir effervescent tablets

Std	Run	X1	X2	X3	Y1	Y2	Y3
1	6	50	20	40	12±2	89.61±0.2	186±18
2	17	100	20	40	19±3	75.42±0.4	198±11
3	13	50	40	40	12±1	95.02±0.3	236±12
4	8	100	40	40	22±5	68.42±0.1	136±17
5	16	50	30	30	15±4	82.19±0.5	210±15
6	4	100	30	30	16±2	86.95±0.6	216±16
7	14	50	30	50	16±1	84.13±0.8	221±14
8	1	100	30	50	32±6	46.35±0.9	106±12
9	12	75	20	30	12±2	94.82±0.7	227±13
10	11	75	40	30	27±1	72.15±0.1	134±14
11	2	75	20	50	31±5	59.84±0.5	118±10
12	3	75	40	50	25±3	76.82±0.3	164±12
13	15	75	30	40	17±4	84.15±0.4	185±14
14	9	75	30	40	16±5	86.42±0.1	192±16
15	10	75	30	40	22±1	78.46±0.6	187±12
16	5	75	30	40	15±2	83.19±0.5	195±15
17	7	75	30	40	18±5	85.07±0.3	188±13

Effect of Disintegration Time

The disintegration time for the formulations varied between 12±1 and 32±6 seconds, with the response equation given as: Time of disintegration = 17.60 + 4.25A + 1.50B + 4.25C + 0.7500AB + 3.75AC - 5.25BC - $2.68A^2$ + $1.33B^2$ + $4.82C^2$. Figure 5 represents the contour plot and 3D response surface plot illustrating the influence of Factors A, B, and C on the disintegration time [30].

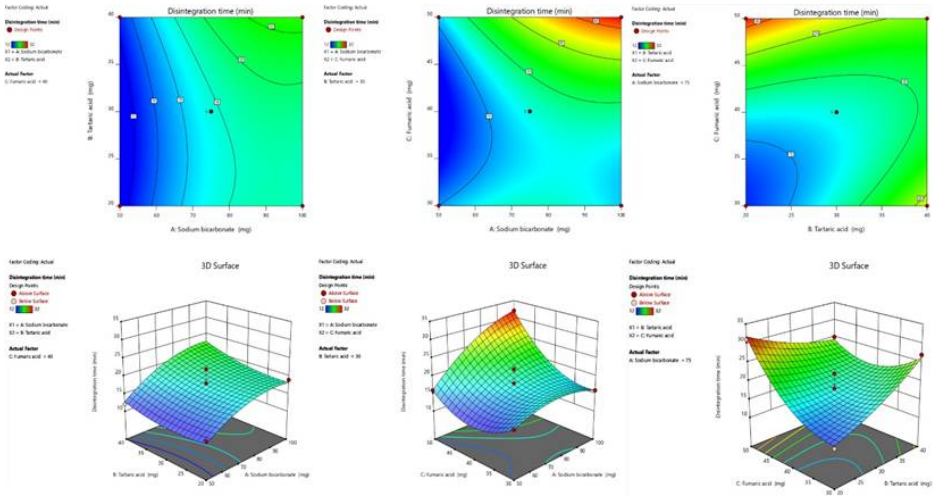

Figure 5: Counter and response 3D Surface Plot for Disintegration Time

Drug Release after 5 min

The drug release after 5 minutes was described by the equation:

Drug Release (%) = 83.46 - 9.23A - 0.9100B - 8.62C - 3.10AB - 10.64AC + 9.91BC - 1.17A^2 - 0.1690B^2 - 7.38C^2.

Figure 6 presents the contour plot and 3D response surface plot, demonstrating the impact of Factors A, B, and C on the drug release percentage [25].

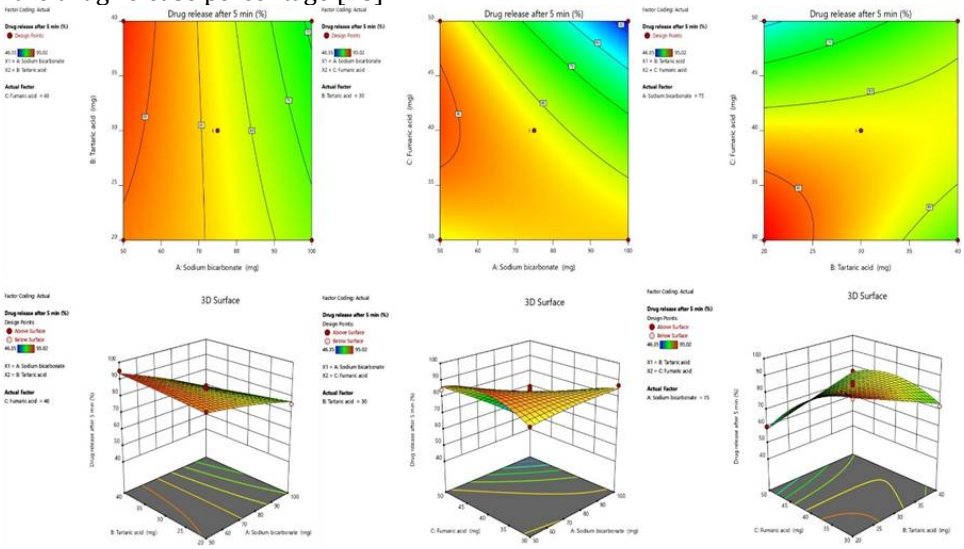

Figure 6: Counter and response 3D Surface Plot for Drug Release after 5 Min

Swelling index studies

The swelling index for all formulations ranged from 106±12 to 236±12, with the response equation: Swelling Index = 189.40 - 24.63A - 7.38B - 22.25C - 28.00AB - 30.25AC + 34.75BC + 13.55A^2 - 13.95B^2 - 14.70C^2. Figure 7 represents the contour plot and 3D response surface plot, highlighting the influence of Factors A, B, and C on the swelling index.

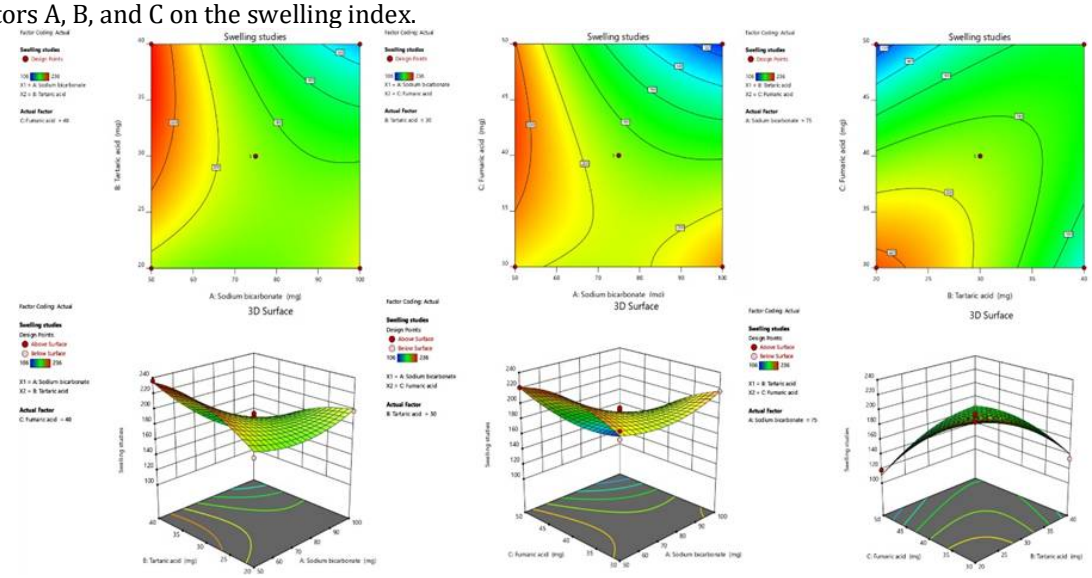

Figure 7: Counter and response 3D Surface Plot for swelling index

Post-compression physicochemical evaluation of cefdinir effervescent tablets

The post-compression evaluation **of** Cefdinir effervescent tablets shown in table 8. Confirmed uniform weight variation (597±0.48 to 602±0.50 mg) and hardness (4.5±0.48 to 5.2±0.52 Kg/cm^2)**.** Friability (0.21±0.81% to 0.41±0.86%) and thickness (4.01±0.32 to 4.45±0.83 mm) were within acceptable limits. Drug content (89.50±0.63% to 98.85±0.65%) ensured uniformity. The floating lag time (1±0.58 to 3±0.83 min) and floating time (8±0.75 to 13±0.76 hours) confirmed efficient gastric retention, demonstrating the formulations' suitability for effervescent drug delivery [31-33].

Table 8: Post-compression parameters

F. no	Weight variation	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Drug content (%)	Floating lag time (min)	floating time (hr)
F1	600±0.50	4.5±0.48	0.29±0.85	4.01±0.32	95.10±0.75	1±0.58	8±0.75
F2	598±0.39	4.8±0.52	0.35±0.78	4.11±0.42	89.50±0.82	2±0.60	10±0.68
F3	599±0.52	4.9±0.47	0.28±0.79	4.21±0.38	91.20±0.56	3±0.72	9±0.71
F4	600±0.43	5.1±0.44	0.31±0.82	4.18±0.53	93.15±0.71	2±0.67	8±0.63
F5	598±0.58	5.2±0.52	0.28±0.83	4.45±0.83	94.20±0.58	2±0.68	9±0.75
F6	600±0.32	4.9±0.49	0.29±0.85	4.19±0.53	92.19±0.53	1±0.70	11±0.72
F7	599±0.39	5.0±0.53	0.30±0.79	4.12±0.55	89.50±0.63	1±0.72	13±0.76
F8	600±0.41	5.1±0.49	0.28±0.78	4.19±0.63	98.85±0.65	2±0.68	12±0.83
F9	599±0.53	5.0±0.52	0.21±0.81	4.20±0.72	97.10±0.71	2±0.78	11±0.85
F10	597±0.48	4.9±0.40	0.22±0.80	4.16±0.68	89.53±0.68	2±0.75	9±0.78
F11	598±0.52	5.0±0.48	0.30±0.77	4.09±0.29	96.30±0.73	3±0.83	8±0.79
F12	600±0.53	4.9±0.53	0.32±0.75	4.20±0.40	91.34±0.69	3±0.79	8±0.78
F13	601±0.48	5.0±0.50	0.40±0.70	4.21±0.52	96.90±0.70	2±0.78	8±0.70
F14	602±0.50	4.8±0.49	0.39±0.91	4.17±0.63	92.21±0.82	3±0.80	9±0.66
F15	599±0.53	4.9±0.47	0.39±0.92	4.19±0.42	93.60±0.78	2±0.87	11±0.53
F16	600±0.58	5.0±0.53	0.41±0.86	4.20±0.49	97.80±0.68	1±0.88	10±0.50
F17	598±0.62	5.1±0.55	0.45±0.82	4.14±0.56	94.40±0.60	2±0.79	13±0.63

Stability analysis

The stability study showed no significant changes in appearance over six months. At 40ºC / 75% RH, drug content decreased from 98.85% to 95.48%, and floating time reduced from 9.9 to 8.6 hours. At 25ºC / 60% RH, drug content declined to 94.38%, with floating time reducing to 8.3 hours. The formulation remained stable with minimal variations shown in table 9.

Table 9: Stability studies of optimized formulation

Stability chamber	Time	Appearance	Drug content	Floating time
40º C ± 2º C / 75% RH	Initial	Brownish colour	98.85±0.65	9.9±0.68
	1 Month	No change	98.82±0.62	9.5±0.62
	2Months	No change	97.78±0.53	9.4±0.58
	3Months	No change	96.52±0.40	8.9±0.52
	6 Months	No change	95.48±0.43	8.6±0.63
25º C ± 2º C / 60% RH ± 5% RH	Initial	No change	98.85±0.65	9.9 ±0.68
	1 Month	No change	97.75±0.58	9.4±0.60
	2Months	No change	96.58±0.45	8.9±0.64
	3Months	No change	95.47±0.40	8.6±0.52
	6Months	No change	94.38±0.38	8.3±0.53

***In vitro* drug release studies**

The *in vitro* drug release study compared the optimized and marketed formulations, with drug release kinetics summarized in Table 10 and Figure 8. The cumulative drug release (%CDR) increased over time, reaching 98.18% at 8 hours. The drug release followed kinetic models, as shown by the **log** transformations and ARA values [21].

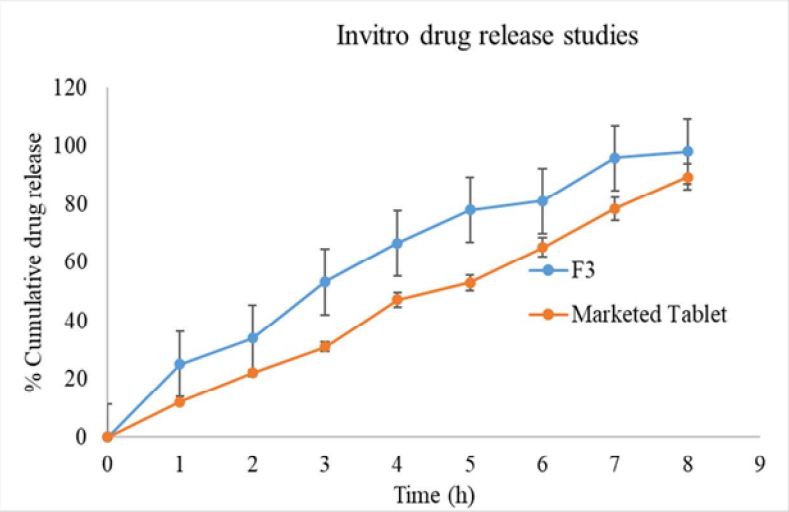

Figure 8: Drug release studies of Optimized and marketed formulation

Table 10: displays the Drug Release Kinetics

TIME	%CDR	SQUARE T	LOG T	LOG%CDR	ARA	LOG%ARA
0.0	0	0	0	0	0	0
1.0	25.23	1	0	1.401917	74.77	1.873727
2.0	34.08	1.415314	0.30103	1.5325	65.92	1.819017
3.0	53.43	1.732051	0.477121	1.727785	46.57	1.668106
4.0	66.62	2	0.60206	1.823605	33.38	1.523486
5.0	78.1	2.236068	0.69897	1.892651	21.9	1.340444
6.0	81.16	2.44949	0.778151	1.909342	18.84	1.275081
7.0	96.10	2.645751	0.835098	1.982723	3.9	0.591065
8.0	98.18	2.828427	0.90309	1.992023	1.82	0.260071

CONCLUSION

According to the study's findings, the production of effervescent tablets using a combination of fumaric acid, tartaric acid, and sodium bicarbonate helps to accomplish cefdinir's faster drug release and faster disintegration. The optimization technique utilized the Box-Behnken design, and the impact of process factors and their interplay on the effervescent preparation was examined. The calibration curve was linear, indicating that 287 nm and 290 nm were the wavelengths employed for cefdinir. According to FTIR and DSC, there was no significant interaction between the components, indicating that the components chosen were perfectly suitable for the formulation. According to the study, it was raised by using Xanthum gum, which has a longer floating time for cefdinir, and by adding more polymer. When assessing the stability of cefdinir cefixime floating tablets, drug release is a crucial component. To shorten the disintegration period, an acid mixture was also tested. Fumaric and tartaric acids together produced rapid breakdown. Box Behnken design was used for additional optimization. The regression value Higuchi's plot showed that the in-vitro release plots of all the cefdinir floating tablet formulations were diffusion-mediated and suggestive of zero-order release.

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