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REVIEW ON ANALYTICAL METHODS OF RUFINAMIDE

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ABSTRACT

Rufinamide is a drug used to treat seizures and also used in combination with other drug to treat Lennox–Gastaut syndrome. Rufinamide particularly prolongation of the inactive state limiting the sustained bursts of high-frequency action potentials and preventing sodium channels from returning to an activated state, therefore decreasing the neuronal hyperexcitability and action potential propagation. For the determination of rufinamide in pharmaceutical dosage form and bulk form, several analytical methods including HPTLC, UV and HPLC has been developed. Developed methods are stability indicating, impurity profiling human plasma are also described for rufinamide. For qualitative and quantitative estimation of rufinamide these analytical methods can be used and it can also be used for its related degradants in bulk formulations and biological fluids. The following study depicts the review on analytical methods which includes to estimate the Anti- Seizures drug.

KEYWORD:- Rufinamide, HPLC, Analytical Methods, seizures, Lennox–Gastaut syndrome.

INTRODUCTION

Epilepsy is one of the most prevalent neurological diseases worldwide, affecting nearly 1 to 2% of the population Currently, there are more than 20 antiepileptic drugs (AEDs) available for clinical use, which are usually divided into three different generations.[1] First-generation of antiepileptic drugs having presently several drawbacks such as narrow therapeutic indices, saturable metabolism, high plasma protein binding (PPB), saturable metabolism, high plasma protein binding (PPB), high potential for drug interactions, complex pharmacokinetic profiles, and may induce antiepileptic hypersensitivity syndrome.[2] Besides the improvements in their pharmacological profiles, third-generation AEDs also present some new chemical structures that allow them to act by new mechanisms of action, interact with different therapeutic targets and modulate different pathways of neuronal excitability that were not covered by first- and second generation AEDs.[3] Thus, to increase therapeutic effectiveness of drug and improve tolerability and decrease toxicity, the initiation of third-generation antiepileptic drugs as auxiliary therapy to patients already treated with other types of AEDs is frequent.[4] This include retigabine (RTG), rufinamide (RFM), stiripentol (STP) and perampanel (PER). RFM and STP are both classified as orphan drugs once their therapeutic indications are specific for treating epileptic syndromes with a very low prevalence in population.[5] Specifically, rufinamide is indicated to treat a severe, chronic, and multiple drug-resistance epileptic encephalopathy mostly characterized by the occurrence of multiple seizure types so called Lennox-Gastaut syndrome.[6] rufinamide also used in the treatment of super-refractory tonic-clonic status epilepticus and as complementary treatment of partial seizures in adults and adolescents.[7] On the other hand, stiripentol is indicated as adjunctive therapy with clobazam and valproic acid to treat Dravet syndrome not only in children, but also during adolescence and adulthood.[8]

Rufinamide is a unique anticonvulsant medication. It is also used in combination with other drug molecule to treat Lennox–Gastaut syndrome and various Anti-seizure (ASD) disorders. Rufinamide therapy is related with a low rate of transient serum enzyme elevations and with rare instances of clinically apparent liver injury.[9] it is a heteroarene and an aromatic amide. Rufinamide is a triazole derivative. Rufinamide was developed in 2004 by Novartis Pharma, AG. In the US Food and Drug Administration (FDA) it was approved on November 14, 2008 for anticonvulsant medication also to treat Lennox–Gastaut syndrome and seizure disorders.[10]

Drug profile
Structure

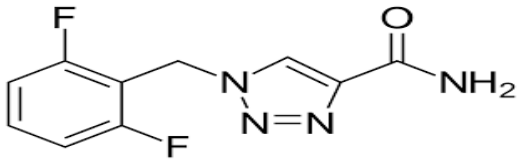

Fig. 1: Structure of rufinamide.

Molecular formula:- $C_{10}H_8F_2N_4O$
Molecular Weight:- 238.19 g/mol
IUPAC Name:- 1-[(2,6-difluorophenyl)methyl]triazole-4-carboxamide.
Brand:- Inovelon, Banzel

Dosage Forms & Strengths
I) Tablet
- 200mg
- 400mg

II) Oral suspension
- 40mg/mL

Mechanism of action: The precise mechanism of action of rufinamide exerts in antiepileptic effect is unknown. Rufinamide is a triazole derivative antiepileptic hence it modulation of activity in sodium channels that prolongs the inactive state of voltage gated sodium channels its activity in sodium channels thus stabilizing membranes, hence ultimately blocking the spread of partial seizure activity.[11] In vitro study, it modulation of activity in sodium channels, prolongation of the inactive state limiting the assist fragment of high-frequency action potentials and it preventing sodium channels from returning to an activated state, therefore decreasing the neuronal hyperexcitability and action potential propagation.[12] A study indicates subtle effects on the voltage-dependence of gating and the time course of inactivation in some sodium channel isoforms that could reduce neuronal excitability. In cultured cortical neurons from immature rats, rufinamide remarkably go slower sodium channel recovery from inactivation after a prolonged prepulse and restricted the sustained repetitive firing of sodium-dependant action potentials. Rufinamide has no effect on benzodiazepine, gamma-aminobutyric acid (GABA) receptors, or adenosine uptake and has no interactions with glutamate, adrenergic, tryptophan, histamine, and muscarinic cholinergic receptors.[13]

Absorption: Rufinamide available in solid and liquid dosage form. The solid dosage form that is oral suspension and solid dosage form tablet are bioequivalent on a mg per mg basis. In study drug well absorbed but the rate is slow hence the extent of absorption decreases as dose is increases. The extent absorption for oral administration was least 85% for a single dose of 600 mg rufinamide tablet under fed condition its based on urinary excretion.[14,15]

Bioavailability: 70%-85% (decreases with increasing doses); Tmax, fed and fasted states= 4-6 hours; Cmax, 10 mg/kg/day= 4.01 µL/mL; Cmax, 30mg/kg/day= 8.68 µL/mL; AUC (0h-12h), 10mg/kg/day= 37.8±47 µg·h/mL; AUC (0h-12h), 30mg/kg/day= 89.3±59 µg·h/mL.[12]

Volume of distribution: Rufinamide was evenly distributed in systemic circulation between erythrocytes and plasma. The observable drug volume of distribution is dependent upon dose and body surface area. The observable volume of distribution of drug was about 50 L at 3200 mg/day. In adults and children Volume of distribution is similar and is non-linear.[16]

Metabolism
Rufinamide is highly metabolized but has no active metabolites. The Metabolism by carboxyesterases by hydrolysis into inactive metabolite CGP 47292, a carboxylic acid derivative, It is the primary biotransformation pathway of metabolism.[17] Rufinamide having a few minor additional metabolites were detected in urine, which appeared to be acyl-glucuronides of CGP 47292. Rufinamide is a weak inhibitor of CYP 2E1. Rufinamide is a weak inducer of CYP 3A4 enzymes. The cytochrome P450 enzyme system or glutathiones are not elaborate with the metabolism of rufinamide.[18]

Hover over products below to view reaction partners
- Rufinamide
  - CGP-47292

Biological Half-Life
half-life, healthy subjects and patients with epilepsy = 6-10 hours.[19]

Route of elimination: The excretion of rufinamide via renally (91%; 66% as CGP 47292, 2% as unchanged drug) and fecally eliminated by (9%).[20]

Toxicity: Headache, dizziness, fatigue, somnolence, and nausea.[21]

Side effect: Sleepiness, headache, loss of coordination, difficulty walking, excessive movement or activity, uncontrollable shaking of a part of the body, uncontrollable movements of the eyes, difficulty paying attention, dizziness, loss of appetite, swelling of the face, yellowing of the skin or eyes, dark-colored urine, nausea, vomiting, back pain, stomach pain.[21]

Reported analytical methods for estimation of rufinamide
K. Harisudha et. al.: Reported A simple, reproducible and efficient high performance liquid chromatographic method was developed for determination of Rufinamide in its pure form as well as in tablet dosage form. Chromatography was performed on a Column: ODS C18 column 250X4.6 mm 5µm, Mode: Isocratic, Mobile phase: Acetonitrile: Buffer pH 4.5 (potassium

dihydrogen phosphate) (30:70 v/v). Flow rate: 1.0 ml/min, Wavelength: 210 nm. The retention time was found 3.18 Min for rufinamide. The developed method validates using System Suitability, Linearity, Accuracy, Method precision, Robustness, Limit of Quantitation (LOQ) and Limit of Detection (LOD). The System suitability Parameter for method was Theoretical plates (N) 3204 3, Tailing factor (T) 1.2. The linearity range for method was 10-60µg/ml, the co-coefficient was found 1. The accuracy was performed on 20, 40 and 60 µg/ml level, the mean Percent recovery was found 98.62, 99.99 and 99.98% respectively. For method precision percent RSD of area found 0.000342%. The LOD 1.52µg/ml and LOQ 4.39 µg/m was found for rufinamide.[22]

Gandla Kumaraswamy et. al.: Reported A simple, precise, rapid and reproducible stability indicating RP - HPLC method was developed and validated for the determination of Rufinamide in pharmaceutical dosage forms. Chromatography was performed on a Column: ODS C18 (4.6×250 mm) 5µ, Mobile phase: Acetonitrile: Triethylamine buffer pH 4.6: Methanol (70:20:10). Flow rate: 0.8 ml/min, Injection volume: 10 µl, Wavelength: 243 nm, Run time: 5 Min. The retention time was found 2.4 Min for rufinamide. The developed method validates using System Suitability, Linearity, Accuracy, Method precision, Limit of Quantitation (LOQ) and Limit of Detection (LOD). The System suitability Parameter for method was Theoretical plates (N) 5342, Tailing factor (T) 1.09. The linearity range for method was 10-50 µg/ml, the co-coefficient was found 0.9999. In accuracy mean Percent recovery was found 99.60, 100.05 and 99.0%. For method precision percent RSD of area found 0.77%. The LOD 1.32 µg/ml and LOQ 3.02 µg/m was found for rufinamide. Force degradation studies shows degradation in Peroxide condition and stable in Acid, Base, Thermal and Photolytic (sunlight) condition.[23]

Habibur Rahman et. al.: Reported development and Validation of Chromatographic and Spectrophotometric Methods for the Quantitation of Rufinamide in Pharmaceutical Preparations Chromatography was performed on a Column: BDS Hypersil C18 (250 mm ×4.6 mm, 5 µm), Mode: Isocratic, Mobile phase: methanol: acetonitrile: dimethylformamide (7:5:8, v/v/v). Flow rate: 1.0 ml/min, Wavelength:210 nm. Injection volume:10 µl. The retention time was found 4.65 Min for rufinamide. Different analytical validation parameters include specificity, linearity, accuracy, precision, the limit of detection, quantification, ruggedness, and robustness, were determined as per ICH guidelines. The linearity range of rufinamide method was 0.15-3.5µg/ml for HPLC and 10-100 µg/ml for spectrophotometric, the co-coefficient 0.9998 and 0.9984 was found respectively. The accuracy was performed on 20, 40 and 60 µg/ml level, the mean Percent recovery was found 99.38, 99.87 and 98.74% respectively for HPLC and 0.8, 1.6, and 2.4 µg/ml level, the mean Percent recovery was found 98.75, 99.58 and 99.06% respectively for HPLC. For method precision percent RSD of area found 0.3% for HPLC and 0.2 for UV spectrophotometric. The LOD 0.061µg/ml and LOQ 0.184µg/m was found for HPLC and LOD 4.07µg/ml and LOQ 12.33µg/m was found for UV spectrophotometric. The statistical analyses of analytical method disclosed no significant differences between the acquired results and reported ones. The proposed method were valuable for rufinamide monitoring and regular analysis in quality control and analytical research laboratories. The UV Visible spectrophotometry implied that it could be a cheap, easy, and alternative method, while the HPLC could be a sensitive one to determine rufinamide with low concentration levels in dosage form.[24]

B. Sai Pavan Kumar et. al.: Reported Development and validation of a stability indicating RP-HPLC method for the determination of Rufinamide. Chromatography was performed on a Column: C18 (250 mm ×4.6 mm, 5 µ m, Mode: Isocratic elution, Mobile phase: acetonitrile and water (60:40, v/v). Flow rate: 0.8 ml/min, Injection volume: 20 µL, Wavelength: 215 nm. The retention time was found 4 Min for rufinamide. The developed method validates using linearity, accuracy, precision, the limit of detection, quantification, ruggedness, and robustness. The System suitability Parameter for method was Theoretical plates (N) 8576, Tailing factor (T) 1.26. The linearity range for method was 1, 5, 10, 20, 50, 100, 150, 200 µg/ml, the co-coefficient was found 0.9997. The accuracy was performed on 18, 20 and 22 mg/mL. level, the mean Percent recovery was found 97.87, 98.70 and 99.25% respectively. % The RSD in precision studies was found to be 0.14–0.29% (Intra-day) and 0.59–0.76% (Inter-day). The LOQ was found to be 0.7346 mg/mL and the LOD was found to be 0.2423 mg/mL. In stability study the acidic degradation, 7.79% of the drug was decomposed. The triazole and carboxamide groups present in the Rufinamide chemical structure hence may be responsible for the degradation. In the alkaline degradation a major degradant was observed at 2.987 mins without interfering the elution of drug peak (3.891 mins) and the percentage of drug decomposition was found to be 2.84%. Rufinamide has undergone thermal, oxidation and UV degradation slightly i.e less than 6.0%.[25]

P.M. Ngumo et. al.: Reported A simple, rapid, isocratic stability indicating reverse phase liquid chromatography method was developed for the assay of rufinamide bulk drug and tablets. Chromatography was performed on a Column: Phenomenex® Hyperclone BDS C-18 (250 × 4.6 mm, 5 µ), Mobile phase: methanol: 0.1 M octane sulfonic acid: 0.1 M Phospate buffer pH 6.5: water (30:10:5:55, % v/v/v/v). Flow rate: 1.0 ml/min, Wavelength: 210 nm. The retention time was found 8 Min for rufinamide. The developed method validates using linearity, accuracy, precision, the limit of detection, quantification, ruggedness, and robustness. The linearity range for method was 0.4, 0.6, 0.8, 1.0 and 1.2 mg/ml, the co-coefficient was found 0.9997. The accuracy was performed, the Average recovery was

found 99.5. For method precision percent RSD of was found 0.9 %. The LOD 156 ng and LOQ 311 ng was found for rufinamide.[26]

Apexa Patel et. al.: Reported development and validation of stability indicating hplc method for estimation of rufinamide in bulk and its pharmaceutical dosage form Chromatography was performed on a Column: phenomenex Luna C18 – (250 x 4.6 mm, 5 µ, Mode: Isocratic elution, Mobile phase: Flow rate: 1.0 ml/min, Injection Volume:20 µL, Wavelength: 210 nm. The retention time was found 3 Min for rufinamide. The developed method validates using The System suitability Parameter for method was Theoretical plates (N) 5584, Tailing factor (T) 0.95. The linearity range for method was 10-80 µg/ml, the co-coefficient was found 0.9999. The accuracy was performed on 10, 20 and 30 µg/ml level, the Percent recovery was found 100.6, 97.15 and 99.3% respectively. The drug has shown more degradation in acid hydrolysis and base hydrolysis. It was less degraded in photolytic, oxidative and thermal degradation. The absence of interference peak indicates that method can be used for routine analysis of Rufinamide in pharmaceutical dosage form.[27]

M Mathrusri Annapurna et. al.: A selective, specific and sensitive stability-indicating high-performance liquid chromatographic method was developed and validated for the determination of Rufinamide in tablet dosage forms. Chromatography was performed on a Column: C18 (250 × 4.6 mm, 5 µ), Mobile phase: methanol and water (52:48, V/V). Mode: Isocratic elution, Flow rate: 1.0 ml/min, Injection Volume: 20 µL, Wavelength: 210 nm. The retention time was found 5.4 Min for rufinamide. The developed method validates using linearity, accuracy, precision, the limit of detection, quantification, ruggedness, and robustness. The linearity range for method was 0.01–160 µg/mL the regression equation for the calibration curve was found to be y = 112887 x + 35285 with correlation coefficient of 0.9998. The accuracy was performed on8, 10 and 12 µg/ml level, the Percent recovery was found 97.25, 97.20 and 97.83 % respectively. The precision was calculated by assaying three samples of each at three different concentration levels (20, 40 and 80 µg/mL) on three different days. The % RSD range was obtained as 0.32-0.40 and 0.57-0.64 for intra-day and inter-day precision studies respectively. The LOD 0.0028 µg/mL and LOQ 0.0086 µg/mL and 0.0028 µg/mL was found for rufinamide. A very slight decomposition was observed on exposure of Rufinamide drug solution to acidic (1.36), alkaline (0.58) and oxidation (0.81). During the oxidative degradation two major degradants were observed at 2.452 mins and 2.784 mins without interfering the elution of drug peak (5.534 mins) and the percentage of drug decomposition was found to be 0.81 % indicating that the drug is highly resistant towards oxidation. Rufinamide has undergone thermal (0.16) and UV degradation (0.77) very slightly i.e less than 1.0 %.[28]

Iolanda Mazzucchelli et. al.: Reported The development of a simple and rapid highperformance liquid chromatography (HPLC) method for the determination of the new antiepileptic drug rufinamide (RFN) in human plasma and saliva. Chromatography was performed on a Column: Spherisorb silica column (250×4.6 mm., 5 µm), Mobile phase: methanol: dichloromethane: n-hexane (10:25:65 v/v/v) mixed with 6 ml ammonium hydroxide. Flow rate: 1.5 ml/min, Injection Volume: 50 µl, Wavelength:230 nm. The developed method validates using Specificity, linearity, accuracy, precision, the limit of detection, quantification. Calibration curves are linear [r 2 =0.998 for plasma and r 2 =0.999 for saliva over the range of 0.25– 20.0 µg ml-1, The accuracy for RFN and IS were 94.1±4.7% and 91.0±3.8% in plasma and 87.2±3.9% and 85.9±1.0% in saliva, respectively. The LOQ 0.25 µg ml-1 was found for rufinamide. The reported assay method is suitable for pharmacokinetic studies in humans and for therapeutic drug monitoring.[29]

P. Jagadeesh et. al.: Reported A simple, precise, selective and affordable spectrphotometric method has been developed and validated for the determination of Rufinamide in its bulk and pharmaceutical dosage form. The reported method was based on ion-pair complex formation between the drug and anionic dye i.e. Bromothymol blue in acidic medium (pH 2.0-4.0). The results obtained due to the tendency of the RFN to form chloroform extractable ion-pair complex with Bromothymol blue under experimental conditions. The form an ion-pair complex held together through electrostatic attraction. The coloured complex formed was quantitatively extracted into chloroform and measured wavelength at 416.5 nm. The stoichiometry of the complexes formed between drug and dye was 1:1 ratio, as determined by job's method of continuous variation. The association constant (Ka) of the ion-pair complexes formed was evaluated using Benesi–Hildebrand equation. Extraction procedure at various pH was measured and maximum absorbance was shown at pH 4.0. This UV method worked on Beer's law, law was obeyed in the concentration range of 10-60µg/ml with correlation coefficient 0.997. The accuracy was performed on 16, 35 and 55 µg/ml level, the Percent recovery was found 81.570, 90.428 and 91.124 % respectively. For precision, Intra- day precision data of proposed method performed on 40 µg/ml the percent RSD was found 0.4 %. And Inter-day precision data of proposed method performed on 30 µg/ml the percent RSD was found 0.8 %. The LOD 3.92 µg/ml and LOQ 11.90 µg/m was found for rufinamide. This method has been successfully applied for the assay of drug in pharmaceutical formulations. No interference was observed from pharmaceutical adjuvants.[30]

Sonia T Hassib et. al.: Reported a validated reversed-phase high-performance liquid chromatography method for simultaneous determination of five antiepileptic drugs used in the treatment of lennox–gastaut syndrome

in their pharmaceutical dosage forms. Chromatography was performed on a Column: RESTEK C18 column (5 µm, 250 mm × 4.6 mm), Mode: Isocratic elution, Mobile phase: Acetonitrile: water (55:45, v/v, adjusted with 0.01 N aqueous solution of o-phosphoric acid to pH = 3.3). Flow rate: 1.0 ml/min, Wavelength:210 nm. The retention time was found 3.102 Min for rufinamide. The linearity range for method was 2–40 µg/ml, the co-coefficient was found 0.9998. The LOD 0.5263 µg/ml and LOQ 1.5948 µg/m was found for rufinamide. Statistical analysis revealed no significant difference between the results obtained and the official or reported ones for each cited drug. The method is simple to be easily implemented in quality control studies of the mentioned drugs in their pharmaceutical preparations.[31]

K Ranjith et. al.: Reported development and validation of stability indicating RP-HPLC method for determination of related substances present in rufinamide tablets. Chromatography was performed on a Column: Inertsil ODS-3V (250 × 4.6 mm, 5 µm), Mode: gradient elution, Mobile phase: Mobile phase-A consists of 0.1% v/v triethylamine in water. pH adjusted to 2.2 with orthophosphoric acid. Mixture of 980 ml of methanol and 20 ml of tetrahydrofuran was used as Mobile phase-B. Flow rate: 1.0 ml/min, Injection volume: 50 µl Runtime: 90 minutes, Column temperature: 35°C, Wavelength:215 nm. The retention time was found 19.89 Min for rufinamide. The developed method validates using specificity, LOQ, LOD, linearity, precision, accuracy, robustness and solution stability. The System suitability Parameter for method was Theoretical plates (N) 47025, Tailing factor (T) 1.05. In linearity the co-coefficient was found 0.9997. The LOD 0.0046 µg/ml was found for rufinamide.[32]

Apexa Patel et. al.: Reported A sensitive, selective, precise and stability indicating a high-performance thin layer chromatographic method for the analysis of rufinamide (Rf) in bulk drug and its formulations was developed and validated. The method employed on aluminum TLC plates precoated with silica gel 60 F254 as the stationary phase. The mobile phase consisted of chloroform: methanol: glacial acetic acid in the ration of (90: 10: 1 v/v/v). The plates were saturated with methanol and activated at 608 °C for 5 min prior to chromatography. Samples were applied as bands 3 mm long, at 5 mm intervals under a stream of nitrogen. The plate dimensions were 3 × 0.1 mm. Linear ascending chromatogram development to a distance of 8 cm was performed in twin trough TLC developing chamber (Camag) at room temperature. The slit previously saturated for 30 min with a mobile phase. Densitometric scanning was performed on the Camag TLC scanner III in the absorbance mode at 210 nm. The developed method validates using specificity, LOQ, LOD, linearity, precision, accuracy. The linearity of response for Rf was assessed in the range of 1,000, 3,500 ng spot^{-1} for standard drug, the co-coefficient was found 0.9989. In the accuracy the mean Percent recovery was found 98.92 %. The intraday precision of the proposed method was determined by estimating the corresponding responses three times on the same day for three different concentrations of Rf (1,000, 2,000 and 3,500 ng spot21) for the method, the percent RSD was found 0.57%. The interday precision of the proposed method was determined by estimating the corresponding responses on three different days over a period of 1 week for three different concentrations of Rf (1,000, 2,000 and 3,500 ng spot^{-1}) for the method. , the percent RSD was found 0.46 %. The LOD 169.59 ng spot^{-1} and LOQ 595.74 ng spot^{-1} was found for rufinamide.[33]

Sonia T. Hassib et. al.: Reported development of two methods for determination of rufinamide (RUF) in presence of 1-[(2,6-difluorophenyl)methyl]-1H-1,2,3-triazole-4 carboxylic acid as its alkaline degradation product in dosage form. Chromatography was performed on a Column: kromasil C8 (250 × 4.6 mm, 5 µm), Mode: isocratic elution, Mobile phase: water: acetonitrile (50:50, v/v), Flow rate: 1.0 ml/min, Injection volume: 20 µl, Wavelength:210 nm. The retention time was found Min for rufinamide. The developed method validates using linearity, accuracy, precision, the limit of detection, quantification. The linearity range for method was 10-90 µg/ml, the co-coefficient was found 0.9999. The accuracy was performed on 10, 20 and 40 µg/ml level, the Percent recovery was found 99.42, 100.17 and 100.15 % respectively. For method precision percent RSD was found for intraday precision 0.139-0.178 % and interday precision 0.156-0.319%. The LOD 0.778 µg/ml and LOQ 2.356 µg/ml was found for rufinamide by HPLC method. In this reported method forced degradation under basic conditions was carried out, the degradation product was isolated and its structure was confirmed. HPLC methods were developed and validated in accordance to ICH guidelines.[34]

CONCLUSION

All these gathered data, herein discussed in an integrated manner, will be useful to support the development and validation of new and improved analytical methods for the determination of these target compounds. The reported methods developed validated RP-HPLC method for estimation of Rufinamide in bulk and in its pharmaceutical dosage form. This reported method can be used for the routine determination of Rufinamide in bulk and its commercial formulations.

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