

Formulation Optimization and Evaluation of Simvastatin Extended-Release Matrix Tablets

K. Thamaraiselvi^{*}, G. Ramya¹, Perli. Kranti Kumar², P. Manikandan³

^{*}**Research Scholar**, (M.Pharmacy), Department of Pharmaceutics, J.K.K.Nattraja College of Pharmacy, Kumarapalayam, Namakkal, Tamil Nadu, India.

¹**co-Research Scholar**, (M.Pharmacy), Department of Pharmaceutics, J.K.K.Nattraja College of Pharmacy, Kumarapalayam, Namakkal, Tamil Nadu, India.

²**Research Guide**, Professor, Department of Pharmaceutical Analysis, J.K.K.Nattraja College of Pharmacy, Kumarapalayam, Namakkal, Tamil Nadu, India.

³**Professor & Head**, Department of Pharmaceutics, J.K.K.Nattraja College of Pharmacy, Kumarapalayam, Namakkal, Tamil Nadu, India.

*Corresponding author: **Ms. K. Thamaraiselvi**
Email: thamaraiselvi.k@jkkn.ac.in

Abstract

This study was carried out with the aim of formulating, optimizing, and assessing Simvastatin extended-release matrix tablets by using different viscosity grades and concentrations of Hydroxypropyl Methylcellulose (HPMC) via the direct compression method. Preformulation investigations, such as determination of the melting point, solubility, and drug-excipient compatibility by means of FTIR spectroscopy, were conducted in order to ascertain the appropriateness of the drug and the excipients. Twelve formulations (F1 to F12) were prepared using HPMC K4M, HPMC K15M and HPMC K100M together with ethyl cellulose and other appropriate excipients. The powder blends and the resulting tablets were examined for their pre-compression and post-compression properties, and in-vitro drug-release studies were then performed. Of the formulations, F12 was chosen as the optimized one since it achieved about 98% cumulative drug release within 24 hours and had acceptable tablet characteristics. The release kinetics of formulation F12 correlated most closely with the Korsmeyer–Peppas model ($R^2 = 0.9969$), then with the Higuchi model ($R^2 = 0.9834$), which indicates that both diffusion and polymer relaxation play a role in the drug release process. Accelerated stability testing, carried out at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH for a period of two months, revealed only slight changes in the parameters under examination, showing that the optimized formulation is stable. The study as a whole showed that HPMC-based hydrophilic matrix technology is a suitable method for extending the in-vitro release of Simvastatin, F12 displaying the most favourable release profile under the experimental conditions.

Keywords: ‘Simvastatin, Extended-release matrix tablet, HPMC, Ethyl cellulose, Direct compression’.

1. Introduction

Hyperlipidemia is a major metabolic disorder characterized by elevated levels of circulating lipids, particularly low-density lipoprotein cholesterol (LDL-C) and triglycerides, and is an important risk factor for atherosclerotic cardiovascular disease. Effective management generally involves lifestyle modification and pharmacological therapy, with statins being the principal agents used for reducing LDL-C and associated cardiovascular risk. [1], [2]

Simvastatin is a widely used statin that acts by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in hepatic cholesterol biosynthesis. Although it is therapeutically effective, simvastatin undergoes extensive first-pass hepatic metabolism and has a relatively short elimination half-life of approximately 2–3 hr. These pharmacokinetic characteristics may limit the duration of drug exposure following conventional immediate-release administration and support the development of a controlled-release dosage form. [3]

Extended-release drug delivery systems are designed to regulate drug release over a prolonged period, thereby reducing fluctuations in drug concentrations and potentially improving dosing convenience and patient adherence. Matrix tablets are a simple, economical, and widely used approach for achieving extended drug release. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) form a hydrated gel layer that controls drug diffusion and matrix erosion, whereas hydrophobic polymers such as ethyl cellulose can provide additional resistance to drug release. [4]

Therefore, the present study was undertaken to formulate and evaluate simvastatin extended-release matrix tablets using different viscosity grades of HPMC (K4M, K15M, and K100M) in combination with ethyl cellulose. The influence of polymer selection on the physicochemical characteristics and in vitro drug-release behaviour of the formulations was investigated to identify a suitable extended-release matrix formulation of simvastatin.

2. Methodology [5], [6], [7]

2.1 Materials

Simvastatin, HPMC K4M, HPMC K15M, HPMC K100M, ethyl cellulose, polyvinylpyrrolidone K30 (PVP K30), microcrystalline cellulose, colloidal silicon dioxide (Aerosil), and magnesium stearate were supplied by Pharmatech Solutions, Hyderabad, India.

2.2 Preformulation Studies

Simvastatin was subjected to preformulation studies to determine its physicochemical properties and suitability for tablet formulation.

2.2.1 Organoleptic Characteristics

The colour, odour, taste, and appearance of Simvastatin were examined and recorded.

2.2.2 Determination of Melting Point

The melting point of Simvastatin was determined in triplicate using the capillary-tube method. Finely powdered drug was filled into a capillary tube sealed at one end and heated gradually in a digital melting-point apparatus. The temperature at which the drug melted completely was recorded, and the average melting point was calculated.

2.2.3 Solubility Studies

The solubility of Simvastatin was assessed in distilled water, methanol, ethanol, phosphate buffer (pH 6.8), and 0.1 N hydrochloric acid. An excess quantity of the drug was separately added to each solvent and stirred continuously at room temperature until equilibrium was reached. The mixtures were filtered, and the solubility characteristics were recorded.

2.2.4 Drug–Excipient Compatibility Study

Drug–excipient compatibility was evaluated using Fourier-transform infrared spectroscopy. Pure Simvastatin, individual excipients, and their physical mixture were prepared by the potassium bromide pellet method and scanned over the wavenumber range of 4000–400 cm^{-1} . The characteristic peaks of pure Simvastatin were compared with those of the physical mixture to identify possible drug–excipient interactions.

2.2.5 UV Spectrophotometric Calibration Curve

A standard stock solution of Simvastatin was prepared in a suitable solvent and diluted to obtain different concentrations. Absorbance was measured at 247.6 nm using the corresponding solvent as the blank. The calibration curve was constructed by plotting absorbance against concentration and was used to determine drug content and in-vitro drug release.

2.3 Preparation of Simvastatin Extended-Release Tablets [7], [8], [15]

Simvastatin, the respective HPMC grade (K4M, K15M, or K100M), ethyl cellulose, PVP K30, and microcrystalline cellulose were accurately weighed and passed through sieve No. 60. The ingredients were blended uniformly, followed by the addition of Aerosil as a glidant. Magnesium stearate was subsequently added as a lubricant and mixed gently for a short period to minimise over-lubrication. The final powder blend was compressed using a rotary tablet-compression machine fitted with suitable punches. The prepared tablets were stored in airtight containers until further evaluation.

Table1. Formulation of Simvastatin extended release tablets

Formulation code/Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Simvastatin	40	40	40	40	40	40	40	40	40	40	40	40
HPMC K 4M	10	20	30	40	-	-	-	-	-	-	-	-
HPMC K 15 M	-	-	-	-	10	20	30	40	-	-	-	-
HPMCK 100 M	-	-	-	-	-	-	-	-	10	20	30	40
Ethyl cellulose	20	20	20	20	20	20	20	20	20	20	20	20
PVP K 30	5	5	5	5	5	5	5	5	5	5	5	5
Microcrystalline cellulose	72.6	62.6	52.6	42.6	72.6	62.6	52.6	42.6	72.6	62.6	52.6	42.6
Aerosil	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Magnesium stearate	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Total	150	150	150	150	150	150	150	150	150	150	150	150

2.4 Evaluation of blend characteristics precompression characteristics of simvastatin matrix tablets. [6], [10]

2.4.1 Evaluation of Powder Blends and Tablets

The powder blends were evaluated for angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner's ratio using standard pharmacopoeial procedures to assess their flowability and suitability for tablet compression.

2.4.2 Angle of Repose

The angle of repose was determined by the fixed funnel method. The powder blend was allowed to flow freely through a funnel fixed at a suitable height onto a flat surface to form a conical heap. The height (h) and radius (r) of the powder cone were measured, and the angle of repose (θ) was calculated using the following equation:

$$\tan \theta = h/r$$

where:

θ = Angle of repose

h = Height of the powder cone (cm)

r = Radius of the powder cone (cm)

Lower values of the angle of repose indicate better flow properties of the powder blend.

2.4.3 Bulk Density

Bulk density was determined by accurately weighing a known quantity of the powder blend and transferring it into a graduated measuring cylinder. The untapped volume (V_0) occupied by the powder was recorded. Bulk density was calculated using the following equation:

$$\text{Bulk Density} = \text{Weight of powder} / \text{Bulk volume}$$

2.4.4 Tapped Density

The same graduated cylinder containing the powder blend was tapped mechanically until a constant volume was obtained. The final tapped volume (V_t) was recorded. Tapped density was calculated using the following equation:

$$\text{Tapped Density} = \text{Weight of powder} / \text{Tapped volume}$$

2.4.5 Carr's Compressibility Index

Carr's Compressibility Index was calculated from the bulk density and tapped density values to assess the compressibility and flowability of the powder blend.

$$\text{Carr's Index (\%)} = [(\text{Tapped Density} - \text{Bulk Density}) / \text{Tapped Density}] \times 100$$

Lower Carr's Index values indicate better flow properties of the powder blend.

2.4.6 Hausner's Ratio

Hausner's ratio was calculated using the bulk density and tapped density values to evaluate the flow characteristics of the powder blend.

$$\text{Hausner's Ratio} = \text{Tapped Density} / \text{Bulk Density}$$

A Hausner's ratio close to 1 indicates good flowability, whereas higher values suggest poor flow characteristics.

2.5 Evaluation of Compressed Tablets (Post-compression Parameters)

The compressed tablets were evaluated for their post-compression characteristics to ensure their quality, mechanical strength, and performance. The tablets were assessed for weight variation, thickness, hardness, friability, drug content uniformity, and disintegration time using standard pharmacopoeial methods. These parameters were evaluated to confirm the physical quality, mechanical strength, uniformity, and suitability of the formulated extended-release matrix tablets.

2.5.1 Weight Variation test

The weight variation test was carried out in accordance with the Indian Pharmacopoeia (IP) guidelines. Twenty tablets were selected at random from each formulation batch and weighed individually using a calibrated digital analytical balance. The average tablet weight was calculated, and the percentage deviation of the individual tablet weights from the mean weight was determined. The results were compared with the pharmacopoeial limits to evaluate the uniformity of tablet weight among the prepared formulations.

Table 2. Weight Variation Limit

Average Weight of Tablet	% Deviation
≤ 80 mg	±10.0
80–250 mg	±7.5
≥ 250 mg	±5.0

2.5.2 Thickness test

The thickness of the compressed tablets was measured using a calibrated digital Vernier caliper. Six tablets were randomly selected from each formulation batch, and the thickness of each tablet was determined by placing it between the measuring jaws of the caliper. The measurements were recorded in millimetres (mm), and the average thickness along with the standard deviation was calculated. The test was performed to ensure uniform tablet dimensions and consistency among the formulations.

2.5.3 Hardness test

The hardness of the compressed tablets was determined to evaluate their mechanical strength and ability to withstand handling during manufacturing, packaging, and transportation. Six tablets were randomly selected from each formulation batch, and the crushing strength of each tablet was measured using a Monsanto hardness tester. The hardness values were recorded in kilograms per square centimetre (kg/cm²), and the average value was calculated for each formulation.

2.5.4 Friability test

The friability of the compressed tablets was evaluated using a Roche friabilator to assess their resistance to mechanical stress during handling, packaging, and transportation. Twenty tablets from each formulation batch were accurately weighed and placed in the friabilator. The instrument was operated at 25 rpm for 4

minutes (100 revolutions). After the test, the tablets were removed, dedusted, and reweighed. The percentage friability was calculated using the following formula

$$\% \text{Friability} = \frac{(\text{Initial Weight} - \text{Final weight})}{\text{Initial Weight}} \times 100$$

A friability value of less than 1% was considered acceptable according to pharmacopoeial specifications.

2.5.5 Drug Content Uniformity

Twenty tablets were randomly selected, weighed, and finely powdered. Powder equivalent to 10 mg of Simvastatin was transferred into a 100 mL volumetric flask containing approximately 70 mL of phosphate buffer (pH 6.8) and sonicated for 15 minutes. The volume was made up to 100 mL with the same buffer, mixed, and filtered through Whatman No. 1 filter paper. After suitable dilution, the absorbance was measured at 247.6 nm using phosphate buffer (pH 6.8) as the blank. Drug content was determined from the standard calibration curve and expressed as a percentage of the labelled claim.

Formula

$$\text{Drug content (\%)} = (\text{Actual amount of drug present} / \text{Label claim}) \times 100$$

2.6 In-Vitro Dissolution Studies [9], [11], [14]

The in-vitro dissolution study of the formulated Simvastatin extended-release tablets was carried out using the USP Dissolution Apparatus II (Paddle Method). The dissolution medium consisted of 900 mL of phosphate buffer (pH 6.8) maintained at $37 \pm 0.5^\circ\text{C}$. One tablet was placed in each dissolution vessel, and the paddle speed was maintained at 50 rpm throughout the study.

At predetermined time intervals, 5 mL of the dissolution medium was withdrawn and filtered through Whatman No. 1 filter paper. An equal volume of fresh dissolution medium, maintained at the same temperature, was added to each vessel to maintain a constant volume. The filtered samples were suitably diluted with phosphate buffer (pH 6.8), and the absorbance was measured at 247.6 nm using a UV-Visible spectrophotometer. The cumulative percentage of drug released at each sampling interval was calculated using the previously prepared standard calibration curve.

2.7 Optimization of Formulation

The formulation of Simvastatin extended-release tablets was optimized by comparing the evaluation results of all prepared formulations. Each formulation was assessed for its pre-compression parameters (angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner's ratio) and post-compression parameters (weight variation, thickness, hardness, friability, drug content uniformity, and *in-vitro* dissolution profile). The formulation that exhibited satisfactory flow properties, acceptable physical characteristics, uniform drug content, and the desired extended-release drug release pattern was selected as the optimized formulation. The optimized formulation was subsequently subjected to stability studies.

2.8 Stability Studies [12]

The optimized formulation of Simvastatin extended-release tablets was subjected to accelerated stability studies in accordance with the International Council for Harmonisation (ICH) guidelines. The tablets were packed in suitable containers and stored in a stability chamber maintained at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ relative humidity (RH) for a period of three months.

Samples were withdrawn at predetermined intervals (0, 1, 2, and 3 months) and evaluated for their physical appearance, hardness, friability, drug content, and *in-vitro* dissolution profile. The results obtained at each interval were compared with the initial values to assess the stability of the optimized formulation under accelerated storage conditions.

3. RESULT AND DISCUSSION

3.1 Preformulation Studies

Simvastatin was observed as a white to off-white, odourless, slightly bitter crystalline powder, and the recorded shape was round. Its melting point was $139.1 \pm 0.1^\circ\text{C}$, which was within the reported range of $138\text{--}140^\circ\text{C}$. The drug was practically insoluble in distilled water, freely soluble in methanol, soluble in ethanol, and slightly soluble in phosphate buffer (pH 6.8).

3.2 Drug-Excipient Compatibility Studies using FTIR Spectroscopy

FTIR spectroscopy was performed to assess the compatibility of Simvastatin with the selected excipients. The FTIR spectrum of pure Simvastatin showed characteristic absorption bands at 3547.03 cm^{-1} , 2951.68, 2929.68 and 2872.24 cm^{-1} , 1695.73 cm^{-1} , 1389.35 and 1368.90 cm^{-1} , and 1264.84, 1224.82 and 1160.52 cm^{-1} , corresponding predominantly to O–H stretching, aliphatic C–H stretching, ester carbonyl stretching, CH_2 bending, and C–O/C–O–C stretching vibrations, respectively. The optimized formulation exhibited corresponding bands at 3547.05, 2928.72, 1694.05, 1466.32, 1389.30, 1368.76, 1264.31, 1159.80, 1054.46, 1010.95 and 990.67 cm^{-1} . The principal characteristic bands of Simvastatin were retained in the optimized formulation with only minor shifts in peak positions. No major disappearance or substantial shift of the characteristic drug bands was observed. These findings suggest that Simvastatin was compatible with the selected formulation excipients under the conditions of the FTIR study.

Table 3. FTIR Interpretation of Simvastatin and Excipients

Function al Group	Simvastat in (cm^{-1})	HPM C K4M (cm^{-1})	HPM C K15 M (cm^{-1})	HPM C K100 M (cm^{-1})	Ethyl Cellulos e	PVP K30	Microcrystalli ne Cellulose	Optimize d formulati on observed peak (cm^{-1})
O–H stretching	3547.03	3550– 3450	3550– 3450	3550– 3450	3500– 3400	3500 – 3200	3500–3200	3547.05
Aliphatic C–H stretching	2951.68, 2929.68, 2872.24	2920– 2850	2920– 2850	2920– 2850	2970– 2850	2970 – 2850	2930–2850	2928.72
Ester carbonyl (C=O) stretching	1695.73	-	-	-	-	-	-	1694.05
CH_2 bending	1465– 1389	1460– 1400	1460– 1400	1460– 1400	1470– 1430	1460 – 1400	1430–1370	1466.32, 1389.30
C–O–C / C–O stretching	1264.84, 1224.82, 1160.52	1155– 1050	1155– 1050	1155– 1050	1250– 1050	1300 – 1000	1160–1050	1264.31, 1159.80
C–O stretching	1070.99, 1042.82, 1011.27	1100– 1000	1100– 1000	1100– 1000	1100– 1000	1100 – 1000	1060–1025	1054.46, 1010.95
Additional fingerprin t-region bands	990.92, 895.76, 624.26, 608.27, 487.91	-	-	-	-	-	-	990.67, 868.57, 737.63, 605.76, 577.74

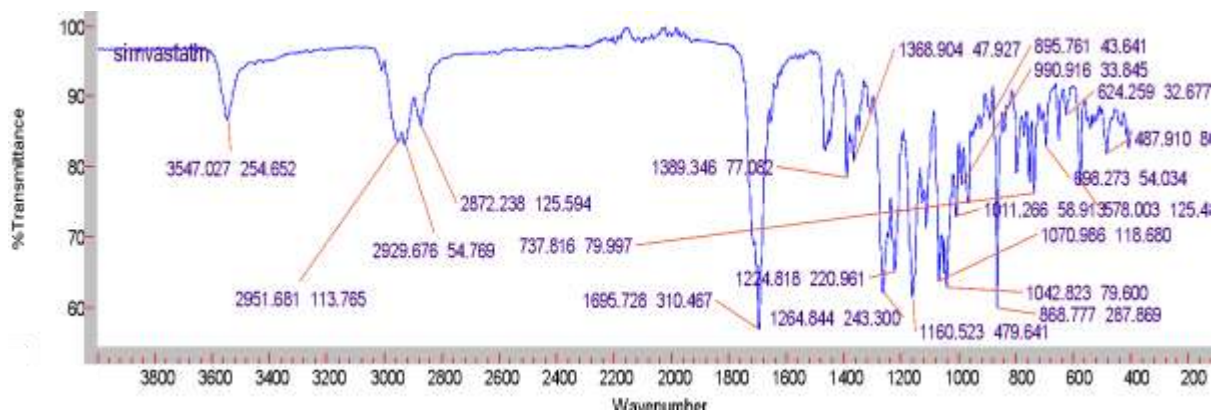


Fig. 1: FT-IR spectra of Simvastatin

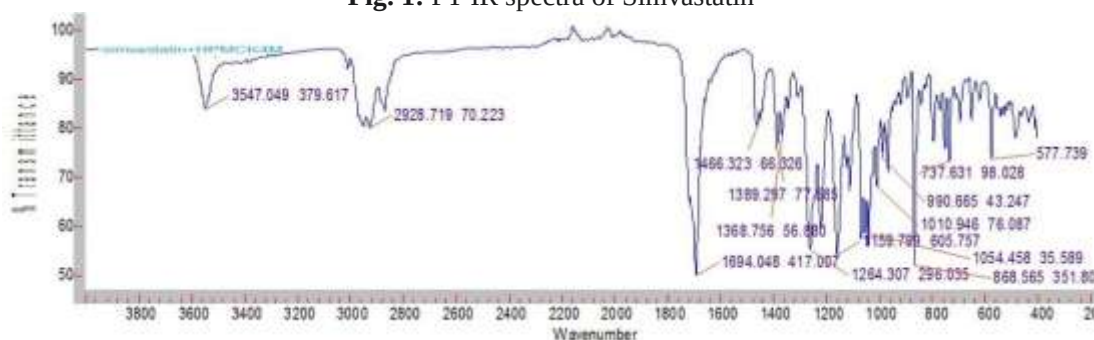


Fig. 2. FT-IR spectra of Optimized formulation

Table 4. Characteristics I.R. Peaks of Drug, Polymers and their Physical Mixtures

S. No.	Drug and Polymers	Characteristic Peaks (cm ⁻¹)
1.	Simvastatin	3460.68 cm ⁻¹ , 3021.53 cm ⁻¹ , 1466.55 cm ⁻¹
2.	Physical mixture of optimized formula	3460.56 cm ⁻¹ , 3150.22 cm ⁻¹ , 1466.11 cm ⁻¹

3.3 Preparation of Standard Calibration Curve of Simvastatin by UV Spectroscopy

3.3.1 Preparation of Standard Calibration Curve of Simvastatin in 0.1 N HCl

Accurately weigh 100 mg of Simvastatin and transfer it into a 100 mL volumetric flask. Dissolve the drug in a small quantity of methanol and make up the volume to 100 mL with 0.1 N HCl to obtain a stock solution of 1000 µg/mL. Dilute the stock solution appropriately with 0.1 N HCl to prepare a working standard solution of 100 µg/mL. Further dilute the working solution to obtain concentrations of 2, 4, 6, 8, 10, and 12 µg/mL. Measure the absorbance of each solution at 238 nm using 0.1 N HCl as the blank. Plot a graph of concentration (µg/mL) versus absorbance to obtain the standard calibration curve.

3.3.2 Standard Calibration Curve of Simvastatin in 0.1 N HCl

The standard calibration curve of Simvastatin in 0.1 N HCl was constructed using concentrations ranging from 0–12 µg/mL. The absorbance increased progressively from 0.000 to 0.708nm with increasing drug concentration, demonstrating a direct proportional relationship between concentration and absorbance. The calibration plot exhibited good linearity within the selected concentration range, indicating that Simvastatin obeys Beer-Lambert's law in 0.1 N HCl. The linear relationship confirms the suitability of the developed UV spectrophotometric method for the quantitative estimation of Simvastatin in acidic dissolution medium.

Table 5. Calibration curve of 0.1N Hcl

Concentration (µg/ml)	Absorbance at 238nm
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0	0
2	0.149
4	0.265
6	0.387
8	0.473
10	0.593
12	0.708

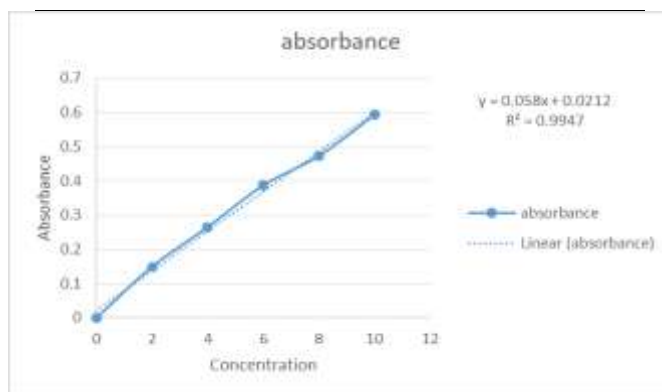


Fig. 3: Standard Calibration Curve of in 0.1N HCl

3.3.3 Preparation of Standard Calibration Curve of Simvastatin in Phosphate Buffer (pH 7.4)

Accurately weigh 100 mg of Simvastatin and transfer it into a 100 mL volumetric flask. Dissolve the drug in methanol and make up the volume with a phosphate buffer (pH 7.4) to obtain a 1000 µg/mL stock solution. Dilute the stock solution to prepare standard solutions of 10, 20, 30, 40, and 50 µg/mL. Measure the absorbance of each solution at 238 nm using phosphate buffer (pH 7.4) as the blank. Plot a calibration curve of concentration (µg/mL) versus absorbance and determine the regression equation and correlation coefficient (R^2).

3.3.4 Standard Calibration Curve of Simvastatin in Phosphate Buffer (pH 7.4)

The standard calibration curve of Simvastatin in pH 7.4 phosphate buffer was prepared over a concentration range of 0–50 µg/mL. The absorbance increased consistently from 0.000 to 0.380nm as the concentration increased, indicating a positive linear relationship between concentration and absorbance. The calibration graph demonstrated satisfactory linearity throughout the selected concentration range, confirming that Simvastatin follows Beer-Lambert's law in pH 7.4 phosphate buffer. These findings indicate that the developed UV spectrophotometric method is reliable and suitable for the quantitative estimation of Simvastatin during in vitro dissolution studies in phosphate buffers.

Table 6. Calibration curve of 7.4 pH phosphate buffer

Concentration (µg/ml)	Absorbance at 238nm
0	0
10	0.072
20	0.151
30	0.221
40	0.294

50

0.38

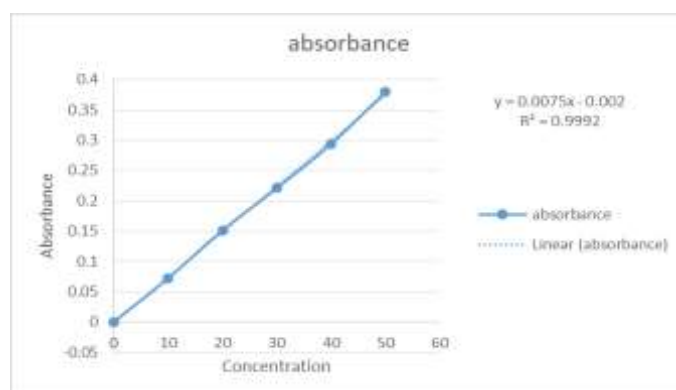


Fig. 4: Standard Calibration Curve of Simvastatin in 7.4 pH Phosphate buffer

3.4 Evaluation of Powder Blend (Pre-compression Parameters)

The pre-compression parameters of the powder blends for formulations F1–F12 were evaluated by determining the angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio. The angle of repose ranged from 22.26° to 26.92°, indicating good flow characteristics of the powder blends. The bulk density and tapped density were found to be in the ranges of 0.42–0.55 g/cm³ and 0.50–0.64 g/cm³, respectively, suggesting acceptable packing properties. The compressibility index varied from 16.36% to 26.19%, while the Hausner's ratio ranged between 1.16 and 1.26. Among all formulations, F9 exhibited the lowest compressibility index (16.36%) and a Hausner's ratio of 1.16, indicating superior flowability and compressibility, whereas F1 showed the highest compressibility index (26.19%) and a Hausner's ratio of 1.26, reflecting comparatively lower flow properties. Overall, the pre-compression results demonstrated that all powder blends possessed acceptable flow and compressibility characteristics, making them suitable for the direct compression process used in the preparation of Simvastatin extended-release tablets.

Table7. Flow properties of granules prepared by different technique

Formulation code/Parameter	Angle of repose	Bulk density	Tapped density	Compressibility index	Hausner's Ratio
F1	23.24± 0.16	0.42± 0.01	0.52± 0.01	26.19± 0.15	1.26± 0.02
F2	22.26 ± 0.14	0.46± 0.01	0.57± 0.02	23.91± 0.18	1.23± 0.01
F3	23.62± 0.13	0.44± 0.02	0.53± 0.01	20.45± 0.10	1.20± 0.02
F4	25.25± 0.15	0.48± 0.02	0.56± 0.02	16.66± 0.11	1.16± 0.01
F5	24.69± 0.15	0.52± 0.02	0.63± 0.02	21.15± 0.12	1.21± 0.01
F6	23.26± 0.16	0.51± 0.02	0.61± 0.02	21.56± 0.12	1.21± 0.01
F7	25.19± 0.15	0.43± 0.01	0.54± 0.01	25.28± 0.17	1.25± 0.02
F8	26.92± 0.12	0.49± 0.01	0.58± 0.03	18.35± 0.14	1.18± 0.01
F9	23.71± 0.11	0.55± 0.01	0.64± 0.02	16.36± 0.11	1.16± 0.01
F10	24.79± 0.15	0.45± 0.01	0.55± 0.02	22.22± 0.12	1.22± 0.01
F11	25.59± 0.18	0.49± 0.01	0.50± 0.02	22.44± 0.12	1.22± 0.01

F12	23.34± 0.16	0.50± 0.01	0.61± 0.02	22.00± 0.13	1.21± 0.01
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3.5 Evaluation of Compressed Tablets (Post-compression Parameters)

The post-compression evaluation of Simvastatin extended-release tablets was carried out by assessing weight variation, thickness, hardness, friability, and drug content uniformity for formulations F1–F12. All formulations successfully complied with the pharmacopoeial limits for weight variation, indicating uniform tablet weight. The tablet thickness ranged from 4.47 to 4.53 mm, demonstrating consistency in tablet dimensions. The hardness values were between 3.0 and 3.2 kg/cm², confirming adequate mechanical strength to withstand handling during manufacturing and storage. The friability values ranged from 0.12% to 0.54%, which were well below the acceptable limit of 1%, indicating satisfactory resistance to abrasion. Drug content uniformity varied from 98.64% to 100.20%, demonstrating uniform distribution of Simvastatin in all tablet formulations. Among the formulations, F4 showed the highest drug content (100.20%), whereas F3 exhibited the lowest (98.64%); however, all values remained within the acceptable pharmacopoeial range. Overall, the post-compression evaluation confirmed that all formulations possessed acceptable physical characteristics and satisfactory drug content, indicating their suitability for further *in-vitro* dissolution and optimization studies.

Table 8. Evaluation of physical parameters

Formulation code/Parameter	Weight variation(mg)	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Drug Content uniformity(%)
F1	150.2 ± 1.2	4.52± 0.03	3.2 ± 0.05	0.17± 0.02	99.17± 0.18
F2	150.1 ± 1.1	4.49± 0.02	3.1 ± 0.05	0.22± 0.02	99.44± 0.20
F3	150.3 ± 1.3	4.51± 0.03	3.2± 0.05	0.42± 0.02	98.64± 0.19
F4	150.2 ± 1.2	4.53± 0.02	3.0± 0.07	0.20± 0.02	100.2± 0.24
F5	149.9 ± 1.1	4.50 ± 0.02	3.2± 0.06	0.25 ± 0.01	99.89± 0.17
F6	149.8 ± 1.4	4.48± 0.03	3.0± 0.05	0.12± 0.01	99.95± 0.18
F7	150.1 ± 1.2	4.52± 0.02	3.2 ± 0.06	0.5± 0.03	99.25± 0.20
F8	150.5 ± 1.0	4.51± 0.03	3.2± 0.07	0.29 ± 0.02	99.72 ± 0.18
F9	149.6 ± 1.2	4.49 ± 0.03	3.1 ± 0.06	0.38 ± 0.03	99.26± 0.20
F10	150.2 ± 1.1	4.50± 0.02	3.2± 0.06	0.25± 0.02	99.48± 0.22
F11	150.4 ± 1.2	4.47 ± 0.02	3.0 ± 0.08	0.54 ± 0.03	98.82 ± 0.21
F12	150.7 ± 1.1	4.48 ± 0.02	3.1 ± 0.07	0.42 ± 0.02	99.82± 0.21

3.5.1 In-Vitro Dissolution Studies

The *in-vitro* dissolution study was carried out to evaluate the release profile of Simvastatin extended-release matrix tablets prepared with different concentrations of HPMC K15M and HPMC K100M. The cumulative percentage drug release of formulations F1-F12 is presented in Table 20.

The results showed that the drug release varied with polymer concentration. Formulations F1 and F5 exhibited faster drug release, achieving approximately 98% cumulative drug release within 10 hours. Formulations F2, F3, F6, F7, F8, and F9 showed sustained drug release over 12–16 hours, whereas F10, F11, and F12 extended the drug release up to 20–24 hours. Among all the formulations, F12 exhibited the slowest release, with approximately 98% cumulative drug release at 24 hours. These findings indicate that increasing the concentration of HPMC polymers effectively prolonged the release of Simvastatin by controlling drug diffusion through the hydrated matrix system.

Table 9. In vitro drug release data

Formulation code/Parameter	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)	F10 (%)	F11 (%)	F12 (%)
1 hr	46	44	34	32	45	43	32	30	44	32	26	19
2 hr	58	56	45	37	58	57	45	42	58	45	35	26
4 hr	69	63	53	49	66	69	54	52	63	55	47	39
6 hr	74	68	68	56	78	75	67	64	67	64	54	48
8 hr	84	78	72	65	92	84	73	68	75	73	63	56
10 hr	98	86	83	73	98	93	86	83	88	85	75	62
12 hr		98	88	87		98	91	87	92	89	84	69
14 hr			96	93			96	91	98	92	89	74
16 hr				98			98	95		98	91	83
18 hr								97			95	87
20 hr											98	91
22 hr												96
24 hr												98

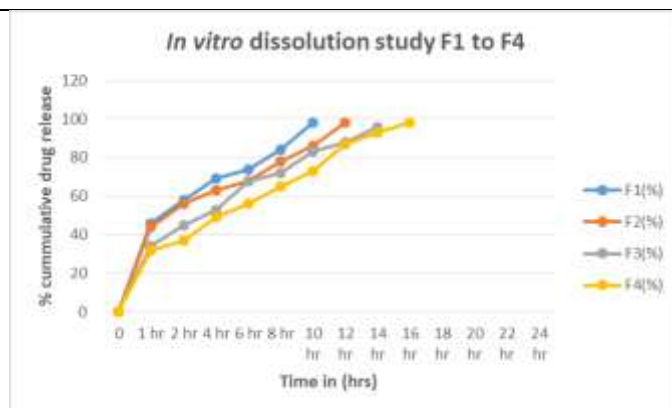


Fig. 5: In-vitro dissolution study F1 to F4

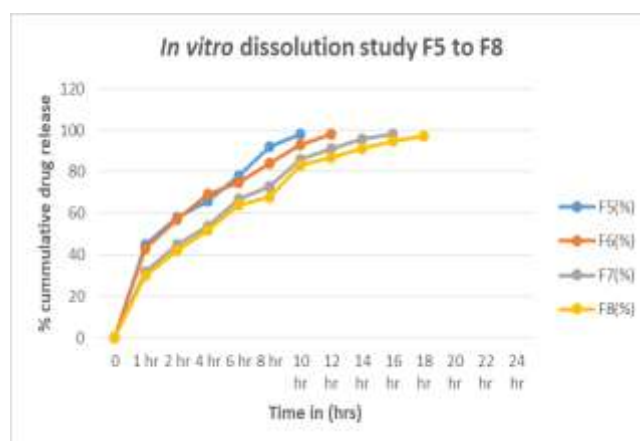


Fig. 6: In-vitro dissolution study F5 to F8

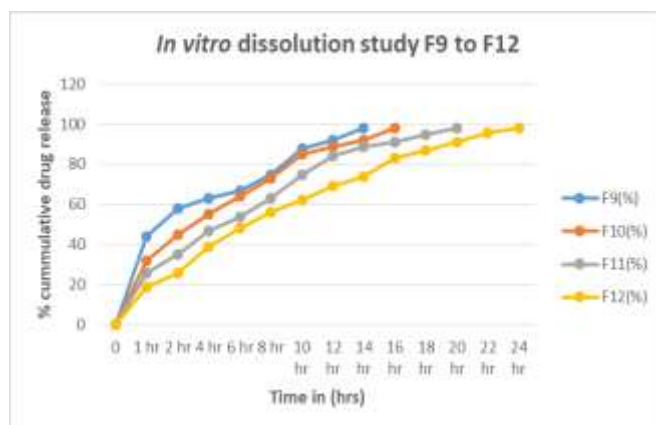


Fig. 7: *In-vitro* dissolution study F9 to F12

3.5.2 IN-VITRO DRUG RELEASE KINETIC STUDY

The *in-vitro* drug release data of the optimized Simvastatin extended-release matrix tablets were fitted to various kinetic models, including Zero-order, First-order, Higuchi, and Korsmeyer-Peppas models, to determine the drug release mechanism. The regression coefficient (R^2) values obtained were 0.9761 for the Zero-order model, 0.8963 for the First-order model, 0.9834 for the Higuchi model, and 0.9969 for the Korsmeyer-Peppas model. Among these, the Korsmeyer-Peppas model exhibited the highest R^2 value, indicating the best fit for the dissolution data. This suggests that the optimized formulation follows a controlled drug release mechanism predominantly governed by diffusion and polymer relaxation, which is characteristic of hydrophilic matrix-based extended-release systems. Therefore, the optimized formulation demonstrated a sustained and predictable release profile throughout the study period.

Table 10. *In-vitro* release kinetic study of simvastatin extended release of matrix tablet from F12

Time (h)	$\sqrt{\text{Time}}$	Cumulative Drug Release (%)	Drug Remaining (%)	Log Drug Remaining	Log Time	Log Cumulative Drug Release
1	1.000	10	90	1.954	0.000	1.000
2	1.414	18	82	1.914	0.301	1.255
4	2.000	30	70	1.845	0.602	1.477
6	2.449	41	59	1.771	0.778	1.613
8	2.828	50	50	1.699	0.903	1.699
10	3.162	58	42	1.623	1.000	1.763
12	3.464	66	34	1.531	1.079	1.820
14	3.742	74	26	1.415	1.146	1.869
16	4.000	85	15	1.176	1.204	1.929
18	4.243	90	10	1.000	1.255	1.954
20	4.472	94	6	0.778	1.301	1.973
22	4.690	98	2	0.301	1.342	1.991
24	4.899	100	0	-	1.380	2.000

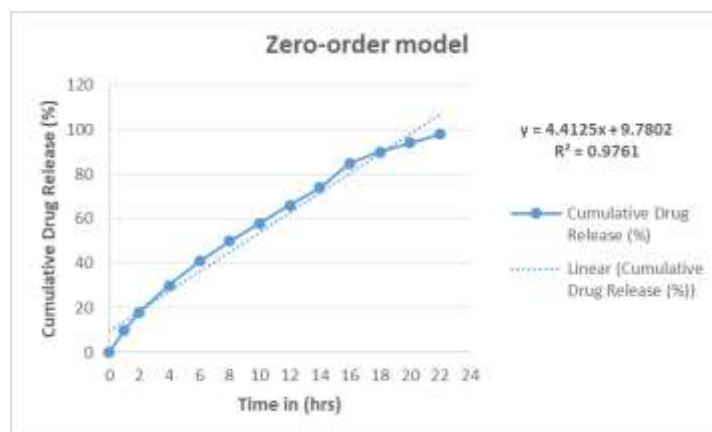


Fig. 8: Zero-order release kinetic plot



Fig. 9: First-order release kinetic plot

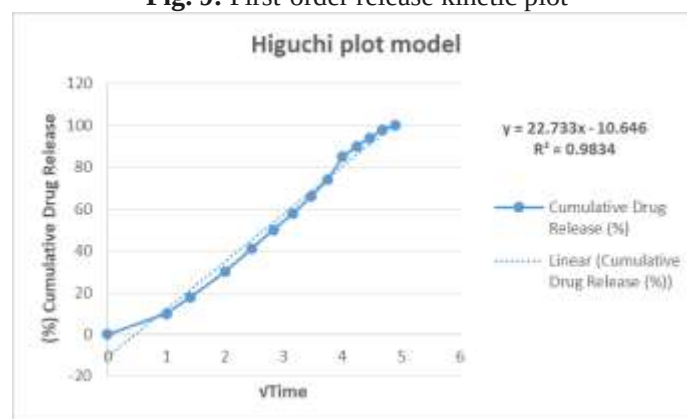


Fig. 10: Higuchi release kinetic plot

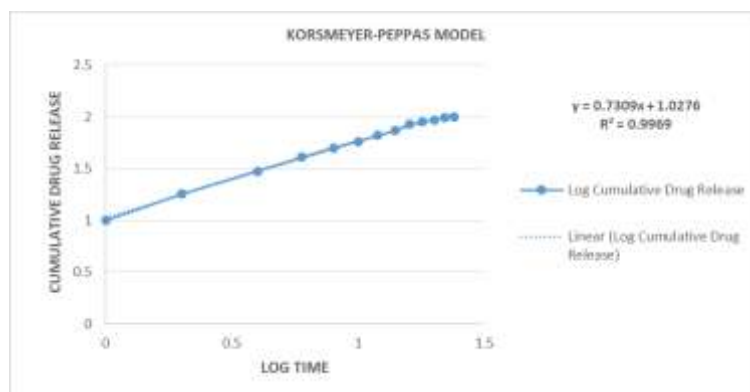


Fig. 11: Korsmeyer-peppas release kinetic plot

3.5.3 Stability Studies

The optimized formulation (F12) was packed in airtight containers and stored under accelerated stability conditions ($40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$) for 2 months according to ICH Q1A(R2) guidelines. Samples were evaluated initially and after 1 and 2 months for physical appearance, hardness, friability, drug content, and *in-vitro* drug release.

Table 11. Stability characteristics of F12

Parameter	Initial	After 1 Month	After 2 Months
Physical appearance	No change	No change	No change
Hardness (kg/cm^2)	6.8 ± 0.2	6.7 ± 0.2	6.6 ± 0.2
Friability (%)	0.42	0.44	0.45
Drug content (%)	99.6 ± 0.4	99.2 ± 0.5	98.9 ± 0.4
Cumulative drug release at 24 h (%)	98.2 ± 0.5	98.0 ± 0.4	97.8 ± 0.6

The optimized formulation (F12) remained stable throughout the 2-month accelerated stability study. No significant changes were observed in the physical appearance of the tablets. The hardness, friability, drug content, and cumulative drug release showed only minor variations during storage and remained within acceptable pharmacopoeial limits. These results indicate that the optimized formulation retained its physicochemical properties and extended-release characteristics under accelerated storage conditions.

4. CONCLUSION

Simvastatin extended-release matrix tablets were successfully formulated by direct compression using different grades and concentrations of HPMC. The preformulation and FTIR findings confirmed the suitability of simvastatin and indicated no significant incompatibility with the selected excipients. Polymer viscosity grade and concentration considerably influenced the drug-release profile. Among the twelve formulations (F1–F12), F12 was selected as the optimized formulation because it maintained acceptable physicochemical properties and achieved approximately 98% cumulative drug release over 24 hours. Its release profile showed the highest correlation with the Korsmeyer–Peppas model ($R^2 = 0.9969$), followed by the Higuchi model ($R^2 = 0.9834$), suggesting that drug release was governed by diffusion and polymer relaxation. F12 also remained stable during two months of accelerated stability testing at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\% \text{ RH}$, with only a minor change in 24-hour drug release from $98.2 \pm 0.5\%$ to $97.8 \pm 0.6\%$. These findings demonstrate that an HPMC-based hydrophilic matrix is a promising approach for extending the *in-vitro* release of simvastatin for approximately 24 hours. Further *in-vivo*, IVIVC, long-term stability, validated analytical, and reference-product comparison studies are required to establish its therapeutic and commercial suitability.

5. NOVEL RESEARCH STATEMENT

“The impact of HPMC viscosity grade and concentration on the *in-vitro* release behavior of directly compressed Simvastatin extended-release matrix tablets is methodically assessed in this work. A comparison of twelve formulations of HPMC K4M, K15M, and K100M revealed that F12 was the best formulation, offering almost 98% cumulative drug release over a 24-hour period and displaying release

behavior best described by the Korsmeyer–Peppas model ($R^2 = 0.9969$). The results show a formulation-specific correlation between the length of Simvastatin release in the studied experimental system and the properties of the HPMC matrix. ”

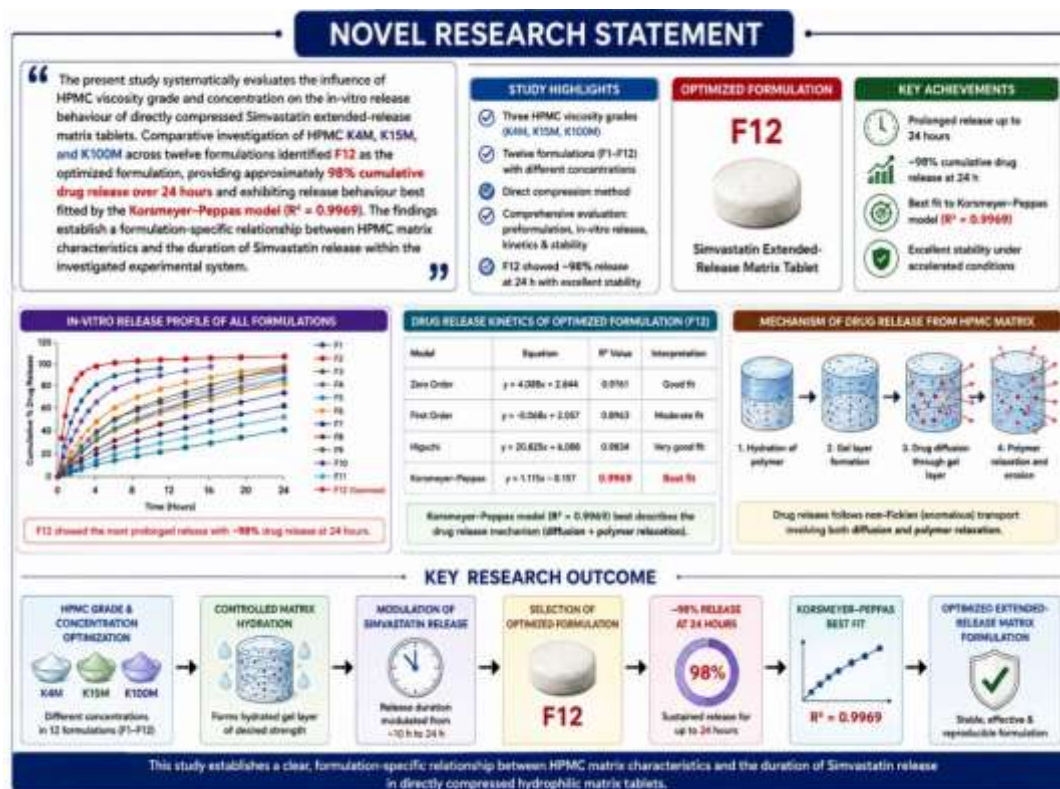


Fig. 12: Graphical Overview of the Optimized Simvastatin Extended-Release Matrix Tablet (F12) and Its Drug Release Mechanism.

KEY RESEARCH OUTCOME

HPMC Grade & Concentration Optimization → Controlled Matrix Hydration → Modulation of Simvastatin Release → Selection of F12 → ~98% Release at 24 h → Korsmeyer–Peppas Best Fit ($R^2 = 0.9969$) → Optimized Extended-Release Matrix Formulation.

Acknowledgements

The authors sincerely thank the management and faculty members of JKKN College of Pharmacy, Kumarapalayam, Namakkal, Tamil Nadu, for providing the necessary facilities, guidance, and support to carry out this research work successfully.

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