

Development and Validation of Related Substances Method by Liquid Chromatography for Analysis of Pregabalin in Tablet Formulations including poly(ethylene oxide)

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Objectives

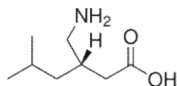
• Develop fast and precise method for the determination of relative substances of Pregabalin in high viscous PEO solution.

• PEO in the formulation make tablet to swell and show high viscosity when it is exposed to water. Due to its viscosity, it is difficult to apply in the HPLC analysis system.

Introduction

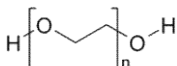
• Pregabalin

- (S)-(+)-4-Amino-3-(2-methylpropyl) butanoic acid



- Soluble in wide range of pH media, such as water, acid, and base.
- Widely used to treat neuropathic diseases, generally anxiety disorder¹.

• Polyethylene oxide (PEO)



- Hydrophilic, white color, and fluidic polymer compound
- Polyether with no electric charge².
- Many different kinds of molecular weights
- Application in pharmaceuticals area
 - muco-adhesive agent, binding agent, lubricant, and coating agent for the tablet³.

• Mechanism of drug release

- Hydrophilic drug : DIFFUSION from PEO gel layer on the tablet surface.
- Hydrophobic drug : EROSION of the tablet

Materials & Methods

• Selection of sodium sulfate aqueous concentration

- Purpose - Find **CRITICAL** concentration of sodium sulfate.
- Range - 0.2-1.0 mol/L of sodium sulfate in 2% PEO solution

• Methods

- **Quantification** - Precipitants from sodium sulfate solution using Raman Spectrometer (B&W Technologies, Newark, USA) at 785 nm wavelength using diode laser.

- **Thermal analysis** - DSC (Mettler Toledo, Swiss) was used for thermal analysis to evaluate property of PEO precipitants.

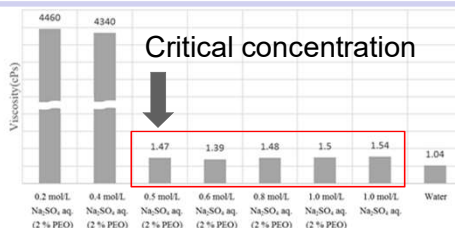
- **Method validation** - Specificity, linearity, accuracy and precision (according to the USP 35 and ICH guideline)

• System suitability confirmation

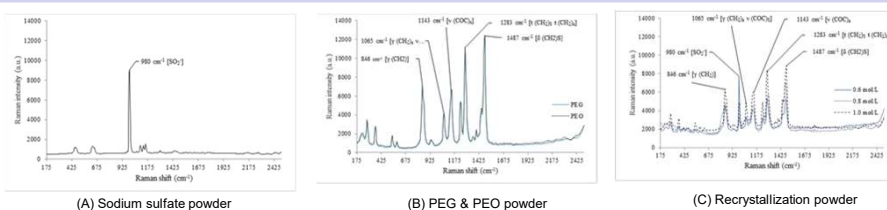
- Peak retention time
- Theoretical plate number

Results

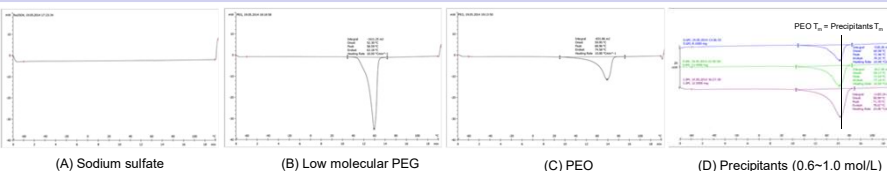
Selection of the concentration of sodium sulfate aqueous solution



Selection of the concentration of sodium sulfate aqueous solution



Determination of thermal characteristics of PEO using DSC analysis



Method validation

(a) Summary data of pregabalin					(B) Summary data of lactam impurity					(C) Summary data of amine amide impurity				
No.	Conc. (µg/mL)	Calibration curve peak area (1 st)	Calibration curve peak area (2 nd)	Calibration curve peak area (3 rd)	No.	Conc. (µg/mL)	Calibration curve peak area (1 st)	Calibration curve peak area (2 nd)	Calibration curve peak area (3 rd)	No.	Conc. (µg/mL)	Calibration curve peak area (1 st)	Calibration curve peak area (2 nd)	Calibration curve peak area (3 rd)
1	1.50	3.84	3.82	3.72	1	1.50	69.12	69.22	68.50	1	1.50	149.12	151.38	151.38
2	4.50	11.23	11.40	11.24	2	4.50	206.18	206.18	205.11	2	4.50	456.40	458.34	456.72
3	9.00	22.42	22.40	22.54	3	9.00	408.72	408.72	412.26	3	9.00	911.54	883.62	924.99
4	13.50	33.55	33.65	33.33	4	13.50	610.81	610.81	608.51	4	13.50	1288.93	1283.90	1373.34
5	18.00	44.58	44.70	44.12	5	18.00	807.72	807.72	810.24	5	18.00	1825.47	1831.52	1834.22
Slope					Slope					Slope				
2.47					44.79					99.65				
Intercept					Intercept					Intercept				
0.14					3.97					-0.44				
Correlation coefficient (r ²)					Correlation coefficient (r ²)					Correlation coefficient (r ²)				
1.000					1.000					0.997				
Mean of slope					Mean of slope					Mean of slope				
2.47					44.95					100.44				
Mean of intercept					Mean of intercept					Mean of intercept				
0.17					3.35					-2.09				
SD of slope					SD of slope					SD of slope				
0.01					0.19					1.31				
SD of intercept					SD of intercept					SD of intercept				
0.04					0.59					3.10				

Conclusions

- **Removal of matrix effect**
 - Sodium sulfate showed **DRAMATIC EFFECT** for the evaluation of Pregabalin in PEO solution
 - Showed **CRITICAL CONCENTRATION** above 0.5 mol/L (For the safety, 0.6 mol/L concentration was used)
- **Method validation results**
 - Linearity - R² of 0.997 or higher
 - Limit of Detection - 0.10 µg/mL
 - Limit of Quantification - 0.31 µg/mL.
 - Recovery rate - between 96.6-107.7% from the three concentration levels (RSD of 0.2-2.3%).
 - Relate Response Factor (RRF) - 95.2-100.8%
- **NOVEL method can be applied to analyze Pregabalin in PEO containing solution**
- **Environmental friendly (No organic solvent)**

* Reference

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