**RESEARCH PAPER**

# QbD-Guided Formulation, Optimization, and Stability Evaluation of Doravirine Solid Dispersions using HPMCAS for Enhanced Solubility and Dissolution

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**Abstract**

**Background:** Doravirine falls under the BCS Class II category, characterized by low solubility in water but high permeability across biological membranes. Due to its limited ability to dissolve in the gastrointestinal environment, its absorption is hindered, resulting in reduced bioavailability. Enhancing its solubility and dissolution rate is crucial to improve its therapeutic performance when administered orally.

**Objective:** This study focused on developing a 100 mg immediate-release doravirine tablet using polymer-assisted top-spray granulation within a Quality-by-Design (QbD) framework. This technique involves spraying a drug-polymer solution onto a fluidized powder bed to enhance the drug's solubility and dissolution properties. The formulation process was carefully optimized by adjusting the levels of polymer, disintegrants, and lubricants to produce tablets with consistent quality and improved drug release profiles. This method not only improves the bioavailability of doravirine, a poorly soluble drug, but also ensures robust manufacturing with controlled granulation and tablet performance, supporting effective oral delivery.

**Methods:** Doravirine, a drug with low water solubility but high permeability, was formulated into a 100 mg immediate-release tablet using a polymer-assisted top-spray granulation technique. This involved spraying a drug-polymer solution onto a fluidized powder bed to enhance solubility and dissolution. The formulation was optimized by adjusting polymer, disintegrant, and lubricant levels through a structured statistical design.

**Results:** The optimized batch of Doravirine Tablets 100 mg exhibited >95% drug release within 60 minutes, with acceptable assay and impurity levels. XRPD confirmed amorphous solid dispersion formation. Stability studies at long-term (30 °C/75% RH) and accelerated (40 °C/75% RH) conditions showed consistent assay (99.3–101.6%), dissolution (>95%), and total impurities (<0.25%) for six months.

**Keywords:** Doravirine; HPMCAS; Fluidized-bed granulation; Quality by Design (QbD); XRPD; Dissolution; Stability; Amorphous solid dispersion

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## Introduction

Doravirine (MK-1439) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) approved in 2018 for the treatment of HIV-1 infection. It is marketed as a 100 mg tablet, either as a single agent or in fixed-dose combinations for treatment-naïve and virologically suppressed adults. As a Biopharmaceutics Classification System (BCS) Class II compound, [1–5] doravirine exhibits low solubility and high permeability, resulting in dissolution-rate-limited absorption. Marketed doravirine tablets show incomplete drug release under acidic conditions, whereas dissolution becomes nearly complete at neutral pH. This pH-dependent solubility contributes to variability in bioavailability and potential food-effect concerns.

Polymer-based amorphous solid dispersion (ASD) methods like spray drying and hot-melt extrusion improve solubility for BCS Class II drugs, but scale-up and solvent issues limit their use. Fluidized-bed top-spray granulation is a scalable alternative that sprays a drug-polymer solution onto a fluidized powder bed, ensuring uniform granules with better flow and dissolution. This process offers precise control over parameters, produces consistent granule quality, and supports efficient, reproducible manufacturing. Using a Quality-by-Design framework and Design of Experiments, key formulation and process variables were optimized to achieve fast, reliable drug release comparable to the original product.[11-12]

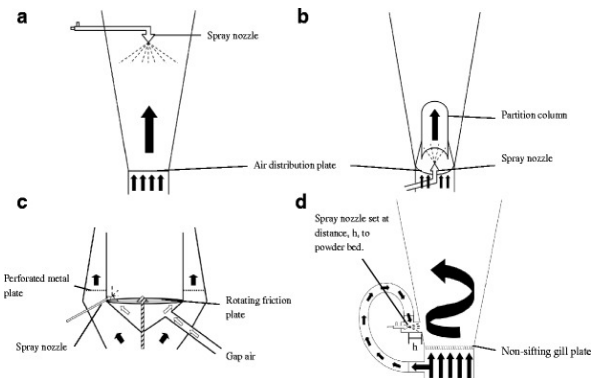


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**Figure 1.** Schematic representation of fluidized-bed granulator configurations. Diagram (a) illustrates the top-spray setup used in this study, where the API/polymer solution is atomized onto a fluidized powder bed. (Other configurations b to d is shown for comparison) The fluid-bed processor (FBP) ensures controlled drying and uniform granule formation.

**Materials and Methods**

Doravirine active pharmaceutical ingredient (API), equivalent to 100 mg per tablet, was obtained from the sponsoring organization. Hypromellose acetate succinate (HPMCAS, Shin-Etsu AQOAT®) was used as a solubility-enhancing polymer. Microcrystalline cellulose (Avicel® PH-101) served as the core excipient, lactose monohydrate as a diluent, croscarmellose sodium as a disintegrant, and magnesium stearate as a lubricant. Analytical-grade acetone and purified water were used as solvents. The US reference product PIFELTRO™[13] (doravirine 100 mg tablet, Merck & Co., USA) was employed for comparative evaluation of the drug product.

**Manufacturing Process:**

The manufacturing process involved the following steps. Doravirine API was dissolved in an acetone–water (90:10) solvent system, followed by dissolution of hypromellose acetate succinate to obtain the drug solution. Microcrystalline cellulose was loaded into the fluidized-bed processor bowl for top-spray granulation under controlled process conditions. The drug solution was sprayed onto the microcrystalline cellulose bed in the fluidized-bed processor. After completion of spraying, the granules were dried to achieve the desired loss on drying (LOD). The dried granules were evaluated for residual solvent content, blended with pre-sifted extra-granular excipients (lactose monohydrate and croscarmellose sodium), followed by lubrication with pre-sifted magnesium stearate. The lubricated granules were compressed into tablets using a suitable compression machine and processing parameters.

Formulation design and optimization were performed using Design-Expert® software (Stat-Ease Inc., Minneapolis, USA) under a QbD[15–18] framework employing factorial, central composite, and Box–Behnken designs. Analytical evaluation for assay, related substances, and dissolution was carried out using a Waters HPLC system equipped with Empower® software. Dissolution testing was performed in 900 mL phosphate buffer (pH 6.8 containing 3% polysorbate 80) using a USP Type II paddle apparatus (Electrolab, India) at 75 rpm.

**Results**

Characterization of the US Reference Product (PIFELTRO™)

The US reference product PIFELTRO™ (doravirine 100 mg tablet, Merck & Co., USA) was evaluated to establish a benchmark for comparative formulation development. The tablets are oval, film-coated, and debossed with "700." They have an average weight of approximately 1024 mg, dimensions of 19.24 × 9.71 mm, thickness of about 7.17 mm, and a disintegration time of 2 minutes and 10 seconds.

The qualitative composition of the US reference tablet includes hypromellose acetate succinate, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, hypromellose, titanium dioxide, and triacetin, which together form a stable and uniform film-coated immediate-release dosage form (Table 1).

**Table 1.** Drug release of PIFELTRO™ in different dissolution media

| Time (min) | pH 6.8 (Mean) | pH 6.8 (Min) | pH 6.8 (Max) | 0.1N HCl (Mean) | 0.1N HCl (Min) | 0.1N HCl (Max) | pH 4.5 (Mean) | pH 4.5 (Min) | pH 4.5 (Max) |
|---|---|---|---|---|---|---|---|---|---|
| 15 | 89 | 86 | 91 | 41 | 40 | 43 | 42 | 41 | 44 |
| 30 | 91 | 89 | 93 | 50 | 48 | 52 | 52 | 49 | 54 |
| 45 | 91 | 89 | 94 | 55 | 54 | 57 | 58 | 55 | 59 |
| 60 | 91 | 89 | 93 | 62 | 61 | 63 | 62 | 59 | 65 |
| 90 | 91 | 89 | 93 | 65 | 64 | 68 | 68 | 65 | 69 |

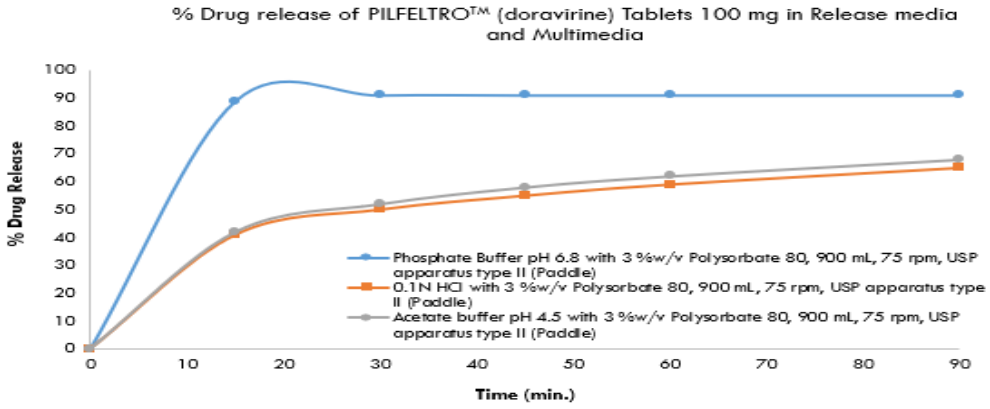



**Figure 2.** Dissolution profiles of PIFELTRO™ tablets in different media.

**Granulation Trials of Doravirine API with HPMCAS polymer**

To improve the solubility and dissolution of Doravirine, the active pharmaceutical ingredient (API) was converted into amorphous solid dispersion–like granules using a fluidized-bed top-spray granulation technique. Hypromellose acetate succinate (HPMCAS) served as the polymeric carrier at a drug-to-polymer ratio of 1:3. The dissolution behavior of these granules was evaluated against that of the micronized API under identical conditions in phosphate buffer (pH 6.8) containing 3% polysorbate 80.

As shown in Table 2 and Figure 3, the micronized API released only about 65% of the drug after 90 minutes, whereas the HPMCAS-based granules achieved more than 95% release within 60 minutes and nearly complete release (~100%) by 90 minutes. These results indicate that incorporation of Doravirine into a polymer matrix significantly enhanced solubility, as reflected in the improved dissolution profile, likely due to the formation of an amorphous-like solid dispersion facilitated by HPMCAS.

**Table 2.** Comparative dissolution of micronized doravirine API and HPMCAS-based granules

| Time (min) | Micronized API (% release) | Granules (Doravirine:HPMCAS in the ratio 1:3) (% release) |
|---|---|---|
| 15 | 35 | 72 |
| 30 | 52 | 85 |
| 60 | 61 | 96 |
| 90 | 65 | 100 |

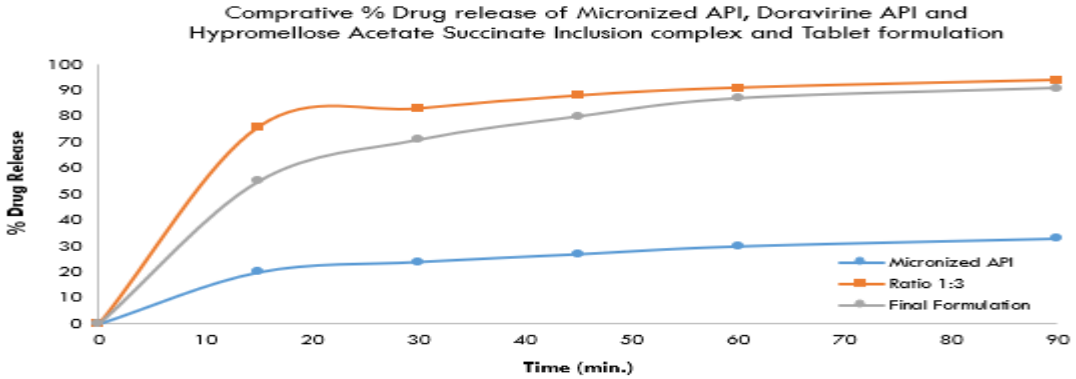



**Figure 3.** Comparative dissolution profiles of Doravirine showing percent drug release from micronized API, Doravirine–HPMCAS (1:3) granules, and final tablet formulation in phosphate buffer (pH 6.8) at 37 ± 0.5 °C.

**X-ray Powder Diffraction (XRPD) Analysis of US Reference Product**

The crystalline characteristics of the US reference product PIFELTRO™ were evaluated using X-ray Powder Diffraction (XRPD). The obtained diffractogram showed several sharp and intense peaks, confirming the material's crystalline nature (Figure 4). Major diffraction peaks appeared at 2θ values of 12.6°, 16.5°, 19.2°, 20.1°, 21.3°, 22.4°, and 23.9°, reflecting a well-ordered crystal lattice.

A detailed summary of the 2θ positions, d-spacing, relative intensities, and I/Imax ratios is presented in Table 3. The most intense peak was observed at 20.07° (2θ), serving as the 100% reference intensity. This diffraction profile offers a distinctive fingerprint confirming the crystalline form of the US reference product.

**Table 3**. XRPD peak list of PIFELTRO™ tablets

| Num. | 2θ (°) | d (Å) | Intensity | I/Imax (%) |
|---|---|---|---|---|
| 1 | 12.5962 | 7.0218 | 1479 | 42.4 |
| 2 | 16.4931 | 5.3704 | 961 | 27.5 |
| 3 | 17.1595 | 5.1634 | 201 | 5.8 |
| 4 | 19.2325 | 4.6113 | 1514 | 43.4 |
| 5 | 19.678 | 4.5078 | 1802 | 51.6 |
| 6 | 20.0748 | 4.4196 | 3489 | 100.0 |
| 7 | 20.9433 | 4.2383 | 767 | 22.0 |
| 8 | 21.3221 | 4.1638 | 1221 | 35.0 |
| 9 | 22.3588 | 3.9423 | 713 | 20.4 |
| 10 | 22.8841 | 3.883 | 826 | 23.7 |
| 11 | 23.8639 | 3.7258 | 746 | 21.4 |
| 12 | 25.3349 | 3.5163 | 395 | 11.3 |
| 13 | 25.6756 | 3.4668 | 255 | 7.3 |
| 14 | 27.581 | 3.2315 | 235 | 6.7 |
| 15 | 28.2724 | 3.154 | 160 | 4.6 |
| 16 | 28.5973 | 3.1189 | 99 | 2.8 |
| 17 | 30.5731 | 2.8748 | 130 | 3.7 |
| 18 | 31.8109 | 2.8108 | 137 | 3.9 |
| 19 | 33.241 | 2.6931 | 151 | 4.3 |
| 20 | 34.6595 | 2.5886 | 187 | 5.4 |
| 21 | 35.0233 | 2.5599 | 187 | 5.4 |
| 22 | 36.5257 | 2.4745 | 124 | 3.6 |
| 23 | 37.01 | 2.427 | 199 | 5.7 |
| 24 | 37.7319 | 2.3822 | 265 | 7.6 |
| 25 | 37.9829 | 2.3763 | 305 | 8.7 |
| 26 | 38.2858 | 2.349 | 211 | 6.0 |
| 27 | 38.6642 | 2.3269 | 171 | 4.9 |
| 28 | 48.0038 | 1.8937 | 107 | 3.1 |

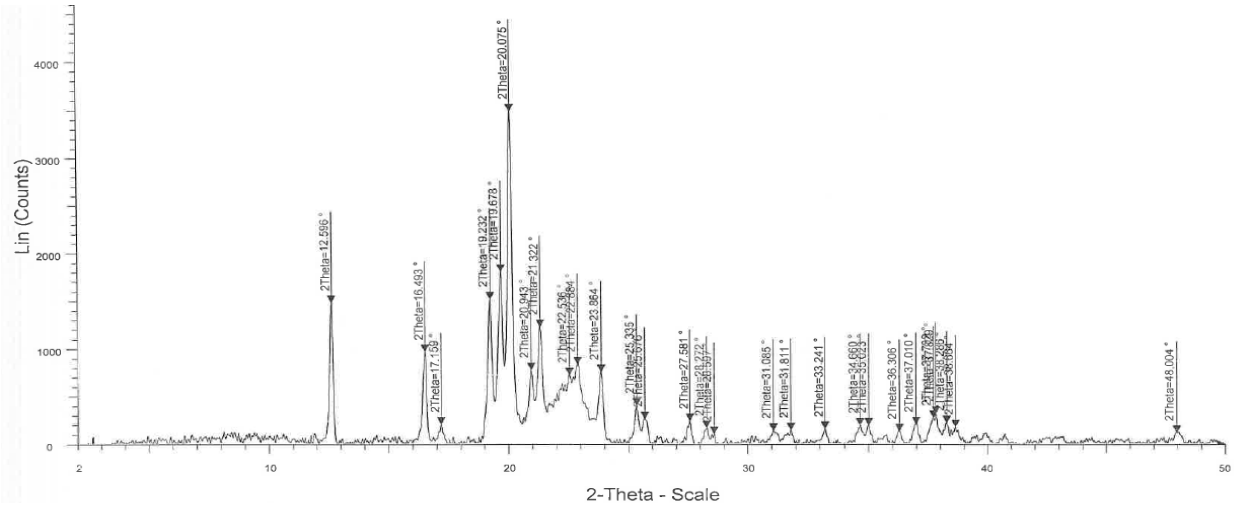



**Figure 4.** XRPD diffractogram of PIFELTRO™ tablets showing characteristic diffraction peaks.

**Granulation of Doravirine by Fluidized-Bed Top-Spray Technique**

Doravirine was processed with hypromellose acetate succinate (HPMCAS) using fluidized-bed top-spray granulation. A drug-polymer solution in acetone–water (90:10) was sprayed onto microcrystalline cellulose to form dried granules, creating an amorphous solid dispersion to boost solubility and dissolution.

Dissolution tests in pH 6.8 phosphate buffer with 3% polysorbate 80 showed the micronized API released about 65% of the drug in 90 minutes, while the HPMCAS granules released over 95% within 60 minutes and fully released by 90 minutes. This confirms the granulation process effectively improved doravirine's dissolution by forming a stable amorphous dispersion.

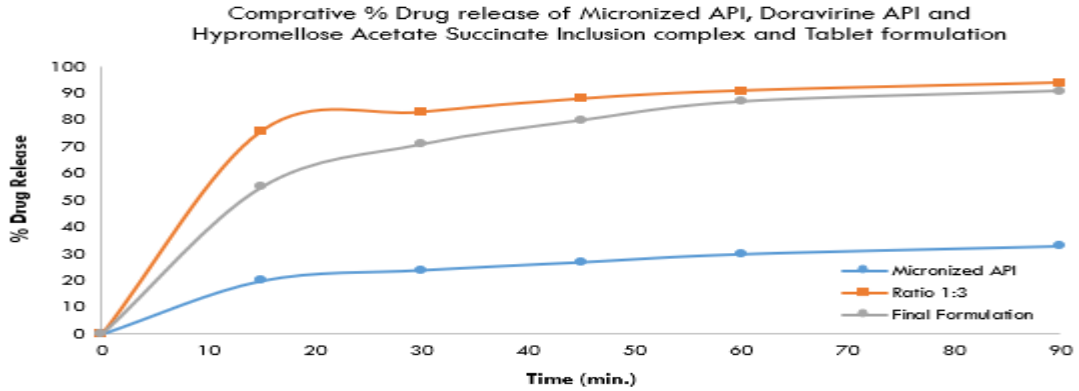



**Figure 5.** Comparative dissolution profiles of Doravirine Spray-Dried Dispersions vs. Micronized API.

**Formulation Optimization and Statistical Evaluation (Formulation Strategy)**

Formulation optimization of Doravirine 100 mg immediate-release tablets was carried out using a Central Composite Face-Centered (CCF) design under the QbD framework to study the effect of polymer (HPMCAS), disintegrant (Croscarmellose Sodium), and lubricant (Magnesium Stearate) concentrations on disintegration time, assay, and dissolution at 30 and 60 minutes.

Thirteen experimental runs were executed as per the design matrix, and the observed responses are summarized in Table 4. Disintegration time ranged from 60–180 seconds, assay from 98.9–101.2%, and dissolution improved from 66–78% at 30 min and 86–95% at 60 min. respectively.

ANOVA analysis showed that the quadratic model was highly significant ($F = 268.84$, $p < 0.0001$), confirming a strong correlation between formulation variables and disintegration behavior (Table 5).

**Table 4.** Analytical results of formulation optimization batches for Doravirine 100 mg immediate-release tablets (Central Composite Face-Centered design).

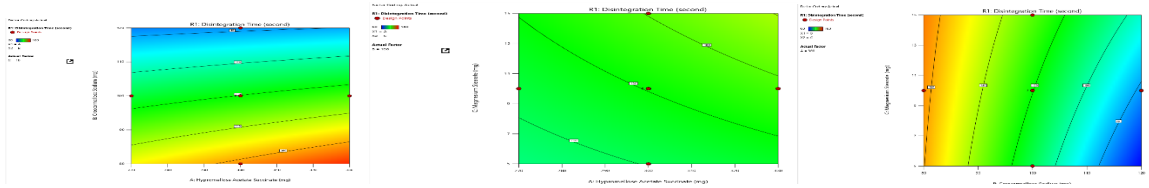
| Batch No. | Hypromellose Acetate Succinate (mg/unit) | Croscarmellose Sodium (mg/unit) | Magnesium Stearate (mg/unit) | Disintegration Time (s) | Assay (%) | Dissolution at 30 min (%) | Dissolution at 60 min (%) |
|---|---|---|---|---|---|---|---|
| Run 1 | 300 | 120 | 10 | 75 | 99.1 | 76 | 93 |
| Run 2 | 330 | 120 | 5 | 60 | 101.2 | 78 | 95 |
| Run 3 | 270 | 120 | 15 | 90 | 98.9 | 74 | 91 |
| Run 4 | 270 | 80 | 5 | 150 | 100.9 | 70 | 86 |
| Run 5 | 300 | 100 | 15 | 130 | 99.6 | 71 | 89 |
| Run 6 | 330 | 80 | 15 | 180 | 100.1 | 66 | 86 |
| Run 7 | 300 | 100 | 5 | 110 | 99.9 | 73 | 90 |
| Run 8 | 300 | 80 | 10 | 160 | 101.0 | 68 | 88 |
| Run 9 | 300 | 100 | 10 | 120 | 100.2 | 72 | 88 |
| Run 10 | 330 | 100 | 10 | 130 | 101.1 | 72 | 89 |
| Run 11 | 300 | 100 | 10 | 120 | 100.6 | 73 | 90 |
| Run 12 | 300 | 100 | 10 | 125 | 100.7 | 71 | 89 |
| Run 13 | 270 | 100 | 10 | 115 | 99.7 | 72 | 90 |

**Table 5.** ANOVA summary for disintegration time of Doravirine 100 mg immediate-release tablets.

| Source | Sum of Squares | df | Mean Square | F-value | p-value (Prob > F) | Remarks |
|---|---|---|---|---|---|---|
| Model | 12925.00 | 6 | 2154.17 | 268.84 | < 0.0001 | Significant |
| A – HPMCAS | 112.50 | 1 | 112.50 | 14.04 | 0.0095 | Significant |
| B – Croscarmellose Sodium | 3612.50 | 1 | 3612.50 | 450.84 | < 0.0001 | Significant |
| C – Magnesium Stearate | 200.00 | 1 | 200.00 | 24.96 | 0.0025 | Significant |
| AB | 33.33 | 1 | 33.33 | 4.16 | 0.0875 | Not significant |
| AC | 8.33 | 1 | 8.33 | 1.04 | 0.3472 | Not significant |

| | | | | | | |
|---|---|---|---|---|---|---|
| BC | 75.00 | 1 | 75.00 | 9.36 | 0.0222 | Significant |
| Residual | 48.08 | 6 | 8.01 | — | — | — |
| Lack of Fit | 31.41 | 4 | 7.85 | 0.94 | 0.5732 | Not significant |
| Pure Error | 16.67 | 2 | 8.33 | — | — | — |
| **Cor Total** | **12973.08** | **12** | — | — | — | — |

The contour and 3D surface plots (Figures 6 and 7) showed a clear relationship between the formulation variables and tablet disintegration. A higher level of disintegrant led to faster tablet breakup, whereas excessive amounts of polymer or lubricant caused a delay, likely due to matrix densification and the hydrophobic nature of magnesium stearate. These graphical trends aligned well with the statistical analysis from the ANOVA results (Table 5), confirming the combined effect of HPMCAS, croscarmellose sodium, and magnesium stearate on disintegration behavior.



**(A)(B) (C)**

**Figure 6.** Contour plots showing the combined effect of formulation variables on the disintegration time of Doravirine 100 mg immediate-release tablets (multi-panel)

(a) A – HPMCAS vs B – Croscarmellose Sodium
(b) A – HPMCAS vs C – Magnesium Stearate
(c) B – Croscarmellose Sodium vs C – Magnesium Stearate

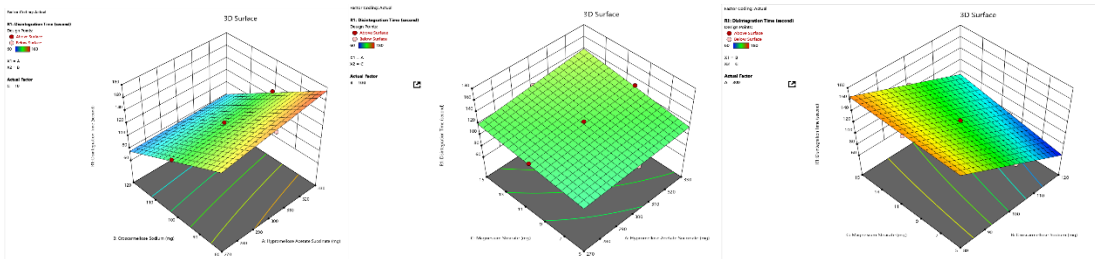


**Figure 7.** 3D response surface plots showing the interactive effect of formulation variables on the disintegration time of Doravirine 100 mg immediate-release tablets (multi-panel).

(a) A – HPMCAS vs B – Croscarmellose Sodium
(b) A – HPMCAS vs C – Magnesium Stearate
(c) B – Croscarmellose Sodium vs C – Magnesium Stearate

Assay Response Model Analysis

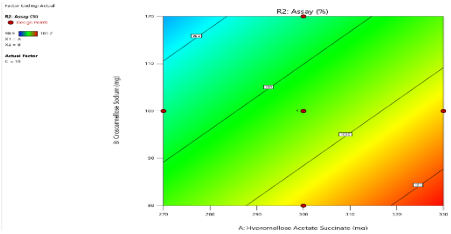
The assay model demonstrated statistical significance with an F-value of 6.01 (p = 0.0156), confirming that the selected factors impacted the assay results. Among these, HPMCAS (A) and magnesium stearate (C) had the strongest effects (Table 6). The non-significant lack-of-fit F-value (4.43) showed that the model was adequate and reliable.

**Table 6.** ANOVA summary for assay response of Doravirine 100 mg immediate-release tablets.

| **Source** | **Sum of Squares** | **df** | **Mean Square** | **F-value** | **p-value (Prob > F)** | **Comments** |
|---|---|---|---|---|---|---|
| Model | 4.63 | 3 | 1.54 | **6.01** | **0.0156** | Significant |
| A – Hypromellose Acetate Succinate | 1.40 | 1 | 1.40 | 5.45 | 0.0443 | Significant |
| B – Croscarmellose Sodium | 1.31 | 1 | 1.31 | 5.08 | 0.0506 | Borderline |
| C – Magnesium Stearate | 1.93 | 1 | 1.93 | 7.50 | 0.0229 | Significant |
| Residual | 2.31 | 9 | 0.2570 | — | — | — |
| Lack of Fit | 2.17 | 7 | 0.3104 | **4.43** | 0.1963 | Not significant |
| Pure Error | 0.14 | 2 | 0.0700 | — | — | — |
| **Cor Total** | **6.95** | **12** | — | — | — | — |

**Contour and 3D Surface Plot Analysis for Assay**

The contour and 3D surface plots (Figures 8 and 9) showed uniform assay values across the design space, confirming homogeneous drug distribution and consistent formulation performance.



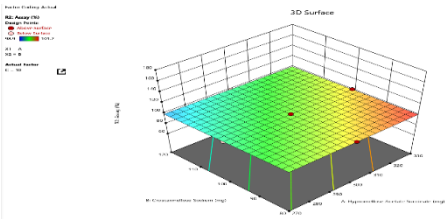




**Figure 8.** Contour plot of % Assay versus the levels of Hypromellose Acetate Succinate and Croscarmellose Sodium.
**Figure 9.** 3D response surface plot of % Assay versus the levels of Hypromellose Acetate Succinate and Croscarmellose Sodium.

**ANOVA Analysis for Dissolution at 30 Minutes**

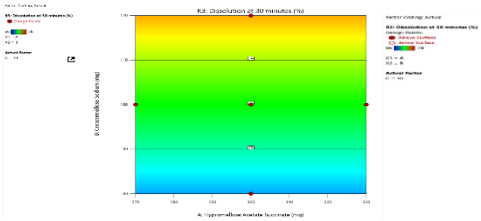
The dissolution model at 30 minutes was highly significant ($F = 101.40$, $p < 0.0001$), indicating a strong effect of formulation variables on drug release. Croscarmellose sodium (B) and magnesium stearate (C) were identified as the main contributing factors (Table 7). The non-significant lack-of-fit value ($F = 0.19$) confirmed the model's reliability and good fit to the data.

**Table 7.** ANOVA summary for dissolution at 30 minutes of Doravirine 100 mg immediate-release tablets.

| Source | Sum of Squares | df | Mean Square | F-value | p-value (Prob > F) | Comments |
|---|---|---|---|---|---|---|
| Model | 112.67 | 3 | 37.56 | **101.40** | **< 0.0001** | Significant |
| A – Hypromellose Acetate Succinate | 0.00 | 1 | 0.00 | 0.00 | 1.0000 | Not significant |
| B – Croscarmellose Sodium | 96.00 | 1 | 96.00 | 259.20 | < 0.0001 | Significant |
| C – Magnesium Stearate | 16.67 | 1 | 16.67 | 45.00 | < 0.0001 | Significant |
| Residual | 3.33 | 9 | 0.37 | — | — | — |
| Lack of Fit | 1.33 | 7 | 0.19 | **0.19** | 0.9595 | Not significant |
| Pure Error | 2.00 | 2 | 1.00 | — | — | — |
| **Cor Total** | **116.00** | **12** | — | — | — | — |

**Contour and 3D Surface Plot Analysis for Dissolution at 30 Minutes**

As seen in the graphical plots (Figures 10 and 11), an increase in disintegrant concentration enhanced drug dissolution, whereas higher lubricant levels slightly reduced the release rate, likely due to hydrophobic film formation on granule surfaces.



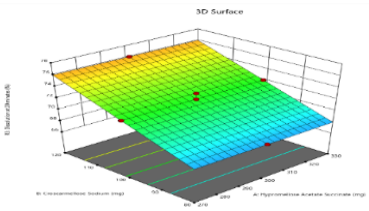



**Figure 10.** Contour plot showing the combined effects of Croscarmellose Sodium and Magnesium Stearate on the dissolution of Doravirine 100 mg immediate-release tablets at 30 minutes.
**Figure 11.** 3D response surface plot illustrating the influence of Croscarmellose Sodium and Magnesium Stearate on the dissolution of Doravirine 100 mg immediate-release tablets at 30 minutes.

**ANOVA Analysis for Dissolution at 60 Minutes**

The model for dissolution at 60 minutes exhibited good predictability ($F = 21.02$, $p = 0.0002$), with croscarmellose sodium (B) identified as the most influential variable. The non-significant lack-of-fit value ($F = 1.06$) confirmed the robustness and adequacy of the model (Table 8).

**Table** 8. ANOVA summary for dissolution at 60 minutes of Doravirine 100 mg immediate-release tablets.

| Source | SS | df | MS | F-value | p-value | Comments |
|---|---|---|---|---|---|---|
| Model | 65.83 | 3 | 21.94 | 21.02 | 0.0002 | Significant |
| A – HPMCAS | 1.50 | 1 | 1.50 | 1.44 | 0.2613 | Not significant |
| B – Croscarmellose Sodium | 60.17 | 1 | 60.17 | 57.62 | < 0.0001 | Significant |
| C – Magnesium Stearate | 4.17 | 1 | 4.17 | 3.99 | 0.0768 | Not significant |
| Residual | 9.40 | 9 | 1.04 | — | — | — |
| Lack of Fit | 7.40 | 7 | 1.06 | 1.06 | 0.5672 | Not significant |
| Pure Error | 2.00 | 2 | 1.00 | — | — | — |
| **Cor Total** | **75.23** | **12** | — | — | — | — |

**Contour and 3D Surface Plot Analysis for Dissolution at 60 Minutes**

The contour and 3D surface plots (Figures 12 and 13) showed that formulations with balanced polymer and disintegrant concentrations exhibited superior dissolution performance, achieving more than 95% drug release within 60 minutes.

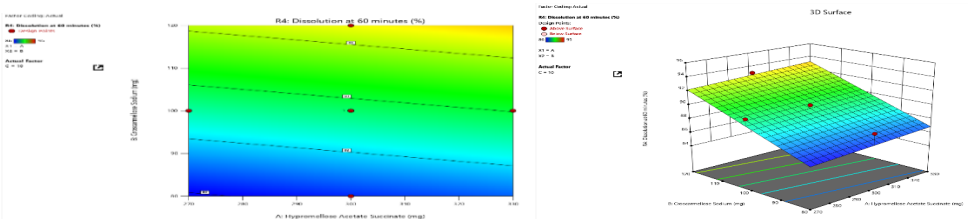
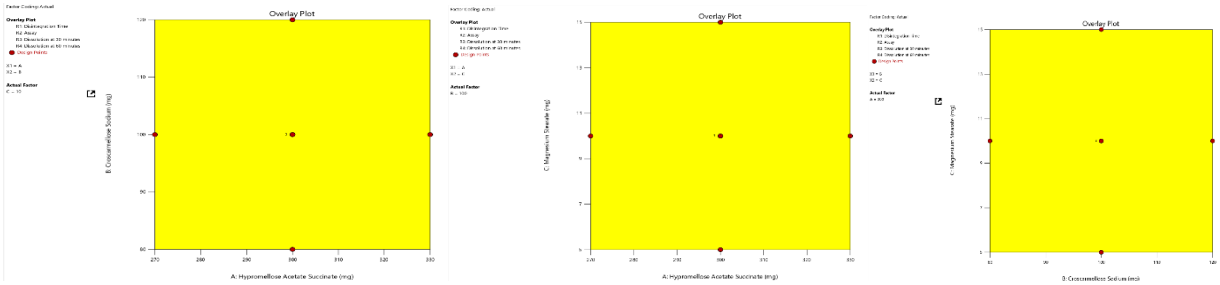


**Figure 12.** Contour plot showing the combined effects of Hypromellose Acetate Succinate and Croscarmellose Sodium concentrations on the dissolution of Doravirine 100 mg immediate-release tablets at 60 minutes.

**Figure 13.** 3D response surface plot illustrating the interactive influence of Hypromellose Acetate Succinate and Croscarmellose Sodium concentrations on the dissolution of Doravirine 100 mg immediate-release tablets at 60 minutes.

**Plot Analysis and Design Space Determination**

Overlay plots, as shown in Figures 14, were used to establish the design space for optimization. The yellow area in the plot indicated the range where all key formulation responses—assay, disintegration time, and dissolution—met specified targets. The center of this region aligned with the final optimized formulation. The optimized tablets demonstrated rapid disintegration, consistent assay values, and nearly complete drug release, validating the design and control strategy.



A B C

**Figure 14.** Overlay plots showing the optimized design space for formulation variables of Doravirine 100 mg immediate-release tablets (multi-panel).

(A) Overlay plot for disintegration time
(B) Overlay plot for assay
(C) Overlay plot for dissolution

The final optimized composition was selected based on the desirability function outcomes, targeting minimum disintegration time, maximum dissolution, and consistent assay. Experimental validation confirmed that the observed results were in close agreement with the predicted values, demonstrating the reliability and robustness of the established optimization model.

**Risk Assessment and Characterization of Doravirine Tablets**

Table 9 provides a summary of risk level assessments in the formulation study. The table shows updated risk evaluations based on the most recent data, but some parameters retained their original risk status because their impact on product quality remained significant. This demonstrates a thorough and justified approach to risk management throughout the development process.

**Table 9:** Risk assessment for formulation variables of Doravirine 100 mg immediate-release tablets.

| Drug Product CQA | Drug Substance Particle Size | Hypromellose Acetate Succinate | Microcrystalline Cellulose | Lactose Monohydrate | Croscarmellose Sodium | Magnesium Stearate |
|---|---|---|---|---|---|---|
| Assay | Low | Low | Low | Low | Low | Low |
| Dissolution | Low | Low | Low | Low | Low | Low |
| Related Substances | Low | Low | Low | Low | Low | Low |

**Final Formulation Composition**

The final prototype formulation composition was established based on the outcomes of the optimization studies and is presented in Table 10. This optimized composition was utilized for the preparation of the final batch of Doravirine 100 mg immediate-release tablets.

**Table10:** Final formulation composition of Doravirine 100 mg immediate-release tablets.

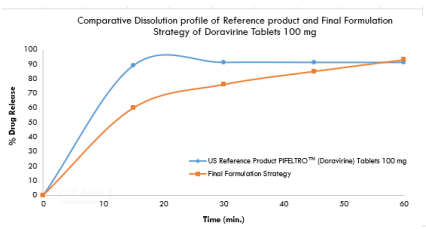
| **Sr. No.** | **Name of Ingredient** | **mg/unit** | **% w/w** |
|---|---|---|---|
| **Drug Dispersion** | | | |
| 1 | Doravirine API | 100.0 | 10.0 |
| 2 | Hypromellose Acetate Succinate | 300.0 | 30.0 |
| 3 | Acetone | Q.S. | – |
| 4 | Purified Water | Q.S. | – |
| **Granulation** | | | |
| 5 | Microcrystalline Cellulose | 300.0 | 30.0 |
| | **Weight of Dried Granules** | **700.0** | **70.0** |
| **Pre-lubrication** | | | |
| 6 | Lactose Monohydrate | 190.0 | 19.0 |
| 7 | Croscarmellose Sodium | 100.0 | 10.0 |
| **Lubrication** | | | |
| 8 | Magnesium Stearate | 10.0 | 1.0 |
| | **Weight of Core Tablets** | **1000.0** | **100.0** |

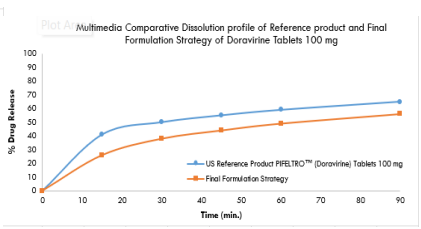
**Analytical Evaluation and Comparative Dissolution Study**

The prototype batch exhibited acceptable assay and impurity results, along with more than 90% of the drug released within 60 minutes, confirming the consistency of the formulation and manufacturing process. A comparative dissolution study with the US reference product was conducted in 900 mL phosphate buffer (pH 6.8), 900 mL acetate buffer (pH 4.5), and 900 mL 0.1 N HCl, each containing 3% polysorbate 80. The results demonstrated similar dissolution behavior across all media (Table 11).

**Table 11.** Comparative dissolution profile of US Reference product and developed formulation of Doravirine 100 mg tablets (N = 12).

| **Time (min)** | **US Reference Product** | | | | **Developed Final Formulation** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Mean** | **Min** | **Max** | **%RSD** | **Mean** | **Min** | **Max** | **%RSD** |
| **Medium:** 25 mM Phosphate buffer pH 6.8 + 3% Polysorbate 80, 900 mL, Paddle, 75 rpm | | | | | | | | |
| 15 | 89 | 86 | 91 | 1.8 | 60 | 54 | 66 | 7.7 |
| 30 | 91 | 89 | 93 | 1.4 | 76 | 72 | 78 | 2.8 |
| 45 | 91 | 89 | 94 | 2.0 | 85 | 81 | 89 | 3.4 |
| 60 | 91 | 89 | 93 | 1.5 | 93 | 90 | 96 | 2.3 |



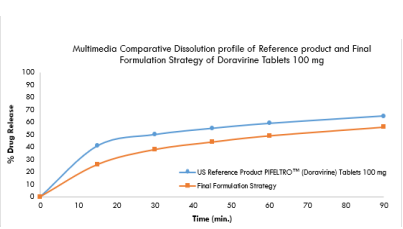



**Figure 15.** Comparative dissolution profiles of US Reference product (PIFELTRO™ 100 mg tablet) and developed formulation of Doravirine 100 mg tablets in different media (multi-panel).

(a) In phosphate buffer (pH 6.8) containing 3% polysorbate 80, the doravirine 100 mg tablet showed a dissolution profile matching the US reference product.
(b) In acetate buffer (pH 4.5) with 3% polysorbate 80, the developed tablet's drug release was comparable to the reference standard.
(c) In 0.1 N HCl containing 3% polysorbate 80, the dissolution behavior of the doravirine tablet remained consistent with the US reference product.
The dissolution profile of Doravirine 100 mg tablets was comparable to that of the US reference product across all three media, confirming bioequivalent dissolution behavior and supporting further stability evaluation.

**X-ray Powder Diffraction (XRPD) Analysis**

Characterization studies using X-ray Powder Diffraction (XRPD) were performed to evaluate the solid-state properties of the Doravirine drug substance, placebo, and final formulation. The Doravirine API was confirmed as crystalline polymorphic Form-I, as indicated by its distinct diffraction peaks (Figure 16). The detailed XRPD data of the API are presented in Table 12, confirming the characteristic 2θ values corresponding to Crystalline Form-I.

**Table 12:** characteristic 2θ values corresponding to Form-I.

| Num. | 2θ (°) | d (Å) | Intensity (Int) | I/Imax (%) | Num. | 2θ (°) | d (Å) | Intensity (Int) | I/Imax (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 5.3647 | 16.46 | 1995 | 21.7 | 21 | 25.9155 | 3.43527 | 187 | 2.0 |
| 2 | 8.7186 | 10.1341 | 866 | 9.4 | 22 | 26.4443 | 3.36776 | 328 | 3.6 |
| 3 | 9.7104 | 9.10109 | 9189 | 100.0 | 23 | 26.9466 | 3.30611 | 651 | 7.1 |
| 4 | 10.7619 | 8.2416 | 2041 | 22.2 | 24 | 27.2103 | 3.27468 | 1396 | 15.2 |
| 5 | 12.4110 | 7.12617 | 2195 | 23.9 | 25 | 27.9054 | 3.19467 | 995 | 10.8 |
| 6 | 13.8203 | 6.4036 | 202 | 2.2 | 26 | 28.2071 | 3.16118 | 3128 | 34.0 |
| 7 | 15.0504 | 5.88185 | 2055 | 22.4 | 27 | 29.3796 | 3.03763 | 531 | 5.8 |
| 8 | 16.5617 | 5.34853 | 6961 | 75.7 | 28 | 30.4148 | 2.93671 | 399 | 4.3 |
| 9 | 17.0809 | 5.18695 | 444 | 4.8 | 29 | 30.9648 | 2.88564 | 281 | 3.1 |
| 10 | 17.5233 | 5.05699 | 3672 | 40.0 | 30 | 31.8650 | 2.80614 | 121 | 1.3 |
| 11 | 18.6262 | 4.75995 | 1393 | 15.2 | 31 | 32.8698 | 2.72511 | 142 | 1.5 |
| 12 | 19.0966 | 4.64374 | 130 | 1.4 | 32 | 33.5291 | 2.67058 | 136 | 1.5 |
| 13 | 19.5247 | 4.54289 | 874 | 9.5 | 33 | 34.6203 | 2.59151 | 543 | 5.9 |
| 14 | 20.9394 | 4.23905 | 182 | 2.0 | 34 | 35.4184 | 2.53234 | 103 | 1.1 |
| 15 | 21.9267 | 4.0535 | 1250 | 13.6 | 35 | 36.9565 | 2.43309 | 116 | 1.3 |
| 16 | 22.7684 | 3.90249 | 498 | 5.4 | 36 | 38.7228 | 2.3235 | 448 | 4.9 |
| 17 | 23.5608 | 3.773 | 1194 | 13.0 | 37 | 41.6692 | 2.1577 | 233 | 2.5 |
| 18 | 24.0288 | 3.70056 | 2089 | 22.7 | 38 | 46.0800 | 1.9682 | 113 | 1.2 |
| 19 | 24.6183 | 3.61327 | 325 | 3.5 | | | | | |
| 20 | 25.0409 | 3.55324 | 1865 | 20.3 | | | | | |

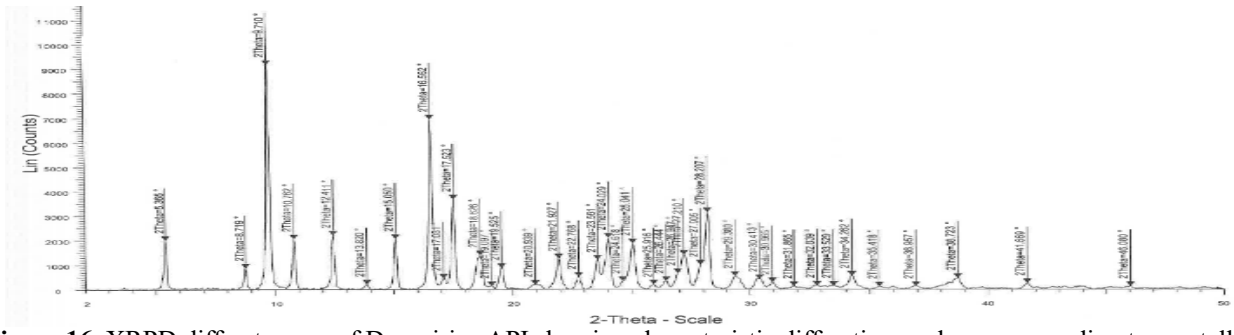



**Figure 16**. XRPD diffractogram of Doravirine API showing characteristic diffraction peaks corresponding to crystalline polymorphic Form-I.

Comparative XRPD patterns were obtained for the placebo, API–placebo physical mixtures (5% and 10%), and the final dried granules of the optimized formulation. As shown in Figure 17 (A–D), the intensity of Doravirine crystalline peaks gradually decreased from the pure API to the final granules, confirming the transition toward an amorphous solid dispersion facilitated by polymer interaction with HPMCAS.

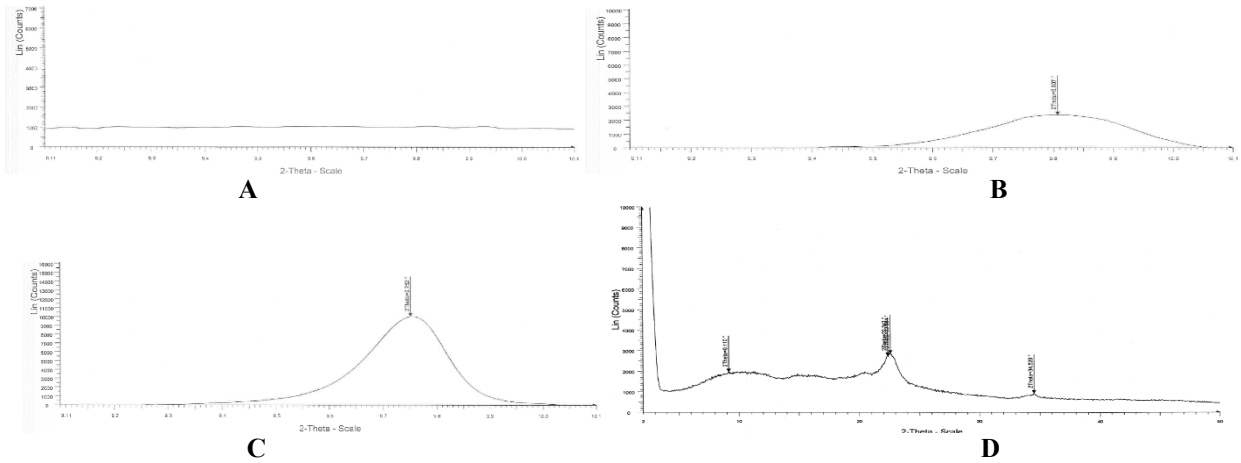



**Figure 17. Comparative XRPD diffractograms of Doravirine formulation components (multi-panel)**.
(A) Placebo of Doravirine Tablets 100 mg
(B) Doravirine API 5 % + Placebo
(C) Doravirine API 10 % + Placebo
(D) Final prototype granules of Doravirine Tablets 100 mg

**Stability Studies**

The stability of the optimized Doravirine tablets 100 mg formulation was evaluated under both long-term (30 °C ± 2 °C / 75% RH ± 5% RH) and accelerated (40 °C ± 2 °C / 75% RH ± 5% RH) storage conditions for six months in HDPE bottles containing 30 tablets with 2 g silica-gel canisters. Samples were tested at the initial, 3-month, and 6-month time intervals for appearance, dissolution, assay, related substances, and water content. The 100 mg doravirine tablets maintained their physical and chemical stability over six months under both long-term and accelerated storage conditions. They showed no change in color, odor, or texture, with assay results between 99.3% and 101.6%, dissolution above 95%, and impurities below 0.25%. Water content was also low, below 4%, indicating good moisture protection. These findings demonstrate the formulation's robustness and suitability for long-term storage, scaling up, and regulatory approval.

**Table 13.** Stability study results of Doravirine Tablets 100 mg (30 °C ± 2 °C / 75 % RH ± 5 % RH; 6 months)

| Test | Specification | Initial | 3 Months | 6 Months |
|---|---|---|---|---|
| Description | White to off-white, oval-shaped, film-coated tablets debossed “EM 70” | Complies | Complies | Complies |
| Dissolution (% of label claim) | NLT 70 % in 30 min | 99 (98–99) | 98 (97–99) | 100 (98–101) |
| Assay (% w/w) | 90.0–110.0 | 99.6 | 101.6 | 100.7 |
| Single unknown impurity | ≤ 0.2 % | 0.050 | 0.057 | 0.061 |
| Total impurities | ≤ 2.0 % | 0.193 | 0.190 | 0.217 |
| Water content (KF, %) | NMT 8.0 % | 3.45 | 3.14 | 3.71 |

**Table 14.** Stability study results of Doravirine Tablets 100 mg (40 °C ± 2 °C / 75 % RH ± 5 % RH; 6 months).

| Test | Specification | Initial | 3 Months | 6 Months |
|---|---|---|---|---|
| Description | White to off-white, oval-shaped, film-coated tablets debossed “EM 70” | Complies | Complies | Complies |
| Dissolution (% of label claim) | NLT 70 % in 60 min | 93 (90–96) | 95 (92–98) | 96 (94–99) |
| Assay (% w/w) | 90.0–110.0 | 99.6 | 99.3 | 100.5 |
| Single unknown impurity | ≤ 0.2 % | 0.050 | 0.066 | 0.061 |
| Total impurities | ≤ 2.0 % | 0.193 | 0.226 | 0.221 |
| Water content (KF, %) | NMT 8.0 % | 3.45 | 3.31 | 3.33 |

**Discussion**

XRPD analysis confirmed the complete conversion of doravirine to an amorphous form in the final formulation, indicated by the absence of crystalline peaks. The optimized tablets maintained strong physical integrity, showed rapid drug dissolution, and preserved stable chemical properties. Stability testing under accelerated conditions (40 °C/75% RH) for 180 days

revealed consistent assay values, dissolution rates, and low impurity levels. Overall, the 100 mg doravirine tablets produced via top-spray granulation demonstrated reliable, reproducible performance, making them well-suited for scale-up and regulatory approval

**Conclusion**

The developed 100 mg immediate-release doravirine tablet, prepared through polymer-assisted top-spray granulation, successfully addressed the solubility and dissolution challenges of the crystalline drug. The optimized formulation exhibited rapid and complete drug release, consistent potency, and maintained chemical stability. Analysis confirmed the drug's conversion to an amorphous form aided by the polymer, enhancing dissolution. Comparative studies showed bioequivalence with the reference product. Stability testing under various conditions demonstrated the formulation's durability, making this method a scalable and reliable option for commercial manufacturing and regulatory compliance.

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