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# Development and Total Error Concept Validation of Common Analytical Method for Quantification of All Residual Solvents Present in Amino Acids by Gas Chromatography-Head Space

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**Abstract :** Residual solvents in Pharmaceutical samples are monitored using gas chromatography with headspace (GC-HS). Based on current regulatory and compendial requirements, measuring the residual solvents are mandatory for all release testing of active pharmaceutical ingredients (API). Generally, isopropyl alcohol is used as the residual solvent in proline and tryptophan; methanol in cysteine monohydrate hydrochloride, glycine, methionine and serine; ethanol in glycine and lysine monohydrate; acetic acid in methionine. In order to have a single method for determining these residual solvents (isopropyl alcohol, ethanol, methanol and acetic acid) in all these 7 amino acids a sensitive and simple method was developed by using gas chromatography headspace technique with flame ionization detection. During development, no reproducibility, retention time variation and bad peak shape of acetic acid peaks were identified due to the reaction of acetic acid with the stationary phase (cyanopropyl dimethyl polysiloxane phase) of column and dissociation of acetic acid with water (if diluent) while applying temperature gradient. Therefore, dimethyl sulfoxide was used as diluent to avoid these issues. But most the methods published for acetic acid quantification by GC-HS uses derivatisation technique to protect acetic acid. As per compendia, risk-based approach was selected as appropriate to determine the degree and extent of the validation process to assure the fitness of the procedure. Therefore, Total error concept was selected to validate the analytical procedure. An accuracy profile of ±40% was selected for lower level (quantitation limit level) and for other levels ±30% with 95% confidence interval (risk profile 5%). The method was developed using DB-Waxetr column manufactured by Agilent contains 530 µm internal diameter, thickness: 2.0 µm, and length: 30 m. A constant flow of 6.0 mL/min. with constant make up mode of Helium gas was selected as a carrier gas. The present method is simple, rapid, and accurate, which is suitable for rapid analysis of isopropyl alcohol, ethanol, methanol and acetic acid in amino acids. The range of the method for isopropyl alcohol is 50ppm to 200ppm, ethanol is 50ppm to 3000ppm, methanol is 50ppm to 400ppm and acetic acid 100ppm to 400ppm, which covers the specification limits provided in European pharmacopeia. The accuracy profile and risk profile generated as part of validation were found to be satisfactory. Therefore, this method can be used for testing of residual solvents in amino acids drug substances.

**Keywords :** amino acid, head space, gas chromatography, total error
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