

Enhancement of Solubility of Terbinafine Hydrochloride by Solid Dispersion

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Abstract: *Terbinafine Hydrochloride is an antifungal drug with poor aqueous solubility, which limits its dissolution and oral bioavailability. The present study aimed to develop amorphous solid dispersions (ASDs) of Terbinafine Hydrochloride using reactive ball milling to improve drug release. Polymer blends of HPMC–Pluronic F127 and PVP K30–Pluronic F127 were used to prepare different formulations. The drug was characterized by melting point, UV spectroscopy, FTIR, DSC, and XRD analysis. Experimental batches were optimized using a Box–Behnken design. The prepared ASDs were evaluated for crystallinity, cumulative drug release, and drug content. The optimized formulation showed a significant improvement in dissolution compared with the pure drug. Drug release reached about 96% within 90 minutes, while drug content remained within acceptable limits. The study demonstrated that reactive ball milling effectively converted the crystalline drug into an amorphous form, resulting in improved dissolution and uniform drug distribution.*

Keywords: Terbinafine Hydrochloride, Amorphous Solid Dispersion, Reactive Ball Milling, Drug Release, Dissolution Enhancement

I. INTRODUCTION

Terbinafine Hydrochloride is a synthetic allylamine antifungal drug widely used for the treatment of fungal infections such as dermatophytosis, candidiasis, and onychomycosis. It acts by inhibiting squalene epoxidase, an important enzyme involved in fungal cell membrane synthesis (1). Although Terbinafine Hydrochloride is highly effective, its poor aqueous solubility limits its dissolution rate and oral bioavailability (2). Improving the dissolution of poorly water-soluble drugs is one of the major challenges in pharmaceutical formulation development (3).

Amorphous solid dispersion (ASD) is a well-established approach for improving the dissolution and bioavailability of poorly soluble drugs. In this technique, the drug is dispersed in a hydrophilic polymer matrix, which reduces crystallinity and enhances wettability and dissolution (4). Reactive ball milling is an effective solvent-free method for producing amorphous solid dispersions by reducing particle size and converting crystalline drug into an amorphous state (5). Hydrophilic polymers such as Hydroxypropyl Methylcellulose (HPMC), Polyvinylpyrrolidone K30 (PVP K30), and Pluronic F127 are commonly used in ASD formulations because they improve drug stability, prevent recrystallization, and enhance drug release (6). Optimization of formulation variables using Design of Experiments (DoE), particularly the Box–Behnken design, provides a systematic approach to achieving the desired formulation with minimum experimental runs (7).

Therefore, the present study was undertaken to develop and optimize Terbinafine Hydrochloride amorphous solid dispersions prepared by reactive ball milling and to evaluate their physicochemical characteristics, dissolution behaviour, crystallinity, and drug content.

Materials and Methods

Terbinafine Hydrochloride was used as the model drug, while Hydroxypropyl Methylcellulose (HPMC), Polyvinylpyrrolidone K30 (PVP K30), and Pluronic F127 were selected as carrier polymers for preparing amorphous solid dispersions (6). The drug and polymers were accurately weighed according to the experimental design and processed



using the reactive ball milling technique. Polymer concentration and milling time were optimized using a Box–Behnken Design generated with Design-Expert software (7).

The pure drug was initially characterized by physical appearance, solubility, melting point, and UV spectroscopy. The maximum absorption wavelength (λ_{max}) of Terbinafine Hydrochloride was determined at 283 nm, and a calibration curve was prepared in methanol for quantitative estimation (8). FTIR spectroscopy was carried out to identify functional groups and evaluate possible drug–polymer interactions. Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD) studies were performed to evaluate thermal behaviour and crystallinity of the prepared formulations (9).

Nine amorphous solid dispersion batches were prepared according to the Box–Behnken experimental design. The prepared formulations were evaluated for cumulative drug release in phosphate buffer (pH 5.5), percentage crystallinity, and drug content. Drug release studies were performed for 90 minutes, and statistical optimization was carried out using analysis of variance (ANOVA). The optimized formulation was selected based on maximum drug release and minimum crystallinity. The optimized batch showed approximately 96.03% drug release within 90 minutes with acceptable drug content, confirming successful formulation development.

Results and Discussion

Preformulation Study:

Identification Test: Terbinafine Hydrochloride

- Physical Appearance: The drug was observed as a white to off-white crystalline powder, odorless or almost odorless in nature.
- Solubility: The drug was found to be slightly soluble in water, soluble in methanol and ethanol, and freely soluble in chloroform. The observed solubility profile was consistent with the reported pharmacopoeial specifications.
- Melting point determination: The melting point was found to be in the range of 204–208°C, which complied with the reported standard value, confirming the identity and purity of the drug.

Analytical Study

- Determination of λ_{max} of Terbinafine Hydrochloride:

A standard solution of Terbinafine Hydrochloride was prepared and scanned in a UV-Visible spectrophotometer. The drug exhibited a maximum absorption wavelength (λ_{max}) at approximately 283 nm.

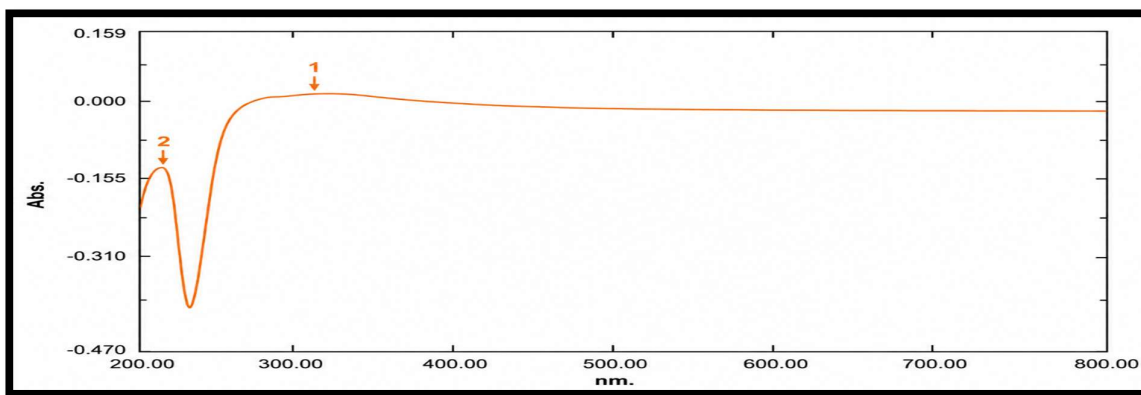


Fig No. 1 λ_{max} Terbinafine Hydrochloride

Table 1: Linearity Data of Terbinafine Hydrochloride

Sr. No.	Concentration ($\mu\text{g/ml}$)	Absorbance (nm)
1.	0.2	0.09



2.	0.4	0.175
3.	0.6	0.31
4.	0.8	0.471
5.	1	0.608

a) Standard Calibration Curve of Terbinafine Hydrochloride in Methanol at 283 nm:

The absorbance of the drug in Methanol was measured at 283 nm.

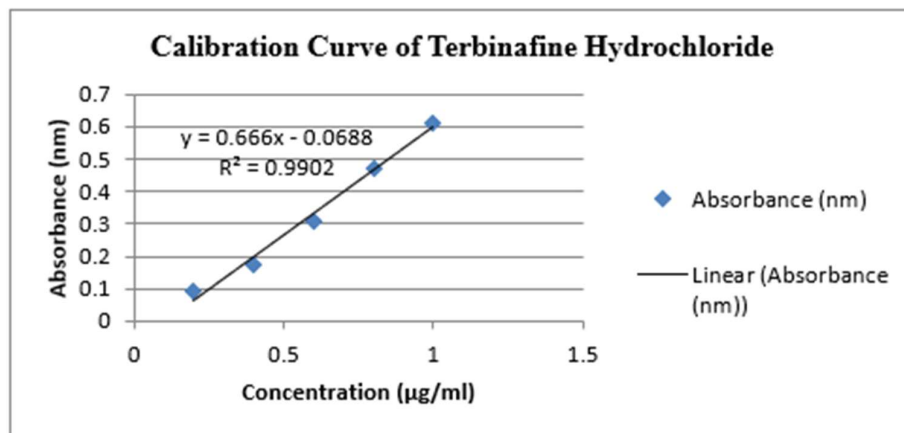


Figure 2: Calibration Curve of Terbinafine Hydrochloride

b) Parameters of Calibration Curve of Terbinafine Hydrochloride

Table 2: Parameters of Calibration Curve of Terbinafine Hydrochloride

Sr. No	Parameter	Values
1.	Slope (m)	0.0666
2.	Intercept (c)	0.0688
3.	Linearity Range	1 to 5µg/ml
4.	Correlation Coefficient	0.9902
5.	λ max	nm

FTIR analysis

The FTIR spectrum of Terbinafine Hydrochloride exhibited characteristic peaks corresponding to aliphatic C–H stretching, aromatic C=C stretching, and C–N stretching vibrations. The observed peaks confirmed the presence of the functional groups of Terbinafine Hydrochloride and indicated the absence of any significant chemical interaction or degradation



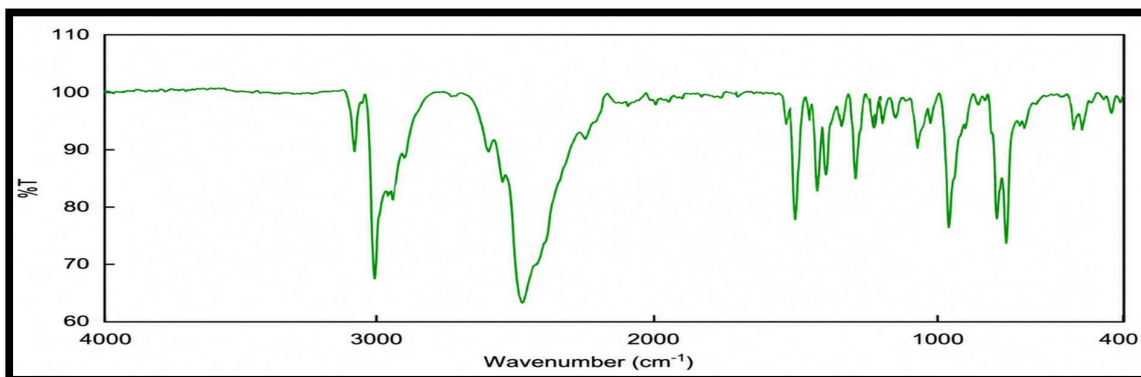


Figure 3: FTIR of Terbinafine Hydrochloride Table

Table 3: FTIR Interpretation Terbinafine Hydrochloride

Sr. No.	Wavenumber Range (cm ⁻¹)	Functional Group	Interpretation
1	2950–2850	C–H Stretching	Aliphatic C–H stretching vibrations of alkyl groups
2	2500–2300	C≡C / C≡N Region	Weak absorption due to alkyne or related vibrations
3	1600–1450	C=C Stretching	Aromatic ring stretching vibrations
4	1350–1200	C–N Stretching	Tertiary amine group vibrations
5	1150–1000	C–O Stretching	Ether/alcohol functional group vibrations
6	900–700	Aromatic C–H Bending	Out-of-plane bending of aromatic ring hydrogen atoms

DSC:

The DSC thermogram of pure Terbinafine Hydrochloride showed a sharp endothermic peak at approximately 204–208°C, corresponding to its melting point. The presence of a distinct melting endotherm confirmed the crystalline nature and purity of the drug. No additional thermal events were observed, indicating the thermal stability of Terbinafine Hydrochloride under the experimental conditions.

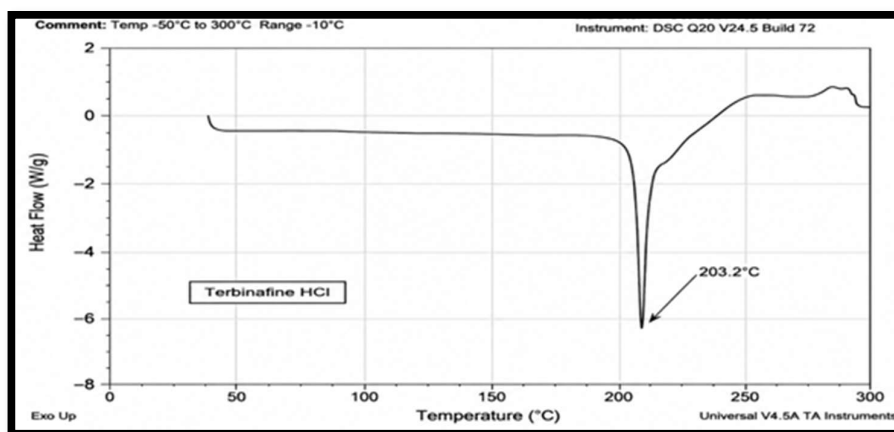


Figure 8.4: DSC thermogram of Pure Terbinafine Hydrochlorid



XRD:

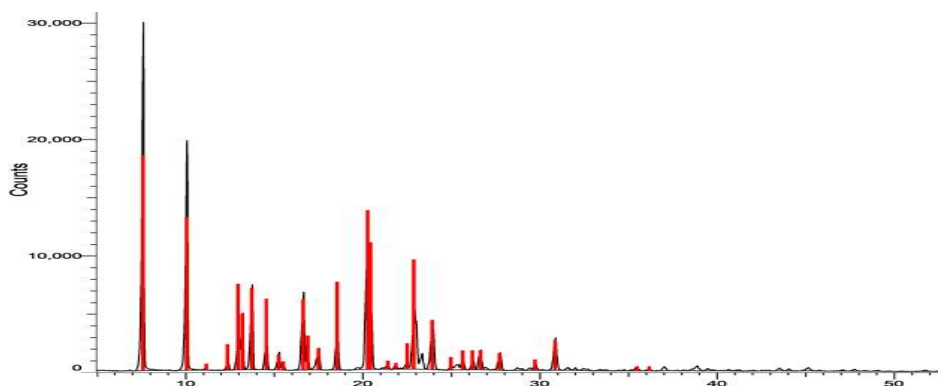


Figure 5: X-ray Diffractogram of Pure Terbinafine Hydrochloride API

XRD pattern of crystalline Terbinafine Hydrochloride is shown in Figure 8.5. Crystalline Terbinafine Hydrochloride displayed their characteristic diffraction peaks at 7.580, 10.060, 13.750, 16.620, 20.240, 22.900 and 30.810 respectively and which are correlating with the previously reportedly reference values which confirms the crystalline nature of Terbinafine Hydrochloride.

Experimental Design

Optimization Study using Design of Experiments:

Table 4: Variable Factors for Box-Behnken design

Factors	Levels for study, As Coded	
	Low (-1)	High (1)
Independent Variables		
X-1= Conc. of Polymer Blend (% w by w)	40	80
X-2=Ball Milling time (Min)	60	180
Dependent Variables		
Y1= Drug Release (%)	Maximize	
Y2= Crystallinity of Terbinafine Hydrochloride (%)	Minimize	

Statistical Analysis:

Full 32 factorial design had chosen, with sufficient two factors examined at three levels each. The independent variables were Polymer Blend Concentration (X1) and Ball Milling Time (min) (X2), while the dependent variables were Drug Release (%) (Y1) and Crystallinity of Terbinafine Hydrochloride (%) (Y2). The collected data was studied using Design Expert 7.1.6 software and statistically evaluated through analysis of variance (ANOVA).

Table 5: Design and Response summary Terbinafine Hydrochloride batches

Sr. No	Batch No	Factor-1 (X1) Conc. Of Polymer Blend (%w/w)	Factor-2 (X2) Ball Milling time (Min)	Response-1 Drug Release (%)	Response-2 Crystallinity of Terbinafine Hydrochloride (%)
1	Terb SD 01	40	60	54.87	10.14
2	Terb SD 02	60	60	70.15	9.36
3	Terb SD 03	80	60	96.03	12.06
4	Terb SD 04	40	120	57.66	9.45
5	Terb SD 05	60	120	78.05	10.96



6	Terb SD 06	80	120	82.85	13.06
7	Terb SD 07	40	180	58.02	8.32
8	Terb SD 08	60	180	74.12	11.58
9	Terb SD 09	80	180	89.45	14.25

Table 6: Response 1 Valeus: Drug Release

Source	Std Dev.	R-Squared	Adjusted R-Squared	Predicted R-Squared	PRESS	
Linear	4.58	0.9268	0.9024	0.8323	288.39	Suggested
2FI	4.52	0.9406	0.9050	0.7797	378.77	
Quadratic	5.73	0.9427	0.8471	0.4300	980.01	
Cubic	6.84	0.9728	0.7826	-3.9520	8514.21	Aliased

ANOVA considering the Quadratic model:

Table 7: Response for Factor No 1: Drug Release of Terbinafine Hydrochloride

Source	Sum of Squares	df	Mean Square	F Value	p-value prob> F	
Model	27.78	5	5.56	11.15	0.0374	Significant
A-conc.of polymer Blend	21.89	1	21.89	43.93	0.0070	
B-Ball Milling time	1.12	1	1.12	2.24	0.2311	
AB	4.02	1	4.02	8.07	0.0656	
A ²	0.67	1	0.67	1.35	0.3293	
B ²	0.084	1	0.084	0.17	0.7088	
Residual	1.49	3	0.50			
Cor Total	29.28	8				

The Model. F-value of 9.86 indicates significance of model. There will be only a 4.42% probability that this such a large. F-value could result from randomness. Model terms with p- values below 0.05 are to eb considered significant.

Table 8: Fit Statistics for % Drug Release

Std. Dev.	5.73	R-Squared	0.9427
Mean	73.47	Adj R-Squared	0.8471
C.V. %	7.80	Pred R-Squared	0.4300
PRESS	980.01	Adeq Precisor	8.002

"Predicted R-Squared" value of 0.4300 deviates from "Adjusted R-Squared" of 0.8471, suggesting a substantial block effect or also a potential issue with the model and/ or data. Factors such as design model simplification, responded transformation, and outlier examination should be taken into account. "Adequate Precision" assesses signal-to-noise ratio, and a ratio over 4.00 is desirable. In this study ratio of 8.002 signifies an acceptable signal suggesting that this model is suitable for the design space.

Table 9: Coefficients of coded factors for the percentage of drug release

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	73.49	1	4.27	59.89	87.09	
A-Conc. Of Polymer Blend	46.30	1	2.34	8.85	23.74	1.00



B-Ball Milling time	0.090	1	2.34	-7.36	7.54	1.00
AB	-2.43	1	2.87	-11.55	6.69	1.00
A ²	-0.96	1	4.05	-13.86	11.94	1.00
B ²	0.92	1	4.05	-11.98	13.82	1.00

The coefficient estimate indicates the anticipated alteration in the response for each unit shift in factor. As a general suggestion, VIFs value below 10.00 is acceptable.

The Final equation expressed in coded factors is as follows:

$$\text{Drug Release} = +73.49 + 16.30 * A + 0.090 * B - 2.43 * A * B - 0.96 * A^2 + 0.92 * B^2$$

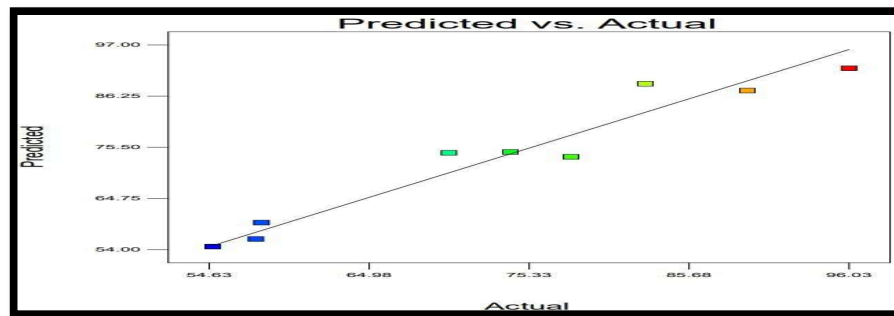


Figure 6: Report for % Drug Release

Source	Std. Dev.	R-Squared	Adjusted Squared	R-Predicted Squared	R-PRESS	
Linear	1.02	0.7858	0.7144	0.3811	18.12	
2FI	0.67	0.9231	0.8770	0.6754	9.50	Suggested
Quadratic	0.71	0.9489	0.8639	0.3908	17.84	
Cubic	0.28	0.9972	0.9778	0.4944	14.80	Aliased

Table 10: Response 2 Values: Crystallinity of Terbinafine Hydrochloride

ANOVA for Quadratic model

Table 11: Response 2: Crystallinity of Terbinafine Hydrochloride

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	27.78	5	5.56	11.15	0.0374	
A-Conc. Of Polymer Blend	21.89	1	21.89	43.93	0.0070	Significant
B-Ball Milling time	1.12	1	1.12	2.24	0.2311	
AB	4.02	1	4.02	8.07	0.0656	
A ²	0.67	1	0.67	1.35	0.3293	
B ²	0.084	1	0.084	0.17	0.7088	
Residual	1.49	3	0.50			
Cor Total	29.28	8				

Significance of this used model is shown by the std F-value of 11.15. Probability that such a high "Model F-Value" could occur due to noise is only 3.74%. Model terms with "Prob > F" values below 0.0500 are considered significant, and in this instance, term A might be significant.



Table 12: Fit statistics for Crystallinity of Terbinafine Hydrochloride

Std. Dev.	0.71	R-Squared	0.9489
Mean	11.02	Adj R-Squared	0.8639
C.V. %	6.41	Pred R-Squared	0.3908
PRESS	17.84	Adeq Precisor	10.107

3 Dimensional Response Surface & Contour Plot:

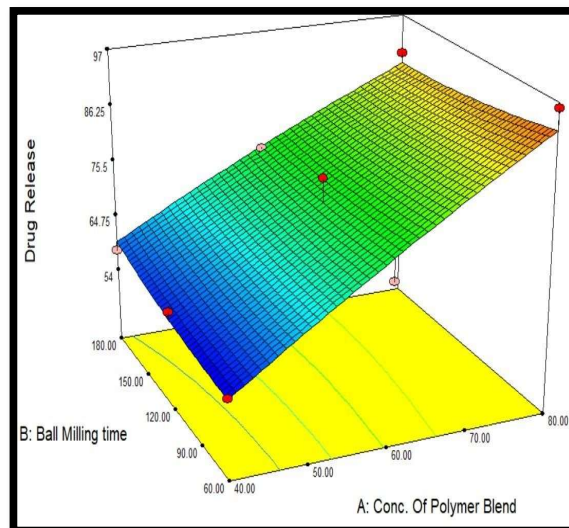
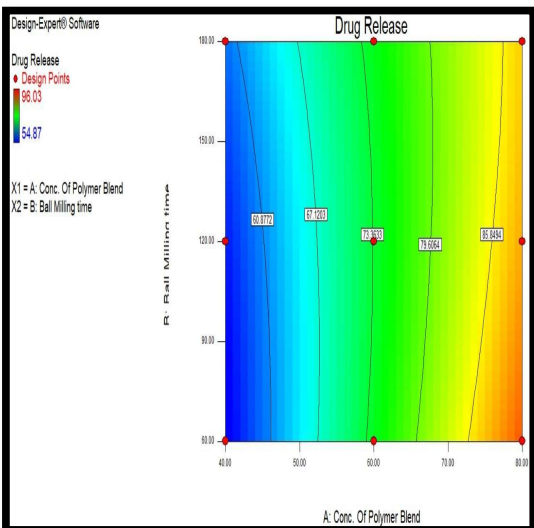


Figure 7: A contour plot illustrates the correlation between different concentrations of the polymer blend and ball milling time with respect to drug release.

Figure 8: Response 3D surface plot show the effect of levels of conc. of polymer blend and ball milling time on drug release

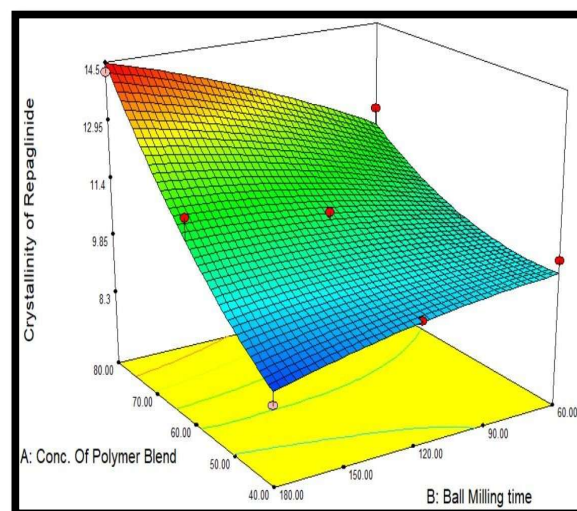
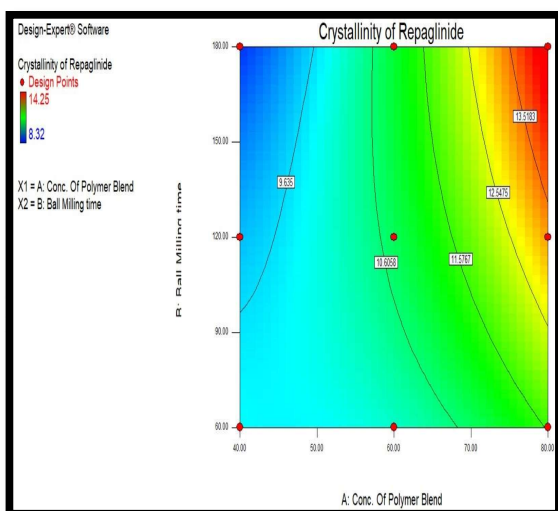


Figure 9: A contour plot demonstrates the connection between different concentrations of the polymer blend and ball milling time concerning the crystallinity of Terbinafine Hydrochloride



Figure 10: Response 3D surface plot show the effect of levels of conc. of polymer blend and ball milling time on crystallinity of Terbinafine Hydrochloride

Evaluation of ASD formulations:

A) Solid- state studies of ball-milled ASDs:

X RD powder diffraction (XRPD):

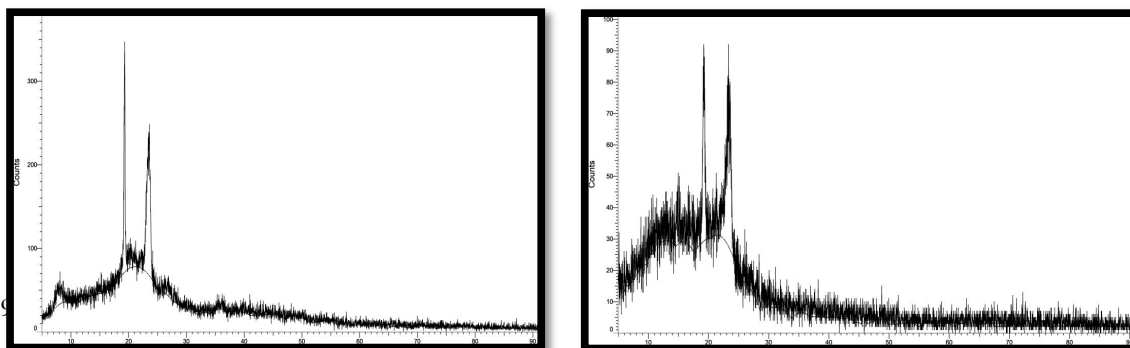


Figure 11: X-RD Diffractogram of Polymer Blend of HPMC + Pluronic F127 developed by Reactive Ball Milling

Figure 12: XRD Diffractogram of Polymer Blend of PVP K30 + Pluronic F127 developed by Reactive Ball Milling

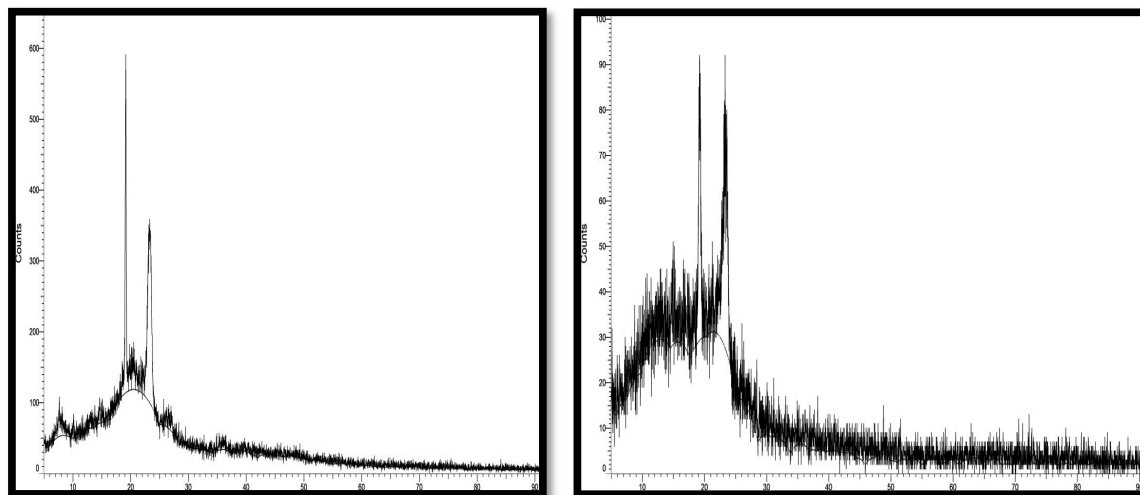


Figure 13: X-ray Diffractogram of Amorphous Solid Dispersion of Terbinafine Hydrochloride + (HPMC + Pluronic F127) developed by Reactive Ball Milling

Figure 14: X-ray Diffractogram of Amorphous Solid Dispersion of Terbinafine Hydrochloride +(PVP K30 + Pluronic F127) developed by Reactive Ball Milling



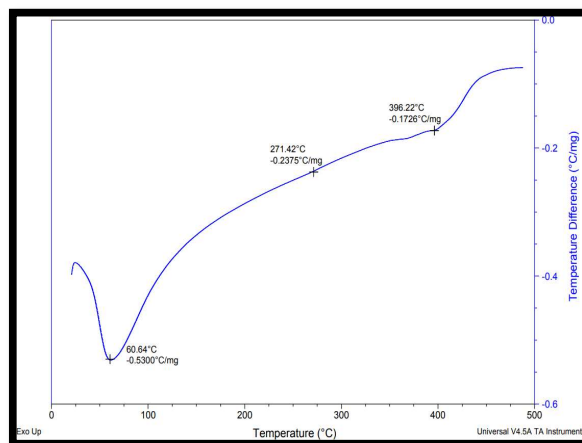
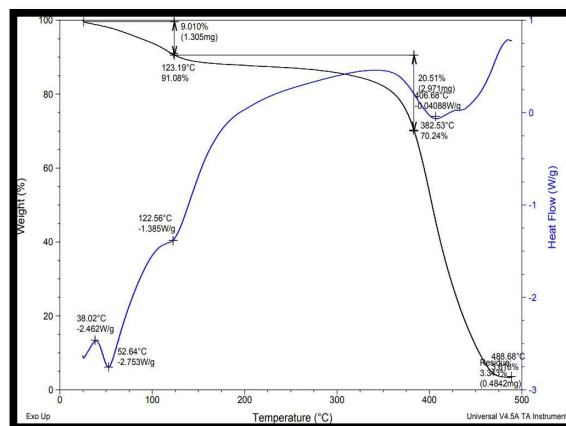


Figure 16: Thermogram of Polymer Blend of PVP K30 + Pluronic F127 developed by Reactive Ball Milling



10	3.45	5.87	10.11	15.78	22.14	9.88	17.05	16.36	7.88	16.87	15.45
20	8.89	11.25	17.12	25.12	31.47	18.15	28.45	30.04	17.22	24.45	31.67
30	15.25	18.89	26.77	33.64	39.85	28.89	36.89	41.89	25.25	35.78	42.38
45	21.12	27.35	35.49	47.32	60.55	36.65	49.19	59.45	35.87	50.15	58.47
60	29.14	36.15	44.38	57.78	78.52	47.89	67.16	71.18	48.00	61.78	72.65
90	36.45	44.28	54.87	70.15	96.03	57.66	78.05	82.85	58.02	74.12	89.45

Figure 19: Cumulative % of drug release of Amorphous solid dispersion Batches (SD- 1 to SD 4), Pure drug, Physical mixture

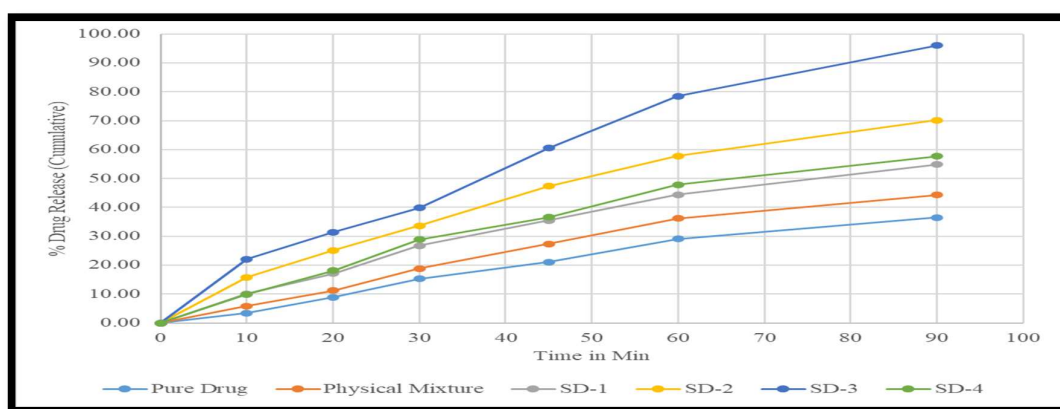
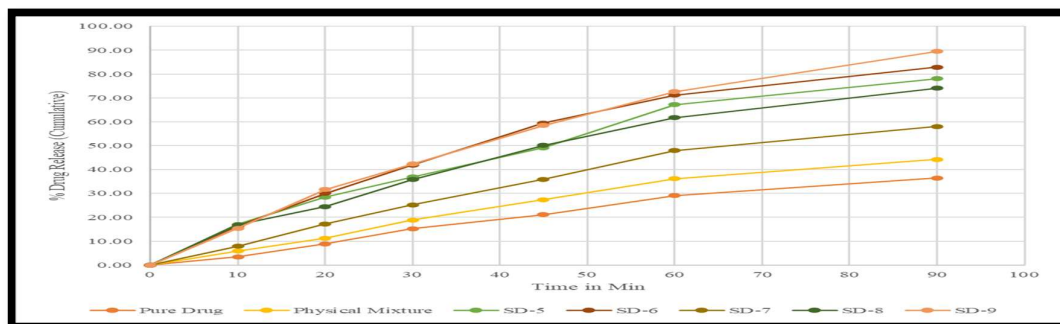


Figure 20: Cumulative % of drug release of Amorphous solid dispersion Batches (SD- 5 to SD-9), Pure drug, Physical mixture



Terbinafine Hydrochloride Drug-Content:

Table 14: % Drug content of Terbinafine Hydrochloride ASD batches

Sr. No	ASD Batches	Drug-Content (%)
1	REP-SD-1	88.45
2	REP-SD-2	98.60
3	REP-SD-3	99.78
4	REP-SD-4	100.05



5	REP-SD-5	92.85
6	REP-SD-6	97.68
7	REP-SD-7	96.25
8	REP-SD-8	98.65
9	REP-SD-9	99.14

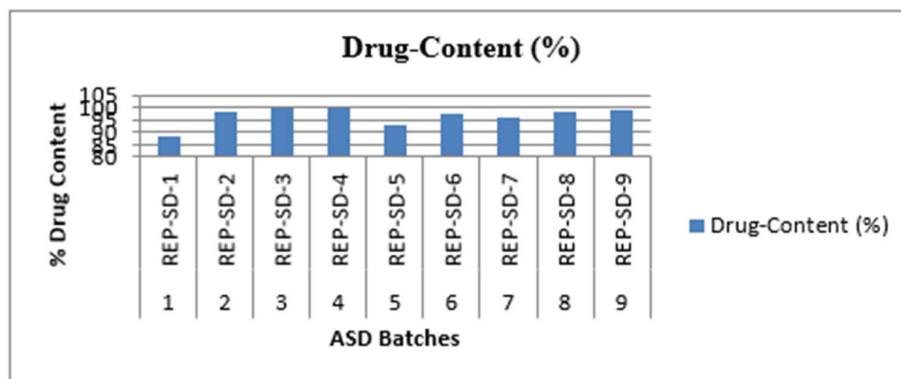


Figure 21: % Drug content of Terbinafine Hydrochloride ASD batches

The Terbinafine Hydrochloride drug content of solid dispersion formulations are within acceptable range. The percentage drug content in the formulations ranged from 88.45 to 100.05, indicating a uniform distribution of drug in ASD's.

II. CONCLUSION

The present study successfully developed Terbinafine Hydrochloride amorphous solid dispersions using the reactive ball milling technique. Characterization studies including UV spectroscopy, FTIR, DSC, and XRD confirmed the identity of the drug and demonstrated successful conversion from the crystalline to the amorphous state without significant drug-polymer interaction. Optimization using the Box-Behnken design identified the influence of polymer concentration and milling time on drug release and crystallinity. The optimized formulation exhibited approximately 96% cumulative drug release within 90 minutes, which was significantly higher than the pure drug. Drug content remained within acceptable limits, indicating uniform drug distribution among all prepared batches. Overall, reactive ball milling proved to be an effective solvent-free technique for enhancing the dissolution performance of Terbinafine Hydrochloride. This approach has potential for improving the oral delivery of other poorly water-soluble drugs and may be useful for future pharmaceutical formulation development.

REFERENCES

1. Katzung BG. Basic and Clinical Pharmacology. 15th ed. New York: McGraw-Hill; 2021.
2. Sweetman SC. Martindale: The Complete Drug Reference. 40th ed. London: Pharmaceutical Press; 2020.
3. Aulton ME, Taylor KMG. Aulton's Pharmaceutics: The Design and Manufacture of Medicines. 6th ed. London: Elsevier; 2022.
4. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water-soluble drugs. Drug Discov Today. 2007;12(23-24):1068-1075.
5. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm. 2000;50(1):47-60.
6. Rowe RC, Sheskey PJ, Quinn ME. Handbook of Pharmaceutical Excipients. 8th ed. London: Pharmaceutical Press; 2017.



7. Montgomery DC. Design and Analysis of Experiments. 10th ed. New York: John Wiley & Sons; 2020.
8. Beckett AH, Stenlake JB. Practical Pharmaceutical Chemistry. 4th ed. CBS Publishers; 2004.
9. ICH Harmonised Guideline Q8(R2). Pharmaceutical Development. International Council for Harmonisation; 2009.

