Formulation Optimization & Evaluation of Fexofenadine Hydrochloride Capsule

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***Abstract*—The present study focused on the formulation optimization and evaluation of Fexofenadine Hydrochloride immediate-release capsules. Preformulation studies were conducted to characterize and establish the analytical profile of the drug. Organoleptic evaluation confirmed that Fexofenadine Hydrochloride was a white, odorless, and bitter powder consistent with standard specifications. The melting point was found to be 195°C, indicating satisfactory purity and compliance with the reported reference range. A UV-Visible spectrophotometric method was developed using 0.1 N HCl as the solvent system. The maximum absorption wavelength (λmax) was observed at 225 nm. A calibration curve was constructed over the concentration range of 0–25 µg/mL and exhibited excellent linearity with the regression equation y = 0.0385x − 0.0242 and correlation coefficient (R^2) of 0.9978. Formulation optimization was performed using Central Composite Design (CCD) under Response Surface Methodology (RSM). Croscarmellose Sodium (X_1) and Crospovidone (X_2) were selected as independent variables, while Disintegration Time (DT) and Percentage Drug Release (%DR) were considered dependent responses. B7 optimized batches (B1–B10) were prepared and evaluated through in-vitro dissolution studies. All formulations demonstrated rapid drug release, achieving 92.34–98.30% release within 60 minutes. Regression analysis indicated that both super disintegrants positively influenced drug release ($\%DR = 96.95 + 1.83X_1 + 1.11X_2$) and negatively affected disintegration time ($DT = 4.01 - 0.6051X_1 - 0.6155X_2$). ANOVA results confirmed the statistical significance of the developed models ($p < 0.05$). The optimized formulation exhibited rapid disintegration and enhanced drug release, demonstrating the effectiveness of super disintegrant optimization in immediate-release capsule development.**

***Index Terms*—Fexofenadine Hydrochloride, Immediate-Release Capsules, Croscarmellose Sodium, Crospovidone.**

I. Introduction

Hard gelatin capsules are one of the most widely used solid dosage forms in pharmaceutical technology. They consist of a two-piece shell made primarily of gelatin, which encloses the drug substance in powder, granule, or pellet form. These capsules are designed for oral administration and offer an efficient and convenient method for drug delivery. The gelatin shell is usually composed of gelatin, water, and sometimes colorants and preservatives to enhance appearance and stability. Hard gelatin capsules are preferred due to their ease of manufacturing, accurate dosing, and ability to mask unpleasant taste and odor of drugs. They also provide flexibility in formulation, allowing combination of multiple ingredients within

a single unit. The shells dissolve rapidly in the gastrointestinal tract, releasing the drug for absorption. Capsule sizes vary depending on the dose requirement, making them suitable for a wide range of therapeutic applications. In addition, they improve patient compliance due to their smooth texture and ease of swallowing. The formulation of hard gelatin capsules requires careful selection of excipients to ensure proper flow, stability, and drug release. Overall, hard gelatin capsules play a crucial role in modern pharmaceutics as a reliable and versatile dosage form.

UV Estimation of Fexofenadine Hydrochloride:

Method of Preparation of 0.1 N HCl:

Preparation of 0.1 N HCl Take ~8.3 mL of concentrated HCl, add it slowly to about 500 ml distilled water (never water to acid), Mix and allow to cool, Make up the volume to 1000 mL with distilled water. Shake well then prepared of 0.1 HCl.

Calibration Curve of Fexofenadine Hydrochloride 0.1N HCl:

Accurately weighed 10 mg of Fexofenadine Hydrochloride was transferred to 100 ml volumetric flask and dissolved in 100 ml of 0.1N HCl to obtain concentration 100 µg/ml. Aliquots 0.5, 1, 1.5, 2, 2.5 ml were pipetted out in 10 ml volumetric flask. The volume was made upto the mark with 0.1N HCl. These dilutions 5,10,15,20 and 25, µg/ml concentration solution of Fexofenadine Hydrochloride respectively. Absorbance of each solution was measured at 225 nm using UV visible spectrophotometer (Shimadzu 1800) and 0.1N HCl as reference standard and the standard curve was generated.

Preparation of Fexofenadine Hydrochloride Capsule Method:

- Weigh all the ingredient properly.
- Pass all powders through #60 mesh sieve to remove lumps and get uniform particle size.
- Mix Fexofenadine HCl + Microcrystalline Cellulose + Croscarmellose sodium thoroughly for minutes.
- Add talc & mix for 2 minutes to improve flow.
- Add magnesium stearate and mix gently for 2–3 minutes (do not overmix).
- Fill the prepared blend into hard gelatin capsules using manual capsule filling machine.

- Remove excess powder from capsule surface.
- Check for defects like weight variation, cracks, improper filling.
- Pack in airtight container and store in a cool, dry place.

Fig No. 1 Manual Capsule Filling Machine

Experimental

Central Composite Design (CCD):

Central Composite Design (CCD) is a statistical optimization method widely used in pharmaceutical research. It is a part of Response Surface Methodology (RSM) and helps study the relationship between multiple variables and their effects on responses. In this study, CCD was used to analyze the effect of formulation variables such as the concentration of Croscarmellose Sodium (X1) and Crosspovidone (X2). These independent variables influence dependent variables like drug release (%) and disintegration time. The concentrations of excipients were varied according to the experimental design, while other factors were kept constant. The responses were evaluated using Design Expert software. CCD helps in optimizing drug formulations, studying drug release behaviour, and improving stability and bioavailability. This method involves conducting experiments with different combinations of variables at

various levels. It includes factorial points (minimum and maximum levels) and axial points to understand curvature effects. The collected data is analysed using statistical tools like regression analysis and ANOVA. CCD helps identify significant factors and their interactions, allowing researchers to determine optimal conditions. It improves formulation efficiency, reduces cost, and enhances product quality. Overall, CCD is a powerful tool for developing effective and robust pharmaceutical formulations.

Table No. 1. Formulation Variables with Their Actual Coded Values

Independent Variables	**Unit**	Actual Coded Value	Levels				
			-α	Low	Medium	High	+α
Croscarmellose Sodium % (X1)	%	X1	0	1.25	6.875	12.5	14.82995
Crossprovidone % (X2)	%	X2	3.4467	5	8.75	12.5	14.0533

Table No. 2: Response Variables with Their Actual Coded Values

Response Variables	**Unit**
Drug Release (Y1)	%
Disintegration Time (Y2)	Minute

Table No.3: Factor combination as per the Experimental Design

Experiment No.	Croscarmellose Sodium		Crossprovidone	
	Actual (mg)	Coded	Actual (mg)	Coded
B1	2.75	-1	5.62132	+α
B2	2.75	-1	1.37868	- α
B3	0	-α	3.5	0
B4	0.5	0	2	-1
B5	0.5	0	5	+1
B6	5	+1	5	+1
B7	2.75	-1	3.5	0
B8	5	+1	2	-1
B9	5.93198	+α	3.5	0
B10	2.75	+1	3.5	0

Table No 4: Composition of Optimized Batches of Fexofenadine HCl Capsule by Central Composite Design

Ingredient (mg/Capsule)	Batches									
	B1	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**	**B10**
Fexofenadine HCl	60	60	60	60	60	60	60	60	60	60
Microcrystalline Cellulose	159.32	169.92	171.5	174	166.5	155.25	164.62	162.75	156.67	164.62
Croscarmellose Sodium	6.8	6.8	0.0	1.25	1.25	12.5	6.8	12.5	14.82	6.8
Crossprovidone	15	4	8.75	5	12.5	12.5	8.75	5	8.75	8.75

Magnesium Stearate	7.25	7.25	7.25	7.25	7.25	7.25	7.25	7.25	7.25	7.25
Talc	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50
Avg.Wt	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Evaluation Parameter of Fexofenadine Hydrochloride Capsules

1.Bulk Density

Bulk density is determined by weighing a known quantity of capsule powder and transferring it into a graduated measuring cylinder. The volume occupied by the powder without tapping is noted as the bulk volume. It is calculated as mass divided by bulk volume (g/mL). This test helps in evaluating flow properties and selecting suitable capsule size.

$$Bulk\ density = \frac{Mass\ of\ powder\ in\ gm}{Bulk\ voulme\ of\ powder\ in\ ml}$$

2.Tapped Density

Tapped density is determined by taking a known weight of capsule powder and placing it in a graduated cylinder. The cylinder is then tapped mechanically (usually 100–500 taps) until the volume becomes constant. The final reduced volume is noted as tapped volume. Tapped density is calculated as mass divided by tapped volume (g/mL). It indicates packing ability and helps evaluate flow properties of the powder.

$$Tapped\ density = \frac{Weight\ of\ powder\ in\ gm}{Tapped\ voulme\ of\ powder\ in\ ml}$$

3.Angle of Repose

Angle of repose is determined by allowing the capsule powder to flow through a funnel to form a conical heap on a flat surface. The height (h) and radius (r) of the heap are measured. The angle of repose (θ) is calculated using tan θ = h/r. It indicates the flow property of the powder. Lower angle shows good flow, while higher angle indicates poor flow.

$$\Theta = \tan - 1\ (h/r)$$

4.Hausner's Ratio

Hausner ratio is determined using bulk density and tapped density of the capsule powder. First, measure the bulk density by noting the initial volume, then determine tapped density after tapping the cylinder until constant volume. The Hausner ratio is calculated as Tapped Density / Bulk Density. It indicates flow property of the powder. A value close to 1 (≤1.25) shows good flow, while higher values indicate poor flow.

$$Hausner, s\ Ratio = \frac{\rho b}{\rho t}$$

5.Carr's Index

Carr's Index is determined using the bulk density and tapped density of the capsule powder blend. First, measure bulk density (initial volume) and then tapped density after tapping until constant volume. It is calculated as:

$$Carr's\ Index = \frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density} \times 100$$

It indicates compressibility and flow property of powder. Values <15% show good flow, while >25% indicate poor flow.

6.Weight Variation

Select 20 capsules or tablets randomly from the batch. Weigh each unit individually using a calibrated analytical balance. For capsules open the capsule, remove the contents, and weigh the empty shell. Calculate the net weight of contents by subtracting shell weight from total weight. Determine the average weight of all units. Compare individual weights with the average weight. Calculate the percentage deviation for each unit. Check whether the deviations fall within pharmacopoeia limits (IP/BP/USP).

$$Percentage\ Deviation = \frac{Individual\ Weight - Average\ Weight}{Average\ Weight} \times 100$$

In-Vitro Dissolution Studies and Disintegration Studies

1. Dissolution Studies

The dissolution test is performed using USP Apparatus II (Paddle method) (Electro lab TDL08L). Use 900 mL of dissolution medium such as 0.1 N HCl maintained at 37 ± 0.5°C. Set the paddle rotation speed at 50 rpm as per protocol. Place one capsule carefully into each dissolution vessel. Start the apparatus and begin timing immediately. Withdraw 5 mL samples at predetermined time intervals (e.g., 5, 10, 15, 30, 45, 60 minutes). Replace each withdrawn sample with equal volume of fresh medium to maintain sink conditions. Filter the samples using Whatman filter paper or membrane filter. Analyze the filtered samples using UV Spectrophotometer at λmax (~220–225 nm for Fexofenadine HCl). Determine the drug concentration using a calibration curve. Calculate the percentage drug release at each time point. Plot a graph of % drug release vs time to obtain dissolution profile. Compare the results with pharmacopeial limits or reference formulation. Ensure the test is performed in triplicate or six units for accuracy and reproducibility.

2. Disintegration Studies

The disintegration test is performed using a USP disintegration test apparatus (basket-rack assembly). Six capsules of fexofenadine hydrochloride 350 are selected randomly. The capsules are placed individually in each tube of the basket. Distilled water or simulated gastric fluid (without enzymes) is used as the immersion medium. The temperature of the medium is maintained at 37 ± 2°C to simulate body conditions. The basket is moved up and down at a constant frequency of 28–32 cycles per minute. Discs may be used if the capsules tend to float during the test. The test is continued until all capsule shells completely disintegrate. Disintegration is defined as the breakdown of the capsule into small particles with no intact core remaining. The time taken for complete disintegration of each capsule is recorded. According to pharmacopeial standards, capsules should disintegrate within 30 minutes unless otherwise specified.

3. Stability Studies

Stability Studies were carried out as per ICH guidelines Q1A (R2). The optimized formulation was wrapped in aluminium pouch & desiccant container. the stability study of formulated Capsule was carried

out at (40c±2°c/75% RH ± 5% RH) conditions and at room temperature for a period of one month. The effect of temperature and time on the physical characteristics of the Capsule were evaluated for assessing the stability of the prepared formulations.

II. RESULT AND DISCUSSION

1. Organoleptic Properties:

Table No.1. Organoleptic Properties of Fexofenadine Hydrochloride Capsule

Sr. No.	Properties	Observation	Standard
1	Color	White	White powder
2	Odor	Odorless	Odorless
3	Taste	Bitter	Bitter

2. Melting Point Determination:

Table No. 2. Melting Point of Fexofenadine Hydrochloride Capsule

Sr. No.	Fexofenadine Hydrochloride	Melting Point
1	Standard	192 -209°C
2	Observed	195°C

3. UV Estimation of Fexofenadine Hydrochloride (0.1 N HCl):

A solution of fexofenadine hydrochloride was prepared in (0.1 N HCl) and UV Spectrum was recorded using UV- Visible Spectrophotometer (Shimadzu-1800), in ranges of 200-400 nm. The wavelength was obtained at 225nm.

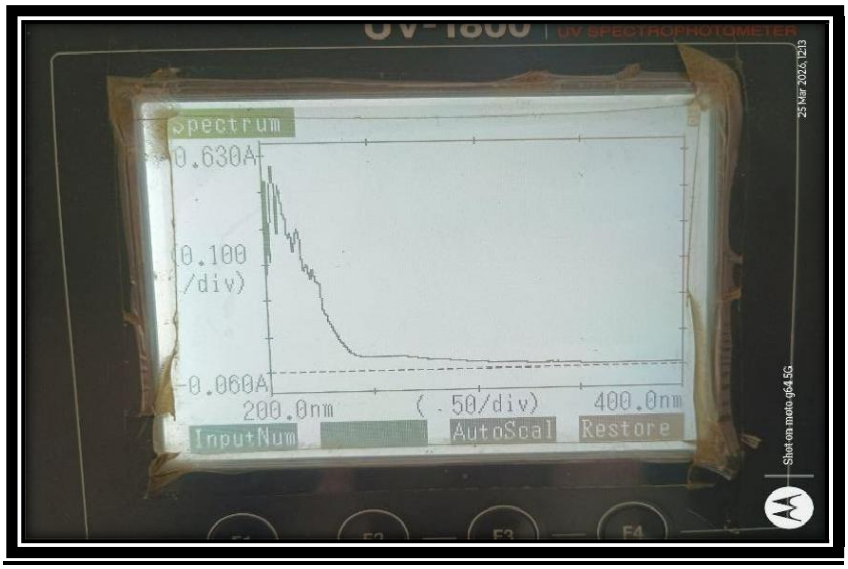

Fig.No.3. Wavelength of Fexofenadine Hydrochloride (0.1 N HCl)

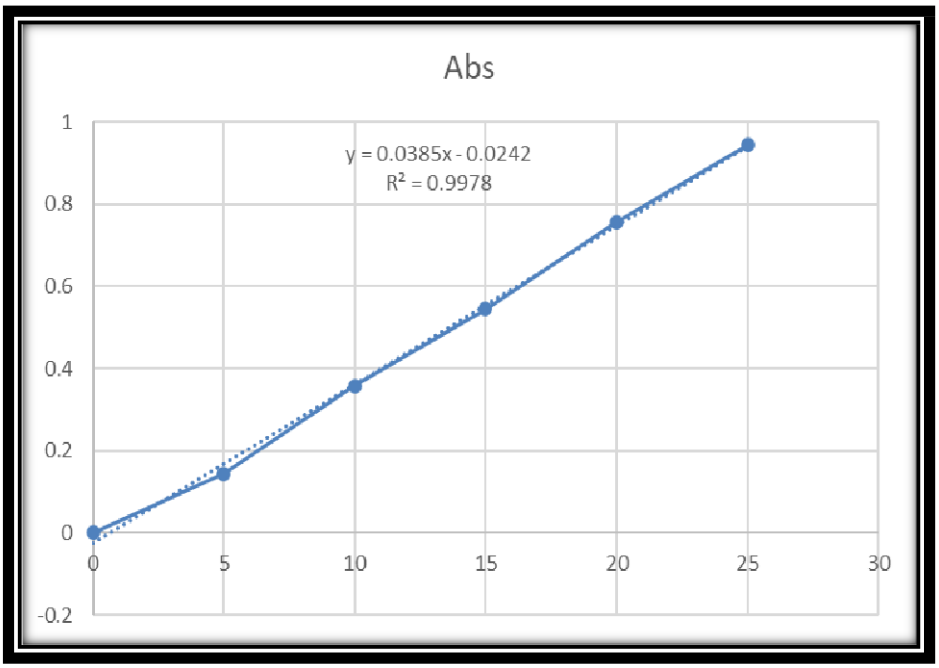

Fig. No. 3.1: Calibration Curve of Fexofenadine Hydrochloride (0.1 N HCl)

4. Fourier Transform Infrared Spectroscopy:

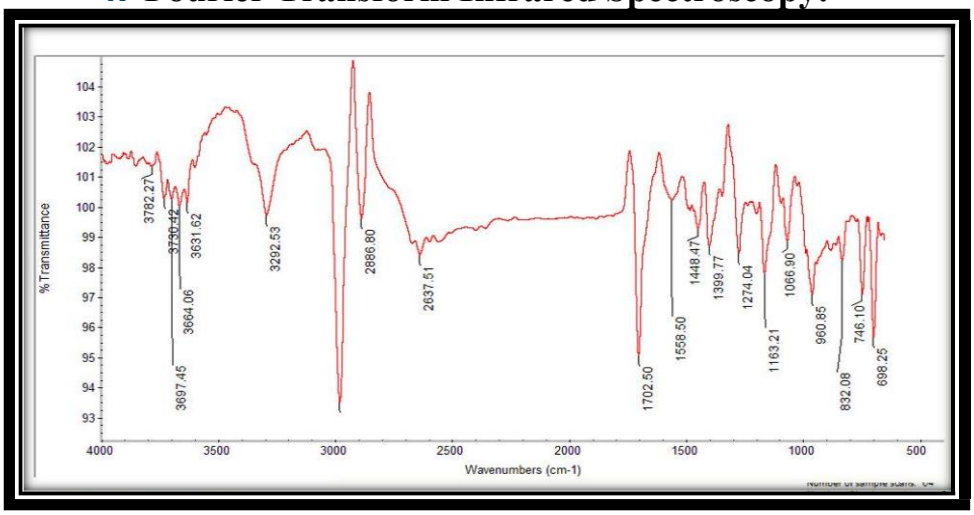

Fig. No. 4.1. FT-IR Spectrum of Fexofenadine Hydrochloride

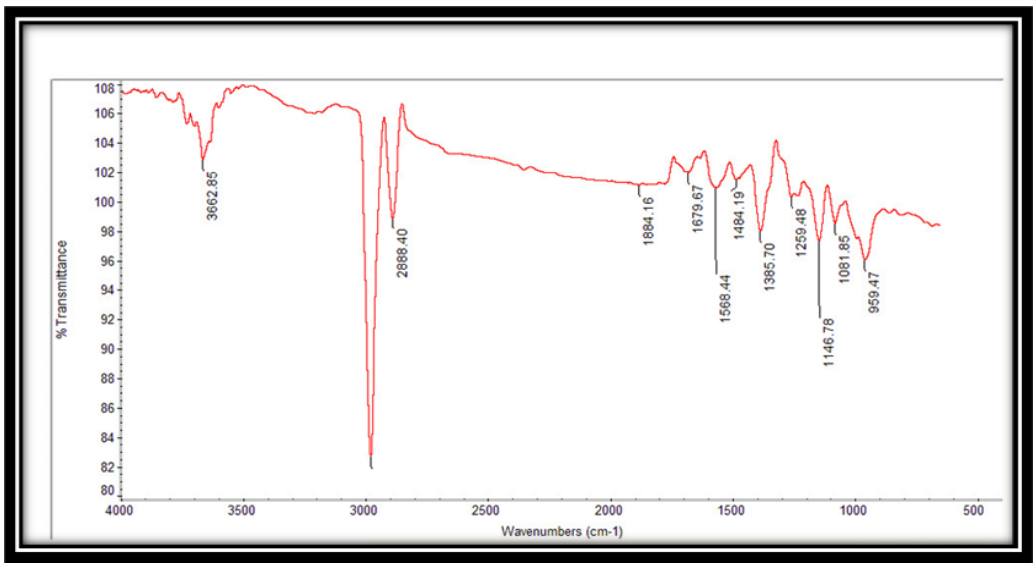

Fig No. 4.2. FTIR Spectrum of Croscarmellose Sodium

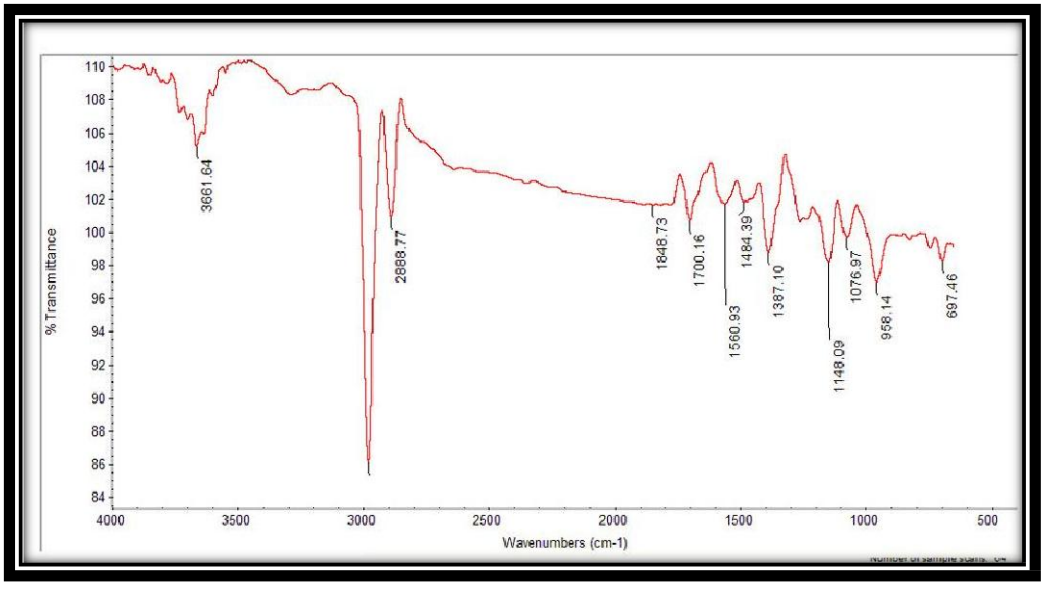

Fig. No. 4.3. FTIR Spectrum of Fexofenadine Hydrochloride + Croscarmellose Sodium

5. Differential Scanning Colorimetry (DSC):

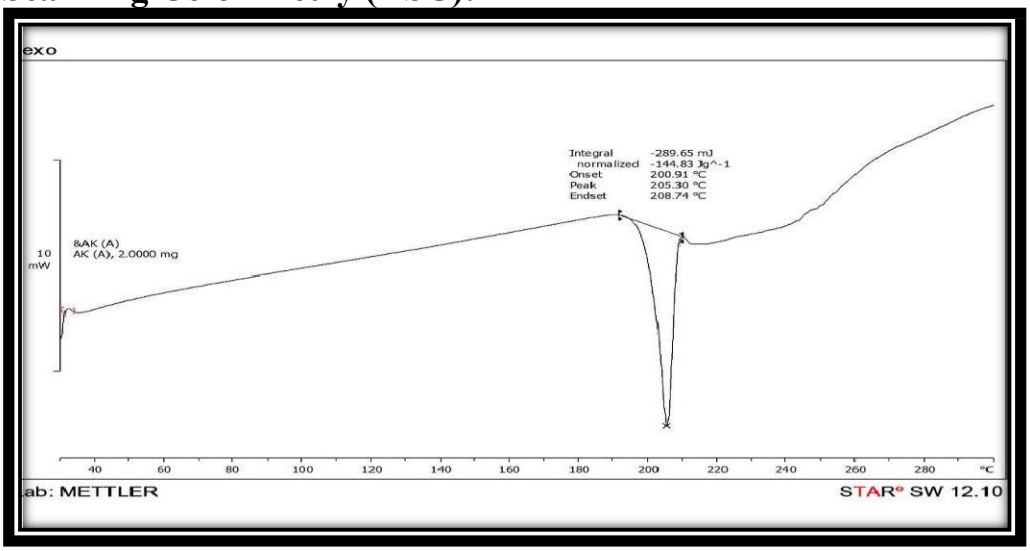

Fig. No. 5.1. DSC Thermogram of Fexofenadine Hydrochloride

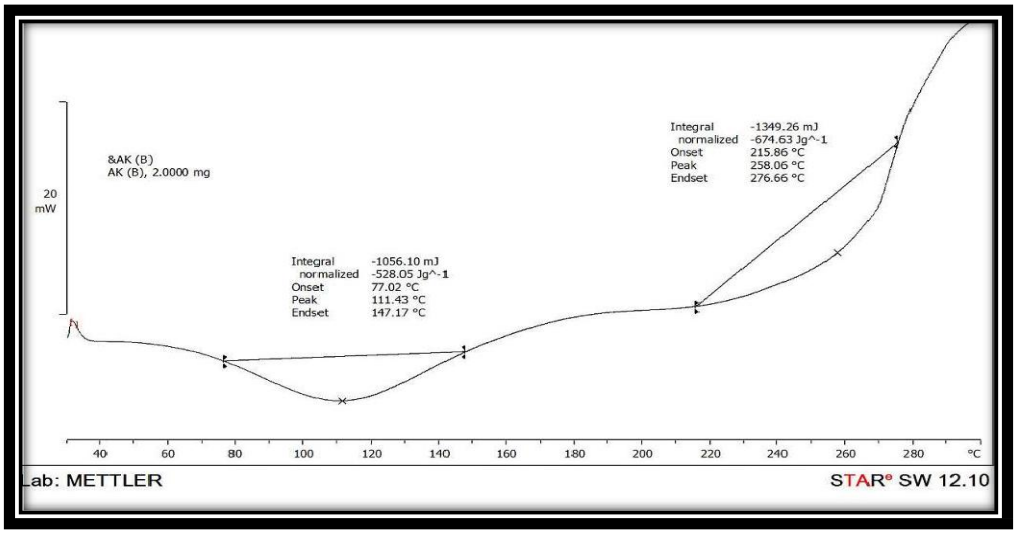

Fig. No. 5.2. DSC Thermogram of Croscarmellose Sodium

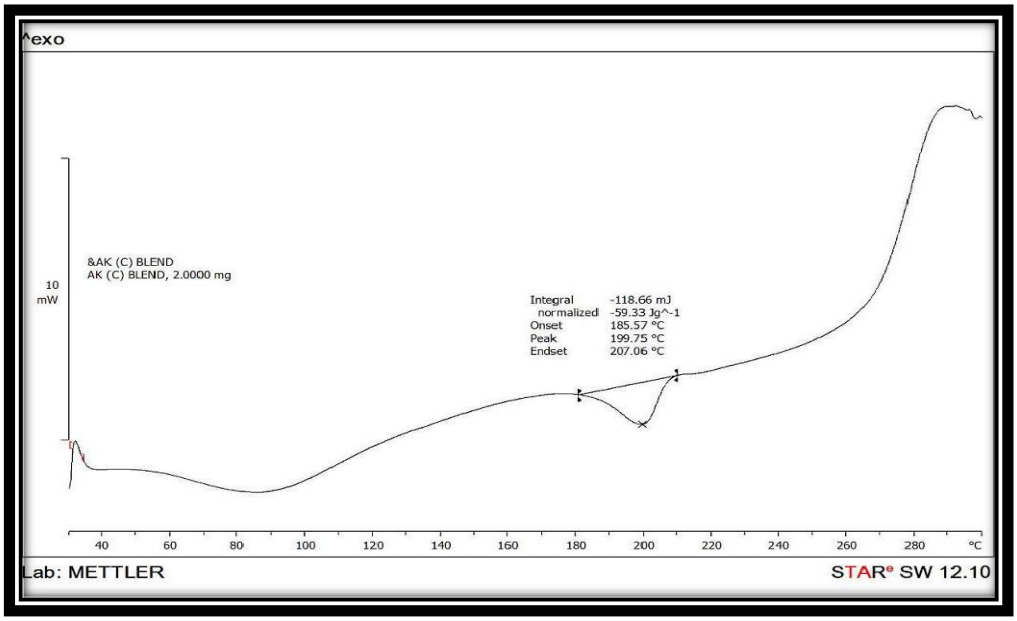

Fig. No. 5.3. DSC Thermogram of Fexofenadine Hydrochloride + Croscarmellose Sodium

Table No.5.4 DSC Values

Sr.no	Chemical	DSC Thermal Transition (°C)	Enthalpy (J/G)
1.	Fexofenadine Hydrochloride	205.30	-144.83
2.	Fexofenadine Hydrochloride + Croscarmellose Sodium	199.75	-59.33

6. Evaluation Parameter of Optimized Batches Fexofenadine Hydrochloride Capsules

Table No. 6.1 Evaluation Parameters of Optimized Batches of Fexofenadine Hydrochloride Capsules

Batches	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (Degree)	Weight Variation (%)
B1	0.40±0.02	0.50±0.02	20.0±0.02	1.25±0.01	36.9±0.01	0.344±0.002
B2	0.42±0.02	0.52±0.03	19.2±0.03	1.24±0.02	36.5±0.02	0.348±0.002
B3	0.39±0.06	0.49±0.04	20.4±0.05	1.26±0.03	37.2±0.01	0.344±0.004
B4	0.41±0.02	0.51±.0.03	19.6±0.06	1.24±0.01	36.9±0.01	0.346±0.003
B5	0.39±0.01	0.48±0.01	18.0±0.02	1.23±0.03	35.5±0.02	0.343±0.001
B6	0.42±0.04	0.53±0.04	20.8±0.02	1.26±0.04	38.3±0.01	0.349±0.001
B7	**0.40±0.01**	**0.50±0.01**	**20.0±0.01**	**1.25±0.02**	**37.8±0.02**	**0.348±0.002**
B8	0.42±0.02	0.52±0.02	19.2±0.03	1.24±0.04	36.5±0.01	0.347±0.001

B9	0.39±0.04	0.49±0.04	20.4±0.04	1.26±0.01	38.1±0.02	0348±0.001
B10	0.40±0.01	0.50±.0.01	20.0±0.01	1.25±.0.02	37.8±0.02	0.348±0.004

7. In-Vitro Dissolution Studies of Optimized Batches of Fexofenadine Hydrochloride Capsules

Table No.7.1: In-Vitro Dissolution Studies of Optimized Batches of Fexofenadine Hydrochloride Capsules

Time (min)	%Drug Release Batches									
	B1	B2	B3	B4	B5	B6	**B7**	B8	B9	B10
0	0	0	0	0	0	0	**0**	0	0	0
5	24.57	26.86	26.86	23.43	26.29	22.28	**30.86**	26.86	33.71	30.86
10	52.58	53.72	54.29	52.00	54.86	50.86	**52.58**	38.86	68.58	52.58
15	70.86	68.58	69.15	66.29	72.01	68.58	**71.44**	68.58	83.44	71.44
30	81.72	80.58	82.29	78.87	84.58	80.01	**83.44**	91.44	88.01	83.44
45	88.58	89.15	86.87	86.30	90.30	89.15	**91.44**	93.15	92.58	91.44
60	97.73	94.30	93.87	94.30	96.58	97.64	**98.30**	97.73	92.34	98.30

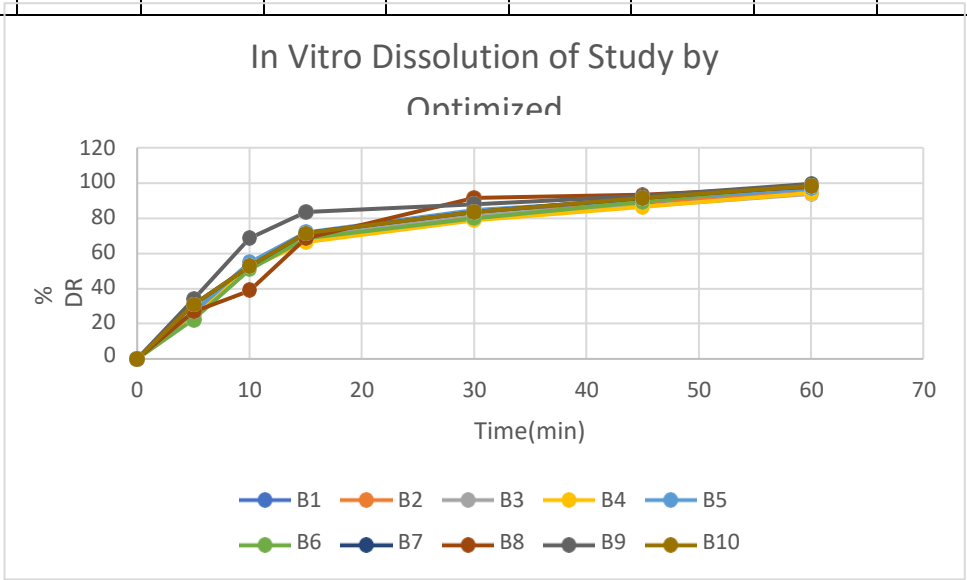

Table No.7.2: In-Vitro Dissolution Studies of Optimized Batches of Fexofenadine Hydrochloride Capsules

8. Optimization and Data Analysis:

Result of Optimization Batches by Central Composite Design

Batches	Variable Level in Coded Form		Dependent variable	
	X1	X2	% Drug Release (%)	Disintegration Time (Sec)
B1	-1	+X	97.73	3.50
B2	-1	-X	94.30	4.50
B3	-X	0	93.73	5.47
B4	0	-1	94.30	5.10
B5	0	+1	96.58	3.46
B6	+1	+1	97.64	2.33
B7	-1	0	98.30	3.54
B8	+1	-1	97.73	4.20
B9	+X	0	92.34	3.50
B10	+1	0	98.30	4.34

Data Analysis:

The general central composite design was applied to optimize the Fexofenadine Hydrochloride Capsules. The response surface methodology analysed data clearly indicate that the DT, % DR. values were mainly depending upon the selected independent variables. The regression equations for the responses fitted in linear model were generated. ANOVA was used to identify the significant effect. Obtained value of F is larger than critical F-value, the result was found to be significant at that level of probability ($p<0.05$). Only statistically significant ($p<0.05$) coefficient was included in regression equation.

A) Drug Release:

Final equation in terms of coded form,

$$\% \text{ Drug Release} = +96.95+1.83\times1+1.11\times2$$

Concerning dissolution, the results of multiple linear regression analysis showed that the coefficients X_1 and X_2 bear positive sign. It revealed that % drug release increases with increase in both Croscarmellose Sodium and Crossprovidone. Higher concentration of both super disintegrants was expected to increase the % drug release due to faster disintegration. ANOVA was used to identify the significant effect. The result was found to be significant at that level of probability ($p < 0.05$)

A) Disintegration Time:

Final equation in terms of coded form,

$$\text{Disintegration Time} = +4.01-0.6051\times1-0.6155\times2$$

Concerning disintegration time, the results of multiple linear regression analysis showed that the coefficients X_1 and X_2 bear negative sign. It revealed that disintegration time decreases with increase in both Croscarmellose Sodium and Crossprovidone. Higher concentration of both super disintegrants was expected to decrease the disintegration time of capsule. ANOVA was used to identify the significant effect. The result was found to be significant level of probability ($p < 0.05$).

Table No. 8.1. Result of Analysis of Variance for Batches by CCD of Fexofenadine Hydrochloride Capsules

	DF*	SS*	MS*	F*	P Value	
Y1 = % DR						
Model	2	34.98	71.49	17.94	0.0018	Significant
Residual	7	6.82	0.9749	-	-	
Total	9	41.80	-	-	-	
Y2 = Disintegration Time						
Model	2	5.77	2.89	11.26	0.0065	Significant

Residual	7	1.79	0.2563	-	-	
Total	9	7.57	-	-	-	

***DF indicates degree of freedom; SS sum of square; MS mean sum of square and F is Fischer's ratio.**

Graphical Representation:

A) % Drug Release:

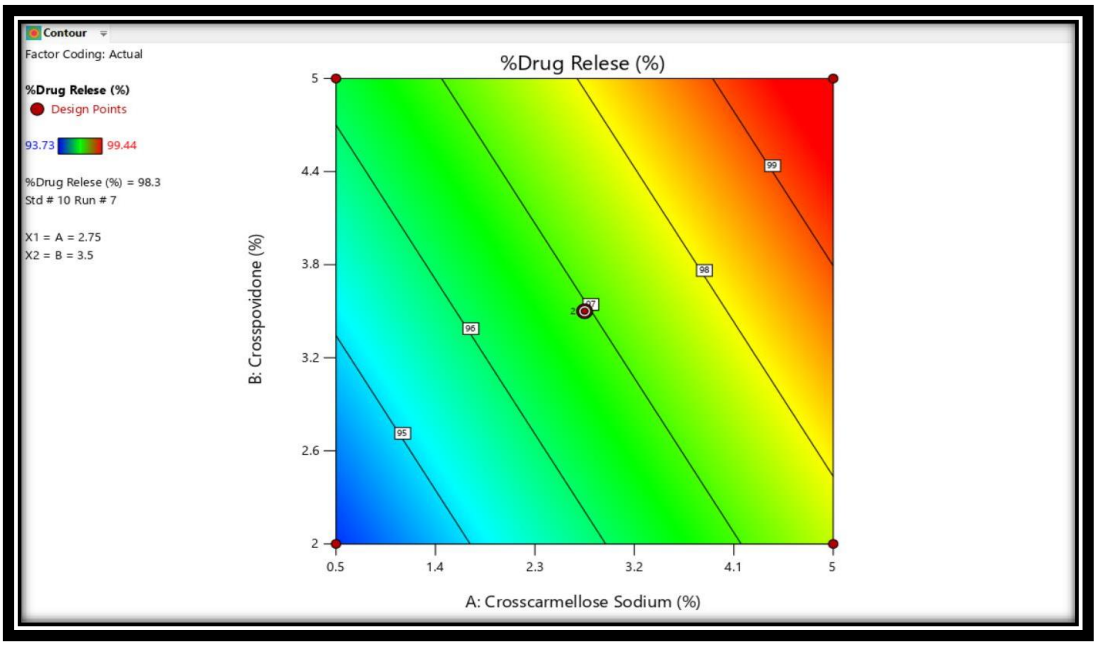

Fig. No. 8.2 3D Response Surface Contour Graph Showing the influence of Croscarmellose Sodium (X1) and Crossprovidone (X2) on % Drug Release (Y1)

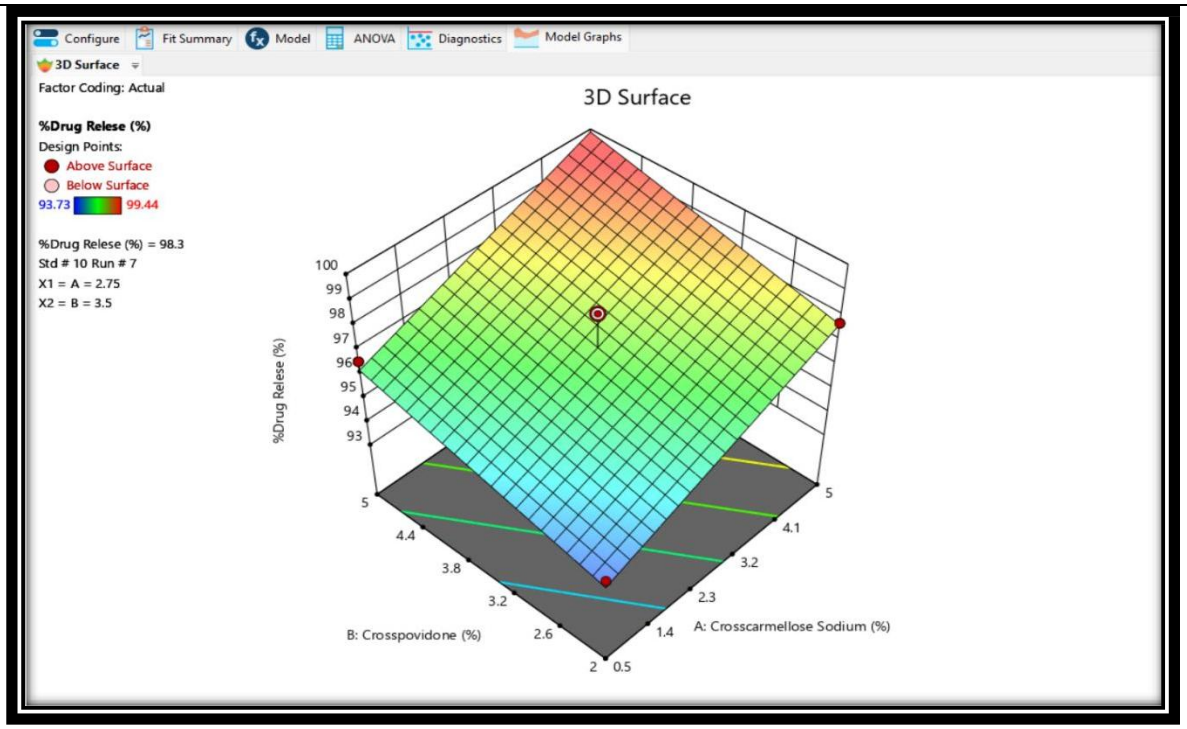

Fig. No. 8.3.3D Response Surface Contour Graph Showing the Influence of Croscarmellose Sodium (X1)

and Crossprovidone (X2) on % Drug Release (Y1)

Disintegration Time:

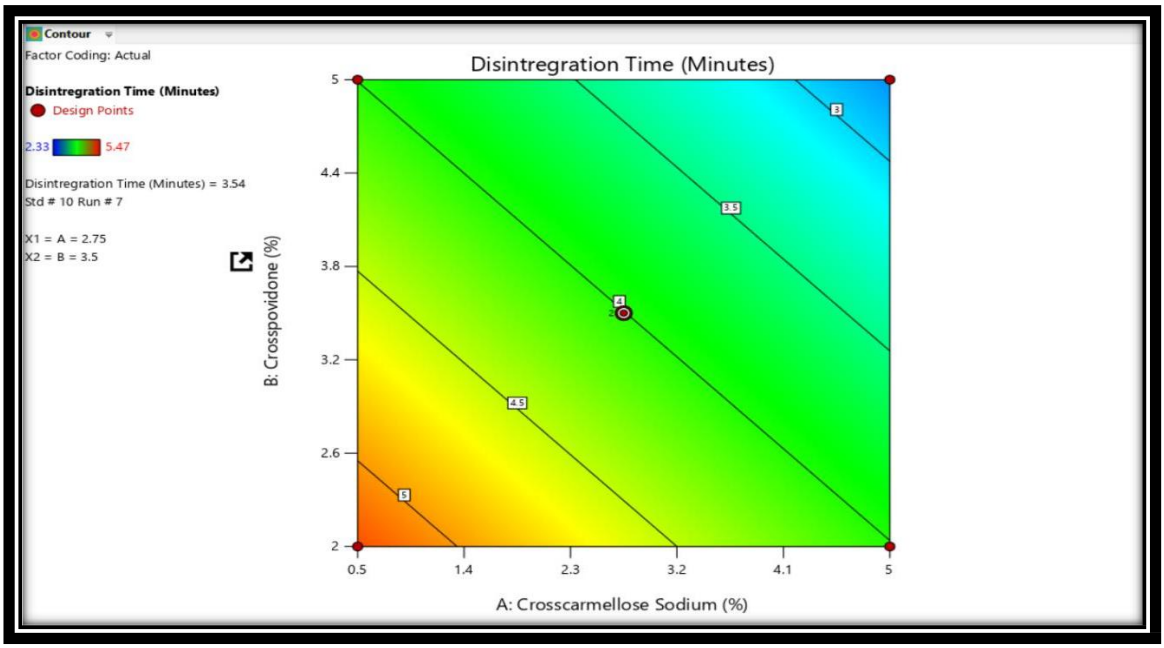

Fig. No. 8.4.3D Response Surface Contour Graph Showing the Influence of Croscarmellose (X1) and Crossprovidone

(X2) on Disintegration Time (Y2)

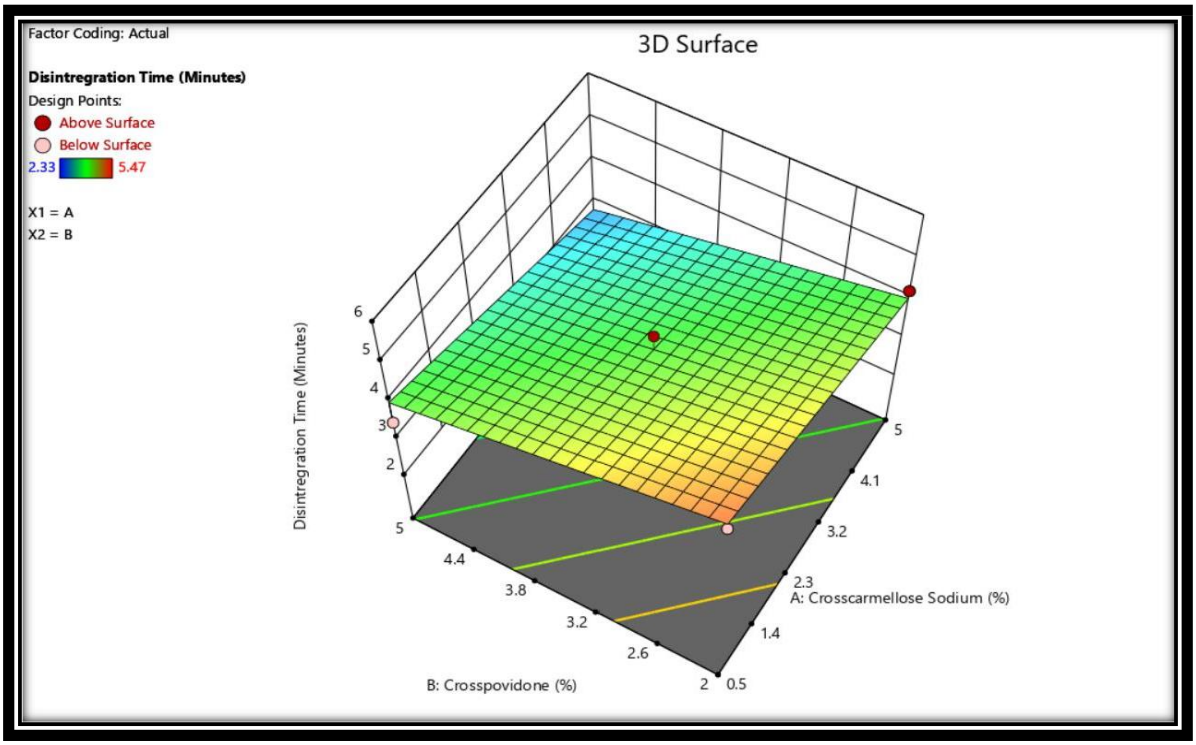

Fig. No. 8.5.3D Response Surface Graph Showing the Influence of Croscarmellose (X1) and Crossprovidone (X2) on Disintegration Time (Y2)

9. Stability Study:

Stability studies were carried out at 40°C ± 2°C and 75% RH ± 5% RH for 1 month. The film was observed for physical changes, weight variation, folding endurance, disintegration time, drug content & % drug release & other parameters. Fexofenadine Hydrochloride Capsule were found to be physically & chemically stable and showed no significant changes in terms of physical characteristics, formulation (B7) was stable and retained their original properties with minor differences in drug content, % DR and other parameter which are in acceptable limits.

Table No. 9.1. Stability Study of Optimized Batch of Fexofenadine Hydrochloride Capsule.

Evaluation Parameter	Batch B7	
	Initial	One Month
Average Weight (mg)	480	482
Capsule Length (mm)	21.5	21.5
Shell Integrity	Intact	Intact
Disintegration Time (min)	6.2	6.4
Moisture Content (%)	4.8	5.1

Chemical	Initial	One Month
Assay (%)	99.2	99.0
Related Substances (%)	0.12	0.18

III. CONCLUSION

Preformulation studies confirmed the **purity and identity** of Fexofenadine Hydrochloride. FTIR and DSC studies showed **no drug–excipient incompatibility** with Croscarmellose Sodium. Powder blends (B1–B10) exhibited **good flow properties** suitable for capsule filling. A **Central Composite Design (CCD)** under the QbD approach was successfully used for formulation optimization. ANOVA results confirmed the **statistical significance and robustness** of the quadratic model (**$p < 0.01$**). Optimized formulations demonstrated **excellent in-vitro drug release** performance. Batches **B7 achieved 98.30% drug release within 60 minutes**. Batch **B7 showed the shortest disintegration time (6.2 min)**, indicating rapid-release characteristics. Stability studies revealed **no significant physical or chemical changes** during one month of storage. Capsule characteristics, including **weight, size, assay, and impurity levels**, remained within acceptable limits.

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