FORMULATION DEVELOPMENT AND EVALUATION OF PROLONGED RELEASE TABLETS OF RUFINAMIDE FOR SUSTAINED ANTIEPILEPTIC THERAPY

Eshita Srivastva, Saurabh Parmar

Rishi Ram Naresh College of Pharmacy

Abstract

The present study aimed to formulate and evaluate prolonged-release tablets of Rufinamide to achieve sustained antiepileptic therapy and improve patient compliance by reducing dosing frequency. Rufinamide, used in Lennox–Gastaut syndrome, was selected due to its short half-life and need for controlled plasma levels. Matrix tablets were prepared using Hydroxypropyl Methylcellulose (HPMC K100M) along with microcrystalline cellulose, magnesium stearate, and talc by direct compression across ten formulations (F1–F10). Preformulation studies confirmed its crystalline nature, melting point of 201 ± 1°C, poor aqueous solubility, and moderate lipophilicity (partition coefficient 1.5 ± 0.05). Powder blends showed good flow and compressibility suitable for direct compression. Post-compression evaluation revealed acceptable hardness, low friability, uniform weight variation, and drug content within pharmacopeial limits (98.5 ± 0.8% to 100.2 ± 0.4%). In vitro studies demonstrated sustained drug release over 12 hours, with formulation F7 identified as optimized, showing 80 ± 0.9% release compared to marketed product (78 ± 0.9%). Stability studies as per ICH guidelines confirmed no significant changes under accelerated and long-term conditions. Overall, the developed HPMC K100M-based matrix tablets successfully provided sustained release of Rufinamide with potential to enhance therapeutic efficacy and patient compliance.

Keywords: *Rufinamide, prolonged-release tablets, sustained release, HPMC K100M, matrix tablets, direct compression*

Corresponding Author

Eshita Srivastva

Received: 07/05/2026
Revised: 24/05/2026
Accepted: 06/06/2026
DOI: http://doi.org/10.66204/GJPSR-966-2026-2-6-7

How to Cite

Srivastva E, Parmar S. Formulation development and evaluation of prolonged release tablets of rufinamide for sustained antiepileptic therapy. Global Journal of Pharmaceutical and Scientific Research. 2026, ISSN: 3108-0103. 2026;2(6):966-972. ISSN: 3108-0103. http://doi.org/10.66204/GJPSR-966-2026-2-6-7

1. Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures due to abnormal, excessive, and synchronous neuronal activity in the brain, significantly affecting patient quality of life and requiring long-term pharmacological therapy (Katzung, 2021; Rang et al., 2019). Despite the availability of several antiepileptic drugs (AEDs), complete seizure control remains difficult due to variability in drug pharmacokinetics, adverse effects at higher doses, and poor patient adherence associated with frequent dosing regimens (Brunton et al., 2022; Goodman & Gilman, 2023).

Rufinamide is a triazole derivative antiepileptic drug approved for the management of Lennox-Gastaut syndrome, a severe and treatment-resistant form of epilepsy characterized by multiple seizure types and cognitive impairment (FDA, 2020; EMA, 2019). It acts primarily by modulating voltage-gated sodium channels and stabilizing their inactive state, thereby reducing neuronal excitability and seizure propagation (Rogawski & Loscher, 2004). However, Rufinamide has a relatively short elimination half-life and requires multiple daily dosing to maintain therapeutic plasma levels, which may lead to fluctuations in drug concentration and reduced patient compliance (Goodman & Gilman, 2023; Patsalos et al., 2018).

To overcome these limitations, prolonged-release drug delivery systems have been widely explored. These systems are designed to release the drug at a controlled rate, maintaining plasma concentration within the therapeutic window for an extended period, thereby minimizing peak–trough fluctuations and improving therapeutic outcomes (Aulton & Taylor, 2018; Chien, 1992). Such systems also reduce dosing frequency and enhance patient adherence, making them highly suitable for chronic conditions such as epilepsy.

Among various controlled-release approaches, hydrophilic matrix tablets are extensively used due to their simplicity, cost-effectiveness, reproducibility, and scalability in industrial manufacturing. Hydroxypropyl Methylcellulose (HPMC), particularly HPMC K100M, is a widely used hydrophilic polymer that hydrates upon contact with gastrointestinal fluids to form a gel barrier, which controls drug diffusion and matrix erosion (Colombo, 1993; Ford, 1999). The drug release behavior from such systems is influenced by polymer concentration, drug solubility, and matrix porosity.

In the present study, Rufinamide was selected as a model antiepileptic drug for the development of prolonged-release matrix tablets using HPMC K100M. The formulation was designed to achieve controlled drug release over an extended period, improve dosing convenience, and enhance therapeutic efficacy. Systematic preformulation, formulation, and

evaluation studies were conducted to ensure the development of a stable, effective, and reproducible prolonged-release dosage form suitable for chronic epilepsy management.

2. Methodology

2.1Selection of Drug and Excipients

2.1.1 Selection of Antiepileptic Drug

Rufinamide was selected as the model antiepileptic drug for the development of prolonged-release tablets. It is a triazole derivative used in treating seizure disorders, particularly Lennox-Gastaut syndrome, and works by modulating voltage-gated sodium channels to reduce neuronal excitability. Due to its short half-life and need for sustained plasma levels, it is suitable for prolonged-release formulation, which helps maintain steady drug levels, reduce dosing frequency, and improve patient compliance.

2.1.2 Selection of Polymers

Polymers are essential for controlling drug release in prolonged-release matrix tablets. In this study, Hydroxypropyl Methylcellulose (HPMC K100M) was used as the main matrix-forming polymer due to its strong swelling, gel-forming ability, and biocompatibility. On contact with gastrointestinal fluids, it forms a gel layer around the tablet that regulates drug diffusion and sustains release. The gel thickness depends on polymer concentration, which directly influences the release profile. Suitable amounts of HPMC K100M were used to achieve the desired sustained release of Rufinamide.

2.1.3 Selection of Excipients

Excipients are essential for achieving good processing and tablet properties. In this study, microcrystalline cellulose was used as a diluent due to its excellent compressibility and flow improvement, contributing to tablet strength. Magnesium stearate acted as a lubricant to reduce friction during compression and ensure smooth tablet ejection, while talc improved flow as a glidant. The proper selection and combination of these excipients ensured uniform blending, efficient compression, and tablets with good physical properties and controlled release behavior.

2.2 Preformulation Studies

2.2.1 Organoleptic Evaluation

Color

Prior to formulation development, an organoleptic evaluation of Rufinamide was performed to assess its basic physical characteristics. The drug’s appearance was visually examined under daylight by placing a small amount on a clean glass slide to check for any discoloration or impurities. Rufinamide was observed as a white to slightly off-white crystalline powder,

consistent with its reported description. The absence of any abnormal color or visible impurities confirmed the purity of the sample and its suitability for further preformulation and formulation studies.

Odor

As part of the organoleptic characterization, the odor of Rufinamide was evaluated to detect any characteristic smell and to identify possible contamination or degradation. A small quantity of the drug was placed on a clean watch glass and gently examined by wafting the vapors toward the nose under standard laboratory conditions. The sample was found to be odorless, confirming the absence of any abnormal or strong smell. This result is consistent with the reported properties of Rufinamide and indicates that the drug is suitable for further formulation development.

Appearance

As part of the organoleptic study, the appearance of Rufinamide was evaluated to determine its visual characteristics and physical nature. A small quantity of the drug was placed on a clean glass slide and examined under daylight. Rufinamide was observed as a fine, uniformly textured crystalline powder with no visible foreign particles, agglomeration, or contamination. These findings were consistent with its reported properties and confirmed the suitability of the drug for further preformulation and formulation studies.

Texture

As part of the organoleptic characterization, the texture of Rufinamide was evaluated to assess its physical powder properties. A small amount of the drug was gently rubbed between the fingertips to examine its tactile characteristics. The sample exhibited a fine, smooth, and powdery texture, indicating uniform particle properties. No lumps or coarse particles were observed. This consistent texture suggests good handling characteristics and confirms the suitability of Rufinamide for further formulation development.

2.2.2 Melting Point Determination

As part of the preformulation study, the melting point of Rufinamide was determined to assess its purity and identity. A small amount of the powdered drug was placed in a capillary tube and heated in a melting point apparatus under controlled conditions. The onset and completion of melting were recorded and compared with the reported literature value. A sharp melting range close to the standard confirmed good purity and suitability of the drug for further formulation studies.

2.2.3 Solubility Studies

The solubility of Rufinamide was evaluated during preformulation studies to understand its dissolution behavior in different solvents. An excess amount of drug was added separately to distilled water, methanol, ethanol, and phosphate buffer (pH 6.8) in clean test tubes and shaken thoroughly, then allowed to stand at room temperature to reach equilibrium. The samples were then visually examined for undissolved particles to determine solubility behavior. The results provided important information about the drug's solubility profile, which is useful for selecting an appropriate dissolution medium and guiding further formulation development.

2.2.4 Partition coefficient

The partition coefficient of Rufinamide was determined using the n-octanol–water system to evaluate its lipophilicity and distribution behavior. Equal volumes of n-octanol and distilled water were taken in a separating funnel and allowed to form two distinct layers. A known amount of Rufinamide was added and shaken thoroughly to allow partitioning between the phases, followed by complete phase separation. The aqueous phase concentration was measured using UV–Visible spectrophotometry, and the partition coefficient was calculated as the ratio of drug concentration in the organic phase to the aqueous phase. The result provided useful information on its lipophilicity and suitability for oral drug delivery.

2.3 Flow Properties of Powder Blend

2.3.1 Bulk density

Bulk density is a key pre-compression parameter used to evaluate the flow and packing behavior of the Rufinamide powder blend. It is defined as the ratio of the mass of powder to its bulk volume, including interparticle spaces. For its determination, a known quantity of powder was gently transferred into a calibrated measuring cylinder without any compaction, and the occupied volume was recorded. Bulk density was then calculated using the formula:

Bulk Density = Weight of Powder / Bulk Volume

This value helps assess the powder's flow properties and suitability for uniform die filling during tablet compression.

2.3.2 Tapped density

Tapped density is an important pre-compression parameter used to evaluate the compressibility and packing behavior of the Rufinamide powder blend. It is defined as the ratio of the mass of powder to its volume after mechanical tapping, which allows particles to settle into a more compact form. For its determination, a known quantity of powder was transferred into a graduated cylinder and the initial volume was recorded. The cylinder was

then placed in a tapped density apparatus and tapped until a constant volume was obtained. The tapped density was calculated using the formula:

Tapped Density = Weight of Powder / Tapped Volume

This value provides important insight into the powder's compressibility, packing ability, and suitability for further tablet compression.

Carr's Index

Carr's Index is an important parameter used to evaluate the flowability and compressibility of the Rufinamide powder blend. It is calculated using bulk density and tapped density values, and reflects the extent of interparticle interaction and packing ability under tapping. Lower values indicate good flow properties, while higher values suggest poor flow behavior. For its determination, the previously obtained bulk and tapped density values were used, and Carr's Index was calculated using the formula:

Carr's Index (%) = [(Tapped Density – Bulk Density) / Tapped Density] × 100

This parameter provides useful insight into the powder's compressibility and suitability for tablet compression.

2.3.4 Hausner's ratio

Hausner's ratio is an important parameter used to evaluate the flow properties and cohesiveness of the Rufinamide powder blend. It is calculated using bulk density and tapped density values and provides an indication of interparticle friction within the powder. Lower values suggest good flowability, while higher values indicate poor flow characteristics. For its determination, the previously measured bulk and tapped densities were used, and Hausner's ratio was calculated using the formula:

Hausner's Ratio = Tapped Density / Bulk Density

This parameter provides useful insight into the powder's flow behavior and suitability for tablet compression.

2.3.5 Angle of repose

The angle of repose is an important parameter used to evaluate the flow properties of the Rufinamide powder blend. It is defined as the maximum angle formed between the surface of a powder heap and the horizontal plane, indicating the extent of interparticle friction. Lower values suggest good flowability, while higher values indicate poor flow behavior. For its determination, the powder was allowed to flow through a funnel fixed at a suitable height to form a conical heap. The height (h) and radius (r) of the heap were measured, and the angle of repose was calculated using the formula:

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

This parameter provides important insight into the powder's flow behavior and suitability for tablet compression.

2.4 Formulation Development of Prolonged Release Tablets

2.4.1 Selection of Polymers

Polymers play a key role in controlling drug release from prolonged-release matrix tablets. In this study, Hydroxypropyl Methylcellulose (HPMC K100M) was selected as the hydrophilic matrix-forming polymer for Rufinamide prolonged-release tablets due to its excellent swelling, gel-forming ability, and biocompatibility. Upon contact with gastrointestinal fluids, HPMC hydrates and forms a gel layer around the tablet, which regulates drug diffusion and ensures sustained release over an extended period. The thickness of this gel barrier and the drug release rate depend on the polymer concentration and viscosity grade. Appropriate amounts of HPMC K100M were incorporated to achieve the desired prolonged-release profile of Rufinamide and maintain therapeutic drug levels.

2.4.2 Preparation of Prolonged Release Tablets

The Rufinamide prolonged-release tablets were prepared using the direct compression method, a simple and cost-effective technique suitable for sustained-release formulations. This method was selected because Rufinamide is stable and the excipients, particularly HPMC K100M, possess good compressibility and flow properties required for direct compression. Accurately weighed quantities of Rufinamide, HPMC K100M, microcrystalline cellulose, magnesium stearate, and talc were used. All ingredients were passed through a #40 mesh to ensure uniform particle size and then blended uniformly using geometric dilution. Magnesium stearate and talc were added as lubricant and glidant, respectively, followed by gentle mixing. The final blend was compressed into tablets using a rotary tablet compression machine under optimized conditions, producing tablets with uniform drug distribution, good mechanical strength, and controlled release characteristics.

Table 1: Formulation Composition of Prolonged Release Rufinamide Tablets

Batch No.	Rufinamide (mg)	HPMC K100M (mg)	Microcrystalline Cellulose (MCC) (mg)	Magnesium Stearate (mg)	Talc (mg)	Total Weight (mg)
F1	200	50	140	5	5	400
F2	200	60	135	5	5	405

F3	200	70	130	5	5	410
F4	200	80	125	5	5	415
F5	200	90	120	5	5	420
F6	200	100	115	5	5	425
F7	200	110	110	5	5	430
F8	200	120	105	5	5	435
F9	200	130	100	5	5	440
F10	200	140	95	5	5	445

2.5 Evaluation of Prolonged Release Tablets

2.5.1 Post-Compression Parameters

Hardness

Hardness (crushing strength) is an important mechanical property of tablets that indicates their ability to withstand physical stress during handling, packaging, and transportation. It also influences drug release, as excessively hard tablets may retard dissolution while overly soft tablets may break easily. To determine hardness, six tablets from each batch were randomly selected and tested using a Pfizer tablet hardness tester. Each tablet was placed between the jaws of the instrument, and the force required to break it was recorded in kg/cm². The mean hardness and standard deviation were then calculated. This evaluation provides important information about the mechanical strength and suitability of the tablets for further handling and performance.

Friability

Friability is a key quality control parameter used to evaluate the ability of tablets to resist abrasion, chipping, and breakage during handling, packaging, and transportation. It reflects the mechanical strength and durability of the formulation. For its determination, ten tablets from each batch were weighed to obtain the initial weight (W_1) and then placed in a Roche friabilator, which was rotated at 25 rpm for 4 minutes (100 revolutions). After the test, tablets

were dedusted and reweighed to obtain the final weight (W_2). Friability was calculated using the formula:

$$\textbf{Friability (\%)} = [(W_1 - W_2) / W_1] \times 100$$

A friability value of less than 1% is considered acceptable, indicating that the tablets possess adequate mechanical strength for handling and distribution.

Weight variation

Weight variation is a key quality control test used to ensure uniformity in tablet weight within a batch, which indirectly confirms dose consistency and proper blending of the formulation. It is particularly important for low-dose drugs where uniform distribution is critical for therapeutic efficacy. For this test, twenty tablets from each batch were randomly selected and individually weighed using a digital analytical balance to determine the average weight. Each tablet weight was then compared with the average, and percentage deviation was calculated using the formula:

$$\textbf{Percentage Deviation} = [(\text{Individual Tablet Weight} - \text{Average Weight}) / \text{Average Weight}] \times 100$$

The results provide important information regarding uniformity of dosing, and tablets within pharmacopeial limits are considered acceptable for consistent drug delivery.

Thickness

Tablet thickness is an important physical parameter that reflects the uniformity, appearance, and packaging suitability of the dosage form. It also indicates consistency in compression force during tablet manufacturing. For its determination, ten tablets from each batch were randomly selected and their thickness was measured using a vernier caliper. The mean thickness and standard deviation were then calculated. This evaluation provides information about compression uniformity and dimensional consistency, ensuring proper handling, packaging, and reproducible drug release characteristics of the prolonged-release tablets.

Drug content uniformity

Drug content uniformity is a key quality control parameter used to ensure that each Rufinamide tablet contains the intended dose, providing consistent therapeutic efficacy and safety. It also confirms uniform drug distribution within the polymer matrix, which is

essential for controlled release performance. For this test, ten tablets from each batch were selected, weighed, and powdered. A quantity equivalent to the label claim was dissolved in phosphate buffer (pH 6.8), sonicated for complete dissolution, and filtered. The drug concentration was then analyzed using a UV-visible spectrophotometer, and the mean content with standard deviation was calculated. This confirms uniform drug distribution in the prolonged-release tablets.

2.6 In-Vitro Drug Release Study

In vitro drug release studies were performed to evaluate the release profile of Rufinamide from prolonged-release tablets and predict their in vivo performance. The study used a USP Type II (paddle) dissolution apparatus under controlled conditions. Phosphate buffer (pH 6.8, 900 mL) maintained at 37 ± 0.5°C was used as the dissolution medium, with paddle rotation set at 50–100 rpm. One tablet was placed in each vessel, and samples were withdrawn at predetermined time intervals (1, 2, 4, 6, 8, 10, and 12 hours) with immediate replacement of fresh medium to maintain sink conditions. The samples were filtered, diluted, and analyzed using UV-visible spectrophotometry, and cumulative drug release was plotted against time.

2.7 Stability Studies as per ICH guidelines

Stability studies were conducted to evaluate the effect of environmental factors such as temperature, humidity, and light on the quality, safety, and efficacy of Rufinamide prolonged-release tablets. These studies help determine the shelf life, storage conditions, and long-term performance of the formulation. The optimized batch was stored in airtight, moisture-resistant containers under ICH-recommended accelerated (40 ± 2°C/75 ± 5% RH) and long-term (25 ± 2°C/60 ± 5% RH) conditions. Samples were analyzed at 0, 15, 30, 45, and 60 days for physical appearance, hardness, friability, weight variation, drug content, and in vitro drug release, and any changes were recorded to assess stability and performance over time.

3. Results

3.1 Preformulation Studies

3.1.1 Organoleptic Evaluation

Rufinamide was evaluated for its organoleptic properties prior to formulation development. It appeared as a white to slightly off-white, fine crystalline powder with no odor, indicating purity and absence of degradation. The sample showed a uniform, smooth, and free-flowing

texture without any visible impurities or agglomeration. Overall, the results confirmed the drug's identity, purity, and suitability for further preformulation studies.

Table 2: Organoleptic Evaluation of Rufinamide

Parameter	Observation
Color	White to slightly off-white crystalline powder
Odor	Odorless
Appearance	Fine crystalline powder with uniform texture
Texture	Fine, smooth powder

3.1.2 Melting Point Determination

Rufinamide's melting point was determined to assess its purity and identity prior to formulation development. The observed melting point was 201 ± 1°C, which closely matches the reported literature range of 200–204°C, indicating good drug authenticity and minimal degradation. The sharp and narrow melting range suggests a crystalline and homogeneous nature with negligible impurities. Overall, the results confirm that Rufinamide is pure, thermally stable, and suitable for further development of prolonged-release tablet formulations.

Table 3: Melting Point of Rufinamide

Parameter	Observed Melting Point (°C)
Rufinamide	201 ± 1

3.1.3 Solubility Studies

Rufinamide's solubility profile was evaluated to understand its dissolution behavior and suitability for formulation development. The drug showed very low solubility in aqueous media, with 0.15 ± 0.01 mg/mL in distilled water and 0.25 ± 0.02 mg/mL in phosphate buffer (pH 6.8), while it exhibited much higher solubility in organic solvents such as methanol (12.5 ± 0.5 mg/mL) and ethanol (10.8 ± 0.4 mg/mL). These results indicate its hydrophobic nature

and poor aqueous solubility. Therefore, formulation strategies such as the use of hydrophilic polymers are necessary to enhance drug release in prolonged-release tablet systems.

Table 4: Solubility of Rufinamide in Different Solvents

Solvent	Solubility (mg/mL)
Distilled Water	0.15 ± 0.01
Phosphate Buffer (pH 6.8)	0.25 ± 0.02
Methanol	12.5 ± 0.5
Ethanol	10.8 ± 0.4

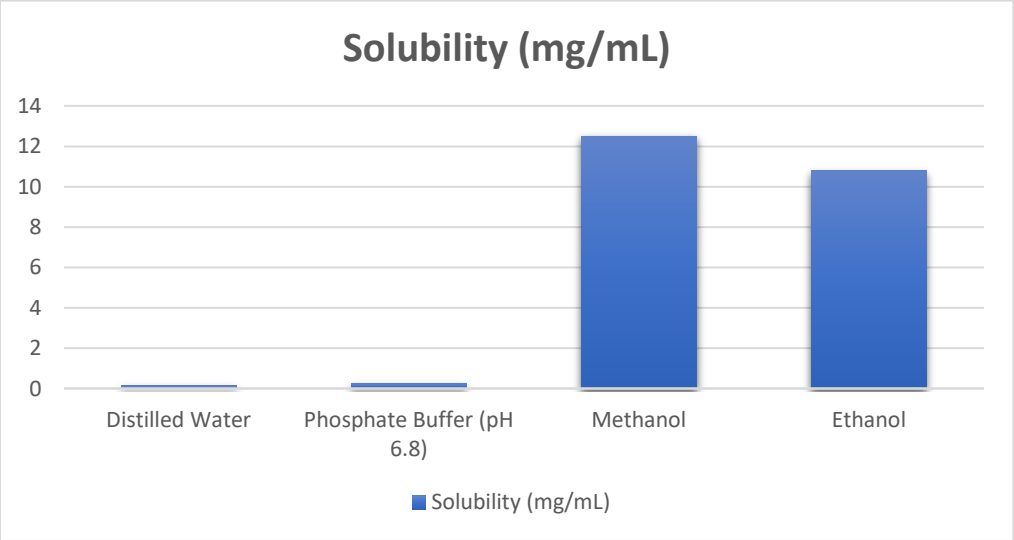

Fig 1: Solubility (mg/mL)

3.1.4 Partition coefficient

Rufinamide's partition coefficient was determined to evaluate its lipophilicity and membrane permeability. The observed value in the n-octanol/water system was 1.5 ± 0.05, indicating moderate lipophilic character. This balanced distribution behavior suggests adequate affinity for both aqueous and lipid phases, which is favorable for oral absorption and passive diffusion across biological membranes. The result also supports its suitability for prolonged-release formulation development, as moderate lipophilicity helps maintain controlled drug release while ensuring sufficient bioavailability.

Table 5: Partition Coefficient of Rufinamide

Parameter	Observed Value
Partition Coefficient (n-octanol / water)	1.5 ± 0.05

3.2 Flow Properties of Powder Blend

Bulk density

Before compression, the bulk density of Rufinamide powder blends was evaluated to assess their flow and packing behavior. The formulations showed comparable values ranging from 0.48 ± 0.01 to 0.54 ± 0.01 g/mL, indicating uniform packing characteristics across batches. A gradual increase in bulk density from F1 to F10 was observed, likely due to variations in formulation composition and polymer content. The commercial product exhibited a bulk density of 0.51 ± 0.01 g/mL, which was comparable to the prepared formulations. Overall, the results confirm acceptable packing properties, ensuring uniform die filling and consistent tablet weight during compression.

Table 6: Bulk Density of Rufinamide Powder Blends and Marketed Product

Batch No.	Bulk Density (g/mL)
F1	0.48 ± 0.01
F2	0.49 ± 0.01
F3	0.50 ± 0.01
F4	0.50 ± 0.01
F5	0.51 ± 0.01
F6	0.52 ± 0.01
F7	0.52 ± 0.01
F8	0.53 ± 0.01
F9	0.53 ± 0.01
F10	0.54 ± 0.01
Marketed Rufinamide	**0.51 ± 0.01**

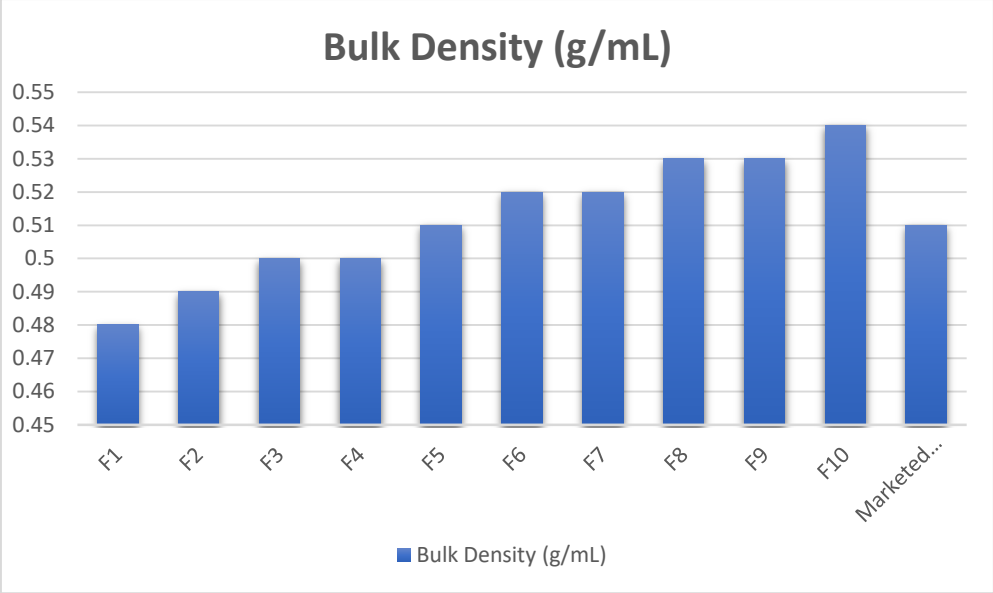

Fig 2: Bulk Density (g/mL)

Tapped density

Tapped density of Rufinamide powder blends was evaluated to assess their compressibility and packing behavior after mechanical tapping. The formulations exhibited values ranging from 0.57 ± 0.01 to 0.66 ± 0.01 g/mL, indicating good particle rearrangement and improved packing efficiency. A gradual increase in tapped density from F1 to F10 was observed, likely due to variations in polymer concentration enhancing compactness. The commercial product showed a tapped density of 0.61 ± 0.01 g/mL, comparable to the developed formulations. Overall, the results confirm good compressibility and uniform packing behavior, supporting suitability for consistent tablet compression.

Table 7: Tapped Density of Rufinamide Powder Blends and Marketed Product

Batch No. / Product	Tapped Density (g/mL)
F1	0.57 ± 0.01
F2	0.58 ± 0.01
F3	0.59 ± 0.01
F4	0.60 ± 0.01
F5	0.61 ± 0.01
F6	0.62 ± 0.01
F7	0.63 ± 0.01
F8	0.64 ± 0.01

F9	0.65 ± 0.01
F10	0.66 ± 0.01
Marketed Rufinamide	**0.61 ± 0.01**

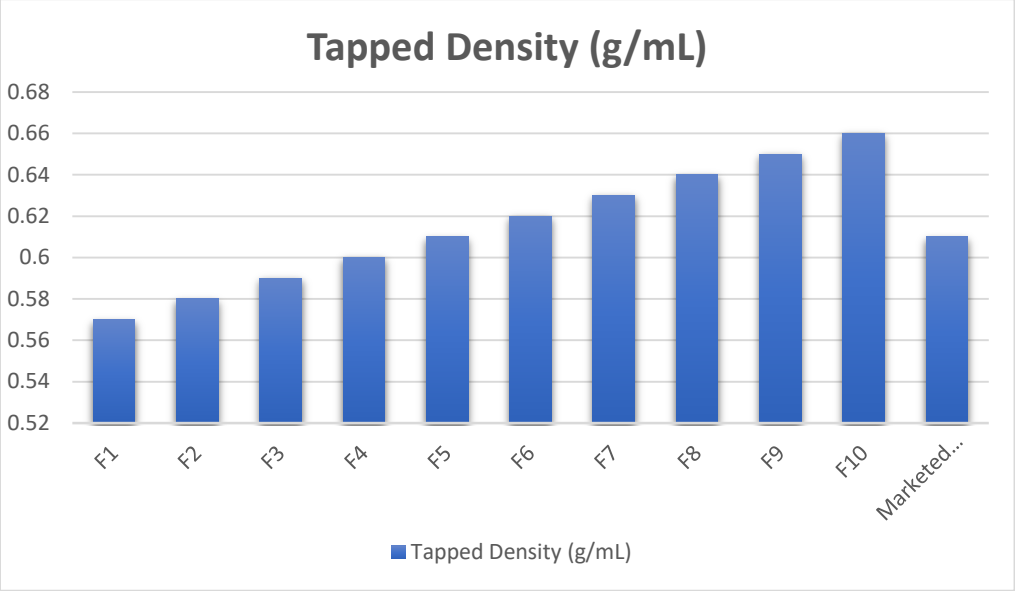

Fig 3: Tapped Density (g/mL)

Carr's Index

Carr's Index was evaluated to assess the flowability and compressibility of Rufinamide powder blends prior to tablet compression. The formulations showed values ranging from 15.3 ± 0.3% to 18.5 ± 0.5%, indicating good to acceptable flow properties suitable for processing. A slight increase in Carr's Index from F1 to F10 was observed, likely due to increased polymer concentration enhancing interparticle cohesion. The commercial product exhibited a value of 16.0 ± 0.4%, which was comparable to the developed formulations. Overall, all values being below 20% confirm satisfactory flow and compressibility, making the blends suitable for direct compression.

Table 8: Carr's Index of Rufinamide Powder Blends and Marketed Product

Batch No. / Product	Carr's Index (%)
F1	15.8 ± 0.5
F2	15.5 ± 0.4
F3	15.3 ± 0.3
F4	16.7 ± 0.4

F5	16.4 ± 0.3
F6	16.1 ± 0.4
F7	17.5 ± 0.5
F8	17.2 ± 0.4
F9	18.5 ± 0.5
F10	18.2 ± 0.4
Marketed Rufinamide	**16.0 ± 0.4**

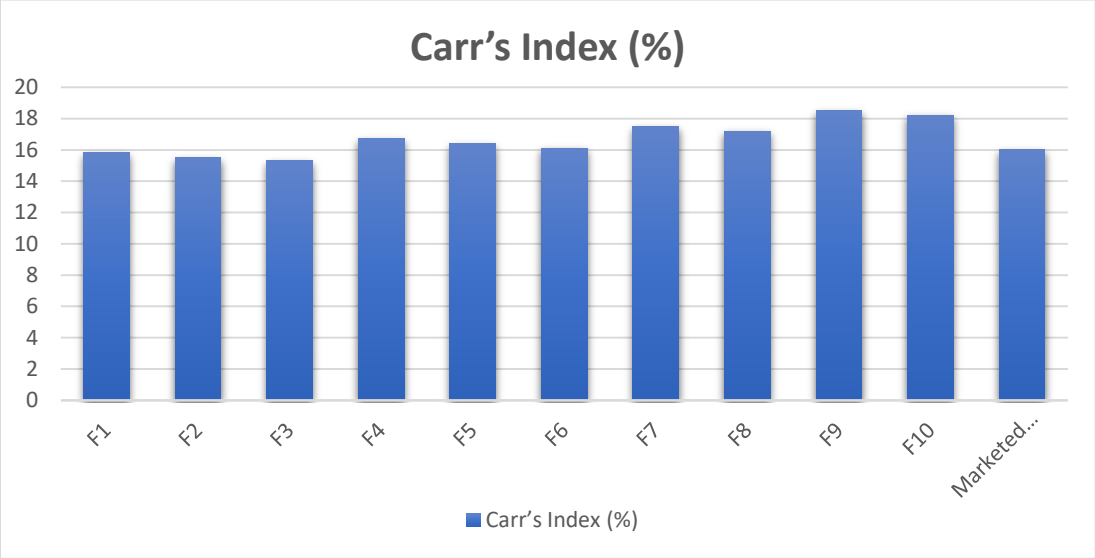

Fig 4: Carr's Index (%)

Hausner's ratio

Hausner's ratio was determined to further evaluate the flow properties of Rufinamide powder blends. The formulations exhibited values ranging from 1.18 ± 0.01 to 1.23 ± 0.01, indicating good flowability and acceptable compressibility. A slight increase from F1 to F10 was observed, which may be due to increased interparticle friction associated with higher polymer concentration. The commercial product showed a comparable value of 1.20 ± 0.01. Since all values were below 1.25, the results confirm that the powder blends possess suitable flow and packing characteristics, making them appropriate for direct compression tablet formulation.

Table 9: Hausner's Ratio of Rufinamide Powder Blends and Marketed Product

Batch No. / Product	Hausner's Ratio
F1	1.19 ± 0.01
F2	1.18 ± 0.01
F3	1.18 ± 0.01

F4	1.20 ± 0.01
F5	1.20 ± 0.01
F6	1.19 ± 0.01
F7	1.21 ± 0.01
F8	1.21 ± 0.01
F9	1.23 ± 0.01
F10	1.22 ± 0.01
Marketed Rufinamide	**1.20 ± 0.01**

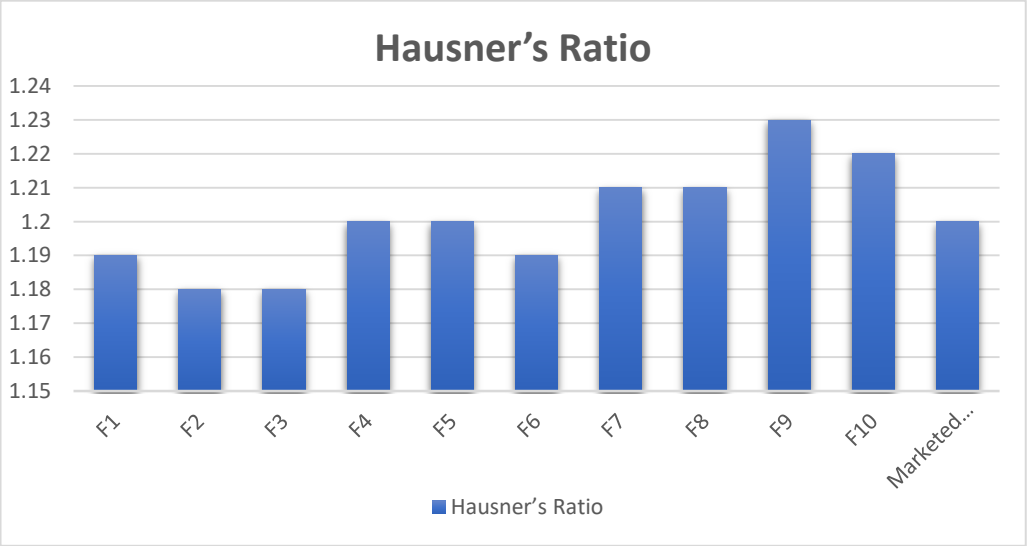

Fig 5: Hausner's Ratio

Angle of repose

The angle of repose was determined to evaluate the flow behavior of Rufinamide powder blends prior to tablet compression. The formulations exhibited values ranging from 28.0 ± 0.3° to 30.0 ± 0.3°, indicating good flow properties suitable for processing. A slight increase from F1 to F10 was observed, likely due to increased interparticle friction with higher polymer concentration. The commercial product showed a comparable value of 28.9 ± 0.3°. Since all values were within acceptable limits (<30°), the results confirm good flowability and suitability of the powder blends for direct compression.

Table 10: Angle of Repose of Rufinamide Powder Blends and Marketed Product

Batch No. / Product	Angle of Repose (°)
F1	28.5 ± 0.3

F2	28.2 ± 0.4
F3	28.0 ± 0.3
F4	29.0 ± 0.3
F5	28.8 ± 0.4
F6	28.7 ± 0.3
F7	29.2 ± 0.4
F8	29.0 ± 0.3
F9	30.0 ± 0.3
F10	29.8 ± 0.4
Marketed Rufinamide	**28.9 ± 0.3**

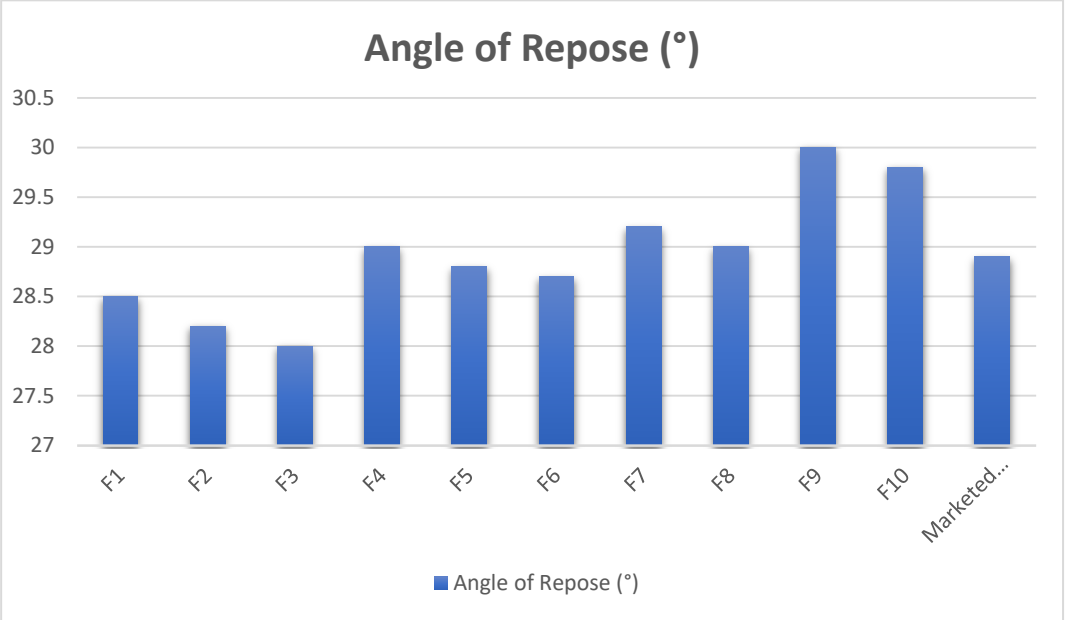

Fig 6: Angle of Repose (°)

3.3 Evaluation of Prolonged Release Tablets

3.3.1 Post-Compression Parameters

The hardness of Rufinamide prolonged-release tablets was evaluated to assess their mechanical strength and resistance to handling and transportation. The formulations showed hardness values ranging from 4.5 ± 0.2 to 5.7 ± 0.2 kg/cm², indicating adequate tablet strength. A gradual increase in hardness from F1 to F10 was observed, likely due to higher polymer content improving interparticle bonding during compression. The commercial product showed a hardness of 5.1 ± 0.2 kg/cm², comparable to the developed formulations.

Overall, all batches demonstrated sufficient mechanical integrity for handling, packaging, and sustained release performance.

Table 11: Hardness of Rufinamide Prolonged Release Tablets

Batch No. / Product	Hardness (kg/cm²)
F1	4.5 ± 0.2
F2	4.7 ± 0.2
F3	4.8 ± 0.3
F4	5.0 ± 0.2
F5	5.2 ± 0.2
F6	5.3 ± 0.3
F7	5.4 ± 0.2
F8	5.5 ± 0.2
F9	5.6 ± 0.3
F10	5.7 ± 0.2
Marketed Rufinamide	**5.1 ± 0.2**

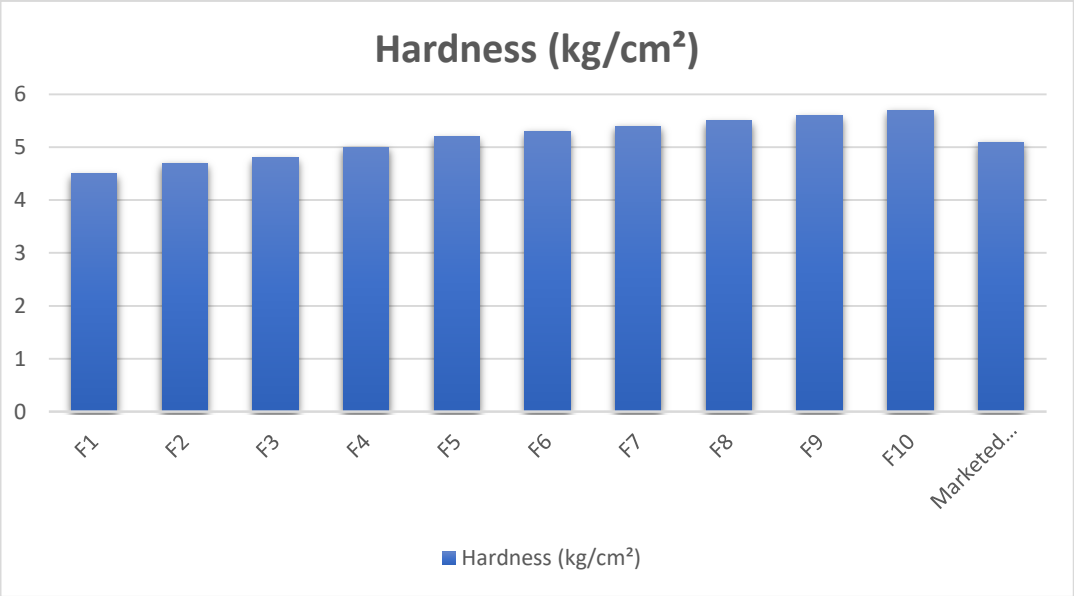

Fig 7: Hardness

3.3.2 Friability

Friability was evaluated to assess the mechanical strength and resistance of Rufinamide prolonged-release tablets to abrasion during handling and transport. The formulations showed low friability values ranging from 0.31 ± 0.02% to 0.45 ± 0.02%, well within the acceptable limit of <1%, indicating good tablet integrity. A slight decrease in friability from F1 to F10

was observed, likely due to increased polymer content enhancing interparticle bonding. The commercial product showed a comparable value of 0.37 ± 0.02%. Overall, the results confirm that all formulations possess adequate mechanical strength and durability.

Table 12: Friability of Rufinamide Prolonged Release Tablets

Batch No. / Product	Friability (%)
F1	0.45 ± 0.02
F2	0.42 ± 0.03
F3	0.40 ± 0.02
F4	0.38 ± 0.03
F5	0.36 ± 0.02
F6	0.35 ± 0.02
F7	0.34 ± 0.03
F8	0.33 ± 0.02
F9	0.32 ± 0.03
F10	0.31 ± 0.02
Marketed Rufinamide	**0.37 ± 0.02**

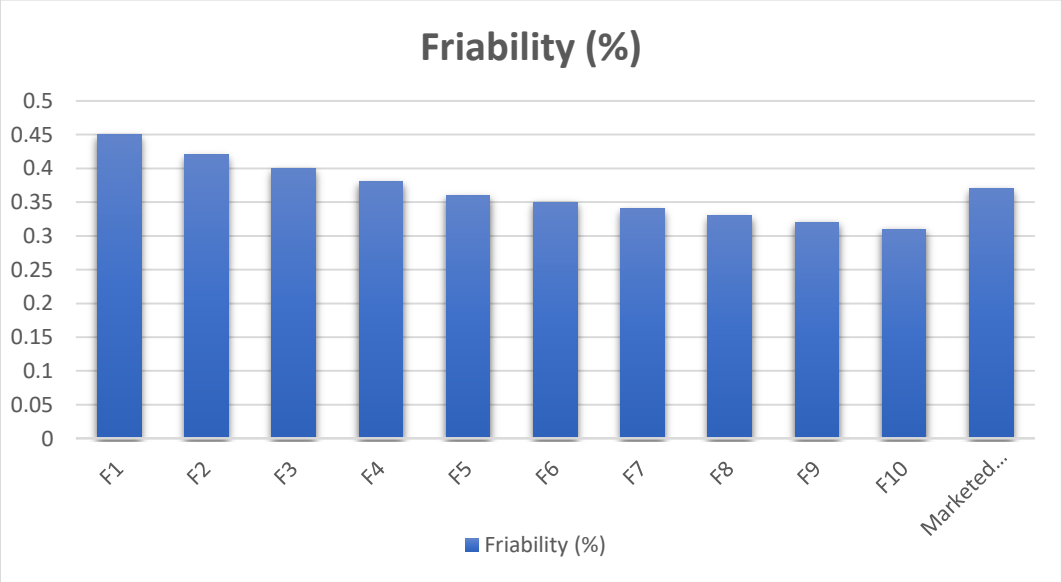

Fig 8: Friability (%)

3.3.3 Weight variation

Weight variation was evaluated to ensure uniformity in tablet weight and drug content of Rufinamide prolonged-release formulations. The average tablet weight ranged from 250 ± 2.5 mg to 259 ± 3.1 mg, with percentage variation between ±1.0% and ±1.2%, which is within

pharmacopeial limits. These results indicate uniform die filling and proper powder blending during compression. The commercial product showed a comparable average weight of 254 ± 2.5 mg with ±1.0% variation. Overall, the findings confirm good weight uniformity across all batches, ensuring consistent dosing and reliable therapeutic performance.

Table 13: Weight variation of Rufinamide Prolonged Release Tablets

Batch No. / Product	Average Weight (mg)	% Deviation
F1	250 ± 2.5	±1.0
F2	252 ± 2.8	±1.1
F3	251 ± 3.0	±1.2
F4	253 ± 2.7	±1.1
F5	254 ± 3.0	±1.2
F6	255 ± 2.9	±1.1
F7	256 ± 3.0	±1.2
F8	257 ± 2.8	±1.1
F9	258 ± 3.0	±1.2
F10	259 ± 3.1	±1.2
Marketed Rufinamide	**254 ± 2.5**	**±1.0**

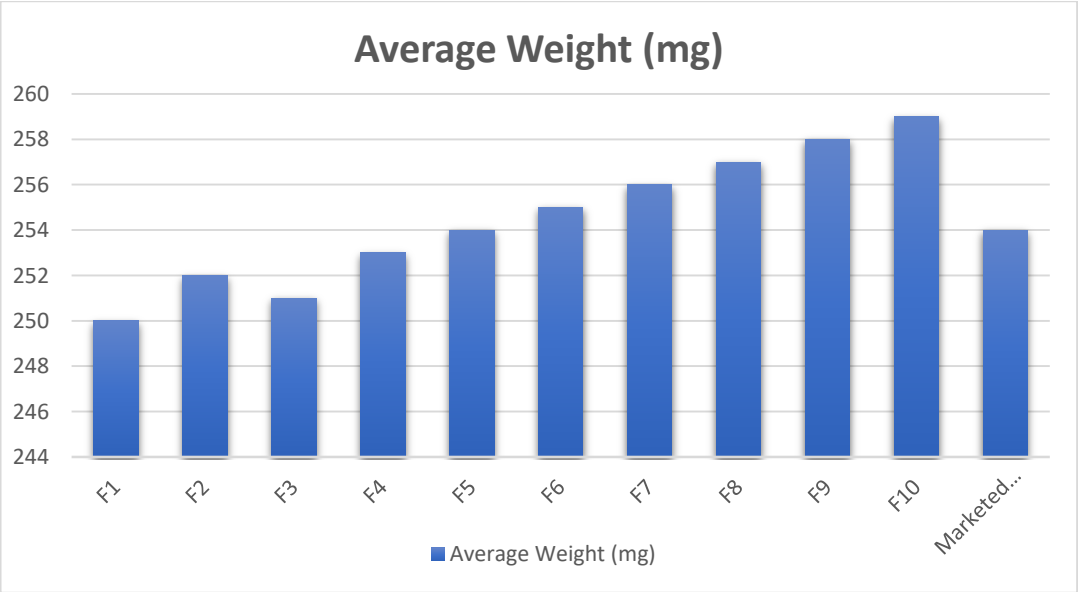

Fig 9: Average Weight (mg)

3.3.4 Thickness

Tablet thickness was evaluated to assess dimensional uniformity and compression consistency of Rufinamide prolonged-release formulations. The formulations showed thickness values ranging from 3.8 ± 0.1 mm to 4.6 ± 0.1 mm, indicating consistent tablet dimensions across batches. A slight increase from F1 to F10 was observed, likely due to variations in polymer concentration affecting tablet compactness. The commercial product showed a comparable thickness of 4.2 ± 0.1 mm. Overall, the results confirm uniform compression and suitability for handling, packaging, and further evaluation.

Table 14: Thickness of Rufinamide Prolonged Release Tablets

Batch No. / Product	Thickness (mm)
F1	3.8 ± 0.1
F2	3.9 ± 0.1
F3	4.0 ± 0.1
F4	4.1 ± 0.1
F5	4.2 ± 0.1
F6	4.3 ± 0.1
F7	4.3 ± 0.1
F8	4.4 ± 0.1
F9	4.5 ± 0.1
F10	4.6 ± 0.1
Marketed Rufinamide	**4.2 ± 0.1**

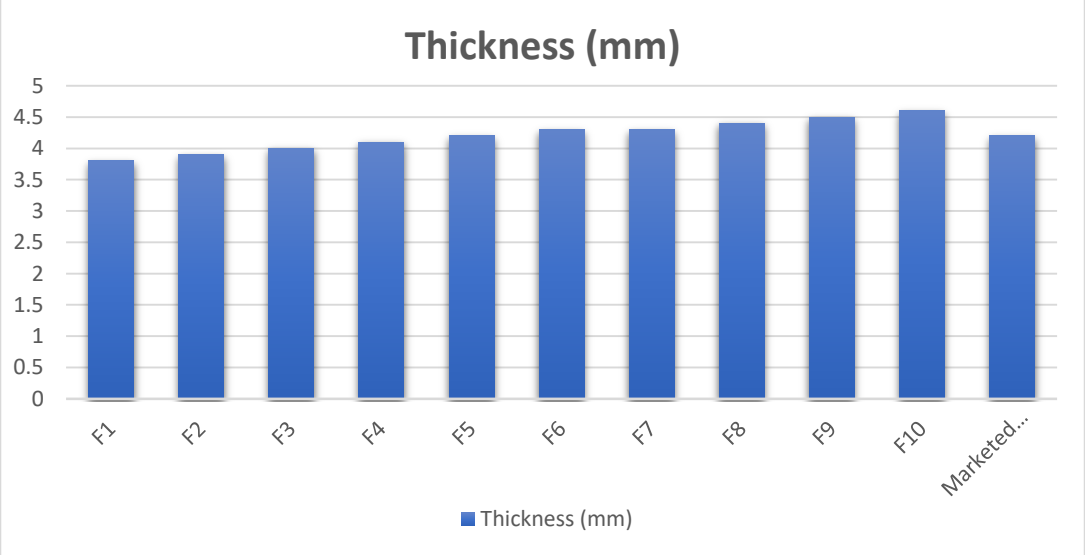

Fig 10: Thickness (mm)

3.4 Drug content uniformity

Drug content uniformity was evaluated to ensure even distribution of Rufinamide within the prolonged-release tablets. The formulations showed drug content ranging from 98.5 ± 0.8% to 100.2 ± 0.4%, which is within the acceptable pharmacopeial limits (98–102%). A slight increase from F1 to F10 indicated uniform mixing and proper drug dispersion within the polymer matrix. The commercial product showed a comparable value of 99.6 ± 0.5%. Overall, the results confirm excellent content uniformity across all batches, ensuring consistent dosing and reliable therapeutic performance.

Table 15: Drug Content Uniformity of Rufinamide Prolonged Release Tablets

Batch No. / Product	Drug Content (%)
F1	98.5 ± 0.8
F2	98.9 ± 0.7
F3	99.2 ± 0.6
F4	99.5 ± 0.7
F5	99.7 ± 0.6
F6	99.8 ± 0.5
F7	100.0 ± 0.5
F8	99.9 ± 0.5
F9	100.2 ± 0.4
F10	100.1 ± 0.5
Marketed Rufinamide	99.6 ± 0.5

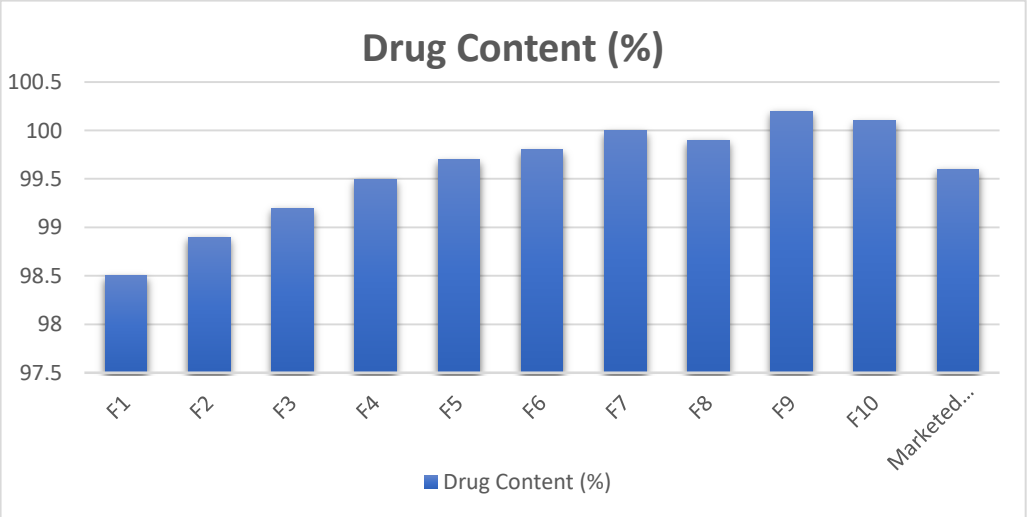

Fig 11: Drug Content (%)

3.5 In-Vitro Drug Release Study

The in-vitro drug release study of Rufinamide prolonged-release tablets was performed over 12 hours to evaluate their release behavior. All formulations showed a controlled and sustained release profile. Faster release was observed in F1–F3, with F1 reaching up to 96 ± 1.1% at 12 hours. In contrast, higher polymer-containing formulations (F4–F10) exhibited more sustained release. The optimized formulation F7 showed 80 ± 0.9% release, while the commercial product showed 78 ± 0.9%. Overall, F6–F8 demonstrated the most desirable controlled release behavior, confirming effective sustained delivery for antiepileptic therapy.

Table 16: In-Vitro Drug Release Profile of Rufinamide Prolonged Release Tablets

Time (h)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)	F10 (%)	Marketed Rufinamide (%)
1	12 ± 0.5	11 ± 0.4	10 ± 0.5	9 ± 0.4	8 ± 0.3	8 ± 0.4	7 ± 0.3	6 ± 0.3	5 ± 0.3	5 ± 0.2	7 ± 0.3
2	22 ± 0.6	20 ± 0.5	19 ± 0.6	18 ± 0.5	17 ± 0.4	16 ± 0.5	15 ± 0.4	14 ± 0.4	13 ± 0.4	12 ± 0.3	15 ± 0.4
4	38 ± 0.7	35 ± 0.6	33 ± 0.7	32 ± 0.6	30 ± 0.5	28 ± 0.6	27 ± 0.5	25 ± 0.5	24 ± 0.5	22 ± 0.4	27 ± 0.5
6	52 ± 0.8	50 ± 0.7	48 ± 0.8	46 ± 0.7	44 ± 0.6	42 ± 0.7	40 ± 0.6	38 ± 0.6	36 ± 0.6	34 ± 0.5	41 ± 0.6
8	68 ± 0.9	65 ± 0.8	63 ± 0.9	60 ± 0.8	58 ± 0.7	55 ± 0.8	53 ± 0.7	50 ± 0.7	48 ± 0.7	45 ± 0.6	54 ± 0.7
10	82 ± 1.0	78 ± 0.9	75 ± 1.0	72 ± 0.9	70 ± 0.8	67 ± 0.9	65 ± 0.8	62 ± 0.8	60 ± 0.8	57 ± 0.7	66 ± 0.8
12	96 ± 1.1	92 ± 1.0	90 ± 1.1	88 ± 1.0	85 ± 0.9	83 ± 1.0	80 ± 0.9	78 ± 0.9	75 ± 0.9	72 ± 0.8	78 ± 0.9

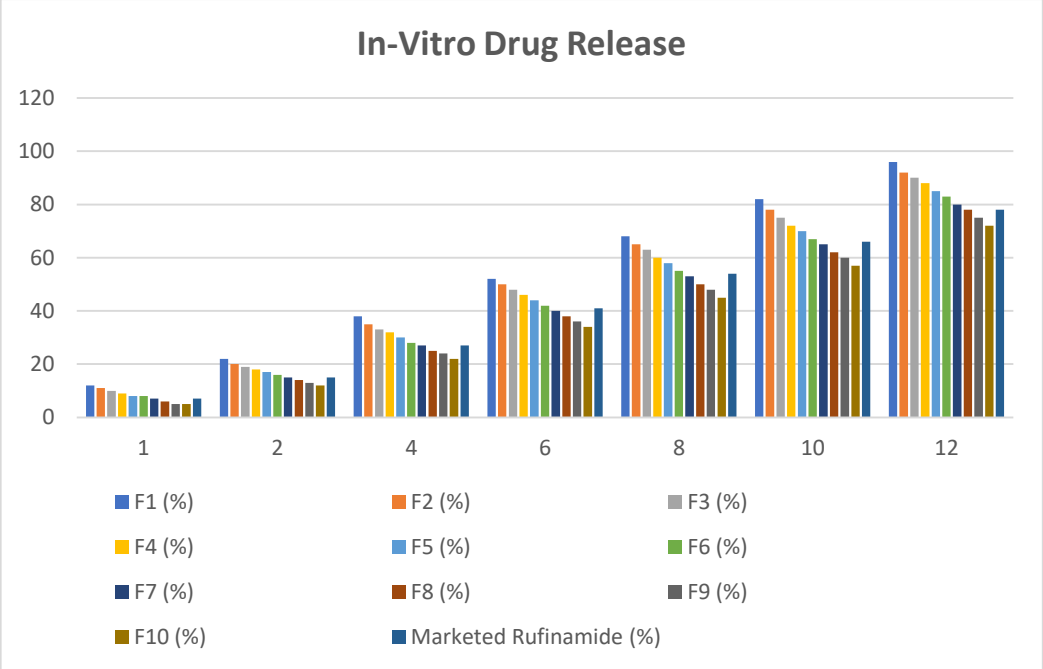

Fig 12: In-Vitro Drug Release

3.6 Stability Studies as per ICH guidelines

A stability study of the optimized Rufinamide prolonged-release formulation (F7) was performed according to ICH guidelines under both room temperature and accelerated conditions. No significant changes in physical appearance were observed, except for slight dullness under accelerated storage. Hardness showed a minor decrease from 5.4 ± 0.2 to 5.1 ± 0.2 kg/cm², while friability remained below 1%, indicating good mechanical integrity. Weight variation remained consistent, confirming batch uniformity. Drug content decreased slightly from 100.0 ± 0.5% to 99.3 ± 0.5%, and in vitro drug release at 12 hours reduced from 80 ± 0.9% to 75 ± 0.8% under accelerated conditions. Overall, the formulation showed good stability with acceptable physicochemical and release properties.

Table 17: Stability Study of Optimized Rufinamide Prolonged Release Tablets (F7)

Parameter	**Initial**	**15 Days (RT)**	**30 Days (RT)**	**45 Days (RT)**	**60 Days (RT)**	**15 Days (Accelerated)**	**30 Days (Accelerated)**	**45 Days (Accelerated)**	**60 Days (Accelerated)**
Appearance	White, smooth	No change	No change	No change	No change	No change	Slight dullness	Slight dullness	No significant change
Hardness (kg/cm²)	5.4 ± 0.2	5.4 ± 0.2	5.3 ± 0.2	5.3 ± 0.2	5.2 ± 0.2	5.3 ± 0.2	5.2 ± 0.2	5.2 ± 0.2	5.1 ± 0.2

Friability (%)	0.34 ± 0.03	0.34 ± 0.03	0.35 ± 0.03	0.35 ± 0.03	0.36 ± 0.03	0.35 ± 0.03	0.36 ± 0.03	0.37 ± 0.03	0.38 ± 0.03
Weight Variation (mg)	256 ± 3	256 ± 3	255 ± 3	255 ± 3	254 ± 3	255 ± 3	254 ± 3	254 ± 3	253 ± 3
Drug Content (%)	100.0 ± 0.5	99.8 ± 0.5	99.7 ± 0.5	99.6 ± 0.5	99.5 ± 0.5	99.6 ± 0.5	99.5 ± 0.5	99.4 ± 0.5	99.3 ± 0.5
% Drug Release (12 h)	80 ± 0.9	79 ± 0.9	78 ± 0.9	78 ± 0.8	77 ± 0.8	78 ± 0.9	77 ± 0.9	76 ± 0.8	75 ± 0.8

4. Conclusion

The present study successfully developed and evaluated prolonged-release matrix tablets of Rufinamide using Hydroxypropyl Methylcellulose (HPMC K100M) as the rate-controlling polymer. The formulations were prepared by direct compression technique and exhibited satisfactory pre- and post-compression characteristics, including good flow properties, uniform weight variation, adequate mechanical strength, low friability, and consistent drug content. In vitro dissolution studies demonstrated that the formulations were capable of sustaining drug release over 12 hours, thereby reducing the frequency of dosing. Among all formulations, F7 was identified as the optimized batch based on its desirable balance of controlled drug release and physicochemical properties. Stability studies conducted as per ICH guidelines confirmed that the optimized formulation remained stable under both accelerated and long-term conditions without significant changes in physical appearance, drug content, or release profile. Overall, the developed HPMC K100M-based prolonged-release tablets of Rufinamide can effectively maintain sustained drug levels and have the potential to improve therapeutic efficacy and patient compliance in the management of epilepsy.

5. Acknowledgement

I express my sincere gratitude to my guide for their valuable guidance and support throughout this research work. I am also thankful to the faculty members, laboratory staff, and my institution for providing necessary facilities and assistance.

6. Conflict of Interest (COI)

The author declares that there is no conflict of interest regarding the publication of this research work.

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