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Analytical method development of pregabalin and related substances in extended release tablets containing polyethylene oxide

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Pregabalin, (S)-3-amino methyl hexanoic acid, is a structural analogue of γ-amino butyric acid (GABA) which has been widely used to treat partial seizures and neuropathic pain [1]. It is soluble in aqueous solution and sparingly soluble in organic solvents such as ethanol, DMSO and DMF. Polyethylene oxide (PEO) has a strong negative effect on analysis of hydrophilic active ingredient and its relative substances due to extremely high viscosity of PEO in aqueous media. The aim of this study is to develop a fast and precise method for the determination of pregabalin and its relative substances in extended release tablets including PEO using sodium sulfate for the treatment of sample solution.

In order to remove effect of PEO in aqueous media, sodium sulfate solution in the range of 0.2–1.0 mol/L was pretreated. Viscosity of solution was evaluated by a viscometer for the determination of optimal concentration of sodium sulfate (Fig. 1). Identification of precipitate after the pretreatment of sodium sulfate was evaluated by Raman spectroscopy [2]. The separation of HPLC for 100 μL of sample solution was accomplished on a Capcellpak C18 (4.6 × 250 mm, 5 μm) column using gradient mobile phase consisting of pH 6.5 ammonium phosphate buffer and acetonitrile at the flow rate of 0.8 mL/min. The wavelength of UV detection was set at 210 nm. The chromatographic parameters monitored were peak retention time and theoretical plate number. The developed method was validated for specificity, linearity, accuracy and precision according to the USP 35 and ICH guideline.

More than 0.5 mol/L of sodium sulfate efficiently precipitated PEO to significantly reduce viscosity of aqueous solution from 4300–4500 g/cm·s to 1.4–1.5 g/cm·s. Precipitated PEO was identified by Raman spectroscopy. The linearity of pregablin and its related substances over the range of 1.5–18.0 μg/mL was proven to show superior correlation coefficient more than 0.997. The limit of detection and quantification were 0.10 μg/mL and 0.31 μg/mL respectively. Recovery between 96.6 and 107.7% at three concentration levels and %RSD of precision between 0.2 and 2.3% were obtained [3]. As a result, this method was proven to be validated. Compared with the previous methods, this pretreatment method using sodium sulfate is superior with

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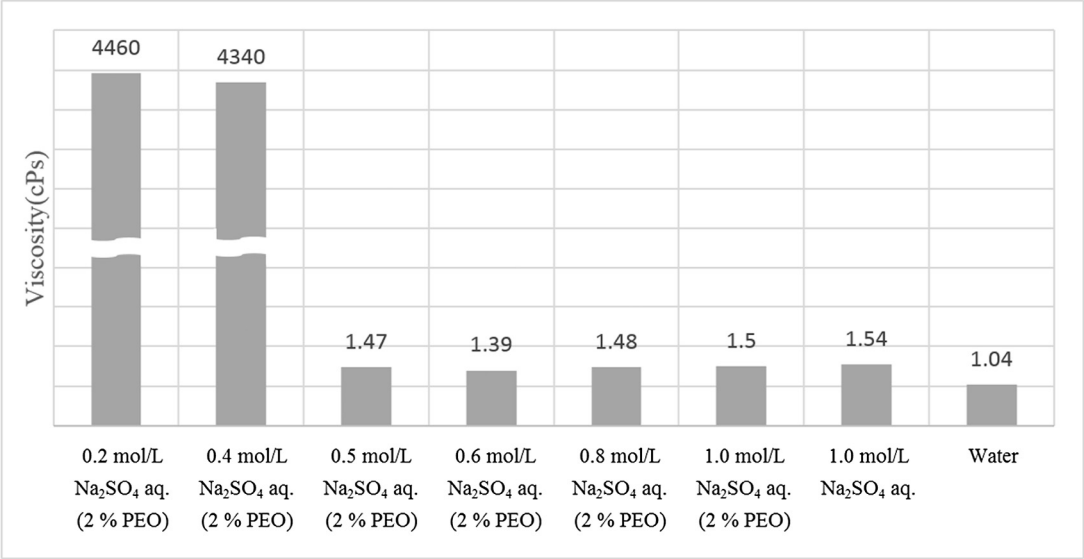

Fig. 1 – Comparison of the viscosity depending on the concentration of sodium sulfate.

respect to efficient removal of PEO effect for analysis of pregabalin and its related substances. This established method from the research is expected to contribute to adequate quality control through accurate and simple analysis of hydrophilic compounds in extended release dosage forms containing PEO.

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