Mini Review

A brief review of various analytical methodologies for quantitative analysis of telmisartan and rosuvastatin calcium in different matrices.

Alaa Ahmed Mostafa [1, *], Michael Gamal Fawzy [1], Abdalla Shalaby [2], Rania Adel Sayed [2]

[1] Pharmaceutical Chemistry Department, Faculty of Pharmacy, Egyptian Russian University, Badr City, Cairo 11829, Egypt.

[2] Analytical Chemistry Department, Faculty of Pharmacy, Zagazig University, Zagazig 44519, Egypt.

*Corresponding author: Alaa Ahmed Mostafa, E-mail: Alaa-azzam@eru.edu.eg, Tel: +201015810943.

ABSTRACT

Cardiovascular diseases including hypertension and hypercholesterolemia considered to be two of the most chronic, age-related risk factors. Both risk factors controlling process may require a combination of lifestyle modification and pharmaceutical medication either single or combined. Appropriate lifestyle changes may help to control some forms of hypertension as excess body fat is a major contributor to hypertension, along with dietary salt, alcohol, and inactivity. Most cases of hypertension accompanied by hypercholesterolemia require a single or combination of antihypertensive agents e.g. diuretics, angiotensin-converting enzyme inhibitors, calcium channels blockers, and/or angiotensin II receptor blockers with antihyperlipidemic agents e.g. fibrates, or statins. The pharmaceutical product contains telmisartan (TMS) and rosuvastatin calcium (RVS) in one tablet under the trade name of Telrose® used for the treatment of cardiovascular including hypertension and hypercholesterolemia. This study examines various analytical approaches, such as UV-visible spectroscopy, spectrofluorimetric, chromatographic, electrochemical, and capillary electrophoresis techniques, for quantifying TMS and RVS in their fixed-dose pharmaceutical formulation and other matrices. The comparative use of various analytical methods for quantifying TMS and RVS is discussed in this review. Further analytical research for estimating TMS and RVS may be successfully conducted using the information presented in this review paper.

Keywords: Telmisartan; rosuvastatin calcium; HPLC; spectrophotometry; cardiovascular.

1. Introduction

Chronic, ubiquitous, and age-related, hypertension accompanied by Hypercholesterolemia frequently has crippling cardiovascular and renal effects. Typically, hypertension is reported together with other cardiovascular risk factors (1).

Both economically developed and developing nations contend with hypertension as a major public health issue(2). Nowadays, more people suffer from hypertension and hyperlipidemia, especially in low- and middle-income countries. Estimates show that 31.1% of adults globally have hypertension. In low and middle-income countries adult hypertension was more prevalent than in high-income ones (28.5%)(3).

The cardiovascular condition controlling process may require a combination of lifestyle modification and pharmaceutical medication either single or combined. Appropriate lifestyle changes may help to control some forms of hypertension as excess body fat is a major contributor to hypertension, along with dietary salt, alcohol, and inactivity(4).

Most cases of hypertension accompanied by hyperlipidemia require a single or combination of antihypertensive agents e.g. diuretics, angiotensin-converting enzyme inhibitors (ACEIs), calcium channels blockers (CCBs), and/or angiotensin II receptor blockers (ARBs)(5) with antihyperlipidemic agent e.g. fibrates, or statins.

TMS (Figure, 1A), under the chemical name of 4c-[4-Methyl-6-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl] methyl] Biphenyl-2-carboxylic acid. A long-acting nonpeptide antagonist of the angiotensin II type 1 (AT1) receptor that is used to treat essential hypertension. It achieves this specifically and irreversibly prevents the activation of the AT1 receptor by angiotensin II without affecting other receptor systems involved in cardiovascular regulation(6). The medicine may have the therapeutically significant advantage of having good tissue penetration because of telmisartan's unusually high lipophilicity and high volume of distribution(7).

TMS is a white or slightly yellowish, crystalline powder. Sparingly soluble in methylene chloride, slightly soluble in methanol, and practically insoluble in water. It dissolves in 1 M sodium hydroxide with a molecular weight (514.6 g/mol)(8,9).

RVS (Figure, 1B), under the chemical name of Calcium (3R,5S, E)-7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido) pyrimidine-5-yl)-3,5-dihydroxyhept-6-enoate salt. A synthetic lipid-lowering medication for high cholesterol. It is a competitive inhibitor of 3-hydroxy-3-methylglutaryl reductase that is selective.

A preliminary and speed-limiting stage in the production of cholesterol(10). This inhibition lowers the levels of low-density lipoprotein in the blood through two different mechanisms: first, by lowering mevalonate levels, which decreases the regulatory sterol pool and causes an increase in the hepatic low-density lipoprotein receptors, which are responsible for removing low-density lipoprotein from the blood; and second, by blocking the synthesis of very low-density lipoprotein in the liver(11). RVS white crystals or crystalline powder. Soluble in organic solvents such as DMSO, and dimethyl formamide. slightly soluble in water and aqueous buffers with a molecular weight (1001.1 g/mol) (8,9).

The review aimed to determine the percentage of analytical methods (chromatographic, spectrophotometric, fluorometric, and electrochemical) that were utilized for the defemination of TMS (Figure, 2) and RVS (Figure, 3). Also, the review illustrated the methods utilized for the determination of the binary pharmaceutical dosage form.

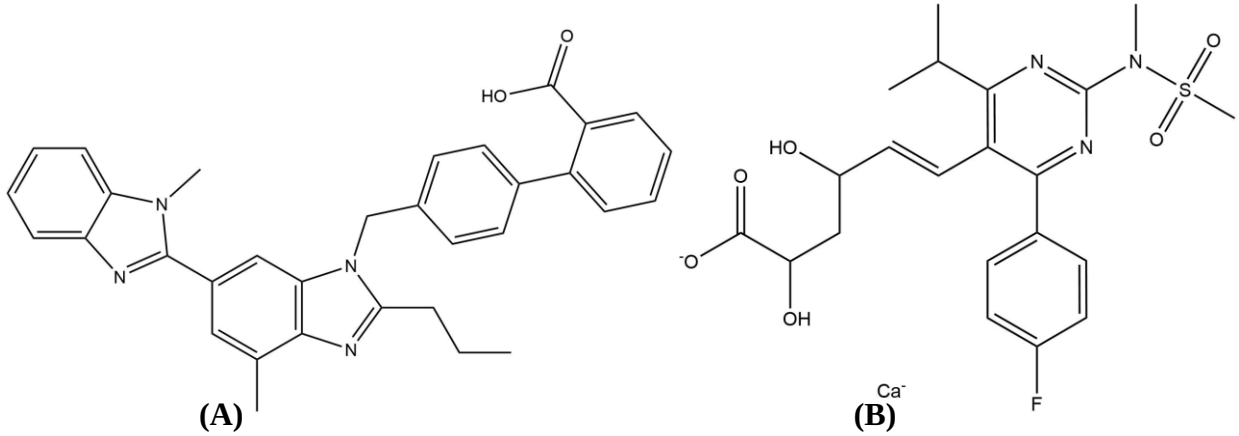

Figure 1: Chemical structures of (A) telmisartan, and (B) rosuvastatin calcium.

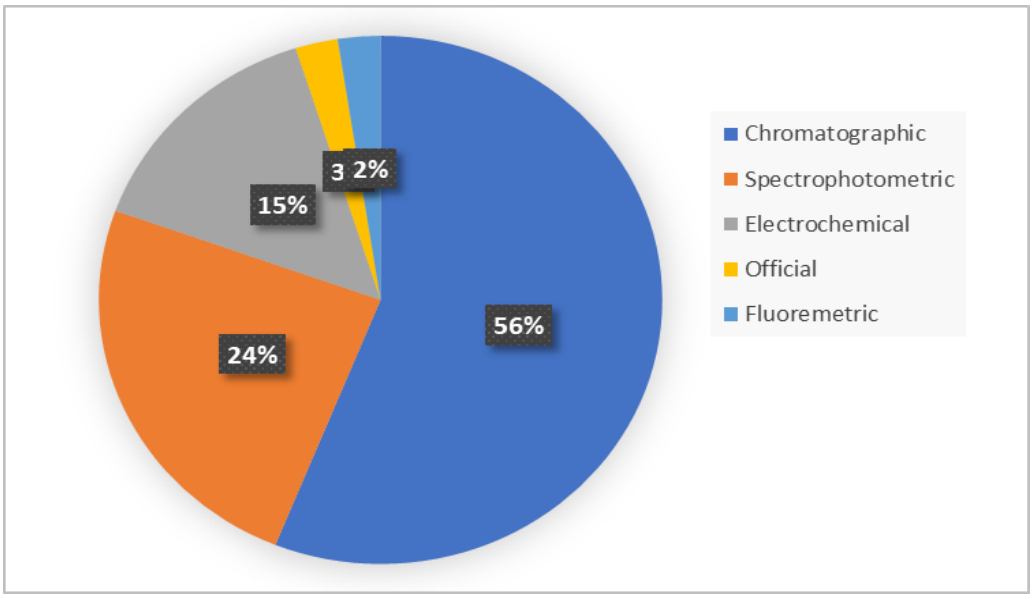

Figure 2: The pie chart represents the percentage of different analytical methods for TMS determination.

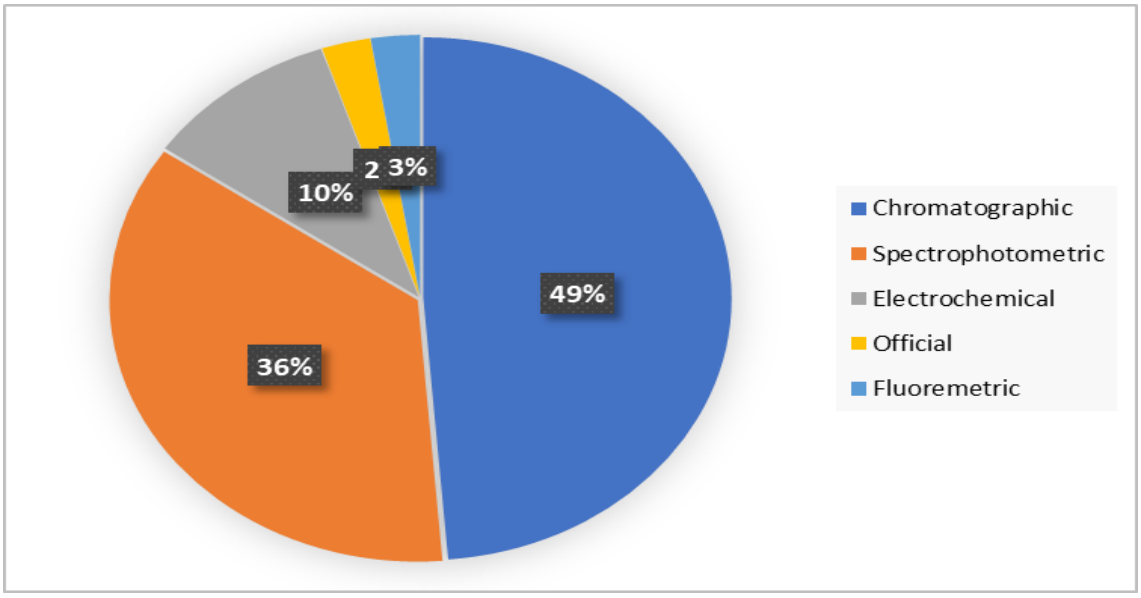

Figure 3: Pie chart represents the percentage of different analytical methods for RVS determination.

2. Analytical techniques

2.1. Official and reported analytical methods for the analysis of TMS

2.1.1. Official analytical method

TMS is identified in BP by Infrared absorption spectrophotometry by dissolving in alcohol and evaporating the solution while the spectrum of the residue is examined. It is determined in USP by titration of where telmisartan is dissolved in 5 ml anhydrous formic acid and diluted with 75 ml of acetic anhydride and titrated against 0.1 M perchloric acids.

2.1.2. Reported analytical methods

a. Spectroscopic methods

UV spectrophotometric methods

- Ten spectrophotometric methods were reported for the estimation of TMS in bulk and tablet (12–21) by utilizing different solvents and different absorbance maxima.
- Four spectrophotometric methods were reported for the estimation of TMS in bulk (22), pharmaceutical dosage form (23,24), and urine samples (25) by colored complex formation.

Spectrofluorimetric method

- The spectrofluorimetric method was developed for TMS determination. The method measured excitation 336 nm at and emission at 475nm utilizing 0.1M NaOH as a solvent (26).

b. Electrochemical methods

- The conductimetric method was developed for the determination of TMS in pure and tablet formulations. The method depends on the weak acid properties of TMS which can be quantified by measuring its conductance in alcoholic media (27).
- The square wave adsorptive stripping voltammetric method was developed for the determination of TMS in tablets and human plasma. The method was applied at pH 10.38 (28).
- The voltammetric method was developed for the determination of TMS. The method was applied using sodium dodecyl sulfate-modified pyrolytic graphite surface (29).
- The cathodic adsorptive stripping voltammetric method was developed for the determination of TMS in pharmaceuticals and biological fluids. The method was applied at pH 10.00 (30).

c. Chromatographic methods

High-performance thin-layer chromatography

- Two HPTLC methods were developed for the determination of TMS in tablets. The methods utilized silica Gel 60 F254 TLC for separation. The first method used a solvent system comprised of Toluene: Methanol (7:3 *v/v/v*). The UV detector was adjusted to 299 nm for the detection of TMS (31). The second method utilized a solvent system comprised of ethyl acetate: dichloromethane: methanol (6:2:1 v/v). The UV detector was adjusted to 295 nm for the detection of TMS (32).

High-performance liquid chromatography

Table 1: The reported chromatographic methods for simultaneous determination of TMS.

Column	Mobil phase	Flow rate	Detector	Sample matrix	Ref
Shimadzu - C18	0.025M potassium dihydrogen phosphate: acetonitrile: methanol (45:50:5, v: v: v).	1.0 ml/min.	UV at 216 nm	Bulk and tablet formulation.	(33)
Chromosil -C18	Methanol: 0.1% Orthophosphoric acid: acetonitrile in the ratio of (80:05:15 v/v/v).	1.5 ml/min.	UV at 256 nm	Tablet formulation.	(34)
sun fire - C18	Pentane sulphonic acid sodium salt monohydrate with Triethyl amine: Methanol in the ratio (40: 60 v/v).	1.2 ml/min.	UV at 230 nm	Bulk and tablet formulation.	(35)
Prontosil ODS -C18	Acetonitrile: Buffer in proportion of (90:10 v/v).	1.0 ml/min.	Fluorescence at 259 nm excitation and 399 nm emission	Bulk and tablet formulation.	(36)
Hypersil - C18	Methanol: water 80:20 (v/v).	1.0 ml/min.	UV at 225 nm	Bulk and tablet formulation.	(37)

Column	Mobil phase	Flow rate	Detector	Sample matrix	Ref
Xterra - C8	Buffer: methanol 40: 60 (v: v)	0.5 ml/min.	UV at 230 nm	Bulk and tablet formulation.	(38)
Chromolith - C18	0.1% trifluoroacetic acid and acetonitrile (83.7:16.3, v/v)	0.5 ml/min.	UV at 230 nm	Drug and related impurities	(39)
Inertsil ODS -C18	Potassium dihydrogen orthophosphate buffer with Triethylamine and phase B of use filter and degas acetonitrile.	1.0 ml/min.	UV at 246 nm	Drug and related impurities	(40)
Waters symmetry - C18	10 mM potassium dihydrogen phosphate: acetonitrile (64:40, v: v).	1.0 ml/min.	UV at 230 nm	Drug and degradation products.	(41)
Kromasil C18	0.1 % ammonium hydroxide solution with acetonitrile: methanol (80:20, v: v).	1.0 ml/min.	UV at 230 nm	Drug and related substances.	(42)
Lichrosphere - C18	20 mM ammonium acetate containing 0.1% (v/v) Triethyl and acetonitrile.	1.0 ml/min.	UV at 254nm	Drug and related compounds.	(43)
Chromosil - C18	Acetonitrile: methanol: sodium dihydrogen orthophosphate (0.01 M) in the ratio of (41:10:49, v: v: v).	1.0 ml/min.	UV at 291 nm	Bulk and plasma.	(44)
Phenomenex Luna - C8	Methanol and acetonitrile (70:30 %v/v).	1.0 ml/min.	UV at 290 nm	Rat plasma.	(45)
Hypurity - C18	Acetonitrile: Ammonium format buffer 2 mM (70:30 v/v).	0.5 ml/min.	MS/MS 513.2/469.3 m/z.	Human plasma.	(46)

Column	Mobil phase	Flow rate	Detector	Sample matrix	Ref
UPLC-MS/MS BEH- C18	Acetonitrile: 8 mM ammonium acetate containing 0.15 % formic acid (70:30, v: v).	0.3 ml/min.	515.27→276.13 m/z.	Human plasma.	(47)
UPLC-BEH - C18	Acetonitrile: methanol : water (75 : 15 : 10 v/v/v).	0.33mL/min	UV at 235	Bulk and its forced degradation products.	(48)
UPLC-Waters Aquity BEH - C18	10mM Ammonium acetate with the addition of 1mL Triethyl amine, and Acetonitrile in the ratio (90:10, v/v);	0.3 mL/min	UV at 235	Bulk and tablet formulation and its related substances.	(49)

2.2. Official and reported analytical methods for the analysis of RVS

2.2.1. Official analytical method

RVS is determined in USP by high-performance layer chromatographic method where the mobile phase consisted of acetonitrile 1%, aqueous trifluoroacetic acid, and water (29:1:70), and the ratio changed to (75:1:24) after 50 minutes. The drug was dissolved in acetonitrile. Elution utilized 3.0-mm × 15-cm; 3-µm packing L1 column at temperature 40º with UV detector at 242 nm. Injection volume 10µL and flow rate 0.75 ml/minute.

2.2.2. Reported analytical methods

a. Spectroscopic methods

UV spectrophotometric methods

- Three spectrophotometric methods for determination of RVS in bulk and pharmaceutical dosage form. The drug was measured at 244 nm (50), at 242.8 nm (51), at 242 nm (52), and at 234.6: 251 nm (53).
- Five spectrophotometric methods were developed for the determination of RVS in pure form and pharmaceutical dosage form by the formation of the ion-pair complex (54–58) utilizing different agents and different absorbance maxima.

- One stability-indicating spectrophotometric method for the estimation of RVS and its oxidative degradation products (59).

Spectrofluorimetric method

- Spectrofluorimetric method for estimation of RVS in bulk and pharmaceutical dosage form. The method depends on the reaction of RVS with sulphuric acid. The drug was measured at excitation 227 nm and emission at 370 nm (60).

b. Electrochemical methods

- The square wave voltammetric method was developed for the determination of RVS in pharmaceuticals and biological fluids (61–64). The methods utilized different pretreated types of electrodes.
- The cyclic voltammetric method was developed for the determination of RVS in human plasma. The method utilized hanging mercury electrode novel nanocomposites prepared from spinel copper ferrite and reduced graphene oxide (65).
- The cyclic voltammetric method was developed for the determination of RVS in human plasma. The method utilized reduced graphene oxide and silver nanocomposite (66).

c. Chromatographic methods

High-performance thin-layer chromatography

- Stability-indicating HPTLC methods for determination of RVS and its oxidative degradation products utilizing mobile phases: Eethyl acetate: methanol: ammonia (7:3:0.01, v/v/v) (59), Chloroform: n-hexane: methanol: glacial acetic acid (8:10.4:1.5:0.1 v/v/v/v) (67). The drug was detected at 245 nm in both methods.

- Stability-indicating HPTLC method for determination of RVS in tablets. Acetonitrile: Ethyl Acetate: Toluene (6:1:3 v/v/v) was utilized as a mobile on silica gel 60 F_{254} as a stationary phase. The drug was detected at 245 nm (68).

High-performance liquid chromatography

Table 2: The reported chromatographic methods for simultaneous determination of RVS.

Column	Mobil phase	Flow rate	Detector	Sample matrix	Ref
Luna - C18	Buffer: Acetonitrile: methanol (45:25:35, v: v: v).	1.0 ml/min	UV at 248 nm	Bulk and tablet formulation.	(69)
Nucleodur - C8	Ethanol: methanol: ethyl acetate (6:3:1 v/v)	1.0 ml/min	UV at 254nm	Bulk and tablet formulation.	(70)
Thermo Hypersil - C18	Methanol: water (90:10, v: v)	0.9 ml/min	UV at 243 nm	Bulk and tablet formulation.	(71)
Thermo scientific C8	Methanol: acetonitrile: water (40:40:20, v/v).	1.0 ml/min	UV at 248 nm	Bulk and tablet formulation.	(72)
YMC - C8	Acetonitrile: water (40:60, v/v).	1.5 ml/min	UV at 242 nm	tablet formulation.	(73)
Nucleodur - C8	0.1M formic acid and methanol (25:75, v/v).	1.0 ml/min	UV at 280 nm	Bulk and tablet formulation.	(74)
Kromasil -C8	Acetonitrile and water (75:25 v/v).	1.0 ml/min	PDAD at 240 nm	Bulk and tablet formulation.	(75)
Phenomenex -C 18	Acetonitrile and buffer (50:50, v: v).	1.0 ml/min	UV at 254nm	Bulk and tablet formulation.	(76)
Phenomenex, Synergi - C18	Acetonitrile: water (40:60, v: v).	1.0 ml/min	Fluorescence at 366 nm excitation and 410 nm emission.	Bulk and tablet formulation.	(77)
Eclipse XDB - C8	Sodium dihydrogen phosphate: acetonitrile (50:50 v/v)	1.2 ml/min	UV at 248 nm	Bulk and tablet formulation.	(78)

Column	Mobil phase	Flow rate	Detector	Sample matrix	Ref
Princeton - C18	A mixture of water and methanol in the ratio (20:80, v: v).	1.0 ml/min	UV at 240 nm	Bulk and tablet formulation with degradation products.	(79)
Sunfire - C18	10 mM ammonium acetate and acetonitrile: methanol (50:50 v/v).	1.0 ml/min	UV at 242 nm	Drug and its lactone impurity.	(80)
C18	Water: acetonitrile: methanol (40: 40: 20, v: v: v).	1.0 ml/min	UV at 245 nm	Drug and its oxidative degradation products.	(59)
Waters Acquity UPLC -C18	Methanol and 0.1% trifluoroacetic acid (50:50, v: v).	0.3 ml/min	UV at 240 nm	Drug and its related impurities.	(81)
LC-MS/MS - Diamonsil C18	Acetonitrile-methanolic acid (0.1%) (60:40, v/v).	0.8 ml/min	MS/MS 482.1 → 258.1 m/z.	Human plasma.	(82)
HiChrom C18	0.1% formic acid in acetonitrile and 0.1% formic acid in water (70:30 v/v).	0.3 ml/min	MS/MS 482.1 → 258.1 m/z.	Human plasma.	(83)
Zorbax-SB Phenyl column.	0.1% v/v glacial acetic acid in 10% v/v methanol in water and 40% v/v methanol in acetonitrile.	0.35 ml/min	MS/MS 470.2 → 276. 2 m/z.	Human plasma.	(84)
Xterra - C18	15 µmol/L ammonium acetate in water and methanol.	0.4 ml/min	MS/MS480.1 → 418.1 m/z.	Human plasma.	(85)
Phenomenex Kinetex- C18	0.1% *v/v* glacial acetic acid in Aqueous formic acid (0.1%) and methanol.	0.2 ml/min	MS/MS 482.3→258.2 m/z.	Human blood.	(86)
Xterra - C18	A mixture of acetonitrile and 10 mM ammonium acetate (55:45, v: v).	0.3 ml/min	MS/MS 481.3→256.0 m/z.	Human blood.	(87)

2.3. Recently reported analytical methodologies for the determination of TMS and RVS in binary mixtures

a. Spectroscopic methods

UV spectrophotometric methods

- Two spectrophotometric methods were developed for the simultaneous determination of TMS and RVS pharmaceutical dosage forms. The first method depends on measuring the absorbance at 243.8nm and 295.3nm for RVS and TMS, respectively (88). The second method utilized four mathematical and ratio spectra manipulations to resolve severely overlapped spectra (89).

b. Chromatographic methods

High-performance liquid chromatography

Table 3: The reported chromatographic methods for simultaneous determination of TMS and RVS in binary mixtures

Column	Mobil phase	Flow rate	Detector	Sample matrix	Ref
Oyster ODS3 - C18	10 mM phosphate buffer with 1.1 g octane-1-sulfonic acid sodium salt and acetonitrile, (50:50, v/v).	1.0 ml/min	UV at 242 nm.	tablet formulation.	(90)
Kinetex - C18	ammonium phosphate monobasic buffer and methanol at a ratio of (30:70, v/v).	1.0 ml/min	UV at 242 nm.	tablet formulation.	(91)

3. Conclusion

The current study provides an overview of the many analytical approaches for TMS and RVS detection in various matrices, including pharmaceutical formulations and serum and plasma samples, that have been reported in the literature. Analytical methods such as spectroscopy, chromatography, and electrochemical processes were used to quantify TMS and RVS both individually and in bulk tablet formulation. According to the results of this study, various methodologies were reported for estimation of TMS and RVS as a single in addition just a few analytical techniques based on UV-Vis spectrophotometry and HPLC are accessible for estimation of the binary mixture. HPLC with UV detection is also the method most frequently used to assess both medicines in the pharmaceutical matrix and other biological matrices since it delivers correct findings with minimal effort, according to the data for TMS and RVS analysis. A suggested HPLC fluorescence or UV could be applied in pharmaceutical dosage forms or biological fluids by utilizing a mobile phase consisting of acetonitrile and *o*-phosphoric acid.

- **Conflict of Interest**

The Authors declare no conflict of interest.

4. References

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