

REVIEW ARTICLE

A Review of Analytical Method Development and Validation of Levetiracetam

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Abstract: Analytical method development and validation are continuous and interdependent tasks associated with research & development, quality control, and quality assurance departments. Analytical procedures play a critical role in equivalence risk assessment and management, helping establish product-specific acceptance criteria and stability of results. Validation determines the suitability of an analytical procedure for its intended purpose. Literature surveys reveal various analytical methods based on UV spectrophotometry for determining Levetiracetam in bulk and in combination with different drugs. The parameters were validated according to ICH guidelines in terms of accuracy, precision, robustness, ruggedness, and other components of analytical validation. The developed methods are simple, sensitive, and reproducible, suitable for the analysis of Levetiracetam in bulk and tablet dosage forms.

Keywords: Levetiracetam; UV Spectroscopy; Validation; ICH guidelines; Analytical method development.

1. Introduction

Levetiracetam, belonging to the pyrrolidone family, is a broad-spectrum antiepileptic and neuroprotective drug [1]. Approved as monotherapy for partial epilepsy with or without secondary generalization, it maintains efficacy and safety during long-term therapy [2]. Levetiracetam can be used alone or in combination with valproate, lamotrigine, or phenobarbital to treat idiopathic generalized epilepsies [3].

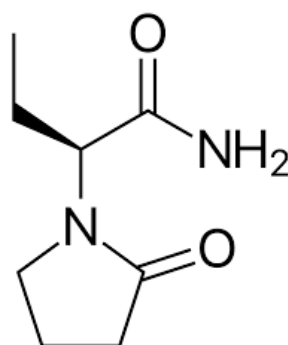


Figure 1. Structure of levetiracetam

Levetiracetam exhibits a good balance between efficacy and tolerability in managing epilepsy, movement disorders, and mood disorders [4]. Interestingly, it may have a neuroprotective role against ischemic brain injury in the elderly, where the incidence of new-onset epilepsy is highest and stroke is the most common cause of symptomatic epilepsy [5]. Although elderly patients often become seizure-free with relatively low doses of antiepileptic drugs (AEDs), comorbidities and comedications frequently raise concerns about potentially detrimental drug interactions [6]. Among recently-introduced AEDs, levetiracetam's favorable characteristics make it an ideal first-choice drug for post-stroke seizures [7].

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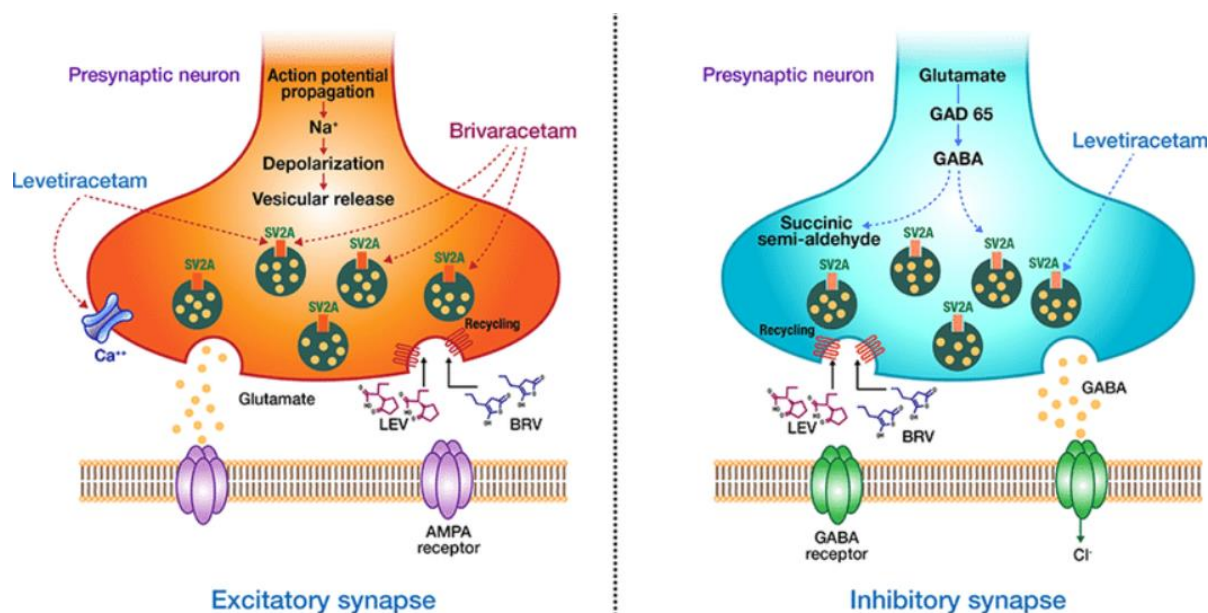


Figure 2. Mechanism of action of Levetiracetam and its congener Brivaracetam

Levetiracetam's mechanism of action does not involve modulation of the three main neurotransmitter systems. Recent evidence suggests that it reduces the inhibitory action of zinc and other negative allosteric modulators (beta-carbolines) on GABA and glycine-gated currents [8]].

2. Literature Review

Numerous studies have investigated analytical method development and validation for levetiracetam. Ravisankar et al. developed a simple, precise, accurate, economical, and reliable UV spectrophotometric method for estimating levetiracetam in tablet dosage form [9]. Kiran Gawale et al. developed and validated suitable UV spectroscopic and RP-HPLC methods for analyzing levetiracetam in single and combined dosage forms [10].

Chakure et al. developed another simple, precise, accurate, economical, and reliable UV spectrophotometric method for levetiracetam estimation in tablet dosage form, with good linearity, sensitivity, and validation per ICH Q2 (R1) guidelines [11]. Santosh V. Gandhi et al. developed and validated a new, simple, accurate, precise, and selective stability-indicating high-performance thin-layer chromatographic (HPTLC) method for levetiracetam determination in pharmaceutical dosage form [12].

Amol Pimpale et al. developed spectrophotometric and HPLC methods for levetiracetam estimation in bulk, optimizing various parameters [13]. Ghada M. Hadad et al. developed a sensitive and rapid flow injection analysis (FIA) method for levetiracetam determination in pharmaceutical formulations, optimizing and validating the method in terms of linearity, range, limit of detection, quantitation, precision, selectivity, and accuracy [14].

Maria P. Hernandez et al. adapted an affordable HPLC-UV method to quantify levetiracetam in plasma for routine use in low-resource settings, validating the method's repeatability, reproducibility, recovery, and limit of detection [15]. Lezitea Antonilli et al. developed a rapid HPTLC method for quantitative determination of levetiracetam in human plasma and compared it with HPLC and LC-MS/MS methods [16].

Kamal M. Matar et al. developed and validated a rapid, selective, reliable, precise, accurate, and reproducible tandem mass spectrometric (MS-MS) method for levetiracetam quantification in human plasma using solid phase extraction (SPE) technique [17]. Aakisetti Siva Sankar et al. developed and validated an effective stability-indicating HPLC procedure to assay levetiracetam in pure and injection formulations, proving the method to be precise, accurate, specific, rugged, robust, and stability-indicating [18].

Farhan Ahmed Siddiqui et al. developed and validated an ultraviolet detection method for simultaneous quantification of piracetam and levetiracetam, evaluating results through statistical parameters which qualify the method's reproducibility and selectivity, proving stability-indicating properties [19]. Juenke, Joetta M Bs et al. developed a method using UPLC-MS/MS for levetiracetam and gabapentin analysis in patient plasma, with a short runtime and baseline-resolved chromatographic separation [20].

Hisham Hashem et al. developed a new simple, rapid, and sensitive reversed-phase high-performance liquid chromatography (RP-HPLC) method employing Quality by Design (QbD) approach for determination of levetiracetam and pyridoxine HCl in prepared tablets, validating the method according to ICH guidelines [21]. Deepak S. Jain et al. validated an extraction method for levetiracetam, examining analyte stability under conditions mimicking sample storage, handling, and analytical procedures, yielding clean extracts with good recovery and evaluating various validation parameters [22].

Lakshmana Rao et al. developed a rapid and sensitive HPLC method for levetiracetam estimation in bulk and pharmaceutical formulations, optimizing chromatographic conditions and validating the method's linearity, limit of detection, quantification, precision, and accuracy [23]. Plaban Bhattacharya et al. developed and validated an HPTLC method for levetiracetam analysis in tablet formulation per ICH guidelines, evaluating linearity, precision, robustness, recovery, LOD, and LOQ [24].

S. Poongothai et al. developed and validated dissolution tests for levetiracetam tablets using a reverse phase HPLC method, optimizing dissolution conditions and evaluating dissolution profiles using difference factor, similar factor, and dissolution efficacy parameters [25]. K. Srinivasu et al. developed three simple, economical, precise, reliable, and reproducible visible spectrophotometric methods for levetiracetam estimation in bulk and tablet formulation based on chloroform extractable complexes with various dyes, optimizing experimental parameters and validating the methods statistically [26].

Table 1. Summary of literature review on various analytical methods reported for levetiracetam

Analytical Technique	Sample Matrix	Validation Parameters	Reference
UV Spectrophotometry	Bulk and Tablet Dosage Form	Linearity, Range, Accuracy, Precision, LOD, LOQ, Ruggedness, Robustness	[9], [10], [11]
RP-HPLC	Bulk and Tablet Dosage Form	Linearity, Range, Accuracy, Precision, LOD, LOQ, Specificity, Robustness	[9], [10], [12], [14], [15], [18], [23]
HPTLC	Pharmaceutical Formulation	Linearity, Precision, Robustness, Recovery, LOD, LOQ	[12], [24]
FIA	Pharmaceutical Formulations	Linearity, Range, LOD, LOQ, Precision, Selectivity, Accuracy	[14]
UPLC-MS/MS	Human Plasma	Runtime, Chromatographic Separation	[17], [20]
RP-HPLC with QbD Approach	Prepared Tablets	Linearity, Precision, Accuracy, Robustness, LOD, LOQ	[21]
HPLC-UV	Plasma (Low-Resource Settings)	Repeatability, Reproducibility, Recovery, LOD	[15]
HPLC-FLD and HPTLC	Human Plasma	Comparative Study with HPLC-UV	[16]
Dissolution Test with RP-HPLC	Tablet Formulation	Dissolution Conditions, Difference Factor, Similar Factor, Dissolution Efficacy	[25]
Visible Spectrophotometry	Bulk and Tablet Formulation	Linearity, Precision, Accuracy, Sensitivity	[26]

3. Conclusion

The literature survey suggests that various UV and simultaneous methods have been developed and reported for levetiracetam analysis. The published methods were validated for various parameters per ICH guidelines, and statistical analysis proved their reproducibility and selectivity. Thus, it can be concluded that the reported and published methods can be successfully applied for the estimation of levetiracetam in pure and pharmaceutical dosage forms.

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