

Optimization of Immediate-Release Fimasartan Tablets Using 3² Factorial Design for Rapid Disintegration and Enhanced Drug Release

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In this study, immediate-release Fimasartan tablets were formulated and optimised by use of a 3² full factorial design with the objective of rapid disintegration and efficient drug release. Croscarmellose sodium (X₁) and microcrystalline cellulose (X₂) were selected as factors, while hardness (Y₁), disintegration time (Y₂), and drug release at 30 min (Y₃) were selected as responses. The tablets were formulated using the direct compression technique and subsequently assessed for both pre-compression and post-compression characteristics, along with disintegration performance and drug release profile. All prepared batches demonstrated satisfactory hardness, friability, uniformity of weight, and drug content values. Statistical analysis indicated that both variables significantly affected tablet performance. Increasing croscarmellose sodium reduced disintegration time and improved drug release, whereas higher MCC levels slightly prolonged disintegration and reduced release. Batch F7 was identified as the optimised formulation, showing hardness of 5.3 ± 0.2 kg/cm², disintegration time of 32 ± 2 s, and $99.8 \pm 4.2\%$ drug release at 30 min. Drug release followed first-order kinetics. Accelerated stability studies at $40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH for three months showed no significant changes, and the similarity factor ($f_2 = 74.13$) confirmed comparable dissolution profiles. The study concluded that optimised immediate-release Fimasartan tablets were successfully developed using a factorial design.

Keywords: Croscarmellose sodium, Factorial design, Fimasartan, Immediate-release tablets, Optimisation.

Hypertension is one of the main worldwide health concerns and a top risk factor for cardiovascular diseases. Effective management of blood pressure is essential to reduce associated morbidity and mortality.¹ Among the therapeutic options available, angiotensin II receptor blockers (ARBs) are widely used due to their efficacy and favourable safety profile. Fimasartan, a relatively newer ARB, has gained attention for

its potent antihypertensive activity and improved pharmacokinetic properties compared to earlier agents. Despite its therapeutic advantages, the formulation of Fimasartan into an effective oral dosage form needs consideration of aspects such as drug release rate, stability, and patient compliance.² Immediate-release (IR) tablet formulations must disintegrate fast after administration, ensuring fast release of drug and fast onset

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of action. Such formulations are particularly beneficial in conditions like hypertension, where a rapid therapeutic response is desirable. The performance of immediate-release tablets is largely influenced by the selection and optimisation of excipients, especially superdisintegrants and binders. Superdisintegrants such as croscarmellose sodium facilitate rapid tablet disintegration through swelling and wicking mechanisms, thereby enhancing drug dissolution. On the other hand, excipients like microcrystalline cellulose (MCC) contribute to tablet hardness and mechanical strength but may also influence disintegration time depending on their concentration. Due to several advantages of the direct compression method, it is widely used for the preparation of immediate-release tablets.³ However, attaining an optimum balance between tablet strength and rapid disintegration is a challenge in formulation development. Statistical optimisation techniques such as factorial design provide a systematic and efficient approach to assess the outcome of formulation variables and their relations on important quality parameters while limiting the number of trials. Therefore, the current study intended to design and optimise immediate-release tablets of Fimasartan using a 3² full factorial design by investigating the effects of croscarmellose sodium and microcrystalline cellulose on tablet properties. The optimised formulation is expected to deliver rapid drug release, better therapeutic efficacy, and improved patient compliance.

MATERIALS AND METHODS

Material

Fimasartan was gifted by Vidisha Analytical Research and Training Centre, Nashik, India. All other excipients and chemicals, including croscarmellose sodium, microcrystalline cellulose (MCC), mannitol, magnesium stearate, talc, and analytical grade reagents, were acquired from Sudarshan Scientific Limited, Nashik, India. In-house prepared distilled water was used wherever necessary.

Methods

Preformulation Studies

To evaluate the physicochemical characteristics of the drug molecule, preformulation studies were performed.

Melting Point Determination

The open capillary method was used to check the melting point.⁴

UV-Visible Spectrophotometric Analysis

A 1000 ppm stock solution of Fimasartan was prepared using methanol and diluted with 0.1 N HCl. A prepared 20 ppm solution was then scanned between 200–400 nm (Shimadzu 1800, Japan) UV-Visible spectrophotometer to determine the λ_{max} .

Calibration Curve Preparation

Suitable dilutions of the stock solution were prepared to obtain 5–25 $\mu\text{g/mL}$ solutions and scanned at the selected λ_{max} using 0.1 N HCl as blank, and a calibration graph of concentration versus absorbance was constructed.⁵

Solubility Study

The shake flask method was used for the determination of solubility. A surplus quantity of API was added to a known volume of solvent (methanol, ethanol, dimethyl sulfoxide, and distilled water) in separate conical flasks. The flasks were securely closed and agitated in a mechanical shaker at $25 \pm 2^\circ\text{C}$ for 24 hours until equilibrium was reached. After equilibrium filtration was carried out through Whatman filter paper and drug concentration was determined by using a UV-Visible spectrophotometer.⁶

Drug-Excipient Compatibility Study

Compatibility study between Fimasartan and the selected excipients was carried out by using FTIR. A physical mixture of the drug and excipients was analyzed using a Shimadzu IRAffinity-1 FTIR spectrophotometer by the KBr pellet method over the range of 4000–400 cm^{-1} .⁷

Formulation of Immediate-Release Tablets

Direct compression was used for the compression of immediate-release tablets of Fimasartan. The accurately weighed materials were passed through a #60 mesh sieve and blended homogeneously. The lubricated blend was then compressed using an 8-station tablet compression machine (VbTech Automation, Ahmedabad, India) with 10 mm punches to obtain tablets.

Experimental Design

A 3² factorial design was used to optimize the immediate-release tablets of Fimasartan. Croscarmellose sodium (X_1) and microcrystalline cellulose (X_2) were selected as independent

variables at three levels (-1, 0, +1), while hardness (Y_1), disintegration time (Y_2), and drug release at 30 min (Y_3) were taken as responses. Based on the design, nine formulations were prepared and evaluated, and the relationship between formulation variables and responses was analysed using a polynomial equation.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2$$

In the polynomial model, Y denotes the response, while b_0 , b_1 , b_2 , and b_{12} represent the intercept, main effects, and interaction effect, respectively. Statistical optimisation was carried out using Design-Expert® software (Version 13) with ANOVA and response surface analysis. The formulation compositions are provided in Table 1.

Evaluation of Powder Blend⁸⁻¹⁰

The powder blend was evaluated for pre-compression parameters to determine its flowability and compressibility characteristics. Bulk and tapped densities were determined by the graduated cylinder method, while flow properties were assessed using the fixed funnel method.

Evaluation of Tablets (Post-Compression Parameters)¹¹⁻¹³

Physical appearance

Visual inspection of the compressed tablets was carried out to evaluate their physical characteristics, including appearance, colour uniformity, shape, and surface quality. The tablets were also checked for manufacturing defects such as chipping, cracking, capping, and lamination. Consistency in these properties reflected proper tablet formulation and effective compression during manufacturing.

Thickness and Hardness

Tablet thickness and hardness were measured using a digital Vernier calliper and a Monsanto hardness tester, respectively. Three tablets from each batch were tested, and the average value was calculated.

Friability

The Roche friabilator was used for checking friability. Previously weighed tablets were subjected to rotation in a friabilator at 25 rpm for 4 minutes, after which the tablets were dedusted and weighed again. The percentage friability was then determined using the appropriate equation.

Friability (%) = [(Initial weight of tablets - Final weight after test) / Initial weight of tablets] × 100

Weight variation

Twenty tablets were selected randomly and weighed individually. The average tablet weight was calculated, and the percentage deviation of each tablet from the average weight was determined using the following equation;

$$\% \text{ Weight Variation} = [(\text{Individual Weight} - \text{Average Weight}) / \text{Average Weight}] \times 100$$

Drug content

Ten tablets were collectively weighed and triturated into a fine powder. A portion of the powder corresponding to 120 mg of Fimasartan was dispersed in 0.1 N HCl, filtered, and quantified using UV-Visible spectrophotometric analysis.

Disintegration Test

Using a USP disintegration test apparatus (Electrolab EDI 2I), six tablets from each batch were tested in 0.1 N HCl kept at $37 \pm 2^\circ\text{C}$. The duration required for total breakdown of the tablets without any intact residue was noted, and the average disintegration time was calculated.¹⁴

In Vitro Dissolution Study

USP Type II dissolution test apparatus (Veritas-08 basic, Electrolab, India) was utilised to check the dissolution performance of the prepared tablet. 0.1 N HCl (900 mL) kept at $37 \pm 0.5^\circ\text{C}$ was used as a medium with a 50 rpm paddle speed. One tablet from each formulation batch was subjected to dissolution testing, and 5 mL samples were collected at specified intervals of 5, 10, 15, 20, 25, and 30 minutes while maintaining sink conditions. The collected dissolution samples were filtered, appropriately diluted, and examined at 256 nm using a UV-Visible spectrophotometer. Drug release at each time point was calculated using the calibration curve data.¹⁵

Statistical Analysis and Optimisation

Design-Expert® (version 13) was used for statistical analysis. The outcome of independent variables, concentration of croscarmellose sodium (X_1) and microcrystalline cellulose (X_2), on the dependent responses, namely tablet hardness and disintegration time, was evaluated. The experimental data were statistically evaluated using

ANOVA to check the significance of the model and formulation variables, with $p < 0.05$ considered significant.

Validation of Optimised Formulation

To validate the reliability of the developed factorial design model, the optimised formulation suggested by the numerical optimisation process was prepared experimentally. The optimised batch (F7) was evaluated for critical quality attributes. The experimentally obtained values were compared with the forecasted responses generated by the software. The percentage prediction error was calculated to assess the accuracy and robustness of the optimisation model. Close agreement between predicted and observed values was considered as confirmation of model validity.

Drug Release Kinetics Study

The release behaviour of the optimized formulation (F7) was evaluated by fitting the dissolution data to various mathematical models, including zero-order, first-order, Higuchi, and Hixson–Crowell models, using cumulative drug release values obtained at different time points.

Accelerated Stability Study

The optimized formulation (F7) was packed in aluminium blister packs and subjected to accelerated stability studies.¹² The tablets were stored at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ relative humidity (RH) in a stability chamber for a period of three

months. Samples were withdrawn at predetermined intervals of 0, 1, 2, and 3 months and evaluated for physical appearance, hardness, friability, disintegration time, drug content, and in vitro drug release. The formulation was considered stable if no significant change in physical appearance was observed, friability remained below 1%, drug content remained within 90–110% of the labeled claim, disintegration time remained within acceptable limits for immediate-release tablets, and drug release at 30 minutes was not less than 85%. Furthermore, the similarity factor (f_2) was calculated to compare the dissolution profiles of the initial and stored samples, and an f_2 value greater than 50 was considered indicative of similarity between dissolution profiles. The results demonstrated that the optimized formulation complied with all predefined acceptance criteria throughout the study period and remained physically and chemically stable under accelerated storage conditions for three months.¹⁶

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

Where n represents the number of dissolution sampling intervals, while R_t and T_t correspond to the percentage drug release from the initial and stability samples, respectively, at a given time point t .

Table 1. Formulation Composition of Batches Prepared Using 3^2 Factorial Design

Component / Batch	F1	F2	F3	F4	F5	F6	F7	F8	F9
Fimasartan (mg)	120	120	120	120	120	120	120	120	120
CCS (mg) (X_1)	5.6	5.6	5.6	11.2	11.2	11.2	16.8	16.8	16.8
MCC (mg) (X_2)	21	31.5	42	21	31.5	42	21	31.5	42
Mannitol (mg)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Talc (mg)	3	3	3	3	3	3	3	3	3
Magnesium stearate (mg)	2	2	2	2	2	2	2	2	2
Total weight (mg)	280	280	280	280	280	280	280	280	280

Table 2. Quantitative Solubility of Fimasartan in Different Solvents

Solvent	Solubility (mg/mL)	Solubility Category
Methanol	28.56 ± 2.67	Freely soluble
Ethanol	23.40 ± 3.02	Freely soluble
Dimethyl sulfoxide (DMSO)	55.78 ± 4.34	Highly soluble
Distilled water	0.0062 ± 0.0003	Poorly soluble

Values are expressed as mean $\pm$ SD ($n = 3$).

RESULTS

Preformulation Studies

Melting Point Determination

The melting temperature of Fimasartan was observed within the range of 154–156°C.

Solubility Study

The drug showed high solubility in methanol, ethanol, and dimethyl, whereas it showed poor solubility in distilled water. The results are presented in Table 2.

UV–Visible Spectrophotometric Analysis

Fimasartan exhibited maximum absorbance (λ_{max}) at 256 nm, showing a sharp and well-defined peak in the UV spectrum (Figure 1).

Calibration Curve

Linear correlation ($R^2 = 0.996$) was found in concentration and absorbance as indicated in Figure 2.

Drug–Excipient Compatibility Study

The FTIR spectrum of pure Fimasartan displayed characteristic absorption peaks associated with its functional groups, such as aromatic C–H and C=O stretching vibrations. Similar prominent peaks were also observed in the FTIR spectrum (Figure 3) of the physical mixture without any noticeable changes, indicating the absence of significant drug–excipient interaction.

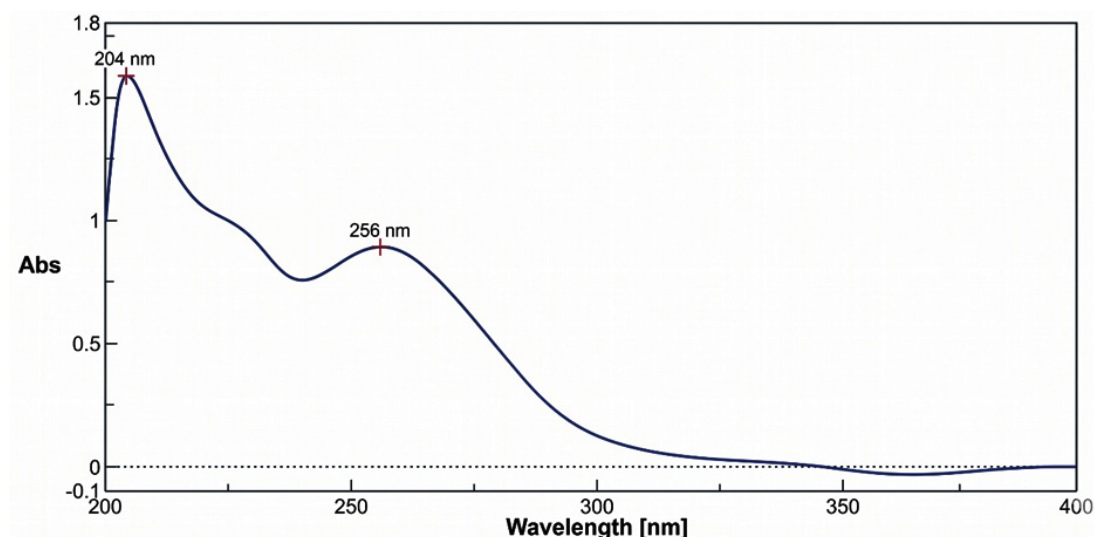


Fig. 1. UV–Visible absorption spectrum of Fimasartan

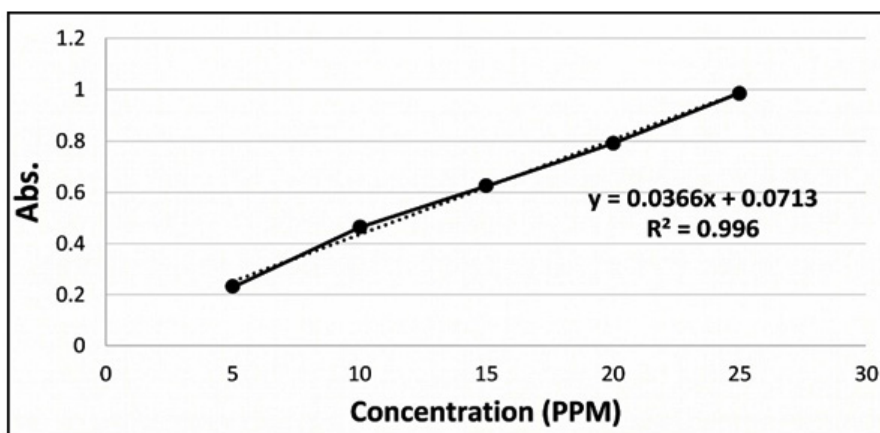


Fig. 2. Calibration curve of Fimasartan in 0.1 N hydrochloric acid (5–25 $\mu\text{g/mL}$)

Evaluation of Powder Blend (Pre-Compression Parameters)

Pre-compression characteristics of formulations F1–F9, including bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose, were determined to assess powder flow and compressibility. The obtained data are summarized in Table 3.

Evaluation of Tablets (Post-Compression Parameters)

The prepared tablets (F1–F9) were assessed for post-compression parameters, including thickness, hardness, friability, weight

variation, and drug content uniformity. The observed results are summarized in Table 4.

Disintegration Test

The disintegration time of F1–F9 was evaluated to assess tablet performance. The results are presented in Table 5.

In Vitro Dissolution Study

The dissolution profile of formulations F1–F9 was studied in 0.1 N HCl, and the corresponding in vitro drug release data are provided in Table 6.

Statistical Analysis and Optimisation

The influence of formulation parameters on the properties of immediate-release tablets

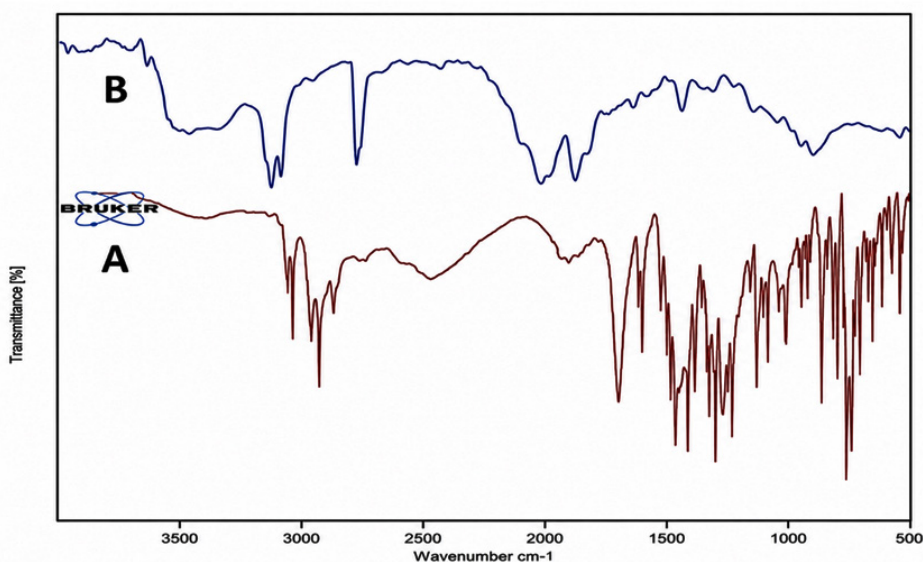


Fig. 3. FTIR spectra of pure Fimasartan (A) and its physical mixture (B) with excipients

Table 3. Pre-Compression Parameters of Powder Blends

Batch	Bulk Density (g/cm ³)	Tapped Density (g/cm ³)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)	Flow Property
F1	0.56 ± 0.03	0.65 ± 0.04	13.97 ± 0.35	1.16 ± 0.02	25.20 ± 0.40	Good
F2	0.56 ± 0.04	0.68 ± 0.05	16.73 ± 0.42	1.20 ± 0.02	27.24 ± 0.45	Good
F3	0.56 ± 0.03	0.66 ± 0.04	14.83 ± 0.36	1.17 ± 0.02	26.36 ± 0.38	Good
F4	0.55 ± 0.03	0.64 ± 0.04	14.50 ± 0.34	1.17 ± 0.02	25.74 ± 0.35	Good
F5	0.53 ± 0.02	0.61 ± 0.03	13.66 ± 0.30	1.16 ± 0.02	24.34 ± 0.30	Good
F6	0.52 ± 0.03	0.63 ± 0.05	18.10 ± 0.48	1.22 ± 0.03	23.45 ± 0.28	Fair
F7	0.53 ± 0.03	0.63 ± 0.04	14.99 ± 0.37	1.18 ± 0.02	25.98 ± 0.36	Good
F8	0.54 ± 0.03	0.65 ± 0.04	16.41 ± 0.40	1.20 ± 0.02	24.34 ± 0.32	Good
F9	0.54 ± 0.03	0.64 ± 0.04	15.07 ± 0.35	1.18 ± 0.02	24.15 ± 0.30	Good

Values are expressed as mean ± SD (n = 3)

was investigated using a 3^2 factorial experimental design. Two formulation components, namely croscarmellose sodium and microcrystalline cellulose, were examined at three different concentrations to study their effect on tablet hardness, disintegration behaviour, and drug release profile. The response values obtained from all nine formulation batches (F1–F9) are provided in Table 7.

Effect of Formulation Variables on Tablet Hardness (Y_1)

The outcome of formulation variables on tablet hardness (Y_1) was analysed using a 2FI model, and the generated polynomial equation was:

$$Y_1 = 4.7889 + 0.25X_1 + 0.0833X_2 - 0.30X_1X_2$$

The response surface plot (Figure 4) shows that hardness increased with increasing

Table 4. Post-Compression Parameters of Tablets

Batch	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Weight Variation (mg)	Drug Content (%)
F1	3.12 ± 0.05	4.2 ± 0.2	0.68 ± 0.04	280 ± 3	98.5 ± 1.2
F2	3.15 ± 0.04	4.5 ± 0.3	0.72 ± 0.05	279 ± 4	99.2 ± 1.0
F3	3.18 ± 0.05	4.8 ± 0.2	0.75 ± 0.04	281 ± 3	99.6 ± 0.9
F4	3.10 ± 0.03	4.6 ± 0.2	0.70 ± 0.03	280 ± 3	98.9 ± 1.1
F5	3.14 ± 0.04	4.9 ± 0.3	0.69 ± 0.04	279 ± 4	99.4 ± 0.8
F6	3.16 ± 0.05	5.1 ± 0.3	0.74 ± 0.05	281 ± 3	99.8 ± 0.7
F7	3.13 ± 0.04	5.3 ± 0.2	0.66 ± 0.03	280 ± 2	100.2 ± 0.6
F8	3.17 ± 0.05	5.0 ± 0.3	0.71 ± 0.04	279 ± 3	99.7 ± 0.8
F9	3.11 ± 0.03	4.7 ± 0.2	0.73 ± 0.05	281 ± 3	99.1 ± 1.0

Values are expressed as mean ± SD (n = 3)

Table 5. Disintegration Time of Tablets

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Disintegration Time(s)	62 ± 3	68 ± 4	75 ± 5	48 ± 3	55 ± 4	60 ± 4	32 ± 2	40 ± 3	45 ± 3

Values are expressed as mean ± SD (n = 3)

Table 6. In vitro drug release profiles of all formulations (F1–F9)

Batch	5 min	10 min	15 min	20 min	25 min	30 min
F1	32.4 ± 2.1	48.7 ± 2.4	65.2 ± 2.8	78.4 ± 3.1	88.9 ± 3.4	94.5 ± 3.6
F2	28.6 ± 1.8	42.3 ± 2.1	58.9 ± 2.5	72.5 ± 2.8	82.3 ± 3.1	89.8 ± 3.3
F3	24.3 ± 1.6	38.6 ± 2.0	52.1 ± 2.3	65.8 ± 2.6	75.6 ± 2.9	82.7 ± 3.1
F4	40.2 ± 2.3	60.4 ± 2.8	78.6 ± 3.2	90.5 ± 3.6	96.2 ± 3.8	98.4 ± 4.1
F5	36.5 ± 2.0	55.7 ± 2.5	72.4 ± 2.9	85.2 ± 3.3	92.8 ± 3.6	96.3 ± 3.9
F6	33.1 ± 1.9	52.2 ± 2.3	69.3 ± 2.8	81.6 ± 3.1	90.1 ± 3.4	93.7 ± 3.6
F7	48.6 ± 2.5	72.5 ± 3.0	88.9 ± 3.5	96.8 ± 3.8	99.2 ± 4.0	99.8 ± 4.2
F8	44.2 ± 2.3	66.8 ± 2.7	82.3 ± 3.1	91.2 ± 3.5	96.5 ± 3.8	97.9 ± 4.0
F9	41.5 ± 2.2	63.4 ± 2.6	79.1 ± 3.0	88.4 ± 3.4	94.3 ± 3.7	96.1 ± 3.9

Values are expressed as mean ± SD (n = 3)

concentration of X_1 , while X_2 had a moderate effect.

Effect on Disintegration Time (Y_2)

The effect on disintegration time (Y_2) was evaluated using a linear model, and the regression equation obtained was:

$$Y_2 = 53.89 - 14.67X_1 + 6.33X_2$$

The response surface plot (Figure 5) indicates that disintegration time decreased with increasing X_1 and increased with higher X_2 .

Effect on Drug Release at 30 min (Y_3)

The effect on drug release at 30 min (Y_3) was analysed using a linear model, and the regression equation obtained was:

$$Y_3 = 94.36 + 4.47X_1 - 3.37X_2$$

The response surface plot (Figure 6) indicated that an increase in X_1 enhanced drug release, whereas higher levels of X_2 resulted in reduced drug release.

Validation of Optimised Formulation

The optimised formulation obtained from the numerical optimisation process was prepared and evaluated. The observed values of hardness, disintegration time, and percentage drug release at 30 min were compared with the predicted values. The results are presented in Table 8.

Drug release kinetics

Drug release data of the optimized batch (F7) were subjected to different mathematical

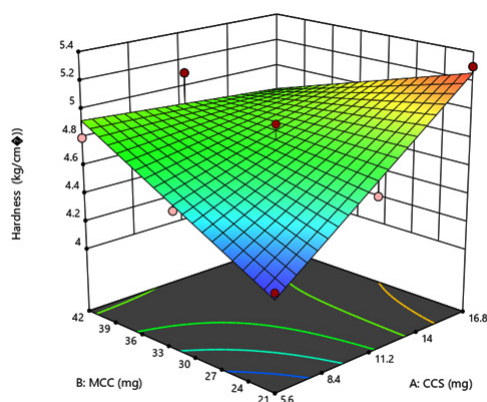


Fig. 4. 3D response surface plot showing the effect of X_1 and X_2 on tablet hardness

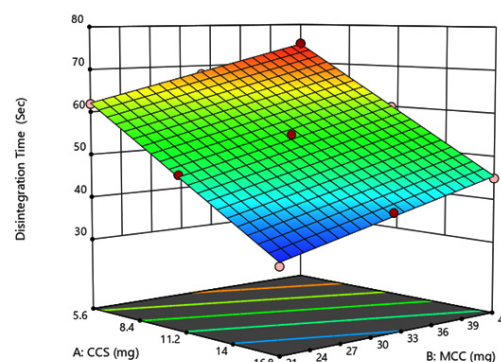


Fig. 5. Three-dimensional response surface plot showing the effect of croscarmellose sodium (X_1) and microcrystalline cellulose (X_2) on disintegration time (Y_2)

Table 7. Experimental design matrix and observed responses

Batch	X_1 : CCS (mg)	X_2 : MCC (mg)	Hardness (kg/cm ²)	Disintegration Time (s)	% Drug Release at 30 min
F1	5.6	21	4.2 ± 0.2	62 ± 3	94.5 ± 3.6
F2	5.6	31.5	4.5 ± 0.3	68 ± 4	89.8 ± 3.3
F3	5.6	42	4.8 ± 0.2	75 ± 5	82.7 ± 3.1
F4	11.2	21	4.6 ± 0.2	48 ± 3	98.4 ± 4.1
F5	11.2	31.5	4.9 ± 0.3	55 ± 4	96.3 ± 3.9
F6	11.2	42	5.1 ± 0.3	60 ± 4	93.7 ± 3.6
F7	16.8	21	5.3 ± 0.2	32 ± 2	99.8 ± 4.2
F8	16.8	31.5	5.0 ± 0.3	40 ± 3	97.9 ± 4.0
F9	16.8	42	4.7 ± 0.2	45 ± 3	96.1 ± 3.9

Values are expressed as mean ± SD (n = 3)

models. The kinetic analysis plots are illustrated in Figure 7, which revealed that the formulation exhibited a first-order drug release pattern.

Accelerated Stability Study

The optimised formulation (F7) was exposed to accelerated stability studies at $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$ for three months. The results are presented in Table 9.

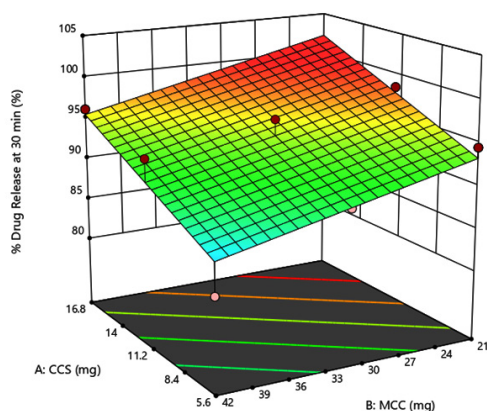


Fig. 6. 3D response surface plot showing the effect of croscarmellose sodium (X_1) and microcrystalline cellulose (X_2) on drug release at 30 min (Y_3).

DISCUSSION

The organoleptic properties of Fimasartan, including its white crystalline appearance and odourless nature, are consistent with reported characteristics, confirming the identity and suitability of the drug for formulation into oral solid dosage forms. The observed melting point range ($154\text{--}156^\circ\text{C}$) is in close agreement with literature values, indicating the purity of the drug. The narrow melting range suggests the absence of significant impurities. The solubility study revealed that Fimasartan is highly soluble in organic solvents such as methanol, ethanol, and dimethyl sulfoxide, but poor soluble in water. This behaviour indicates the hydrophobic nature

Table 8. Comparison of predicted and observed responses of optimised batch F7

Response	Predicted Value	Observed Value
Hardness (kg/cm^2)	5.2	5.3 ± 0.2
Disintegration Time (s)	34	32 ± 2
% Drug Release at 30 min	98.9	99.8 ± 4.2

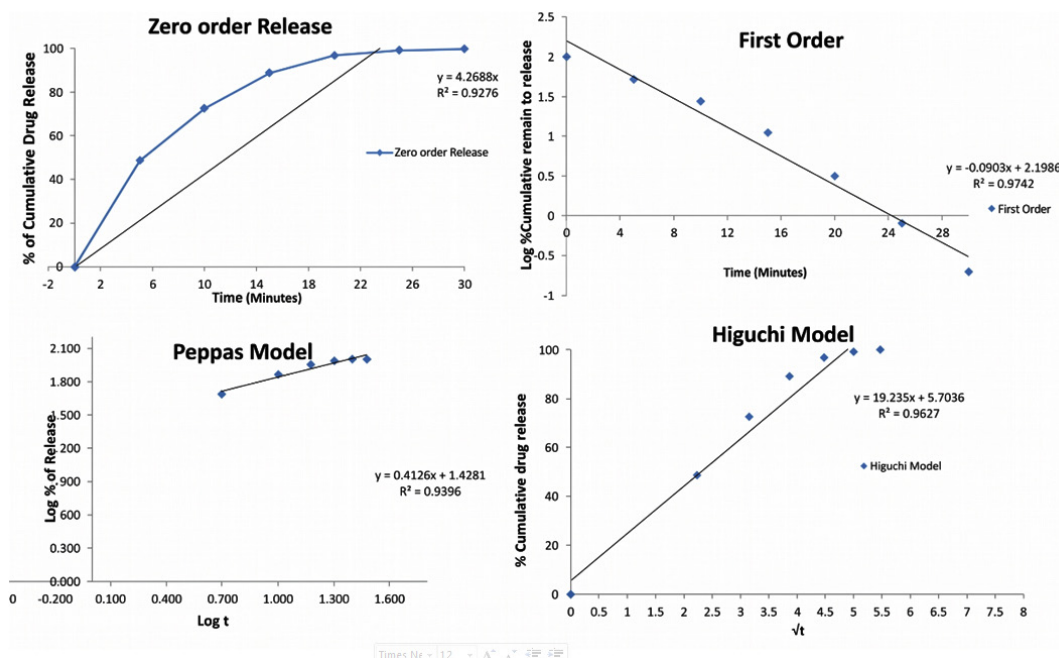


Fig. 7. Comparative drug release kinetic plots of optimised formulation F7 fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models.

Table 9. Stability study data of optimised formulation (F7) stored at $40 \pm 2^\circ\text{C}$ / $75 \pm 5\%$ RH for 3 months

Parameter	Initial	1 Month	2 Months	3 Months
Appearance	White, intact tablets	No change	No change	No change
Hardness (kg/cm ²)	5.3 ± 0.2	5.2 ± 0.2	5.2 ± 0.3	5.1 ± 0.2
Friability (%)	0.42 ± 0.03	0.44 ± 0.02	0.44 ± 0.03	0.45 ± 0.02
Disintegration Time (s)	32 ± 2	33 ± 2	35 ± 3	35 ± 2
Drug Content (%)	99.4 ± 0.6	99.1 ± 0.5	98.8 ± 0.7	98.5 ± 0.6
% Drug Release at 30 min	99.8 ± 4.2	99.2 ± 4.0	98.9 ± 3.8	98.4 ± 3.7

of the drug and suggests that it belongs to the class of poorly water-soluble compounds. The limited aqueous solubility highlights the necessity for preparation approaches to enhance drug dissolution and improve bioavailability. The higher solubility in organic solvents also supports their use in analytical and formulation development.

For calibration curve confirms that the drug follows Beer–Lambert’s law within the considered concentration range.

The compatibility study confirmed that the characteristic FTIR peaks of Fimasartan remained unchanged in the physical mixture, suggesting no major interaction between the drug and the excipients. This confirms the compatibility of Fimasartan with croscarmellose sodium, microcrystalline cellulose, mannitol, magnesium stearate, and talc, and suggests that the excipients are suitable for formulation without affecting the stability of the drug.

Evaluation of powder blend revealed that the obtained bulk density and tapped density values indicate good packing ability of the powder blends. Carr’s index values within the acceptable range suggest good compressibility, while Hausner’s ratio further confirms satisfactory flow characteristics. The angle of repose below 30° indicates good flowability. Overall, the results demonstrate that the powder blends possess suitable flow and compression properties, making them appropriate for direct compression.

Evaluation of tablets revealed that all formulations exhibited uniform thickness, indicating consistent die filling during compression. The hardness values were within acceptable limits, suggesting adequate mechanical strength of the tablets. Friability values below 1% indicate good abrasion resistance. The weight variation complied

with pharmacopeial limits, confirming uniformity in tablet weight. The drug content values were within the acceptable range, demonstrating uniform drug distribution throughout the formulations. Overall, these findings demonstrate that all formulations possess satisfactory post-compression characteristics.

Disintegration test revealed that time of disintegration decreased with an increase in the concentration of croscarmellose sodium due to its swelling and wicking mechanism, which promotes rapid water uptake and tablet breakup. In contrast, formulations containing higher levels of microcrystalline cellulose showed slightly increased disintegration time, which may be attributed to the formation of a more compact tablet matrix. Among all formulations, F7 exhibited the fastest disintegration, indicating an optimal balance between superdisintegrant and binder concentration. All formulations complied with pharmacopeial limits for immediate-release tablets, confirming their suitability for rapid drug release.

In vitro dissolution study revealed that drug release was significantly influenced by the concentration of croscarmellose sodium and microcrystalline cellulose. Formulations with higher levels of croscarmellose sodium showed enhanced drug release due to rapid disintegration and improved wettability, whereas higher concentrations of microcrystalline cellulose resulted in comparatively slower drug release due to increased matrix compactness. Among all formulations, F7 showed the highest drug release, indicating optimal formulation composition. The enhanced release can be attributed to the balanced concentration of superdisintegrant and binder, resulting in efficient tablet disintegration and drug dissolution. Overall, all formulations

demonstrated satisfactory drug release, confirming their suitability for immediate-release dosage forms.

Statistical analysis and optimisation revealed that both formulation variables significantly influenced the performance of immediate-release Fimasartan tablets. Croscarmellose sodium (X_1) exhibited a positive effect on tablet hardness, while microcrystalline cellulose (X_2) showed a comparatively lesser influence; however, their interaction affected hardness behaviour, indicating the importance of combined variable effects.

The disintegration study demonstrated that increasing croscarmellose sodium markedly reduced disintegration time due to its swelling and wicking mechanism, whereas higher levels of microcrystalline cellulose increased disintegration time because of enhanced matrix compactness.¹⁷

Drug release analysis revealed that higher concentrations of croscarmellose sodium improved drug release and increased wettability, while increased levels of microcrystalline cellulose slightly hindered drug release owing to the preparation of a denser tablet structure.¹⁸

Overall, the developed models showed good agreement between predicted and observed responses, confirming the suitability of the factorial design for optimisation. Considering the overall tablet performance, formulation F7 was selected as the optimized batch as it exhibited satisfactory hardness, rapid disintegration, and maximum drug release, achieved through an optimal combination of superdisintegrant and binder levels.¹⁹⁻²²

Validation of optimised formulation revealed that the experimental responses were in close agreement with the predicted values, confirming the adequacy and reliability of the developed factorial design model.

Kinetic analysis demonstrated that the drug release from the formulation primarily followed first-order kinetics, indicating concentration-dependent release behaviour. The fitting to the Higuchi and Peppas models suggested that diffusion, along with other release mechanisms, contributed to the overall drug release process.²³

Accelerated stability study revealed that the optimised formulation remained stable under accelerated storage conditions. No major changes in appearance were observed, and the tablets retained their mechanical strength with friability

within acceptable limits. Minor variations in hardness and disintegration time were observed but remained within acceptable limits for immediate-release tablets. Drug content and dissolution profiles were maintained throughout the study period, indicating good chemical stability.

The obtained similarity factor (f_2) indicated that the dissolution profile remained unchanged after stability storage, confirming the stability of the formulation. Hence, the optimized batch F7 exhibited satisfactory stability characteristics and can be considered suitable for further development studies.

CONCLUSION

The present study successfully developed and optimized immediate-release Fimasartan tablets using a 3^2 full factorial design. Croscarmellose sodium and microcrystalline cellulose significantly influenced tablet hardness, disintegration time, and drug release behaviour. The optimized formulation (F7) exhibited satisfactory mechanical strength, rapid disintegration, and maximum drug release, while accelerated stability studies confirmed its physical and chemical stability over three months. The developed formulation therefore demonstrates potential as an effective immediate-release oral dosage form of Fimasartan.

Strengths of the study include the systematic optimization of formulation variables using a factorial design approach, comprehensive evaluation of pre- and post-compression parameters, validation of the optimization model, assessment of drug release kinetics, and stability testing of the optimized formulation. These findings provide a robust foundation for the development of immediate-release Fimasartan tablets.

Limitations of the study include the relatively short duration of accelerated stability testing and the absence of *in vivo* pharmacokinetic or bioavailability evaluation. Furthermore, the study was limited to *in vitro* characterization and did not establish an *in vitro*–*in vivo* correlation (IVIVC). Therefore, future studies should focus on long-term stability assessment under real-time storage conditions, *in vivo* performance evaluation, and IVIVC development to further confirm the therapeutic potential of the optimized formulation.

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Not Applicable.

Author Contributions

Snehal Anil Khare: Experimental work, Data Collection, Investigation, Writing – Original Draft; Abdul Kalam Abu Bakar: Data Analysis, Validation, Statistical Analysis; Shivraj Popat Jadhav: Conceptualization, Methodology, Supervision, Writing – Review and Editing; Deepak Devidas Sonawane: Methodology, Visualization, Project Administration

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