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Formulation and Evaluation of Ranolazine Extended-Release Matrix Tablets Employing Eudragit® L100-55

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Abstract

Background: Ranolazine is an anti-anginal agent widely used for the management of chronic stable angina. However, its relatively short biological half-life and high solubility in acidic gastric conditions result in rapid drug release, frequent dosing requirements, and fluctuations in plasma drug concentrations. The present study aimed to develop and evaluate an extended-release matrix tablet of Ranolazine using a pH-dependent polymer system to achieve controlled drug release over 24 hours.

Methods: Extended-release matrix tablets containing 500 mg of Ranolazine were formulated by wet granulation using Eudragit L100-55 as a pH-dependent release-retarding polymer, Hydroxypropyl Methylcellulose (HPMC 5 cps) as a pH-independent binder, and sodium hydroxide as a neutralizing agent. The prepared formulations were evaluated for pre-compression and post-compression parameters, including flow properties, hardness, friability, weight variation, drug content, and in vitro dissolution characteristics. Drug–excipient compatibility was assessed using Fourier Transform Infrared Spectroscopy (FTIR). Dissolution profiles were analyzed using various kinetic models, and the optimized formulation was compared with a marketed extended-release product (Ranozex®) using similarity (f_2) and difference (f_1) factors. Accelerated stability studies were performed according to ICH guidelines.

Results: FTIR studies confirmed the absence of significant drug–excipient interactions, indicating compatibility between Ranolazine and the selected excipients. All formulations exhibited acceptable pharmaceutical characteristics and complied with pharmacopoeial specifications. Among the developed formulations, the optimized batch demonstrated sustained drug release extending up to 24 hours with 97.72% cumulative drug release. Drug-release kinetics were best described by the Higuchi model, indicating diffusion-controlled release behavior. The Korsmeyer–Peppas release exponent (n = 0.776–0.950) suggested a non-Fickian anomalous transport mechanism involving both diffusion and polymer relaxation. The optimized formulation exhibited dissolution profile similarity with the marketed product, showing an f_2 value of 85.95 and an f_1 value of 2.29. Stability studies revealed no significant changes in physical appearance, drug content, or dissolution characteristics after storage under accelerated conditions.

Conclusion: The study successfully developed a stable and effective extended-release matrix tablet of Ranolazine employing Eudragit L100-55 and HPMC 5 cps. The optimized formulation provided controlled drug release over 24 hours, exhibited diffusion-controlled release kinetics, and demonstrated dissolution

equivalence to the marketed product. These findings support the potential application of the developed formulation as a once-daily oral extended-release dosage form for improved management of chronic stable angina.
Keywords: Ranolazine; Extended-release tablet; Eudragit L100-55; HPMC; Wet granulation; Controlled drug delivery; Matrix tablet; Drug release kinetics; Higuchi model; Chronic stable angina.

1. Introduction

Drug delivery systems are designed to optimize the therapeutic efficacy of pharmaceutical agents by controlling the rate, time, and site of drug release. Based on release characteristics, these systems are broadly classified into immediate-release and modified-release dosage forms. While immediate-release formulations rapidly release the active pharmaceutical ingredient to achieve a prompt therapeutic effect, modified-release systems are engineered to alter drug release profiles through delayed, sustained, controlled, or targeted delivery mechanisms.

Extended-release (ER) drug delivery systems represent a significant advancement in pharmaceutical technology by maintaining therapeutic drug concentrations over prolonged periods. These systems minimize fluctuations in plasma drug levels, reduce dosing frequency, improve patient compliance, and decrease the incidence of adverse effects associated with peak drug concentrations. ER formulations typically combine an initial loading dose with a maintenance dose that is released at a controlled rate to sustain therapeutic activity.

Various approaches have been developed for extended drug delivery, including dissolution-controlled, diffusion-controlled, osmotically controlled, ion-exchange, and pH-independent systems. Among these, matrix-based delivery systems are widely employed due to their simplicity, cost-effectiveness, and ability to provide predictable drug release profiles. Depending on the polymeric material used, matrix systems may be hydrophobic, hydrophilic, lipid-based, biodegradable, or mineral-derived, each influencing drug release through mechanisms such as diffusion, swelling, erosion, or dissolution.

The successful design of an extended-release dosage form depends on several physicochemical and biological factors, including drug solubility, stability, molecular size, partition coefficient, biological half-life, absorption characteristics, and metabolic behavior. Careful consideration of these parameters enables the development of formulations that enhance therapeutic outcomes while improving patient convenience and treatment adherence.

2. Materials and Methods

2.1 Materials

Ranolazine was obtained from Virdev Intermediates, Surat, India. Methacrylic acid copolymer (Eudragit® L100-55) was procured from Evonik Industries, Germany and used as a pH-dependent release-retarding polymer. Microcrystalline cellulose (Avicel PH101) was obtained from FMC Biopolymer, India and employed as a diluent. Hydroxypropyl methylcellulose (HPMC 5, 15, and 50 cps) was supplied by Colorcon, Goa, India and used as pH-independent binders. Sodium hydroxide was obtained from Cadila Pharmaceuticals, Dholka, India and utilized as a neutralizing agent. Magnesium stearate was procured from Skant Healthcare Ltd., Mumbai, India and used as a lubricant. Opadry® II Brown 85G86605 (Colorcon, Goa, India) was used as the film-coating material. All other chemicals and reagents used in the study were of analytical grade.

2.2 Methodology

Ranolazine belongs to Biopharmaceutical Classification System (BCS) Class II, characterized by low aqueous solubility and high permeability. The drug exhibits pH-dependent solubility, showing greater solubility in acidic conditions and limited solubility at intestinal pH. It has a relatively short elimination half-life of approximately 2–3 hours, making it a suitable candidate for extended-release dosage forms. Following oral administration, Ranolazine undergoes extensive hepatic metabolism primarily via CYP3A4 and CYP2D6 enzymes and is eliminated through both urinary and fecal routes.

2.3 Rationale for Developing Extended-Release Ranolazine Tablets

Despite its therapeutic efficacy, Ranolazine exhibits a relatively short biological half-life and significant plasma concentration fluctuations following conventional administration. Frequent dosing may reduce patient adherence and increase variability in therapeutic response. Extended-release matrix tablets are

therefore developed to maintain plasma drug concentrations within the therapeutic window for prolonged periods while reducing dosing frequency.

The use of pH-dependent polymers such as Eudragit L100-55 and hydrophilic polymers such as Hydroxypropyl Methylcellulose (HPMC) can effectively control drug release by combining diffusion and matrix swelling mechanisms. Such systems are expected to reduce initial burst release in the stomach and sustain drug release throughout the gastrointestinal tract.

2.4 Preformulation Studies

Preformulation studies were performed to evaluate the physicochemical properties of Ranolazine, including appearance, melting point, partition coefficient, aqueous solubility, loss on drying (LOD), assay, particle size, bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose.

2.4.1 FTIR Analysis

Drug–excipient compatibility studies were performed using Fourier Transform Infrared Spectroscopy (FTIR). Spectra of pure Ranolazine and physical mixtures containing individual excipients were recorded over a range of 4000–400 cm^{-1} using an FTIR spectrophotometer.

2.4.2 Loss on Drying

Loss on drying was determined using a moisture balance at 105°C until constant weight was achieved.

2.4.3 Assay of Ranolazine

The assay of Ranolazine was determined by HPLC using a HYPERSIL ODS column (250 × 4.6 mm, 5 µm). The mobile phase consisted of phosphate buffer (pH 7.5) and acetonitrile (40:60 v/v). Detection was carried out at 225 nm with a flow rate of 1.0 mL/min.

2.4.4 Micromeritic Evaluation

Particle size distribution was determined using a Malvern Zetasizer. Bulk density, tapped density, Carr's compressibility index, Hausner's ratio, and angle of repose were determined using standard pharmacopoeial procedures.

2.5 Preparation of Preliminary Formulations

Preliminary formulations were prepared by incorporating Eudragit L100-55 as the pH-dependent polymer and different grades of HPMC (5 cps, 15 cps, and 50 cps) as pH-independent binders. Tablets were prepared by wet granulation and compressed to obtain tablets with an average weight of 660 mg.

2.6 Evaluation of Tablets

The prepared tablets were evaluated for appearance, thickness, weight variation, hardness, friability, and drug content according to pharmacopeial methods.

2.7 Construction of Calibration Curve

A stock solution of Ranolazine was prepared in methanol and diluted with distilled water to obtain concentrations ranging from 2–10 µg/mL. Absorbance was measured at 272 nm using a UV–Visible spectrophotometer, and a calibration curve was constructed by plotting concentration against absorbance.

2.8 In Vitro Dissolution Studies

Drug release studies were performed using USP Dissolution Apparatus II (Paddle Method). Dissolution testing was carried out in 900 mL of 0.1 N hydrochloric acid maintained at 37 ± 0.5°C and stirred at 50 rpm. Samples were withdrawn at predetermined intervals (0.5, 2, 4, 8, 12, 20, and 24 h), filtered, and analyzed spectrophotometrically.

2.9 Drug Release Kinetics

Dissolution data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas kinetic models to determine the mechanism of drug release.

2.10 Comparison of Dissolution Profiles

The dissolution profile of the optimized formulation was compared with that of the reference product using similarity factor (f_2) and difference factor (f_1) analyses according to SUPAC and FDA recommendations.

Table 2.4: Preliminary Formulation Composition

Ingredient	P1 (mg)	P2 (mg)	P3 (mg)
Ranolazine	506	506	506
Eudragit L100-55	100	100	100
Sodium Hydroxide	5.2	5.2	5.2
HPMC 5 cps	13	–	–
HPMC 15 cps	–	13	–
HPMC 50 cps	–	–	13
Avicel PH101	22.8	22.8	22.8
Magnesium Stearate	13	13	13
Total Weight	660	660	660

2.11 Formulation of Ranolazine Extended-Release Matrix Tablets

Based on the results obtained from preliminary formulation studies, HPMC 5 cps was selected as the pH-independent binder for further formulation development. Extended-release matrix tablets of Ranolazine were formulated using Eudragit® L100-55 as a pH-dependent release-retarding polymer and sodium hydroxide as a neutralizing agent. A total of fourteen formulations (F1–F14) were prepared by varying the concentrations of Eudragit® L100-55 and sodium hydroxide while maintaining the drug content constant. The composition of the formulations is presented in Table X.

Table 2.5: Composition of Ranolazine Extended-Release Matrix Tablets (mg/tablet)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Ranolazine	506	506	506	506	506	506	506	506	506	506	506	506	506
Eudragit® L100-55	67	83.5	100	67	83.5	100	67	83.5	100	83.5	83.5	83.5	83.5
HPMC 5 cps	13	13	13	13	13	13	13	13	13	13	13	13	13
Sodium Hydroxide	2.6	2.6	2.6	3.9	3.9	3.9	5.2	5.2	5.2	3.9	3.9	3.9	3.9
Magnesium Stearate	13	13	13	13	13	13	13	13	13	13	13	13	13
Avicel PH101	58.4	41.9	25.4	57.1	40.6	24.1	55.8	39.3	22.8	40.6	40.6	40.6	40.6
Opadry® II Brown 85G86605	20	20	20	20	20	20	20	20	20	20	20	20	20
Total Weight (mg)	**680**	**680**	**680**	**680**	**680**	**680**	**680**	**680**	**680**	**680**	**680**	**680**	**680**

2.12 Preparation of Extended-Release Matrix Tablets

Extended-release matrix tablets were prepared by the wet granulation technique. Ranolazine, Eudragit® L100-55, Avicel PH101, and HPMC 5 cps were individually passed through a #20 sieve and blended uniformly in a rapid mixer granulator (RMG). Sodium hydroxide was dissolved in purified water and HPMC 5 cps was dispersed under continuous stirring to prepare the binder solution.

The prepared binder solution was gradually added to the powder blend with continuous mixing. The wet mass obtained was kneaded until uniform granulation was achieved. The granules were dried in a fluidized bed dryer at 60°C until the loss on drying was below 2%. The dried granules were passed through a #16 sieve and lubricated with magnesium stearate previously passed through a #60 sieve.

The lubricated granules were compressed using a tablet compression machine equipped with 16.4 × 8 mm capsule-shaped, sub-concave punches. The compressed tablets were subsequently coated with Opadry® II Brown 85G86605 using a conventional pan coating process to improve tablet appearance and patient acceptability.

Table 2.6: Granulation Parameters

Process Step	Time (s)	Impeller Speed (rpm)	Chopper Speed (rpm)
Dry Mixing	180	75	Off
Binder Addition	120	75	Off
Kneading	60	75	1500

Table 2.7: Film Coating Parameters

Parameter	Value
Inlet Temperature	55–65°C
Outlet Temperature	35–45°C
Atomization Pressure	2.5 bar
Pan Temperature	48°C
Spray Rate	2.1 rpm
Pan Speed	10 rpm

2.13 Evaluation of Granules

The prepared granules were evaluated for pre-compression characteristics including bulk density, tapped density, Hausner's ratio, and compressibility index using standard pharmacopoeial procedures. These parameters were determined to assess the flowability and compressibility of the granules prior to tablet compression.

2.14 Evaluation of Tablets

The compressed tablets were evaluated for physical appearance, dimensions (length, width, and thickness), weight variation, hardness, friability, and drug content according to official pharmacopoeial methods. Tablet dimensions were measured using a digital Vernier caliper, hardness was determined using a hardness tester, and friability was assessed using a Roche friabilator. Drug content was determined by a validated analytical method.

2.15 In Vitro Drug Release Studies of Optimized Formulations

All formulations (F1–F14) were subjected to in vitro dissolution testing using USP Dissolution Apparatus II (Paddle Method). Dissolution studies were carried out under the conditions described previously. Samples were withdrawn at predetermined intervals and analyzed spectrophotometrically. The release profiles of all formulations were compared with the target dissolution profile of the marketed reference product.

2.16 Drug Release Kinetic Analysis

The dissolution data obtained from all formulations were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas kinetic models to elucidate the mechanism of drug release. The model showing the highest correlation coefficient (R^2) was considered to best describe the release kinetics of the developed formulations.

2.17 Comparison with Reference Product

The dissolution profile of the optimized formulation was compared with that of the marketed extended-release Ranolazine tablet (Ranozex®, Sun Pharma). Similarity factor (f_2) and difference factor (f_1) analyses were performed according to FDA and SUPAC guidelines to evaluate the equivalence of dissolution profiles between the optimized formulation and the reference product.

2.18 Accelerated Stability Studies

The optimized formulation (F14) was subjected to accelerated stability testing in accordance with International Council for Harmonisation (ICH) guidelines. The tablets were stored at 40 ± 2°C and 75 ± 5% relative humidity (RH) for a period of one month. Samples were withdrawn at the end of the study period and evaluated for physical appearance, drug content, and in vitro dissolution characteristics.

Physical stability was assessed by visual examination for any changes in color, shape, or surface characteristics. Chemical stability was evaluated by determining the assay of Ranolazine, while dissolution testing was performed to assess any changes in drug release behavior during storage.

Table 2.8: ICH Accelerated Stability Conditions

Study Type	Storage Condition	Minimum Duration
Long-term	25 ± 2°C / 60 ± 5% RH	12 months
Intermediate	30 ± 2°C / 65 ± 5% RH	6 months
Accelerated	40 ± 2°C / 75 ± 5% RH	6 months

3. Results

3.1 Preformulation Characterization of Ranolazine

Preformulation studies were conducted to evaluate the physicochemical properties of Ranolazine and to establish its suitability for the development of an extended-release matrix tablet. The drug was obtained as a white, odorless crystalline powder with a melting point of 120°C. The measured partition coefficient (1.116) indicated moderate lipophilicity, while the aqueous solubility was found to be 3.285 mg/mL.

The assay value of 99.2% confirmed the purity of the drug substance and complied with pharmacopeial specifications. The loss on drying was only 0.3%, indicating minimal moisture content and good storage stability.

Table 3.1: Physicochemical Properties of Ranolazine

Parameter	Result
Appearance	White crystalline powder
Melting point	120°C
Partition coefficient	1.116
Aqueous solubility	3.285 mg/mL
Loss on drying	0.3%
Assay	99.2%
Potency	506 mg

Micromeritic characterization revealed poor flowability of the pure drug. The bulk density and tapped density were 0.4166 g/mL and 0.6578 g/mL, respectively. Carr's index (36.67%) and Hausner's ratio (1.5789) indicated very poor flow properties, suggesting the need for granulation prior to compression. The average particle size (D90) was 12.44 µm.

Table 3.2: Micromeritic Properties of Ranolazine

Parameter	Result
Bulk density (g/mL)	0.4166
Tapped density (g/mL)	0.6578
Carr's index (%)	36.67
Hausner's ratio	1.5789
Particle size (D90)	12.44 µm

The poor flow behavior of Ranolazine can be attributed to its fine particle size and cohesive nature. Therefore, wet granulation was selected as the manufacturing technique to improve flowability and compressibility during tablet production.

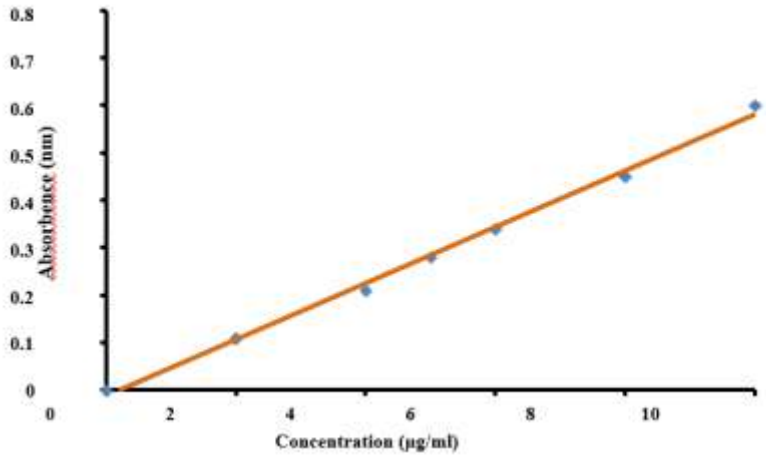

Fig 3.1: Calibration Curve of Ranolazine by U.V Spectrophotometric Method

3.2 Analytical Method Development

The UV spectrophotometric method developed for Ranolazine analysis exhibited good linearity over the concentration range of 2–10 µg/mL. The calibration curve demonstrated a direct relationship between concentration and absorbance, with a correlation coefficient (R^2) of 0.996.

Table 3.3: Calibration Data of Ranolazine

Concentration (µg/mL)	Absorbance
2	0.11
4	0.21
6	0.34
8	0.45
10	0.56

The high correlation coefficient confirmed compliance with Beer–Lambert's law and demonstrated the suitability of the method for quantitative estimation of Ranolazine during dissolution and assay studies.

3.3 Drug–Excipient Compatibility Studies

The compatibility of Ranolazine with formulation excipients was evaluated through physical observation and FTIR spectroscopy. No visible changes in color, texture, or physical appearance were observed in any drug–excipient mixture after storage at 60°C for one week and 40°C/75% RH for one month.

Table 3.4: Physical Compatibility Study of Ranolazine with Excipients

Mixture	Observation
Drug	No change
Drug + HPMC 5 cps	No change
Drug + Eudragit L100-55	No change
Drug + Avicel PH101	No change
Drug + Magnesium Stearate	No change
Drug + Sodium Hydroxide	No change

FTIR analysis further confirmed compatibility between Ranolazine and the selected excipients. The characteristic absorption peaks of Ranolazine observed at 3330 cm^{-1} (N–H stretching), 2832 cm^{-1} (C–H stretching), and 1683 cm^{-1} (amide C=O stretching) remained unchanged in all binary mixtures.

Table 3.5: Characteristic FTIR Peaks of Ranolazine

Wavenumber (cm^{-1})	Functional Group
3330	N–H stretching
2832	C–H stretching
1683	Amide C=O stretching
1591	Aromatic C–C stretching
1456	Aromatic C–C stretching

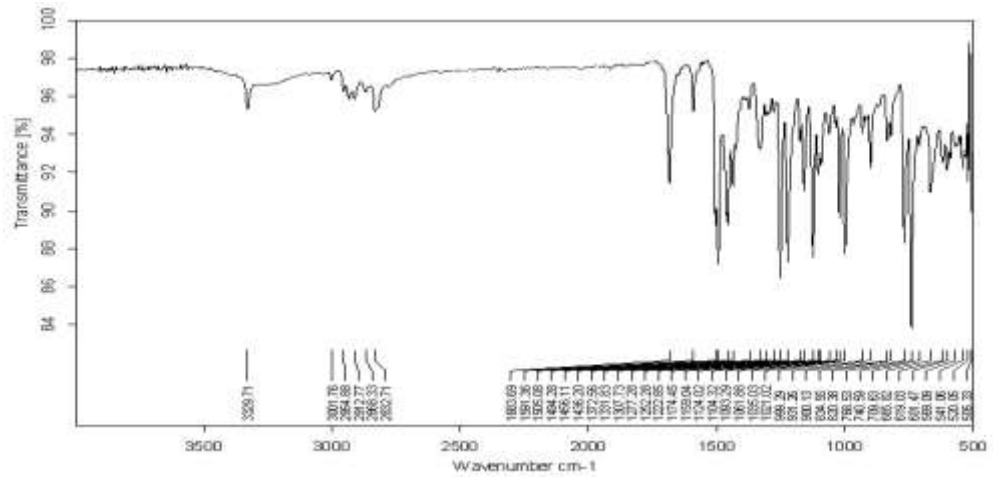

Fig 3.2: Infrared Spectrum of Ranolazine Pure Drug

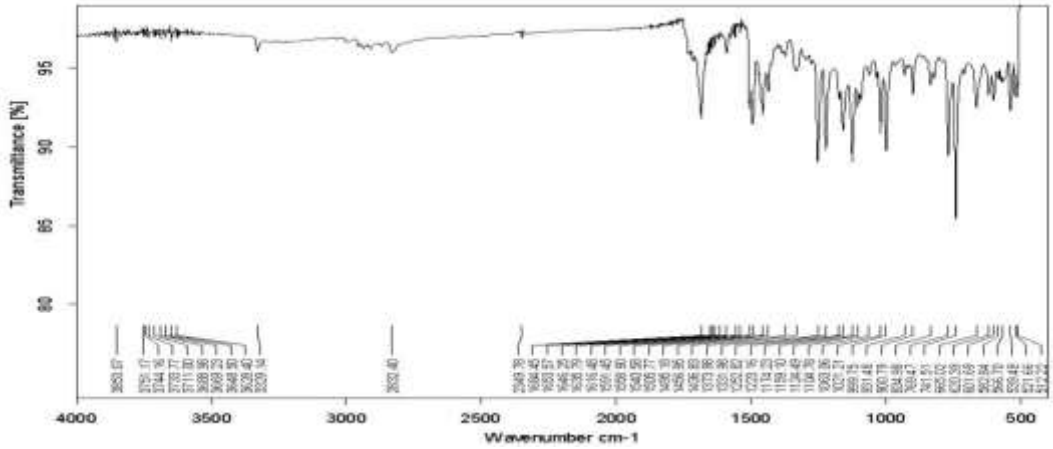

Fig 3.3: FTIR Spectrums - Mixture of Drug and Eudragit L 100-5

The retention of characteristic peaks without significant shifts or disappearance indicated the absence of chemical interactions between the drug and excipients. Therefore, Eudragit L100-55, HPMC 5 cps, Avicel PH101, sodium hydroxide, and magnesium stearate were considered suitable for formulation development.

3.4 Selection of Release-Control Polymer

Preliminary formulations containing Eudragit L100-55 and different grades of HPMC (5 cps, 15 cps, and 50 cps) were prepared to identify the most suitable polymer system for extended drug release.

Table 3.6: Composition of Preliminary Formulations

Ingredients	P1 (HPMC 5 cps) (mg)	P2 (HPMC 15 cps) (mg)	P3 (HPMC 50 cps) (mg)
Ranolazine	506	506	506
Eudragit L100-55	100	100	100
Sodium Hydroxide	5.2	5.2	5.2
HPMC 5 cps	13	–	–
HPMC 15 cps	–	13	–
HPMC 50 cps	–	–	13
Avicel PH 101	22.8	22.8	22.8
Magnesium Stearate	13	13	13

Total Weight (mg)	660	660	660

Table 3.7: Dissolution Profile of Preliminary Formulations

Time (h)	P1 (HPMC 5 cps)	P2 (HPMC 15 cps)	P3 (HPMC 50 cps)
0	0.0	0.0	0.0
0.5	17.1 ± 0.046	16.4 ± 0.066	15.6 ± 0.041
2	31.15 ± 0.023	28.8 ± 0.054	27.9 ± 0.079
4	45.2 ± 0.016	41.2 ± 0.046	40.2 ± 0.031
8	60.45 ± 0.031	57.25 ± 0.094	55.75 ± 0.065
12	75.7 ± 0.049	73.3 ± 0.025	71.3 ± 0.016
20	87.95 ± 0.075	86.1 ± 0.013	84.45 ± 0.053
24	100.2 ± 0.015	98.9 ± 0.045	97.6 ± 0.084

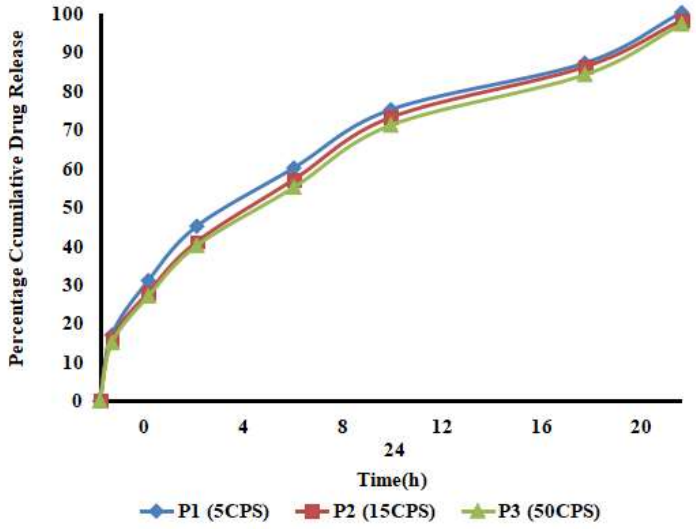

Fig 3.4: Dissolution Profile Comparisons of Preliminary Batches

All preliminary batches demonstrated sustained drug release over 24 h. The cumulative drug release at 24 h was 100.2%, 98.9%, and 97.6% for formulations containing HPMC 5 cps, HPMC 15 cps, and HPMC 50 cps, respectively. The similarity of dissolution profiles indicated that polymer viscosity had minimal influence on release behavior.

Consequently, HPMC 5 cps was selected for further formulation development because it provided comparable release characteristics while offering easier processing and lower viscosity during granulation. Eudragit L100-55 was selected as the primary release-retarding polymer due to its pH-dependent dissolution properties and superior stability compared with other enteric polymers.

3.5 Evaluation of Granules

The granules prepared by wet granulation were evaluated for their flow and compressibility characteristics prior to compression. Bulk density values ranged from 0.43 to 0.46 g/cm³, while tapped density values ranged from 0.54 to 0.57 g/cm³ for most formulations. The Hausner's ratio values were generally below 1.25, indicating acceptable flow properties suitable for tablet compression. Similarly, the compressibility index values ranged from 16.66% to 21.81%, suggesting fair to good compressibility of the granules.

The improved flow properties observed after granulation may be attributed to the increase in particle size and reduction in interparticle friction. These characteristics ensured uniform die filling and consistent tablet weight during compression.

Table 3.8: Pre-Compression Evaluation of Granules

Batch	Bulk Density	Tapped Density	Hausner's Ratio	Compressibility

	(g/cm³)	(g/cm³)		Index (%)
F1	0.43 ± 0.03	0.54 ± 0.06	1.24 ± 0.05	20.37 ± 0.01
F2	0.45 ± 0.04	0.55 ± 0.02	1.22 ± 0.04	18.18 ± 0.03
F3	0.43 ± 0.02	0.55 ± 0.04	1.24 ± 0.01	21.81 ± 0.04
F4	0.44 ± 0.01	0.54 ± 0.04	1.22 ± 0.05	18.51 ± 0.07
F5	0.46 ± 0.01	0.57 ± 0.01	1.23 ± 0.02	19.29 ± 0.01
F6	0.45 ± 0.01	0.54 ± 0.03	1.20 ± 0.02	16.66 ± 0.06
F7	0.46 ± 0.01	0.57 ± 0.06	1.23 ± 0.01	19.29 ± 0.05
F8	0.46 ± 0.02	0.54 ± 0.02	1.23 ± 0.04	21.46 ± 0.02
F9	0.43 ± 0.03	0.54 ± 0.06	1.24 ± 0.05	19.15 ± 0.01
F10	0.46 ± 0.01	0.54 ± 0.06	1.20 ± 0.02	21.81 ± 0.04
F11	0.45 ± 0.01	0.55 ± 0.01	1.23 ± 0.01	18.51 ± 0.07
F12	0.46 ± 0.01	0.55 ± 0.04	1.23 ± 0.04	19.29 ± 0.01
F13	0.46 ± 0.02	0.54 ± 0.04	1.24 ± 0.05	16.66 ± 0.06
F14	0.45 ± 0.03	0.55 ± 0.06	1.22 ± 0.03	18.78 ± 0.04

3.6 Post-Compression Evaluation of Tablets

All formulations produced brown-colored, capsule-shaped, biconvex film-coated tablets with a break line on one side and a plain surface on the other. The tablets exhibited satisfactory physical appearance and mechanical integrity.

The average tablet weight ranged from 678.2 ± 2.31 mg to 683.1 ± 3.27 mg, complying with pharmacopoeial specifications for weight variation. Tablet dimensions were found to be uniform among all batches, indicating consistency in compression parameters. Hardness values ranged from 17.1 ± 0.1 to 17.8 ± 0.5 kg/cm², demonstrating adequate mechanical strength for handling and packaging. Friability values were below 0.1% for all formulations, confirming excellent resistance to abrasion.

Drug content ranged from 98.32 ± 0.20% to 100.81 ± 0.36%, indicating uniform distribution of Ranolazine within the matrix tablets and satisfactory content uniformity.

Table 3.9: Post-Compression Evaluation of Ranolazine Extended-Release Tablets

Batch	Average Tablet Weight (mg) (n=20)	Hardness (kg/cm²) (n=10)	Length (mm) (n=6)	Width (mm) (n=6)	Thickness (mm) (n=6)	Friability (%)	Assay (%) (n=5)
F1	682.6 ± 2.88	17.2 ± 0.5	16.40 ± 0.01	8.01 ± 0.02	5.71 ± 0.02	0.064	99.80 ± 0.10
F2	679.2 ± 2.38	17.5 ± 0.2	16.42 ± 0.01	8.02 ± 0.01	5.72 ± 0.01	0.073	98.32 ± 0.20
F3	683.1 ± 3.27	17.8 ± 0.4	16.39 ± 0.03	8.01 ± 0.03	5.75 ± 0.03	0.068	100.44 ± 0.23
F4	681.4 ± 2.25	17.4 ± 0.3	16.41 ± 0.01	7.99 ± 0.03	5.84 ± 0.01	0.066	99.61 ± 0.33
F5	678.5 ± 2.60	17.3 ± 0.1	16.38 ± 0.03	7.98 ± 0.02	5.77 ± 0.02	0.055	99.21 ± 0.19
F6	680.3 ± 2.96	17.1 ± 0.1	16.41 ± 0.03	8.01 ± 0.03	5.85 ± 0.01	0.062	98.68 ± 0.22
F7	682.6 ± 3.20	17.4 ± 0.4	16.42 ± 0.04	7.99 ± 0.01	5.74 ± 0.01	0.059	100.34 ± 0.30
F8	679.8 ± 2.49	17.3 ± 0.2	16.38 ± 0.02	8.03 ± 0.01	5.72 ± 0.03	0.053	100.81 ± 0.36
F9	678.2 ± 2.31	17.1 ± 0.4	16.41 ± 0.03	8.02 ± 0.02	5.81 ± 0.01	0.056	99.48 ± 0.20
F10	682.6 ± 2.84	17.8 ± 0.4	16.43 ± 0.01	8.01 ± 0.02	5.71 ± 0.03	0.073	99.61 ± 0.33

F11	679.2 ± 2.58	17.4 ± 0.3	16.42 ± 0.02	8.01 ± 0.01	5.73 ± 0.01	0.068	99.21 ± 0.19
F12	683.1 ± 2.99	17.3 ± 0.1	16.39 ± 0.01	8.02 ± 0.03	5.76 ± 0.02	0.066	98.68 ± 0.22
F13	681.4 ± 2.34	17.1 ± 0.1	16.41 ± 0.03	7.98 ± 0.01	5.79 ± 0.01	0.055	100.34 ± 0.30
F14	680.3 ± 2.48	17.7 ± 0.4	16.38 ± 0.06	8.01 ± 0.03	5.76 ± 0.02	0.066	99.34 ± 0.45

3.7 In Vitro Drug Release Studies

The in vitro dissolution profiles of formulations F1–F14 were evaluated and compared with the reference product. Drug release was found to be significantly influenced by the concentration of Eudragit® L100-55 and sodium hydroxide. Formulations containing lower concentrations of Eudragit® L100-55 exhibited relatively faster drug release, whereas increasing the polymer concentration effectively retarded drug dissolution.

Eudragit® L100-55, a pH-dependent polymer, restricted the high solubility of Ranolazine under acidic conditions and facilitated sustained drug release in the intestinal environment. Sodium hydroxide acted as a neutralizing agent and further contributed to modulation of the release profile.

Among all formulations, F14 demonstrated a dissolution profile most closely matching that of the reference product. The optimized formulation released 17.45%, 32.10%, 46.74%, 60.43%, 74.12%, 85.92%, and 97.72% of drug at 0.5, 2, 4, 8, 12, 20, and 24 h, respectively.

Table 3.10: Comparative Drug Release Profiles of Formulations F1–F14

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	20.51 ± 0.04	16.62 ± 0.06	8.36 ± 0.01	17.53 ± 0.09	15.03 ± 0.11	5.41 ± 0.12	13.73 ± 0.11	12.86 ± 0.11	3.53 ± 0.04
2	28.60 ± 0.09	30.32 ± 0.12	19.99 ± 0.09	32.23 ± 0.09	28.33 ± 0.17	16.36 ± 0.14	26.01 ± 0.11	25.52 ± 0.05	10.60 ± 0.13
4	49.56 ± 0.11	44.02 ± 0.06	31.62 ± 0.16	46.93 ± 0.10	41.63 ± 0.10	27.31 ± 0.13	38.29 ± 0.11	38.18 ± 0.11	17.66 ± 0.19
8	64.11 ± 0.10	58.74 ± 0.06	46.025 ± 0.10	61.20 ± 0.11	55.53 ± 0.12	41.385 ± 0.09	51.81 ± 0.11	52.17 ± 0.10	31.06 ± 0.09
12	78.65 ± 0.12	73.46 ± 0.08	60.43 ± 0.12	75.46 ± 0.12	69.42 ± 0.01	55.46 ± 0.10	65.32 ± 0.12	66.15 ± 0.08	44.45 ± 0.11
20	88.84 ± 0.10	84.45 ± 0.07	75.17 ± 0.10	87.06 ± 0.04	80.67 ± 0.12	72.86 ± 0.16	78.49 ± 0.11	78.04 ± 0.12	62.35 ± 0.11
24	99.02 ± 0.01	95.45 ± 0.09	89.91 ± 0.07	98.66 ± 0.09	91.92 ± 0.12	90.26 ± 0.06	91.66 ± 0.09	89.93 ± 0.11	82.06 ± 0.11

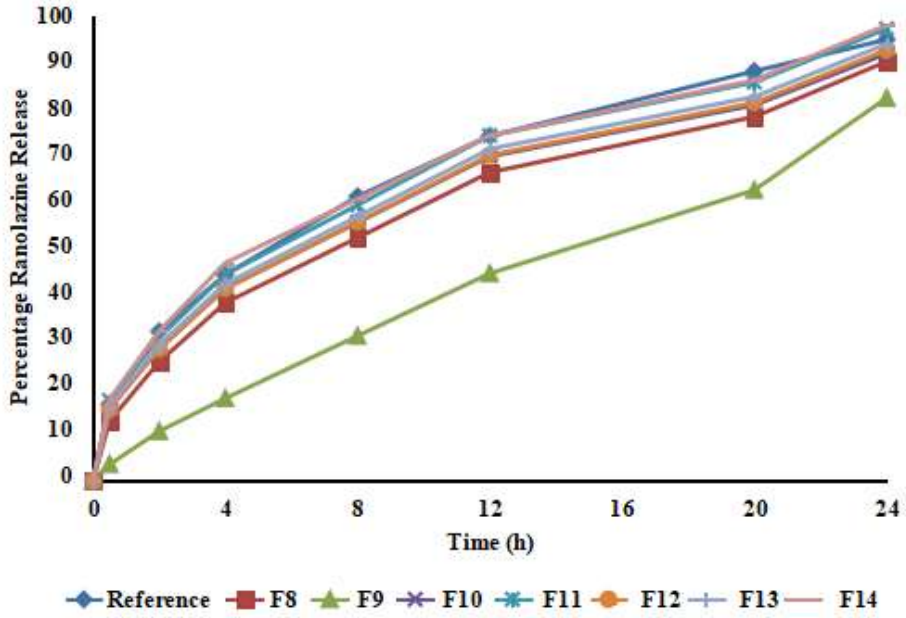

Fig 3.5: Comparative Dissolution Profiles of Formulations F1–F7 and Reference Product

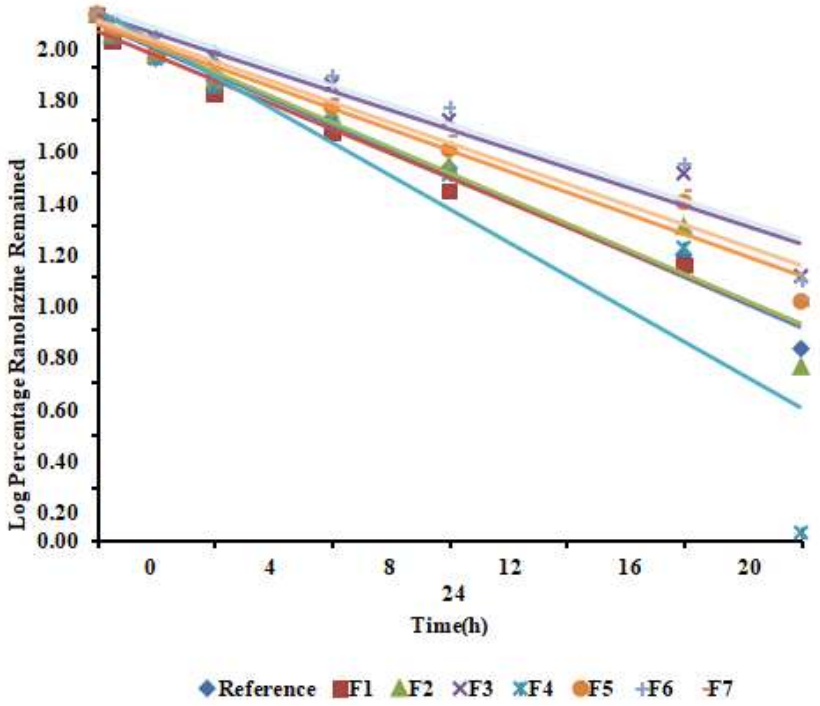

Fig 3.6: Comparative Dissolution Profiles of Formulations F8–F14 and Reference Product

The dissolution results clearly demonstrated that the combination of Eudragit® L100-55 and sodium hydroxide effectively controlled drug release over a period of 24 h. Formulation F14 showed the closest agreement with the dissolution profile of the marketed product and was therefore selected as the optimized formulation for further evaluation.

3.8 Drug Release Kinetics

To elucidate the mechanism of drug release, dissolution data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas kinetic models. The correlation coefficient (R^2) values obtained for the Higuchi model were consistently higher than those observed for the other models, indicating that drug release from the developed matrix tablets predominantly followed diffusion-controlled kinetics.

The optimized formulation (F14) exhibited a Higuchi correlation coefficient (R^2) of 0.992, confirming diffusion as the primary release mechanism. Furthermore, the release exponent (n) obtained from the Korsmeyer–Peppas model was 0.783, indicating a non-Fickian anomalous transport mechanism involving both diffusion and polymer relaxation.

Table 3.11: Release Kinetic Parameters of Formulations F1–F14

Batch	Zero-Order Model (R^2)	First-Order Model (R^2)	Higuchi Model (R^2)	Korsmeyer–Peppas Model (R^2)	Release Exponent (n)
Ranozex®	0.881	0.987	0.993	0.559	0.794
F1	0.868	0.888	0.984	0.529	0.776
F2	0.888	0.955	0.993	0.557	0.789
F3	0.952	0.959	0.993	0.699	0.881
F4	0.882	0.885	0.992	0.546	0.787
F5	0.896	0.971	0.995	0.573	0.793
F6	0.973	0.936	0.982	0.778	0.950
F7	0.921	0.960	0.997	0.595	0.803
F8	0.913	0.974	0.997	0.606	0.813
F9	0.991	0.940	0.950	0.857	0.992
F10	0.896	0.973	0.995	0.567	0.788
F11	0.891	0.932	0.994	0.551	0.786
F12	0.898	0.969	0.995	0.571	0.792
F13	0.895	0.964	0.994	0.563	0.788
F14	0.882	0.912	0.992	0.545	0.783

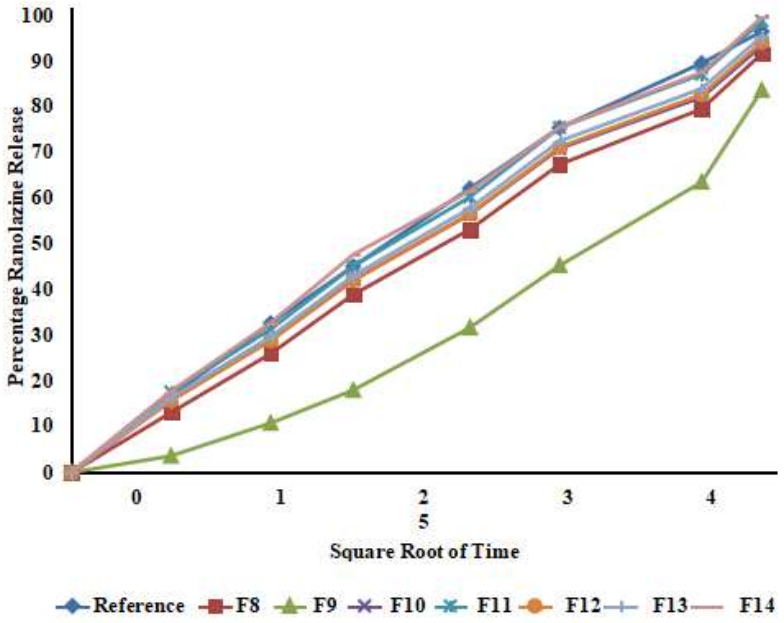

Fig 3.7: Higuchi Release Plot of Optimized Formulation (F14)

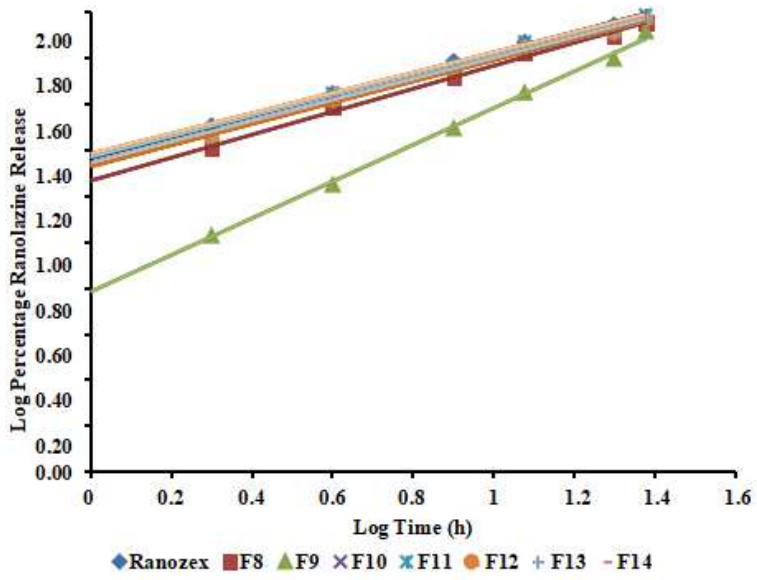

Fig 3.8: Korsmeyer–Peppas Release Plot of Optimized Formulation (F14)

These findings suggest that the developed extended-release matrix system achieved controlled drug release through a combination of diffusion and matrix relaxation mechanisms, which is characteristic of hydrophilic polymer-based matrix tablets.

3.9 Comparison with the Marketed Product

The dissolution profile of the optimized formulation (F14) was compared with that of the marketed extended-release product, Ranozex®. The release profiles of both formulations were highly comparable throughout the 24-h study period.

Table 3.12: Dissolution Profile Comparison between Optimized Formulation (F14) and Reference Product

Time (h)	Optimized Formulation (F14) (%)	Reference Product (%)
0	0.00	0.00
0.5	17.45 ± 0.015	16.28 ± 0.33
2	32.10 ± 0.041	32.04 ± 0.46
4	46.74 ± 0.049	44.23 ± 0.66
8	60.43 ± 0.084	60.99 ± 0.14
12	74.12 ± 0.034	74.00 ± 0.79
20	85.92 ± 0.097	87.87 ± 0.84
24	97.72 ± 0.078	94.66 ± 0.27

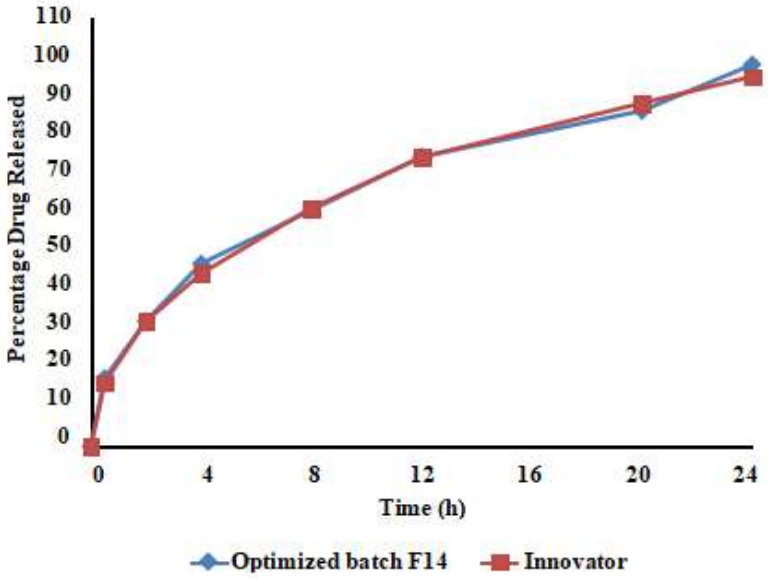

Fig 3.9: Comparative Dissolution Profiles of Optimized Formulation (F14) and Ranozex®

The similarity factor (f_2) and difference factor (f_1) were calculated to assess dissolution profile equivalence. The optimized formulation exhibited an f_2 value of 85.95 and an f_1 value of 2.29, satisfying FDA acceptance criteria for similarity ($f_2 > 50$ and $f_1 < 15$). These results confirmed that formulation F14 successfully reproduced the release characteristics of the reference product.

Table 3.13:. Similarity and Difference Factors for Optimized Formulation

Parameter	Value
Similarity Factor (f_2)	85.95
Difference Factor (f_1)	2.29

The high similarity observed between the optimized formulation and the marketed product demonstrates the suitability of Eudragit® L100-55 as an effective release-retarding polymer for the development of once-daily extended-release Ranolazine tablets.

3.10 Accelerated Stability Studies

The optimized formulation (F14) was subjected to accelerated stability testing at **40 ± 2°C/75 ± 5% RH** for one month to evaluate its physical and chemical stability.

Table 3.14: Stability Evaluation of Optimized Formulation (F14)

Parameter	Initial	After 1 Month
Physical Appearance	Brown-colored capsule-shaped, biconvex film-coated tablets with break line on one side and plain surface on the other side	No change observed
Assay (%)	100.34	100.14

No visible changes in tablet appearance, color, shape, or coating integrity were observed after storage under accelerated conditions. Similarly, the assay value remained within acceptable limits, indicating minimal degradation of Ranolazine during the study period.

Table 3.15: Dissolution Profile of Optimized Formulation During Stability Study (Mean ± SD, n = 3)

Time (h)	Initial (%)	After 1 Month (%)
0	0.00	0.00
0.5	17.45 ± 0.015	17.35 ± 0.085

2	32.10 ± 0.041	31.83 ± 0.011
4	46.74 ± 0.049	45.98 ± 0.052
8	60.43 ± 0.084	59.49 ± 0.021
12	74.12 ± 0.034	75.64 ± 0.032
20	85.92 ± 0.097	86.21 ± 0.094
24	97.72 ± 0.078	96.46 ± 0.064

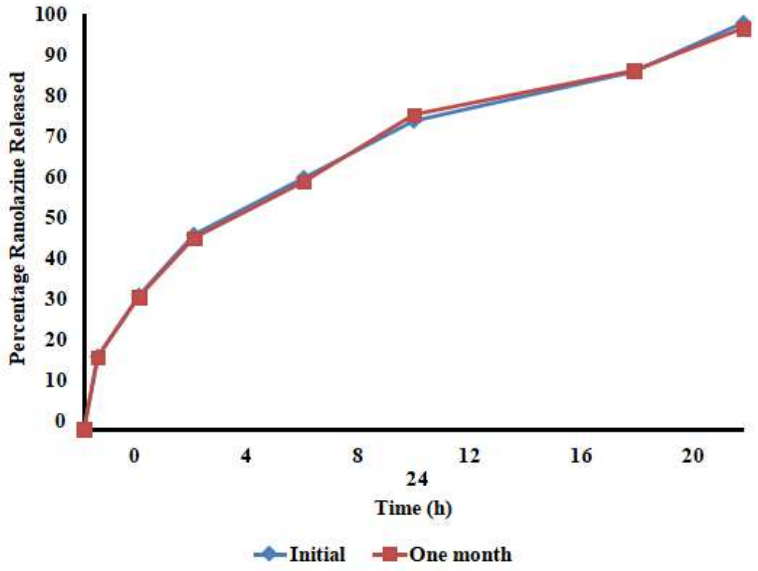

Fig 3.10: Comparative Dissolution Profiles of Optimized Formulation Before and After One Month Stability Storage

The dissolution profile remained essentially unchanged after one month of accelerated storage, indicating good formulation stability.

4. Discussion

The present study aimed to develop an extended-release matrix tablet of Ranolazine using Eudragit® L100-55 as a pH-dependent release-retarding polymer. Preliminary characterization demonstrated that Ranolazine possesses poor flow properties, as indicated by high compressibility index and Hausner's ratio values, necessitating the use of wet granulation for improving processability and ensuring uniform tablet compression. FTIR analysis confirmed the compatibility of Ranolazine with all selected excipients, indicating the absence of significant drug–excipient interactions that could affect formulation stability or drug release behavior.

The preliminary formulation studies revealed that variations in HPMC viscosity grades (5, 15, and 50 cps) produced only minor differences in dissolution behavior. Therefore, HPMC 5 cps was selected for further development owing to its satisfactory performance and ease of processing. The formulation strategy was subsequently focused on optimizing the concentrations of Eudragit® L100-55 and sodium hydroxide to achieve a release profile comparable to the marketed reference product.

All developed formulations exhibited acceptable pre-compression and post-compression characteristics. The granules showed adequate flowability and compressibility for large-scale manufacturing, while the compressed tablets complied with pharmacopoeial requirements for weight variation, hardness, friability, dimensions, and drug content. These findings confirmed the robustness of the wet granulation process and the suitability of the selected excipients for extended-release tablet formulation.

Dissolution studies demonstrated that drug release was significantly influenced by the concentration of Eudragit® L100-55 and sodium hydroxide. Eudragit® L100-55 effectively restricted the rapid dissolution of Ranolazine under acidic conditions and facilitated controlled release in the intestinal environment due to its pH-dependent solubility characteristics. The incorporation of sodium hydroxide further enhanced the release-retarding effect by modulating the ionization behavior of the methacrylic acid

copolymer. As the concentration of Eudragit® L100-55 increased, a gradual reduction in drug release rate was observed, confirming its critical role in controlling matrix integrity and diffusion pathways.

Among the investigated formulations, F14 exhibited the most desirable release profile and closely matched the dissolution behavior of the marketed reference product. The optimized formulation achieved sustained drug release over 24 h, releasing 97.72% of Ranolazine at the end of the dissolution study. Statistical comparison using similarity factor (f_2) and difference factor (f_1) analyses yielded values of 85.95 and 2.29, respectively, indicating excellent equivalence with the reference product according to FDA acceptance criteria.

Drug release kinetic analysis revealed that the dissolution data were best described by the Higuchi model, as evidenced by the highest correlation coefficient values among the tested kinetic models. This finding indicates that diffusion was the predominant mechanism governing drug release from the matrix system. Furthermore, the Korsmeyer–Peppas release exponent values (n = 0.776–0.950) suggested a non-Fickian anomalous transport mechanism, indicating that both diffusion of dissolved drug and polymer relaxation contributed to the overall release process. Similar release behavior has been reported for hydrophilic matrix systems employing combinations of methacrylic acid copolymers and cellulose-based polymers for extended drug delivery.

Overall, the results demonstrate that Eudragit® L100-55 is an effective release-retarding polymer for the development of once-daily Ranolazine extended-release tablets. The optimized formulation exhibited satisfactory pharmaceutical properties, controlled drug release over 24 h, and dissolution profile equivalence to the marketed product, highlighting its potential as a suitable alternative for the management of chronic stable angina.

The dissolution profiles obtained before and after storage under accelerated conditions were found to be highly comparable. The optimized formulation exhibited 97.72% drug release initially and 96.46% drug release after one month of storage, indicating negligible changes in release characteristics. Similarly, assay values remained within acceptable pharmacopeial limits, with only a marginal reduction from 100.34% to 100.14%.

No significant changes were observed in the physical appearance, drug content, or dissolution behavior of the tablets during the storage period. These findings demonstrate that the optimized formulation maintained its integrity and performance under accelerated storage conditions. Therefore, the developed Ranolazine extended-release matrix tablet can be considered physically and chemically stable under the tested conditions.

5. Conclusion

The present study successfully developed an extended-release matrix tablet of Ranolazine using Eudragit® L100-55 as a pH-dependent release-retarding polymer. The formulated tablets exhibited satisfactory pre-compression and post-compression characteristics and complied with pharmacopeial quality requirements. Drug–excipient compatibility studies confirmed the absence of significant interactions between Ranolazine and the selected excipients.

The concentration of Eudragit® L100-55 and sodium hydroxide significantly influenced the drug release profile. Among the investigated formulations, formulation F14 demonstrated the most desirable release characteristics and closely matched the dissolution profile of the marketed reference product. Drug release followed the Higuchi kinetic model and exhibited a non-Fickian diffusion mechanism, indicating the combined contribution of diffusion and polymer relaxation to the release process.

The optimized formulation achieved controlled drug release over 24 h and demonstrated dissolution profile equivalence with the innovator product (f_2 = 85.95, f_1 = 2.29). These findings suggest that Eudragit® L100-55 is an effective polymer for the development of once-daily extended-release Ranolazine tablets and may serve as a suitable alternative to commercially available formulations for the management of chronic stable angina.

6. Declarations

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Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Ethical Approval

This study did not involve human participants, human tissues, animals, or clinical investigations. Therefore, ethical approval was not required.

Informed Consent

Not applicable.

Data Availability Statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

ERADATH REVATHI: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Writing – Original Draft Preparation

MS.A. Suneetha Devi: Writing – Review and Editing, Supervision

All authors have read and approved the final manuscript.

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