ROBUST MIXED-MODE CHROMATOGRAPHY METHOD DEVELOPMENT USING ANALYTICAL QUALITY BY DESIGN APPROACH FOR ANALYSIS OF SELECTED DRUGS

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Mixed-Mode Liquid Chromatography (MMLC) includes several separation mechanisms in a single column, which is why MMLC can analyze compounds in a broad range of polarities and ionization potentials in a single run (1). Acclaim Mixed-Mode WCX-1 column with the ability to expose hydrophobic and weak cation exchange interactions was thus selected to analyse a challenging mixture of neutral and cationic forms: ergotamine, mecloxamine, camylofin, caffeine and propyphenazone, used as a fixed combination. MMLC method was developed in line with Analytical Quality by Design (AQbD) approach implying the scientifically-based understanding of process properties and risk-based management of the method life cycle. AQbD refers to pre-definition of the method's Analytical Target Profile (ATP) by means of baseline separations within the shortest possible time, as well as definition of Critical Method Attributes (CMAs) as a measure of method quality and Critical Method Parameters (CMPs) affecting CMAs (2). Acetonitrile content, pH and acetate buffer concentration were selected as CMPs since retention mechanism expression in MMLC strongly depends on the mobile phase characteristics. The dependence of CMAs on CMPs was revealed following a face-centred central composition design plan of experiments and accompanying mathematical models, coefficients and standard error values. Design Space in which ATP is achieved with a high level of reliability (π = 90%), was determined by Monte Carlo simulations taking error distribution into account. Its margins pointed out to the working point that assures proper method robustness (pH 5.2, 90 mM acetate buffer solution and 48% (v/v) of acetonitrile).

References

1. Zhang K, Liu X. Mixed-mode chromatography in pharmaceutical and biopharmaceutical applications. J. Pharm. Biomed. Anal. 2016; 128: 73–88.
2. Dispas A, Avohou HT, Lebrun P, Hubert Ph, Hubert C. 'Quality by Design' approach for the analysis of impurities in pharmaceutical drug products and drug substances. TrAC - Trends Anal. Chem. 2018; 101: 24-33.

ROBUSTAN RAZVOJ METODE MULTIMODALNE HROMATOGRAFIJE PRIMENOM PRINCIPA UGRAĐIVANJA KVALITETA KROZ DIZAJN ZA ANALIZU ODABARNIH LEKOVA

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Multimodalna tečna hromatografija (*Mixed-Mode Liquid Chromatography* – MMLC) uključuje nekoliko mehanizama razdvajanja u jednoj koloni, zbog čega se ova tehnika može koristiti za simultanu analizu jedinjenja širokog opsega polarnosti i jonizacionog potencijala (1). *Acclaim Mixed-Mode WCX-1* kolona sa sposobnošću ekspresije hidrofobnih i interakcija slabe katjonske izmene, je odabrana za analizu izazovne smeše neutralnih i katjonskih oblika analita: ergotamina, mekloksamina, kamilofina, kofeina i propifenazona, koji se primenjuju u fiksnoj kombinaciji. MMLC metoda je razvijena u skladu sa pristupom ugradnje kvaliteta kroz dizajn (*Analytical Quality by Design* – AQbD) koji podrazumeva naučno zasnovano razumevanje svojstava procesa i upravljanje životnim ciklusom metode prema riziku. AQbD se odnosi na unapred definisanje analitičkog ciljanog profila metode (*Analytical Target Profile* - ATP) odnosno razdvajanje na baznoj liniji za što kraće vreme, kao i na definisanje kritičnih osobina metode (*Critical Method Attributes* - CMA) kao mere kvaliteta metode i kritičnih parametara metode (*Critical Method Parameters* - CMP) koji utiču na CMA (2). Sadržaj acetonitrila, pH i koncentracija acetatnog pufera izabrani su kao CMP, pošto ekspresija MMLC retencionih mehanizma zavisi od karakteristika mobilne faze. Zavisnost CMA od CMP definisana je pomoću plana eksperimenata usklađenim sa centralnim kompozicionim dizajnom, ka centru orijentisanim i pratećim matematičkim modelima, koeficijentima i vrednostima standardne greške. Prostor dizajna u kome se ATP postiže sa visokim nivoom pouzdanosti (π = 90%) određen je Monte Karlo simulacijama uzimajući u obzir distribuciju grešaka. Njegov okvir ukazuje na radnu tačku koja obezbeđuje odgovarajuću robusnost metode (pH 5,2, 90 mM rastvor acetatnog pufera i 48% (v/v) acetonitrila).

Literatura

1. Zhang K, Liu X. Mixed-mode chromatography in pharmaceutical and biopharmaceutical applications. J. Pharm. Biomed. Anal. 2016; 128: 73–88.
2. Dispas A, Avohou HT, Lebrun P, Hubert Ph, Hubert C. 'Quality by Design' approach for the analysis of impurities in pharmaceutical drug products and drug substances. TrAC - Trends Anal. Chem. 2018; 101: 24-33.