3. REVIEW OF LITERATURE

Few methods have been reported for the analysis of newer antiepileptic agents. Those include both classical and instrumental methods. The methods have been developed keeping in view the requirements. Consequently, certain methods are also focused on the analysis of the drug from biological fluids along with stress degradation studies and chemical kinetic study. Table 3.1.1-3.1.5 gives an account on some of the methods available in the literature.

Table 3.1: Review of Methods for Analysis of Gabapentin

<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Experimental Condition</th>
<th>Ref. No.</th>
</tr>
</thead>
</table>
| 1.  | High Performance Liquid Chromatography                                | **Column**: Strong cation exchange column bonded with phenyl sulfonic acid  
**Mobile phase**: Ammonium dihydrogen orthophosphate buffer: Methanol (60:40)  
**Detection wavelength**: 200 nm                                         | 23       |
| 2.  | HPLC method with pre-column fluorescence derivatization using 4-fluoro 7-Nitrobenzofurazan | **Column**: Inertsil C(18)  
**Mobile phase**: Methanol:Water (80:20, v/v)  
**Flow rate**: 1.2 ml/min  
**Internal standard**: Mexiletin  
Excitation wavelength: 458 nm  
Emission wavelength: 521 nm                                               | 24       |
| 3.  | HPLC method for assay of Gabapentin capsule                          | **Column**: Beckman ultrasphere C18  
**Mobile phase**: Water: Acetonitrile: Methanol: Phosphate buffer solution (55:35:10:0.1)  
**Flow rate**: 1.0 ml/min  
**Detection wavelength**: 210 nm                                           | 25       |
<p>| | | | |</p>
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</thead>
</table>
| 4. | Non-derivatization method for determination of Gabapentin in formulation, rat serum & rate urine using HPLC coupled with charged aerosol detection | **Column:** Gracesmart RP C18 packed column  
**Mobile phase:** Methanol: Water (55:45, v/v)  
**Flow rate:** 1.1 ml/min | 26 |
| 5. | Derivatization HPLC for vigabatrin & gabapentin with fluorescence detection | **Column:** 5 micro ASTM BANsil CN  
**Mobile phase:** Acetonitrile: TBAH (20:80)  
**Detection wavelength:** 390 nm | 27 |
| 6. | Development and validation of new HPLC method for determination of gabapentin | **Column:** C18  
**Mobile phase:** Methanol: potassium dihydrogen orthophosphate (20:80, v/v) pH 6.2  
**Flow rate:** 1.0 ml/min  
**Detection wavelength:** 275 nm | 28 |
| 7. | Validated simultaneous estimation of gabapentin in presence of methylcobalamine in tablet using HPLC | **Mobile phase:** potassium dihydrogen orthophosphate: acetonitrile: methanol (7.5:1.5:1.0)  
**Detection wavelength:** 500 nm | 29 |
| 8. | UV-Visible spectroscopy method for estimation of gabapentin and methylcobalamin in bulk and tablet | **Instrument:** UV Visible spectrophotometer  
**Solvent Used:** Distilled water  
**Reagent:** 0.2% ninhydrin in N,N’-dimethylformamide  
**Wavelength:** 351 nm for methylcobalamin and 405 nm for gabapentin | 30 |
### Chapter 3

<table>
<thead>
<tr>
<th>Section</th>
<th>Method</th>
<th>Reagent</th>
<th>Wavelength</th>
<th>Buffer</th>
<th>Detection wavelength</th>
<th>Excitation wavelength</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.</td>
<td>Visible spectroscopic methods for determination of gabapentin in tablet and capsule</td>
<td><strong>Method I</strong>&lt;br&gt;&lt;span&gt;Reagent: Bromocresol green in phosphate buffer of pH 4.0&lt;/span&gt;</td>
<td><strong>Wavelength:</strong> 416 nm</td>
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<td></td>
<td><strong>Method II</strong>&lt;br&gt;&lt;span&gt;Reagent: Bromothymol blue in phosphate buffer of pH 4.0&lt;/span&gt;</td>
<td><strong>Wavelength:</strong> 421 nm</td>
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<tr>
<td>10.</td>
<td>Spectrofluorimetric determination of vigabatrin and gabapentin in urine and dosage form through derivatization with fluorescamine</td>
<td><strong>Buffer:</strong> Borate, pH 8.2</td>
<td></td>
<td></td>
<td><strong>Detection wavelength:</strong> 472 nm</td>
<td><strong>Excitation wavelength:</strong> 390 nm</td>
</tr>
<tr>
<td>11.</td>
<td>Spectrofluorimetric determination of vigabatrin and gabapentin in dosage forms and spiked plasma samples through derivatization with 4-chloro-7-nitrobenzo-2-oxa-1,3-diazole.</td>
<td><strong>Buffer:</strong> Borate, 7.1</td>
<td></td>
<td></td>
<td><strong>Detection wavelength:</strong> 532 nm</td>
<td><strong>Excitation wavelength:</strong> 465 nm</td>
</tr>
<tr>
<td>12.</td>
<td>Sensitive Spectrofluorimetric Method of Analysis for Gabapentin in Pure and Pharmaceutical Preparations</td>
<td><strong>Reagent:</strong> 4-fluoro 7-nitrobenzofurazan pH 9.5</td>
<td></td>
<td></td>
<td><strong>Detection wavelength:</strong> 521 nm</td>
<td><strong>Excitation wavelength:</strong> 458 nm</td>
</tr>
<tr>
<td>No.</td>
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<td>Experimental Condition</td>
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</tbody>
</table>
| 1.  | Liquid Chromatography and Ultraviolet spectrophotometric (UV)                                                                         | **Column**: ACE RP-C18  
**Mobile phase**: 0.3% triethylamine in water (v/v) pH 4.0: methanol (62:38, v/v)  
**Detection wavelength**: 279 nm                                                                                                           | 35       |
| 2.  | Measurement of Serum Lamotrigine by HPLC method using Phenyltriazine as internal standard                                              | **Column**: Phenomenex ODS3 column  
**Mobile Phase**: Methanol Phosphate buffer pH – 3  
**Detection wavelength**: 225nm                                                                                                                     | 36       |
| 3.  | Development and validation of new HPLC method for Lamotrigine and related compounds in tablet formulation                              | **Column**: C18 mu Bondapack column(250mm x 4.6 mm)  
**Mobile phase**: Acetonitrile: Monobasic Potassium Phosphate solution (35:65, v/v)  
**Flow rate**: 1.5 ml/min  
**Detection wavelength**: 210 nm  
**Column Temperature**: 40°C                                                                                                                      | 37       |
| 4.  | RP-HPLC Method Development and validation of Lamotrigine                                                                            | **Column**: Supelco C18 column (25cm X 4.6mm and i.d., 5µm)  
**Mobile phase**: methanol and 0.05 M potassium dihydrogen orthophosphate (65: 35v/v)  
**Detection wavelength**: 270 nm  
**Flow rate**: 1 ml/min                                                                                                                                   | 38       |
|   |   | Rapid HPLC analysis of the antiepileptic Lamotrigine and its metabolites in human plasma | Column: C18- RP column  
**Mobile phase:** methanol and a 0.45 mM, pH 3.5 phosphate buffer containing 0.17% triethylamine (24:76 v/v)  
Melatonin - internal standard (IS)  
**Detection wavelength:** 220 nm | 39 |
|---|---|---|---|
|   |   | A new simultaneous RP-HPLC method for development and validation of Lamotrigine tablets | Column: Xterra C18 (4.6 X 100 mm) column  
**Mobile phase:** methanol and Potassium dihydrogen phosphate (50:50v/v)  
**Detection wavelength:** 225 nm | 40 |
|   | Solid-Phase Extraction Study and RP-HPLC Analysis of Lamotrigine in Human Biological Fluids and in Antiepileptic Tablet Formulations | Method 1:  
**Column:** C₈ Bond Elut cartridges (200mg/3ml)  
**Solvent:** Acidic Acetonitrile  
Method 2:  
**Column:** octylsilica, using a Lichrosorb RP-8, 5µm, 250x4.6 mm  
**Mobile phase:** 0.05M acetate buffer pH5.6 and acetonitrile (72:28 v/v) | 41 |
|   | A sensitive HPLC method for estimation of lamotrigine in human plasma and saliva: application to plasma-saliva correlation in epileptic patients. | **Column:** Reverse Phase column  
**Mobile phase:** Acetonitrile and 20 mM ammonium acetate buffer pH 6.5 (30:70)  
**Flow rate:** 1 ml/min | 42 |
| 9. | High-performance liquid chromatography quantitation of plasma Lamotrigine concentrations: application measuring trough concentrations in patients with epilepsy. | **Column:** Silica column (5 µm)  
**Mobile phase:** 94% methanol, 5.92% water, and 0.08% NH₄H₂PO₄  
**Flow rate:** 1 ml/min  
**Detection wavelength:** 280 nm | 43 |
| --- | --- | --- | --- |
| 10. | Determination of Lamotrigine and its metabolites in human plasma by liquid chromatography-mass spectrometry. | **Column:** Reversed phase  
**Mobile phase:** Gradient elution  
**Internal Standard:** 3,5-diamino-6-(2-methoxyphenyl)-1,2,4-triazine and morphine-3-glucuronide-D₃ | 44 |
| 11. | A rapid cost-effective high-performance liquid chromatographic (HPLC) assay of serum Lamotrigine after liquid-liquid extraction and using HPLC conditions routinely used for analysis of barbiturates. | **Column:** LC-18 column(15 cm x 4.6 mm)  
**Mobile phase:** Prepared by mixing 750 ml of potassium dihydrogen phosphate, 550 ml of deionized water, 430 ml of methanol, and 100 microliters of triethylamine as an ion pairing reagent  
**Internal Standard:** Thiopental | 45 |
| 12. | Validated HPTLC Method for Estimation of Lamotrigine in Tablets | **Stationary phase:** Precoated silica gel G60 F254  
**Mobile phase:** acetone: toluene: ammonia (70:30:5.0 v/v)  
**Quantification:** Densitometry at 312 nm | 46 |
|   | Validated Densitometric Method for the Quantification of Lamotrigine in Dosage Form | **Stationary phase:** Precoated silica gel G60 F254  
**Mobile phase:** ethyl acetate: chloroform: water in the ratio of 9.0: 3.0: 2.5 v/v  
**Quantification:** 240 nm | 47 |
|---|---|---|---|
| 13. | Validated spectrofluorimetric method for the determination of lamotrigine in tablets and human plasma through derivatization with o-phthalmaldehyde. | **Florescent Derivative:** Measured at 448nm  
**Limit of detection (LOD):** 0.02 µg/ml  
**Limit of quantification (LOQ):** 0.06 µg/ml | 48 |
| 14. | Identification and assay of lamotrigine in human milk with gas chromatography and densitometry. | **GC Range:** 2-20 µg/ml  
**Densitometry Range:** 2-10 µg/ml  
Densitometry measurement at 217nm  
**Detector:** Flame-ionizing detector | 49 |
<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Experimental Condition</th>
<th>Ref. No.</th>
</tr>
</thead>
</table>
| 1   | HPLC-UV analysis of Rufinamide, Zonisamide, Lamotrigine, Oxcarbazepine monohydroxy derivative and Felbamate in deproteinized plasma of patients with epilepsy | **Column**: Synergi 4µm Hydro-RP  
**Mobile phase**: potassium dihydrogen phosphate buffer (50 mM, pH 4.5) : acetonitrile : methanol (65:26.2:8.8, v/v/v)  
**Flow rate**: 0.8 ml/min  
**Internal standard**: citalopram  
**Detection wavelength**: 210 nm | 63       |
| 2   | Validation of Zonisamide and its Four Related Substances by HPLC and UV-Spectrophotometry | **Column**: Perfectsil Target C18 column  
**Mobile phase**: Disodium hydrogen phosphate buffer: acetonitrile:methanol (650 : 150 : 200, v/v/v)  
**Flow rate**: 1.2 ml/min  
**Detection wavelength**: 240 nm | 64       |
| 3   | Spectorphotometric Determination of Zonisamide Bulk And In Tablet Dosage Form By Using P-Dimethyl amino benzaldehyde | **Instrument**: UV-Visible spectrophotometer  
**Solvent Used**: Acetonitrile and acidic solution of P-dimethyl amino benzaldehyde  
**Detection Wavelength**: 420nm  
**% RSD**: 0.27 | 65       |
| 4   | Determination of Furosemide and Zonisamide as a Drug Substance and in Dosage Form by Ion Pair Reversed Phase Liquid Chromatographic Technique | **Column**: ODS chromatographic column  
**Mobile phase**: methanol: Tetrabutyl ammonium hydrogen sulphate40:60 ,v/v)  
**Flow rate**: 1.0 ml/min  
**Detection wavelength**: 240 nm | 66       |
|   | HPLC Method for the Determination of Zonisamide as Bulk Drug and in Pharmaceutical Dosage Form | Column: Waters X-Terra RP 18  
Mobile phase: acetonitrile :sodium dihydrogen phosphate monohydrate pH 3.0, 18:82 ,v/v)  
Detection wavelength: 240 nm | 67 |
|---|---|---|
| 5. | Simultaneous Analysis of Lamotrigine, Oxcarbazepine, 10-Hydroxycarbazepine, and Zonisamide by HPLC–UV and a Rapid GC Method | Detector: Nitrogen-phosphorus detector  
Detection wavelength: 230 nm | 68 |
| 6. | Analysis of Lamotrigine, Oxcarbazepine, 10-hydroxycarbazepine, and Zonisamide by HPLC-UV and a rapid GC method | Detector: Nitrogen-phosphorus detector  
Detection wavelength: 230 nm | 69 |
| 7. | Development and validation of UV-Spectrophotometric method for determination of Quetiapine Fumarate in tablets | Instrument: UV Visible spectrophotometer  
Solvent Used: 0.1 N HCl  
% R.S.D:0.20% (Quetipin tablet: 200 mg , 0.16% (Quetipin tablet: 300 mg)  
D-values: at 254.76nm | 70 |
| 8. | Drug Monitoring and Toxicology: A Procedure for the Monitoring of Levetiracetam and Zonisamide by HPLC-UV | Instrument Used: HPLC  
Detection wavelength: | 71 |
Table 3.4: Review of Methods for Analysis of Pregabalin

<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Experimental Condition</th>
<th>Ref. No.</th>
</tr>
</thead>
</table>
| 1.  | Development And Validation Of HPLC Method For The Determination Of Pregabalin In Capsules | **Column:** Hypersil BDS, C8, 150×4.6 mm, 5 μm column  
**Mobile phase:** phosphate buffer pH 6.9 and acetonitrile (95:05)  
**Flow rate:** 1 ml/min  
**Detector:** photodiode array detector | 73       |
| 2.  | Determination Of Pregabalin In Bulk Pharmaceutical Formulations And Human Urine Samples using Reverse Phase High Performance Liquid Chromatography (RP-HPLC) | **Column:** Chromosil C18 (250×4.6mm, 5μm In Particle Size)  
**Mobile phase:** methanol acetonitrile - 0.02 M di - potassium hydrogen orthophosphate (K2HPO4) (pH - 7.00) (3: 1: 16, v/v/v)  
**Flow rate:** 1.0 ml/min  
**Detector:** UV Detector  
**Detection wavelength:** 210 nm | 74       |
| 3.  | Analytical RP-HPLC Method for Development and Validation of Pregabalin and Methylcobalamin in Combined Capsule Formulation | **Column:** Waters allaiance 2695 seperation module,C18 column (250 x 4.6 mm,5 mcg/ml)  
**Mobile phase:** ammonium dihydrogen-o-phosphate (buffer 6.0), acetonitrile and methanol(75:15:10)  
**Flow rate:** 1 ml/min  
**Detector:** UV visible PDA detector  
**Detection wavelength:** 210 nm | 75       |
<table>
<thead>
<tr>
<th>No.</th>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
</table>
| 4.  | Development And Validation of Rapid HPLC Method For Determination of Pregabalin In Bulk Drug And dosage Forms. | Column: waters spherisorb 5μ ODS 24.6mm x 250mm column  
Mobile phase: acetonitrile:buffer (30:70 V/V)  
Flow rate: 1.ml/min  
Detection wavelength: 210nm |
| 5.  | Determination Of Optical Impurity Of Pregabalin By HPLC With Pre-Column Chiral Derivatization. | Column: Inertsil ODS-2.5 microm, 250 mmx4.6 mm i.d.)  
Mobile phase: Phosphoric acid buffer and acetonitrile (55:45, v/v)  
Flow rate: 1.0 ml/min  
Detection wavelength: 340 nm |
| 6.  | Stability Indicating RP-HPLC Method For Determination Of Pregabalin          | Column: Phenomenex C_{18} column (250 x 4.6 mm i.d.,5 μm particle sizes)  
Mobile phase: acetonitrile and phosphate buffer pH3.5 (60:40 v/v)  
Flow rate: 1.ml/min  
Detection wavelength: 210 nm |
| 7.  | Analysis of Pregabalin at therapeutic concentrations in human plasma/serum by reversed-phase HPLC. | Column: Inertsil ODS-2.5 micron, 250 mmx4.6 mm i.d.) |
| 8.  | A Sensitive Spectrophotometric Method For The Determination Of Pregabalin In Bulk, And In Human Urine Samples | Method: The method was based on the reaction of drug with the mixture of potassium iodate and potassium iodide.  
Wavelength: 353nm. |
### Table 3.5: Review of Methods For Analysis of Levetiracetam

<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Experimental Condition</th>
<th>Ref. No.</th>
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</thead>
</table>
| 1.  | Validated Method For the Determination Of Levetiracetam In Plasma Of Patients With Epilepsy Using High Performance Liquid Chromatography With UV Detection. | **Column:** Synergi 4-microm Hydro-RP (150mm x 4 mm I.D. column)  
**Mobile phase:** mixture of potassium dihydrogen phosphate buffer (50 mM, pH 4.5) and acetonitrile (94:6,v/v)  
**Flow rate:** 1.5ml/min  
**Detector:** UV Detector  
**Detection wavelength:** 205 nm | 108      |
| 2.  | Developed And Validated Method For Assay Of Levetiracetam In Formulations Using Reverse Phase High Performance Liquid Chromatography (RP-HPLC) | **Column:** Chromosil C18 (250x4.6mm, 5µm In Particle Size)  
**Mobile phase:** Methanol: Water: Triethyl acetate 75:25:05 (v/v)  
**Flow rate:** 1.0 ml/min  
**Detection wavelength:** 214 nm | 109      |
| 3.  | Simple and reproducible method developed for estimation of Levetiracetam In Tablet Dosage Form Using Reverse Phase High Performance Liquid Chromatography (RP-HPLC) | **Column:** prontosil C18 column (150X4.6mm; 5µm)  
**Mobile phase:** buffer solution (pH 2.8) and acetonitrile(90:10)  
**Flow rate:** 1.2ml/min  
**Detection wavelength:** 215 nm | 110      |
| 4.  | Determination of Levetiracetam using Ultra-High-Performance Liquid Chromatography | **Column:** BEH C18 column (1.7 µm particle size and 100 × 2.1 mm i.d.)  
**Mobile phase:** acetonitrile-phosphate buffer (pH = 6.6; 0.01 M) (10/90 v/v) | 111      |
### Chapter 3

- **Column:** conventional Phenomenex Gemini C18 (100 x 4.6 mm, 5 microm) and Merck Chromolith Performance RP18e (100 x 4.6 mm, macropore size 2 mm, micropore size 13 nm) monolithic silica.
- **Mobile phase:** Water: Acetonitrile (90:10, v/v)
- **Flow rate:** 1 ml/min
- **Detection wavelength:** 210 nm

#### 6. Quantitative Determination Of Levetiracetam By Gas Chromatography Using Ethyl Chloroformate As A Derivatizing Reagent In Pure And Pharmaceutical Preparation
- **Column:** an Rtx-5 capillary column (cross bond 5% diphenyl/95% dimethyl polysiloxane)
- **Flow rate:** 120 Kpa/4min
- **Detector:** flame ionization detector

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Department of Pharmaceutical Sciences, Bhagwant University.

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