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REVIEW ON HYPHENATED ANALYTICAL TECHNIQUES IMPLEMENTED FOR ANALYSIS OF ROSUVASTATIN

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Abstract:

Rosuvastatin calcium [RSV] specifically inhibit the enzyme 3-hydroxy-3-methylglutaryl-Co-enzyme A [HMG-CoA] reductase. It belongs to family of cholesterol lowering medications which are denoted as statins and useful in treatment of dyslipidemia where it helps in reducing the chances of arthrosclerosis development by decreasing the level of bad cholesterol and hence eliminating the possibilities of heart diseases. RSV was developed by Astra-Zeneca and it was granted approval in 2003 by US-FDA. This article presents a literature review on hyphenated analytical techniques implemented for the estimation of RSV in pharmaceutical preparations and biological fluids.

Keywords: *Analytical methods; LC–MS/MS; GC-MS; CE-MS; LC-NMR; Rosuvastatin.*

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INTRODUCTION:

Illinois University in the 1950s led to innovation of 3-hydroxy-3-methylglutaryl-CoA [HMG CoA] by the investigators Bimal Kumar Bachhawat and Minor J. Coon, similarly recognized as β-Hydroxy β-methylglutaryl-CoA, which is a transitional in the ketogenesis and mevalonate pathways. It is made by acetoacetyl CoA and acetyl CoA from HMG-CoA synthase[1,2].HMG-CoA is a transitional metabolic in the metabolism of the amino acid chain, isoleucine, leucine and valine are included[3]. Its immediate precursors are β-hydroxy β-methylbutyryl-CoA [HMB-CoA] and β-methylglutaconyl-CoA [MG-CoA], produces mevalonic acid from HMG-CoA[4-6]. The reductase of HMG-CoA is a cholesterol biosynthesis measurement step. Statins specifically constrain the enzyme 3-hydroxy-3-methylglutaryl - coenzyme A [HMG - CoA], thus preventing the reduction of cholesterol in cardiovascular events[7].In pharmacokinetics and drug interaction studies, the development of analytical methods for the measuring of statins in biological fluids is a key determinant[8]. To produce reliable pharmacokinetic records, it is essential to use fine - categorized and completely authorized analytical methods. For the quantitation of each HMG-CoA reductase inhibitor, several analytical methods have also been developed in pharmaceutical formulations, which are crucial during the process of quality control of pharmaceutical products. In addition, analytical methods have been developed for the quantification of mevalonate acid to be used as a biomarker for statin inhibition of the enzyme. Statins specifically inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA] hence prevention of cardiovascular events due to the cholesterol reduction[9-12].

The purpose of this review is to provide an overview of relevant published literature and to discuss methods for determining RSV alone or in mixtures, in pure form, formulations and biological samples using the analytical procedure LC – MS / MS.

ROSUVASTATIN CHEMISTRY:

RSV is a synthetic compound produced as monocalcium bis [+]-7-[4-[4-fluorophenyl]-6-isopropyl-2-[N-methylN-methansulfonylaminopyrimidine]-5-yl]-[3R, 5S]-dihydroxy-[E]-6 heptenoate[13,14]. RSV configuration comprises on its own enantiomer [3R, 5S], expressed and administered as the active hydroxy acid calcium salt[15]. The chemical formula is C44H54Ca F2N6O12S2 and molecular weight is 1001.141 g/mol RSV is a white amorphous powder that is sparingly soluble in methanol [MeOH] and water and slightly soluble in ethanol [EtOH][14,16]. The pharmacophore consists of a portion of dihydroxy heptenoic acid, which binds the target enzyme HMGCoA reductase to the active position[17]. Differently from other statins, the addition of a stable polar methane sulfonamide group in the RSV structure confers relatively low lipophilicity[17,18]. The log D [distribution of the drug into octanol: water] measured at pH 7.4 is -0.33, which is comparable to pravastatin and lower than other statins [atorvastatin, fluvastatin, simvastatin, and cerivastatin][18]. The commercial formulations of RSV tablets available contain 5, 10, 20, or 40 mg of RSV[16].

PHARMACODYNAMICS, EFFICACY, AND SAFETY:

RSV showing effects on lipid profile by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase, a limiting enzyme in cholesterol biosynthesis that liable for conversion of HMG-CoA to mevalonate. RSV is a competitive inhibitor of HMG-CoA reductase, having a chemical structure very similar to HMG portion of HMG-CoA. Olsson et al.[19] have reported that a dosage of RSV starting 1 to 80 mg above 6 weeks has given rise to in LDL - C reductions ranging from 34 percent to 65 percent. There are some reports have been published on effectiveness of RSV over the other statins on reduction of LDL-C[20-22] and it shows that RSV is more effective than other statins in increasing HDL-C and lowering LDL-C at same dose[23]. RSV can be administered along with other drugs to for better management of high-risk patients whose cholesterol level cannot be controlled with RSV monotherapy[24]. In literature it is reported that, RSV showing the adverse effect such as myalgia, myopathy, rhabdomyolysis and acute liver injury[25,26].

PHARMACOKINETICS:

RSV oral bioavailability is about 20 percent and pea plasma concentration [Cmax] is reached 3-5 hours after 10-80 mg oral dose is given[27]. Cmax and area under the plasma concentration-time curve [AUC] increase proportionally to the dose. RSV administration with food decreased the ratio of drug absorption by 20 percent as assessed by Cmax; however the extent of absorption is not affected when measured by AUC[28,29]. The average volume of distribution at steady state of RSV is approximately 134 L. RSV is 88% bound to plasma proteins, mainly albumin. RSV undergoes minimal metabolism with

approximately 10% of radio- labeled dose recovered as metabolite [30-33]. RSV recovery is primarily through fecal elimination route with about 72% of absorbed RSV being eliminated through bile secretion and 28% through renal excretion. The half-life of the circulating plasma is about 20 hours [34]. No effects on RSV pharmacokinetics were observed with deference to age, sex, or daytime [morning or evening] of administration[35,36].

LIQUID CHROMATOGRAPHY-MASS SPECTROMETRY METHODS:

Liquid Chromatography / Mass Spectrometry [LC/MS] is rapidly becoming liquid chromatographers' preferred tool. It's a powerful technique of analysis combining the solving power of LC with mass spectrometry detection specificity[37-39]. Sample components are separated by LC and then introduced to the MS. The MS creates charged ions and detects them. The LC / MS data can be used to deliver information about specific sample components ' molecular weight, identity, structure and quantity[40]. LC-MS/MS method is the most explored technique for quantitative analysis of RSV alone or in mixture.

Table 1[41-60] express the LC-MS/MS technique for RSV analysis alone or in mixture with other drugs determined in biological fluids. Most LC-MS/MS analyses were performed in +ve ion mode [ESI+] for the quantification of RSV in human plasma. LC-MS/MS methods were performed with a C18 analytical column and the mobile phase was composed by MeOH or ACN as organic solvent and water with volatile additives including acetate and formic acid, which were added to enhance ionization and increase the method's sensitivity. Multiple reaction monitoring [MRM] was the most commonly used method and the selected [MRM] precursor ion was [M+H+] at m / z 482.RSV can be detected in both +ve and -ve ionization modes of a mass spectrometer, since its structure contains a pyrimidine ring and a carboxylic ring. In order to improve sensitivity, electrospray ionization in the negative mode [ESI-] could be used for MS/ MS detection of RSV in plasma that produced abundant deprotonated molecule [M-H-] at m/z 480 as demonstrated by Gao et al. Retention times were very short, including methods for simultaneous analysis with other drugs, ranging from 0.9 minutes up to 4.1 minutes. Isocratic elution was applied in most cases. More sensitive methods have been developed using LC–MS/MS with linearity ranging from 0.02 ng/mL to 512 ng/mL. A method using LC-MS/MS equipped with an ESI interface and operated in -ve ionization mode was employed with this aim contrast to the most usual method that uses positive ionization mode for RSV detection. RSV retention time was 4.18 minutes, and the final analysis eluted at 4.95 minutes. Kosek et al. recently reported a sensitive LC - MS / MS method to quantify all statins in human plasma simultaneously. The mass spectrometry was conducted in negative ion electrospray mode for RSV determination and it showed retention time at 3.08 minutes and the lower concentration in the linearity range of 0.4 ng/mL.

Gandla et al. LC - MS / MS technique for RSV resolution in human plasma was studied and certified. RSV d6 has been used as an internal standard [IS]. The method employs lesser plasma volume [100 µL] processed by simple solid-phase extraction [SPE] procedure. This method possesses a suitable degree of precision and accuracy in accordance with US FDA guidelines. The runtime was also set at 2 min, which is fast and more samples can be studied in a day. This analytical method can be obliging for estimating the pharmacokinetics of oral RSV for a pharmacokinetic or bioavailability/bioequivalence studies[41]. **Bai X et al.** has developed rapid and susceptible ultra-performance liquid chromatography-tandem mass spectrometry [UPLC-MS/MS] assay was established and certified for the simultaneous quantification of RSV, RSV-5 S-lactone [RSV-LAC], and N-desmethyl RSV in human plasma. Mass spectrometry detection was performed through positive ion electrospray ionization [ESI][42]. **Kumar et al.** were developed LC-MS / MS technique for simultaneous resolution of RSV and metformin [MET] in human plasma. Simple protein precipitation with acetonitrile [ACN] involved the assay procedure. The portion of supernatant was transferred after precipitation and vaporized under a mild flux of nitrogen [40°C]. The mobile phase residue was reconstituted and injected[43].**B. Siddartha et al.** has reported the LC-MS/MS method stands validated and is suitable for estimation of plasma RSV concentrations as a single analytical run, in clinical samples from Bioequivalence studies following oral administration of RSV fixed dose [5/10/20mg] tablets in healthy human subjects[44].**A. Narapusetti et al.** established and certified a rapid, selective and sensitive LC - MS / MS method in MRM mode to determine RSV and amlodipine [AML] in human plasma simultaneously. The proposed technique was fast with a 2.5 min of chromatographic run time and simultaneously suitable for high - performance bioanalysis of RSV and AML. In addition, the method demonstrated suitability for human clinical studies. Furthermore, the sample reanalysis incurred

effectively proves that the assay is reproducible[45].**Varghese and Ravi** studied simultaneous quantitation of RSV and ezetimibe [EZE] in biological fluid [human plasma] by LC-ESI/MS method Selected ion observing using their particular [M-H] - ions, m/z 480, m/z 408, and m/z 557 respectively for RSV, EZE and Atorvastatin [ATV] as IS was performed on a mass spectrometer. This method was used for pharmacokinetic, bioavailability, or bioequivalent studies of RSV and EZE in human plasma[48].**R.K. Trivedi et al.** has reported validated LC-MS/MS described herein for the simultaneous estimation of RSV and fenofibric acid [FEA] in human plasma is specific, accurate, precise and reproducible. In addition, the present technique utilizes a single step liquid/ liquid extraction technique with a commercially available IS. The assay was positively applied in a clinical pharmacokinetic study to simultaneously determine the concentration - time profiles of RSV and FEA[59]. **C.K. Hull et al.** has reported sensitive, accurate, reproducible and specific LC-MS/MS technique for the quantification of RSV in human plasma. With a 0.1 ng/ml lover limit of quantification [LLOQ], the desired sensitivity for RSV was achieved. When stored at -220 and -270 ° C, RSV was shown to be stable in routine analytical conditions and human plasma and buffered plasma for up to 6 months. A number of thousands of human plasma samples from a series of human RSV clinical studies were successfully analyzed using the method[60].

CAPILLARY ELECTROPHORESIS-MASS SPECTROSCOPY:

Mohemad Dowod et al. has studied method with the EOF reversal agent, polybrene, in monoammonium carbonate electrolyte, pH 9.00. The ionic power and the quantity of MeOH in buffer were optimized in a multivariate manner use of artificial neural complexes, with optimum conditions being 60mM monoammonium carbonate containing 60 percent MeOH, providing baseline determination within 20 min of the five hypolipidaemics. Using electrokinetic supercharging, the sensitivity of the technique was 1000-fold improved over conventional injections under field-amplified fraction stacking conditions with 180 ng / L LODs. This is the 1st report of CE separation of hypolipidaemics[Pravastatin, Fluvastatin, Atorvastatin, gemfibrozil, Rosuvastatin]. The method was validated and then applicable to the determination of objective drugs in water fractions from Hobart city[61].

GAS CHROMATOGRAPHY-MASS SPECTROSCOPY:

B. H. Woollen et al. has explained study of 3,5-Dihydroxy-3-methylvaleric acid [MVA] in human urine including transformation to MVA lactone [MVAL] and examination by GC-MS. A strategy was explained to achieve a low limit of quantitation to overcome the constraint that calibration must be executed in urine [since MVAL is adsorbed in the absence of matrix] and control urine every time contains significant amounts of MVA. Information are presented for authentication of the technique over the range 75-300 ng mL-1 and for application of the method to a clinical studied with the drug rosuvastatin[62].**Ali Ismail et al.** determined the residual solvents present in some statins. A selective Gas chromatography with headspace and Mass Spectrometer detectors [HS-GC-MS] has been developed and validated according to different aspect of validation as per ICH. The method has been found to be simple, sensitive, rugged, reliable and reproducible for the quantitation of n-hexane and ethanol widely used during synthesizing of atorvastatin and rosuvastatin or formulating into dosage form. The limit of detection was calculated to be 2.53 ppm and 1.63 ppm per sample for ethanol and n-hexane, respectively. Limit of quantification was 7.59 ppm ethanol, LOQ= 4.89 ppm for n-Hexane. Correlation factor was 0.999 for both ethanol and n-hexane. The percentage recovery was calculated and the value was 99.29 % and 96.01% for ethanol and *n*-hexane, respectively. The total run is 16 minutes[63].

LIQUID CHROMATOGRAPHY-NUCLEAR MAGNETIC RESONANCE:

Shahu A. et al. studied forced degradation behavior of rosuvastatin under conditions prescribed by ICH. Under acid hydrolytic and photolytic circumstances, the drug was originated to be labile, while base / neutral hydrolytic, oxidative and thermal stress was stable. A total of 11 degradant were prepared, performed on a C-18 column with a stability-indicating technique. LC-MS analyzes specified that five degradation products had the similar molecular mass as the drug, while the remains six had 18 Da less than the drug. Structural elucidation of all the degradant products was performed with the help of sophisticated and modern structural description tools, viz. LC-MS/TOF, LC-MS, on-line H / D exchange and Liquid Chromatography-NMR. The drug's mechanisms of degradation and degradation pathway were delineated. In addition, toxicity in-silico was predicted and equaled with the drug for all degradation products with the help of DEREK and TOPKAT software[64].

CONCLUSIONS:

The present review article gives the comprehensive details about LC-MS/MS, CE-MS, GC-MS, LC-NMR methods applied for the analysis of RSV in pharmaceutical formulation and various biological matrices. Most of these validated hyphenated methods are specific, sensitive, reproducible and accurate. These bioanalytical methods are support to estimation of pharmacokinetic or bioavailability or Bioequivalence studies of oral solid dosage form containing RSV. In this review, the bioanalytical data support the utility of the methods for therapeutic drug monitoring and also for routine chemical sample analysis with desired analogues.

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Chemical formula-

$C_{44}H_{54}CaF_2N_6O_{12}S_2$

Molecular weight-

1001.141 g/mol

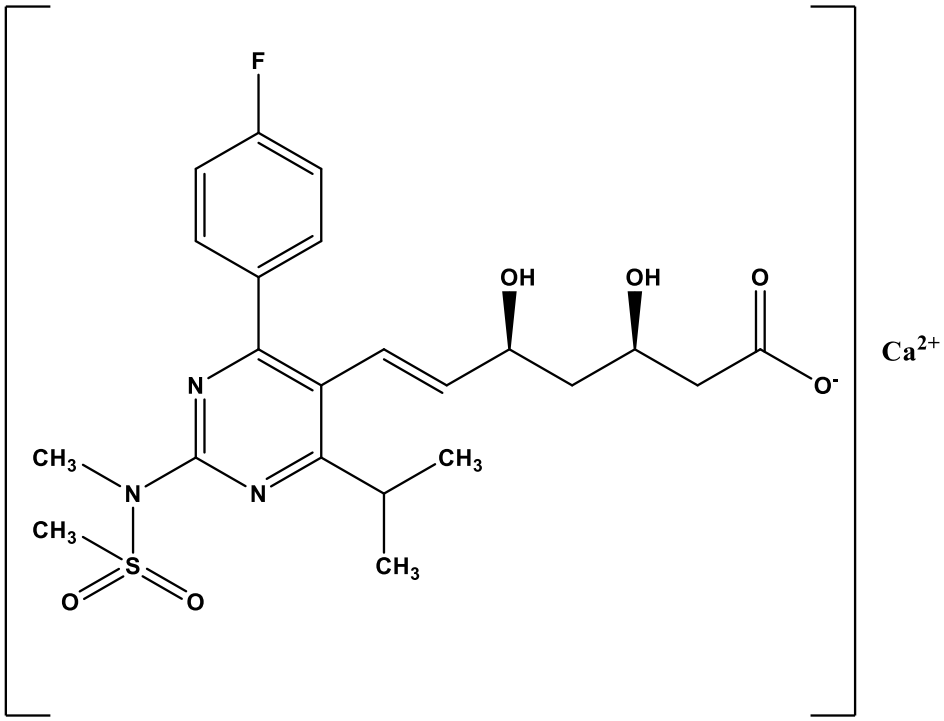

Figure 1. Chemical structure of rosuvastatin calcium

TABLE 1- LIQUID CHROMATOGRAPHY-MASS SPECTROSCOPY

Drug	Matrices	Interface	Extraction method	Column & Mobile Phase	Flow Rate [ml/min]	Rt [min]	Linearity range	LLOQ	Reference
2017									
RSV	Human plasma	Turboionspray [ESI]	Simple solid phase extraction method, Rosuvastatin d6 as internal standard	Discovery HS C18 [50 mm×4.6 mm, 5µm] column & Ammonium acetate [5mM, pH 3.5]: acetonitrile [20:80, v/v]	0.7	0.85	0.51-100.9 ng/mL	0.51 ng/mL	41
RSV & RSV-LAC & N-Desmethyl RSV	Human plasma	ESI	Liquid-liquid extraction with ethyl acetate from 100 µL acidulated buffered plasma	Acquity UPLC HSS T3 column [100 mm×3.0 mm, 1.8 µm] & 0.1 % gradient formic acid [A]: acetonitrile [solvent B] in gradient elution	0.3	2.69 & 3.10 & 2.33	0.1-50 ng/ml & 0.2-100 ng/ml	0.1 ng/ml & 0.2 ng/ml	42
2015									
RVS & MET	Human plasma	ESI	fortified postextracted sample	Thermo Hypurity C18column [50 mm×4.6 mm, 5 µm] & 0.1% v/v formic acid in water: acetonitrile [30:70 v/v]	0.4	2.01 & 1.43	0.5-200 ng/mL & 2-2000 ng/mL	0.5 ng/mL & 2 ng/mL	43
2014									
RSV	Human plasma	Turboionspray	Solid Phase Extraction; and extracted from human plasma	C18 column [50 mm×4.6 mm, 3 µm] & Acetonitrile: 10 mM ammonium acetate at pH 3.1 [55:45 v/v]	1	1.34	0.5-512 ng/mL	0.5 ng/mL	44

RSV & AML	Human plasma	Turboionspray at 550℃	Liquid-liquid extraction using a mixture of ethyl acetate and n-hexane [80:20, v/v]	Zorbax SB C18 column [50 mm×4.6 mm, 3.5 µm] & 0.1% formic acid in 5 mM ammonium acetate: methanol: acetonitrile [20:20:60 v/v/v]	0.75	1.30 & 1.7	0.52-51.77 ng/mL & 0.10-10.07 ng/mL	0.52 ng/mL & 0.10 ng/mL	45
RSV & N-Desmethyl RSV	Human plasma	ESI	Liquid-liquid extraction using acetonitrile	HiChrom C18 [150mm×3.0mm, 3 µm] & 0.1% formic acid in acetonitrile: 0.1 % formic acid in water [70:30 v/v]	0.3	3.38 & 2.64	0.2-20 ng/mL & 0.1-10 ng/mL	0.1,0.2 ng/mL & 0.03, 0.1 ng/mL	46
2013									
RSV & N-Desmethyl RSV	Human plasma	ESI	Liquid-liquid extraction using diethyl ether	X-Terra MS C-18 column [50 mm×4.6mm, 5.0 µm] & 15 µmol/L ammonium acetate in water [solution A] and in methanol [Solution B], adjusted to pH 6 with aqueous ammonia [2 mol/L]	0.4	5.061 & 4.226	0.05-42 µg/mL & 0.02-14 ng/mL	0.05 µg/mL & 0.02 µg/mL	47
RSV & EZE	Human plasma	ESI	Liquid-liquid extraction, atorvastatin as internal standard	Luna C18 column [150×4.60 mm, 5 µm] & 0.1% [v/v] formic acid: methanol [20:80 v/v]	1	2.7 & 3.4	0.1-10 ng/mL	0.10 ng/mL	48
2011									
RSV	Human plasma	ESI	Liquid-liquid extraction and solid-phase extraction and extracted with ethyl acetate	Diamonsil C18 column [150 mm×4.6 mm,5 mm] & Acetonitrile: Methanoic acid [0.1%] [60:40 v/v]	0.8	3 .0	0.1-60 ng/mL	0.1 ng/mL	49

RSV	Tablet	ESI	Solid-phase extraction and extracted with methanol	C8 [50 mm×4.6 mm, 5µm] & 0.2% acetic acid: methanol [60:40 v/v]	0.3	6.5	1–6 µg/mL	1 µg/mL	50
RSV & RSV-LAC & N-Desmethyl RSV	Human plasma	ESI	Liquid-liquid and solid-phase extractions and extracted from 50 µL of buffered human plasma by protein precipitation	Zorbax-SB Phenyl column [100 mm×2.1 mm, 3.5 µm] & 0.1% v/v glacial acetic acid in 10% v/v methanol in water [solvent A] and 40% v/v methanol in Acetonitrile [solvent B]	0.35	3.3 & 2.8 & 3.8	0.1-100 ng/mL DM-RSV-0.5-100 µg/mL	0.1 ng/mL DM-RST-0.5	51
2009									
RSV	Human plasma	Turboionspray	Automated liquid-liquid extraction	Symmetry shield RP18 column [50mm×4.6 mm,3.5 µm] & A:Water: methanol [35:65 v/v]; ammonium formate 5mM; B: 100% methanol, gradient elution	1	0.90	50-25000 pg/ml	100 pg/ml	52
2007									
RSV	Human plasma	Turboionspray 475℃	solid-phase extraction and internal standard from plasma with acetonitrile	Inertsil ODS 3 column [100mm × 4.6mm, 3.0 µm] & 0.05 mol/L formic acid: acetonitrile [20:80 v/v]	0.5	1.8	0.5-50 ng/mL	1 ng/mL	53
RSV	Human plasma	Turboionspray [ESI]	liquid–liquid extraction with ethyl ether	Zorbax XDB-C18 [150mm×4.6mm, 5 µm] column & methanol–water [75:25v/v] adjusted to pH 6 by aqueous ammonia	0.5	2.36	0.02-60 ng/mL	0.02 ng/mL	54

RSV	Human plasma	ESI	Liquid-liquid extraction, Internal standard estrone	Phenomenex Luna C18 5µm [150 mm×4.6mm] & 2% formic acid: methanol [20:80 v/v]	1	2.3	0.1-20 ng/mL	0.1 ng/mL	55
2006									
RSV	Human plasma	ESI	Liquid-liquid extraction internal standard Cilostazol extracted with ether	Atlantis C18 column [150mm×2.1mm, 5.0 µm] & 0.2% formic acid: methanol [30:70 v/v]	0.2	4.13	0.2-50 ng/mL	0.2 ng/mL	56
RSV	Human plasma	Turboionspray	Solid-phase extraction	Microbore columns packed with Luna C18 [5cm×2.0, 1.0 and 0.5 mm]3µm & Methanol: water [7:3 v/v] with 0.2% [v/v] formic acid	0.06	1.8	0.05-50 ng/mL	0.05 ng/mL	57
2005									
RSV	Human plasma		Solid phase extraction	YMC J' Sphere ODS H-80 column[150 mm×4.6 mm, 4.0 µm] & 0.2% formic acid in Water: acetonitrile [40: 60 v/v]	1	2.5	1-50 ng/mL	0.25 ng/mL to 100 µL	58
RSV & FEA	Human plasma	Turboionspray At 400℃	Liquid-liquid extraction, Carbamazepine as internal standard from plasma into ethyl acetate	X-Terra MS C-18 column [50 mm×4.6mm, 5.0 µm] & 0.05M formic acid: acetonitrile [45:55 v/v]	0.4	2.35 & 4.70	1-50 µg/mL	1 µg/mL	59
2002									
RSV	Human plasma	Turboionspray	Automated solid-phase extraction	Luna C18 [150 mm×4.6 mm,5 µm] & Methanol: 0.2% formic acid in water [70:30 v/v]	1	3.63	0.1-30 ng/mL	0.1 ng/mL	60

Abbreviation: RSV-LAC: RSV-5S-lactone; MET: metformin; AML: amlodipine; EZE: ezetimibe; FEA: fenofibric acid; ESI: electrospray ionization; Rt: retention time; LLOQ: lower limit of quantification